ASG
Anästhesie & Schmerztherapie

DIVI-Sektion
„Klinische Hämotherapie und
Hämostasemanagement“

Gerinnungsmanagement beim Polytrauma

FOAM-Live e.V.

Webinar, 05. November 2024

Heiko Lier

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Interessenskonflikte ?

Bild: https://gracegrapevine.wordpress.com

h.lier@asg-online.com

Vortragshonorare,
Reisekostenerstattungen o.ä.
erhielt ich von:

AstraZeneca
Bayer Vital
CSL Behring
DRK-Blutspendedienst West
Ferring
Mitsubishi Pharma
NovoNordisk
Werfen

“evidence-based“

evidence-based medicine = Evidenz-basierte Medizin

im Sinne von „Nachweise, Belege, Beweismaterial“

odds ratio (OR) *
Chancenverhältnis, relative Chance, Quotenverhältnis

relative risk oder risk ratio (RR) *
Verhältnis der Risiken in zwei Gruppen

hazard ratio (HR) *
Quotient zweier Ausfallraten

confidence interval (CI) **
Konfidenzintervall, Vertrauensintervall, Konfidenzbereich, Vertrauensbereich, Erwartungsbereich

* Wert von 1 heißt, beide Gruppen sind (statistisch) gleich
** Bereich von <1 bis >1 heißt, (statistisch) keine eindeutige Aussage möglich

⇒ statistische Wahrscheinlichkeiten, **aber nicht** absolute Gewissheit !!

Die Problematik?

TR-DGU® 2023: Hintergrund

Jahresbericht 2024

(S) Patient und Unfall	TR-DGU 2023		TR-DGU 10 Jahre	
Patienten im **Basiskollektiv** (n)	31.217		320.909	
Patientendaten	MW ± SA*/ %	n	MW ± SA*/ %	n
Alter [Jahre]	**54,5** ± 22,9	31.217	**52,8** ± 22,7	320.909
Kinder unter 16 Jahre	**3,8 %**	1.171	**3,9 %**	12.536
Ältere ab 70 Jahre	**30,1 %**	9.401	**27,7 %**	89.015
Geschlecht männlich	**69,6 %**	21.729	**69,6 %**	223.502
ASG 3-4 vor Trauma	**23,8 %**	6.994	**19,7 %**	57.844
BG-Fall (ab 2020)	**16,0 %**	4.030	**16,2 %**	15.829
Unfallmechanismus	%	n	%	n
Stumpf	**95,6 %**	28.073	**96,0 %**	292.151
Penetrierend	**4,4 %**	1.278	**4,0 %**	12.102
Unfallart / Ursache	%	n	%	n
Verkehrsunfall: Auto	**16,1 %**	4.964	**18,7 %**	59.195
... als PKW-Insasse (ab 2020)	**15,4 %**	4.746	**5,6 %**	17.607
... als LKW-Insasse (ab 2020)	**0,6 %**	181	**0,2 %**	715
... als Bus-Insasse (ab 2020)	**0,1 %**	37	**0,0 %**	149
Verkehrsunfall: Motorrad	**10,9 %**	3.354	**11,8 %**	37.421
Verkehrsunfall: Fahrrad	**11,8 %**	3.661	**10,6 %**	33.511
... mit unterstützem Fahrrad (ab 2020)	**1,7 %**	534	**0,6 %**	1.741
Verkehrsunfall: Fußgänger	**4,9 %**	1.518	**5,3 %**	16.808
Verkehrsunfall: E-Scooter	**0,8 %**	235	**0,2 %**	707
Sturz aus großer Höhe (> 3m)	**14,4 %**	4.451	**15,1 %**	47.878
Sturz aus niedriger Höhe (≤ 3m)	**29,0 %**	8.970	**26,9 %**	85.149
... ebenerdig (ab 2020)	**10,6 %**	3.284	**3,4 %**	10.877
Verdacht auf Suizid	**4,5 %**	1.383	**4,4 %**	13.859
Verdacht auf Verbrechen	**3,0 %**	918	**2,6 %**	8.093

* MW = Mittelwert; SA = Standardabweichung

Eine 10er Potenz mehr Alte als Kinder

immer ältere Patienten !

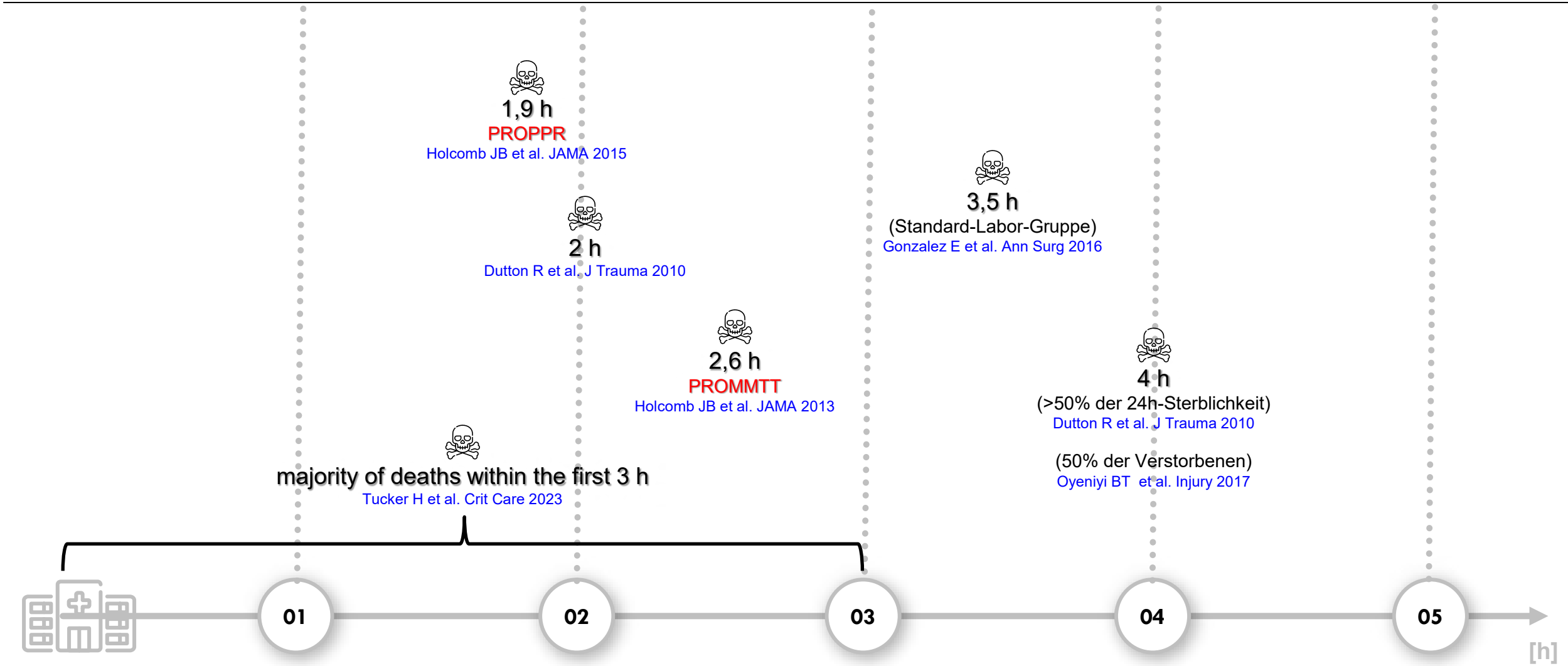
immer mehr deutlich vorerkrankte Patienten !

(noch) wenig Stich- und Schussverletzungen !

Verkehrsunfälle: 44,5%

größte Gruppe an Patienten !

Trauma & Tod durch Verbluten



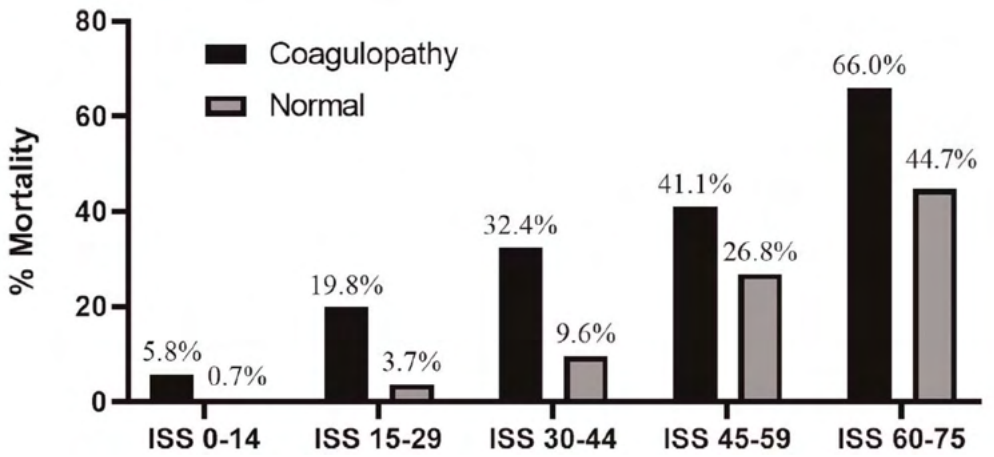
Trauma-Induced Coagulopathy:
Prevalence and Association with Mortality Persist Twenty Years Later.

Teeter W et al. Shock 2024

retrospective cohort study from 1/1/2018 to 12/31/2022 using prospectively collected institutional trauma registry data on all trauma admissions from two level 1 trauma centers (n=20,107); historical comparison with the study by MacLeod et al. J Trauma 2003 using MacLeod's definition for coagulopathy (initial prothrombin time (PT) or partial thromboplastin time (PTT) above normal per each center's reference range).

Current study patients were notably older (36±19 vs. 54±21 years), with less on-scene hypotension (26% vs. 10%), an overall lower mortality (8.9% vs. 6%) at comparable ISS (9 [4-16] vs. 10 [5-18]).
The **prevalence of eTIC remained high**: overall rate of **33.4%**, abnormal PT 32%, abnormal PTT 10.0%.

Koagulopathische Patienten haben ein **erhöhtes Sterberisiko.**
Je höher der ISS, desto häufiger eine Koagulopathie.
ABER: wenn bei geringer Verletzungsschwere eine Koagulopathie auftritt, bedeutet das ein besonders erhöhtes Sterberisiko !



Coagulopathy had a major impact on mortality over all ISS ranges, with the greatest impact in the lower ISS ranges. There was an 8.3-fold increase in mortality in coagulopathic patients with ISS ≤14, a 5.3-fold with ISS 15–29, while only a 1.2 -old increase with ISS ≥ 30.

Time to Early Resuscitative Intervention Association with Mortality in Trauma Patients at Risk for Hemorrhage.

Deeb AP et al. J Trauma Acute Care Surg 2023

combined secondary analysis of PAMPer and STAAMP; **time to early resuscitative intervention (TERI)** as time from emergency medical services arrival to packed red blood cells (pRBC), plasma, or TXA initiation in the field or within 90-minutes of trauma center arrival; 1504 propensity matched patients; median ISS 17

- Among the 1504 propensity matched patients, every 1-minute delay in TERI was associated with
  - 1.5% increase in odds of 24h mortality (aOR 1.015; 95%CI 1.001-1.029, p=0.03) and
  - 2% increase in the odds of 30d mortality (aOR 1.020; 95%CI 1.006-1.033, p<0.01).

- Among the 799 patients receiving an early resuscitative intervention, every 1-minute increase in TERI was associated with a
  - 2% increase in the odds of 24-hour mortality (aOR 1.023; 95%CI 1.005-1.042, p=0.01) and 30-day mortality (aOR 1.021; 95%CI 1.005-1.038, p=0.01).

TERI for **24-Hour Mortality**

- *pre-hospital*: adj. OR 0.423; 95%CI 0.217–0.836; p=0.028
- *hospital*: adj. OR 0.588; 95%CI 0.197–1.753; p=0.341

TERI for **30-Day Mortality**

- *pre-hospital*: adj. OR 0.365; 95%CI 0.227–0.576; p<0.001
- *hospital*: adj. OR 0.419; 95%CI 0.192–0.915; p=0.002

"… support should focus on increased availability of blood products and TXA in **areas with prolonged transport times** …"

“The treatment of bleeding is to stop the bleeding!”

Boffard KD et al. Transfusion 2009

Und das so schnell wie möglich!!

zunächst die vorübergehende **Versorgung stärkster, lebensbedrohlicher Blutungen** (das vorgestellte C / X), später dann Versorgung weiterer, **nicht-lebensbedrohlicher Blutungen** (das zweite C):

militärisch	<**C**>ABC (*„**c**atastrophic haemorrhage“*) Hodgetts TJ et al. Emerg Med J 2006
zivil	**c**ABCDE (*„**c**ritical haemorrhage“*) Maegele M. Dtsch Arztebl Int 2019
	xABCDE (*„e**x**anguinating haemorrhage“*) Ruggero JM et al. 2022

Comparing outcomes in patients with exsanguinating injuries: an Eastern Association for the Surgery of Trauma (EAST), multicenter, international trial evaluating prioritization of circulation over intubation (**CAB over ABC**).

Ferrada P et al. World J Emerg Surg 2024

prospective observational study; 6 international trauma centers; 278 trauma patients with a systolic blood pressure lower than 90 mm Hg, intubated within 30 min of arrival: 171 (61.5%) CAB vs.107 (38.5%) ABC;

cABC group had

- **significantly lower 24-hour mortality rate** (11.1% vs. 69.2%, P<0.001)
- lower rate of renal failure (14.6% vs. 22.4%, P=0.107)
- higher rate of ARDS (4.7% vs. 0.9%, P=0.160)

In multivariable logistic regression, **cABC group** had

- **91% reduction in the odds of mortality within 24 h** (aOR: 0.09; 95% CI: 0.04–0.18; P<0.001; AUROC of 0.86 [95% CI 0.81–0.90])
- **89% reduction in the odds of mortality at 30 days** (aOR: 0.11; 95% CI: 0.05–0.23; P<0.001; AUROC of 0.83 [95% CI 0.78–0.88])

"CAB approach it is likely to be more useful in **patients with penetrating injuries** and **without traumatic brain injury**."

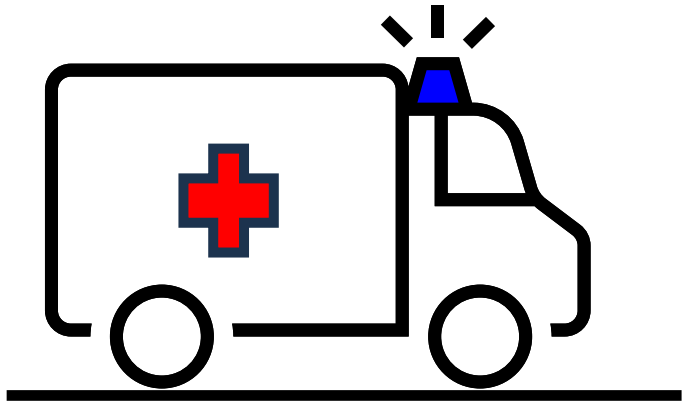
Short-term versus long-term trauma mortality: A systematic review.

Frydrych LM et al. J Trauma Acute Care Surf 2019

16 studies, between 1991 and 2017; 208,412 trauma patients; 11 studies (186,864 patients) were from United States cohorts, two were from Canada, and one each from Germany, Switzerland and Sweden.

	postdischarge general mortality	postdischarge trauma mortality
3-6 months	1.3%	4.6%
2-3 years	2.2%	15.8%
5-25 years	15.6%	26.3%

Was ist präklinisch?



TR-DGU® 2023: präklinische Dauer

Jahresbericht 2024

2010
72 ± 52 [min]
6.249

Jahr	2019	2020	2021	2022	2023
TR-DGU	62 [min]	64 [min]	65 [min]	66 [min]	66 [min]
n:	10.944	11.135	10.518	11.284	11.400
Min. – Max.	5-240 [min]	5-240 [min]	5-240 [min]	5-240 [min]	5-240 [min]

… es wird nicht (mehr) schneller …

TR-DGU® 2023: Unfallort

Jahresbericht 2024

Zeitpunkt A: Befund am Unfallort	TR-DGU 2023		TR-DGU 10 Jahre	
Primär versorgte Patienten (n) (%-Anteil vom Basiskollektiv)	28.718 (92 %)		293.047 (91 %)	
Glasgow Coma Scale (GCS) [Punkte]	**12,8** ± 3,2	2[illegible]7	**12,7** ± 3,9	2[illegible]383
Befunde	%	n	%	n
Schock (systolischer Blutdruck ≤ 90 mmHg)	**8,2 %**	1.952	**8,3 %**	20.855
Bewusstlos (GCS ≤ 8)	**15,1 %**	3.876	**16,0 %**	42.995
Therapie	%	n	%	n
Herzdruckmassage	**3,0 %**	871	**2,9 %**	8.483
Präklinische Thorakotomie (seit 2020)	**0,2 %**	64	**0,1 %**	181
Endotracheale Intubation	**18,0 %**	5.181	**19,6 %**	57.544
Alternativer Atemweg	**0,8 %**	237	**1,1 %**	3.124
Chirurgischer Atemweg (seit 2020)	**0,1 %**	19	**0,0 %**	63
HWS-Immobilisierung (seit 2020)	**58,3 %**	14.258	**61,7 %**	56.476
Analgosedierung **	**49,0 %**	14.086	**35,8 %**	104.952
Thoraxdrainage (mit und ohne Nadeldekompression) **	**3,0 %**	867	**1,9 %**	5.687
... nur mit Nadeldekompression (seit 2020)	**0,7 %**	199	**0,2 %**	622
Katecholamine **	**8,3 %**	2.384	**5,3 %**	15.649
Beckengurt **	**16,0 %**	4.581	**8,0 %**	23.326
Tourniquet (seit 2020)	**1,6 %**	461	**0,5 %**	1.476
IO-Zugang (seit 2020)	**1,5 %**	440	**0,5 %**	1.611
Tranexamsäure	**16,3 %**	4.691	**8,9 %**	25.962
Volumengabe	**MW** ± SA*/ %	n	**MW** ± SA*/ %	n
Patienten ohne Volumengabe	**22,3 %**	5.749	**19,6 %**	53.367
mit Volumengabe	**77,7 %**	20.047	**80,4 %**	219.095
mit Kolloidgabe	**1,9 %**	465	**2,9 %**	7.549
Menge bei Pat. mit Volumen [ml]	**572** ± 509	25.796	**615** ± 530	272.462
bei Pat. mit und ohne Volumengabe [ml]	Median **500**		Median **500**	

deutliche Zunahme!

deutliche Zunahme!

deutliche Zunahme!

* MW = Mittelwert; SA = Standardabweichung

** im reduzierten QM-Datensatz nicht verfügbar

European Trauma 6th ed.
Rossaint R et al. Crit Care 2023
SI ≥ 0.9–1.0 (Rec. 5; 1C)

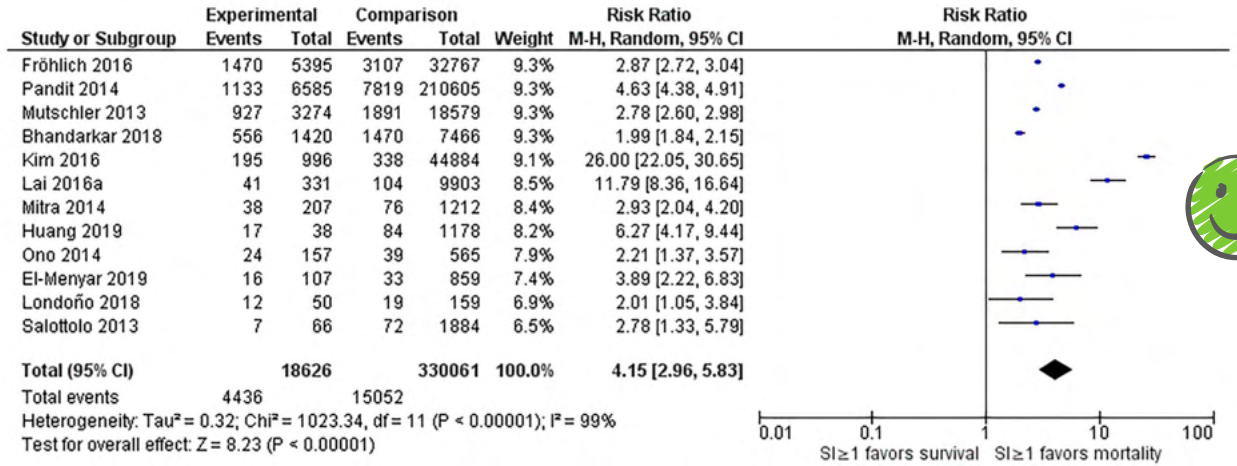
Shock index as a predictor for mortality in trauma patients: a systematic review and meta-analysis

Vang M et al. Eur J Trauma Emerg Surg 2022

dito
Gianola S et al.
J Trauma Acute Care Surg 2022

systematic review; reporting according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); using PICOS (population, intervention, comparison, outcome and study design) format; until 30 June 2021; 12 studies including a total of 348,687 participants

Shock Index (SI) is defined as heart rate divided by SBP.



Study or Subgroup	Experimental Events	Experimental Total	Comparison Events	Comparison Total	Weight	Risk Ratio M-H, Random, 95% CI
Fröhlich 2016	1470	5395	3107	32767	9.3%	2.87 [2.72, 3.04]
Pandit 2014	1133	6585	7819	210605	9.3%	4.63 [4.38, 4.91]
Mutschler 2013	927	3274	1891	18579	9.3%	2.78 [2.60, 2.98]
Bhandarkar 2018	556	1420	1470	7466	9.3%	1.99 [1.84, 2.15]
Kim 2016	195	996	338	44884	9.1%	26.00 [22.05, 30.65]
Lai 2016a	41	331	104	9903	8.5%	11.79 [8.36, 16.64]
Mitra 2014	38	207	76	1212	8.4%	2.93 [2.04, 4.20]
Huang 2019	17	38	84	1178	8.2%	6.27 [4.17, 9.44]
Ono 2014	24	157	39	565	7.9%	2.21 [1.37, 3.57]
El-Menyar 2019	16	107	33	859	7.4%	3.89 [2.22, 6.83]
Londoño 2018	12	50	19	159	6.9%	2.01 [1.05, 3.84]
Salottolo 2013	7	66	72	1884	6.5%	2.78 [1.33, 5.79]
Total (95% CI)		**18626**		**330061**	**100.0%**	**4.15 [2.96, 5.83]**
Total events	4436		15052			

Heterogeneity: Tau² = 0.32; Chi² = 1023.34, df = 11 (P < 0.00001); I² = 99%
Test for overall effect: Z = 8.23 (P < 0.00001)

- **in-hospital mortality**: SI ≥1 RR 2.16 (95%CI 1.57–2.97).
- **30-day mortality**: SI ≥1 RR 2.73 (95% CI 2.08–3.57) and SI ≥0.9 RR 3.02 (95% CI 1.83–4.96).
- **massive blood transfusion**: SI ≥1 and SI ≥0.9 2x ↑ prehospital and 3x ↑ in ED
- **ICU admission**: SI ≥1 RR 1.43 (95% CI 1.05–1.95).

"Due to statistical heterogeneity and risk of bias across studies, the overall quality of evidence was low, and the effect size should as a result be interpreted with care."

Cave: SI ≥0,9 bzw. 1 (d.h., HF ≥ SBP) deutet auf ein Risiko hin; SI <0,9 heißt nicht, dass kein Risiko besteht.

Schockindex und Überleben

Shock index as predictor of massive transfusion and mortality in patients with trauma: a systematic review and meta-analysis

Carsetti A et al. Crit Care 2023

systematic review; reporting according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P); using quality assessment of diagnostic accuracy studies (QUADAS-2) and Grading of Recommendations Assessment, Development and Evaluation (GRADE); 35 studies (10x pre-hospital, 22x in-hospital, 3x both; only 1 prospective) including a total of 670,728 participants

Shock Index (SI) is defined as heart rate divided by SBP.

Caveat: chronic hypertension, diabetes mellitus, coronary heart disease, age (**age-SI** = SI x age in years; risk if >50)

- **Prediction of massive transfusion** (15 studies):
  - *overall*: sensibility 0.68 [0.57; 0.76]; specificity 0.84 [0.79; 0.88]; AUC 0.85 [0.81; 0.88]
  - *prehospital*: sensitivity 0.67 [0.50; 0.81]; the specificity 0.83 [0.75; 0.89]; AUC 0.84 [0.81; 0.87]
  - *in-hospital*: sensitivity 0.771 [0.584;0.890]; specificity 0.775 [0.674; 0.852]; AUC 0.841

- values correlated with the degree of shock and impaired tissue perfusion
- SI > 1 → suspect hemorrhagic shock

- **Prediction of mortality** (26 studies, different timepoint for mortality definition):
  - *overall*: sensibility 0.358 [0.238; 0.498]; specificity 0.742 [0.656; 0.813]; AUC 0.553
  - *prehospital*: sensitivity 0.886 [0.064; 0.998]; specificity 0.389 [0.072; 0.837]; AUC 0.590
  - *in-hospital*: sensitivity 0.462 [0.349; 0.580]; specificity 0.780 [0.699; 0.855]; AUC 0.638
  - *hospital mortality* (most frequently reported timepoint for mortality assessment, 12 studies): sensitivity 0.325 [0.161; 0.547]; specificity 0.736 [0.600; 0.838]; AUC 0.5315

- normal SI may be useful to identify patients with a low risk of mortality

"… not … as the sole parameter …"

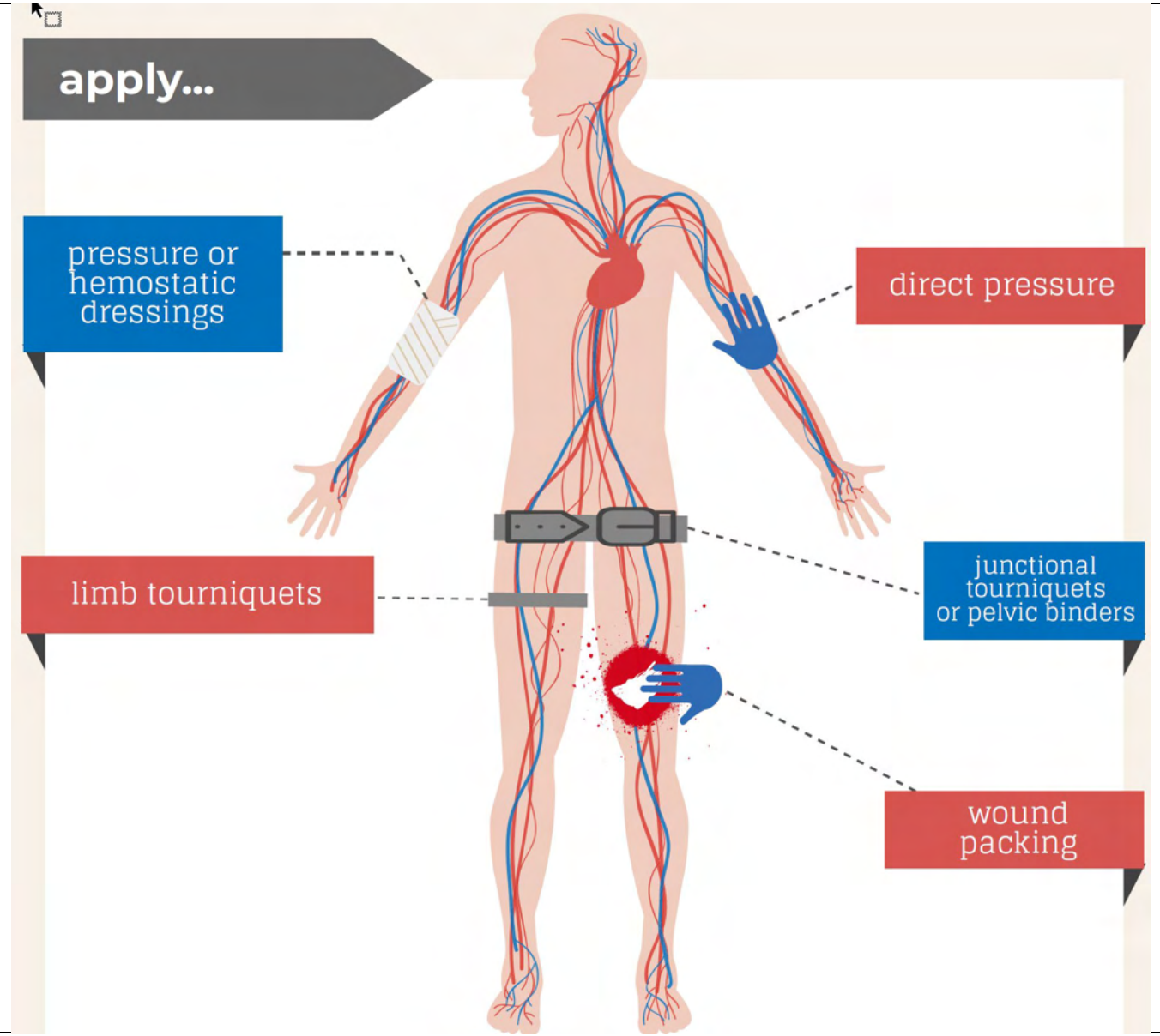
Basismaßnahmen?

externe Blutstillung

To stop or reduce hemorrhage as close to time-of-injury as possible,

Joint Trauma System

Clinical Practice Guidelines



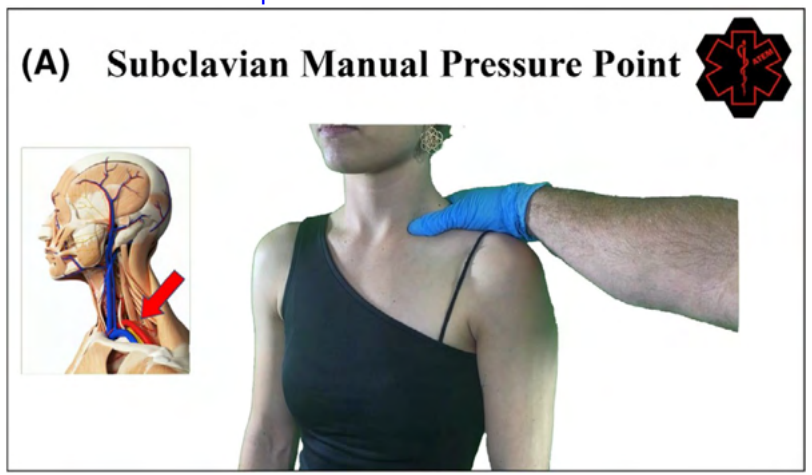
Stufenschema bei aktiven Blutungen

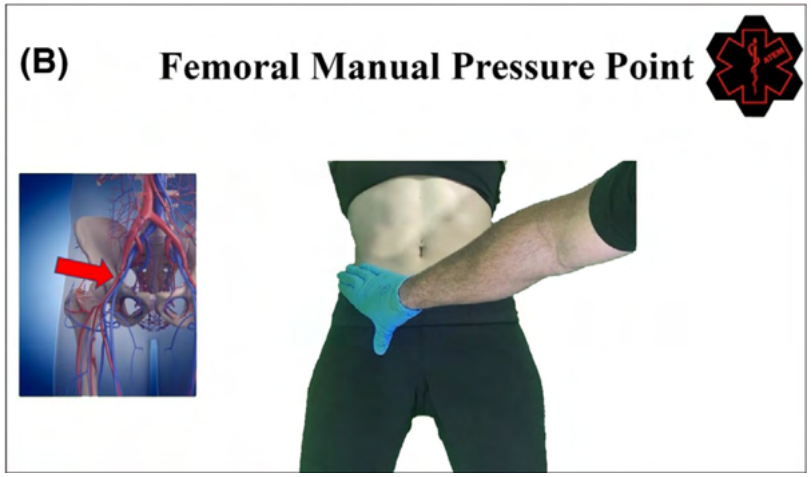
manuelle Kompression	• Repetitive Kontrollen, ob die Blutung zum Stillstand gekommen ist, sollten nicht durchgeführt werden. (1.1.6; **GPP**)
Kompressionsverband	• bei penetrierendem Trauma mit nach außen blutenden Verletzungen am Torso und an den Extremitäten (1.1.7; **GoR B**) • an Torso und an den Extremitäten nach stumpfem Trauma (1.1.8; **GPP**)
Hämostyptikum	• Hämostyptika auf jeder Stufe ergänzend (1.1.13; **GoR 0**) • Bei blutenden Stichwunden, … Fremdkörper bereits wieder entfernt … Länge von mind. 3 cm … direkte Wundtamponade mit Chitosan. (1.1.11; **GoR A**) • Bei Schuss- und Explosionsverletzungen mit aktiver Blutung … Verbände mit Chitosan. (1.1.12; **GoR B**) • Bei Kopfschwartenverletzungen mit aktiver Blutung sollten Chitosan-Wundauflagen. (1.1.14; **GoR B**)
Tourniquet	• wenn eine lebensgefährliche Blutung mit anderen Maßnahmen nicht zeitgerecht gestoppt werden kann. (1.1.9; **GoR A**) • sollte, …, die Fortsetzung der Maßnahme und ein möglicher Verfahrenswechsel kritisch geprüft werden. (1.1.10; **GPP**)

Abdrückpunkte am Stamm

The effectiveness of the manual pressure points technique for hemorrhage control—The 2022 THOR pre-conference meeting experience.

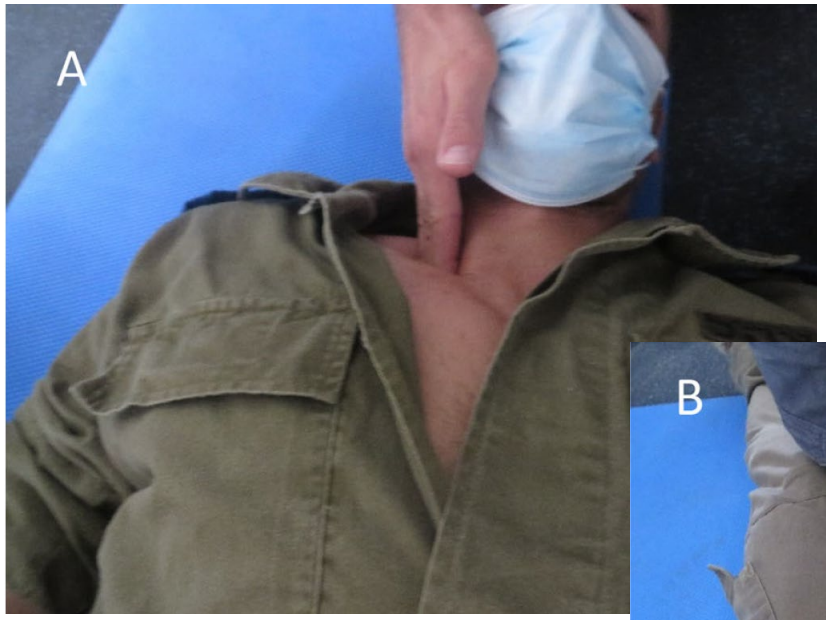
Thompson P et al. Transfusion 2023





Manual Pressure Points Technique for Massive Hemorrhage Control—A Prospective Human Volunteer Study.

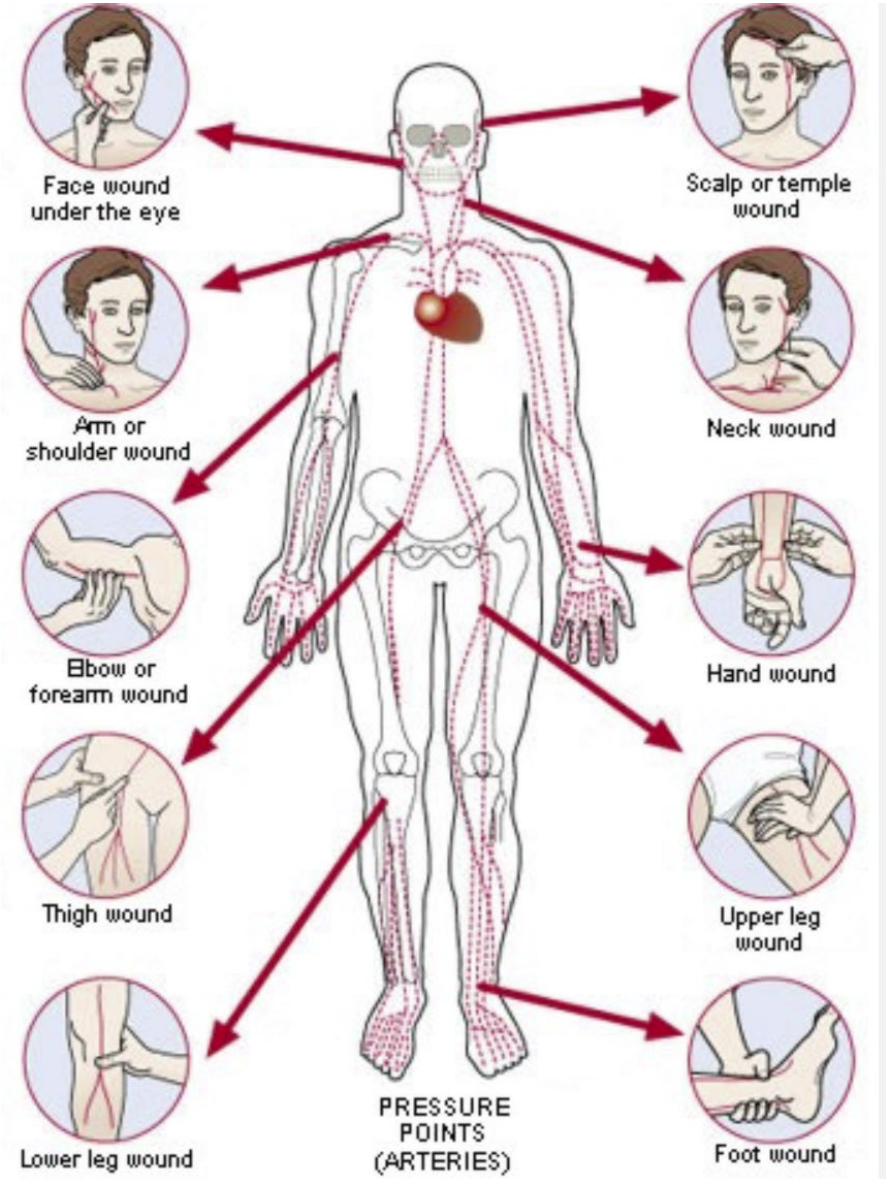
Gravriely RP et al. Prehosp Emerg Care 2022



- subclavian artery pulsation in the supra-clavicular fossa.
- arm in the neutral anatomic position
- pressure with their second through fourth digits inferiorly **against the first rib** to stop blood flow

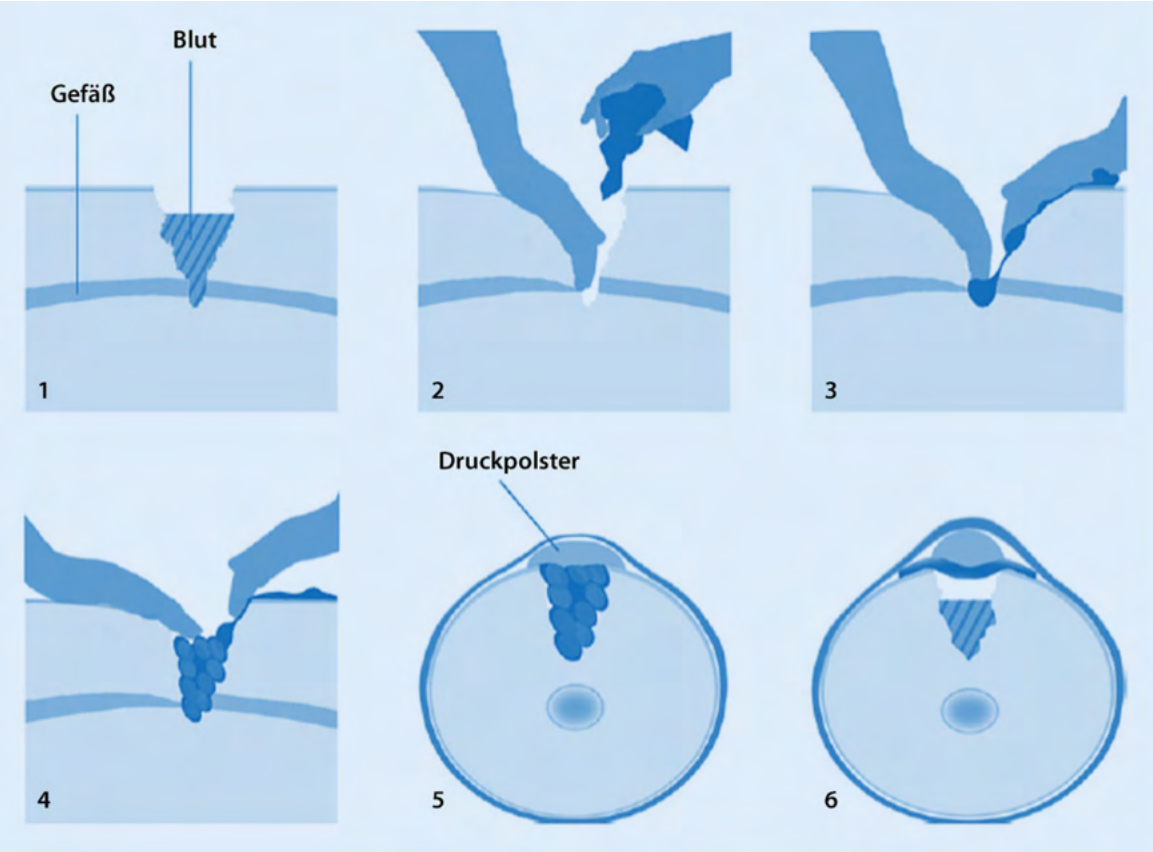
- femoral artery pulse at the femoral crease
- thigh in slight external rotation
- pressure posteriorly using either the metacarpo-phalangeal or the proximal interphalangeal joints **against the pelvic bone**

Abdrückpunkte



U.S. Navy Training Manual 14191

externe Blutstillung
präklinisches „wound packing“



Blutungsquelle in der Tiefe der Wunde

↓

„wound packing“

↓

Austamponieren der Wunde bzw. der Wundhöhle mit flexiblem, sterilem Verbandmaterial mit folgendem Druckverband

Üben
Üben
Üben !

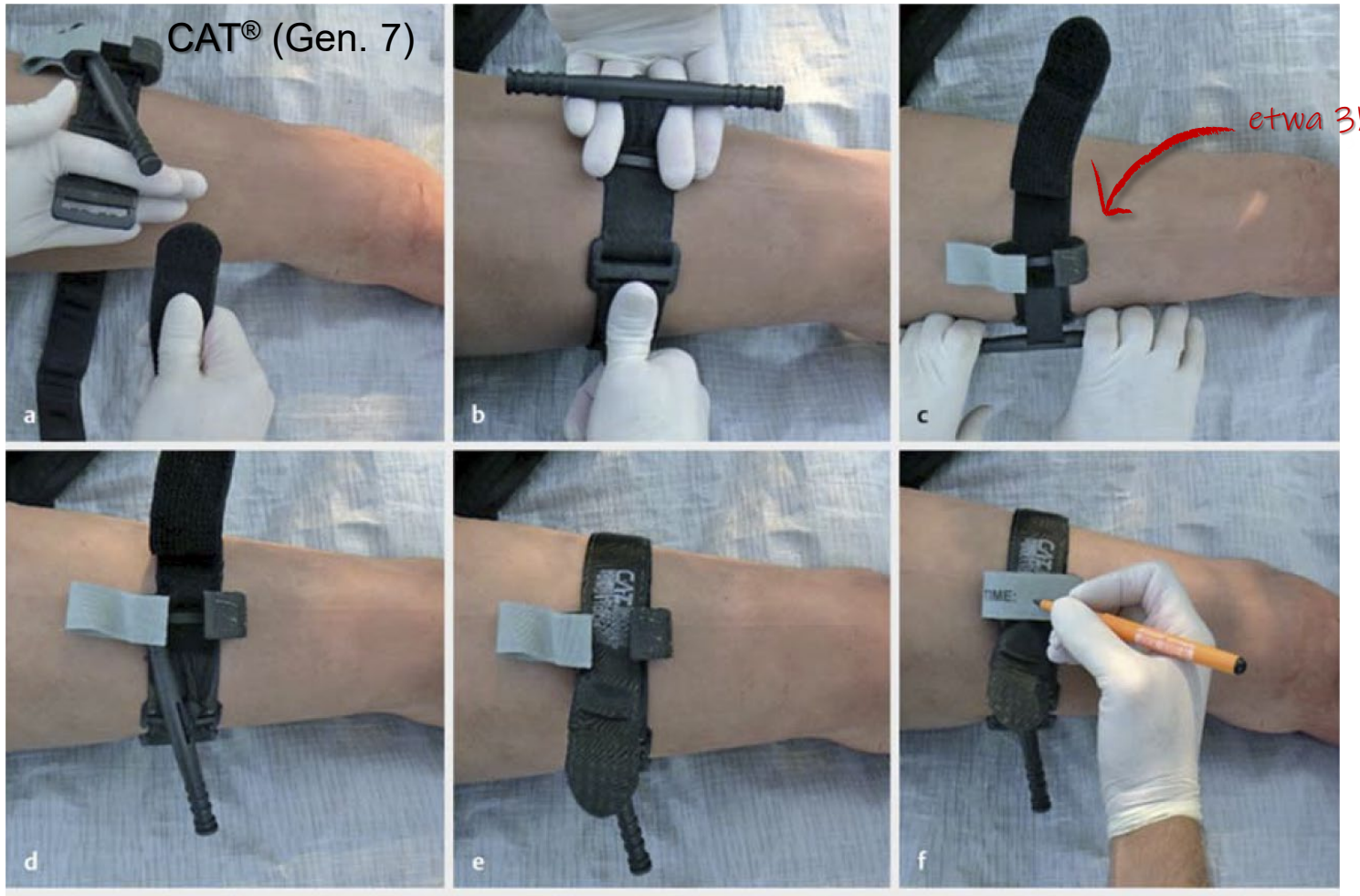
Realitätsnahes Training des „Packings“ an Schlachtteilen. Quelle: Florent Josse.

Helm M et al. Notfall Rettungsmed 2018 und Josse F et al. AINS 2020

Wissenschaftlicher Arbeitskreis Notfallmedizin
Arbeitsgruppe „Taktische Medizin"

Prähospitale Strategien zur Minimierung des Blutverlustes.

Josse F et al. Anästh Intensivmed 2020



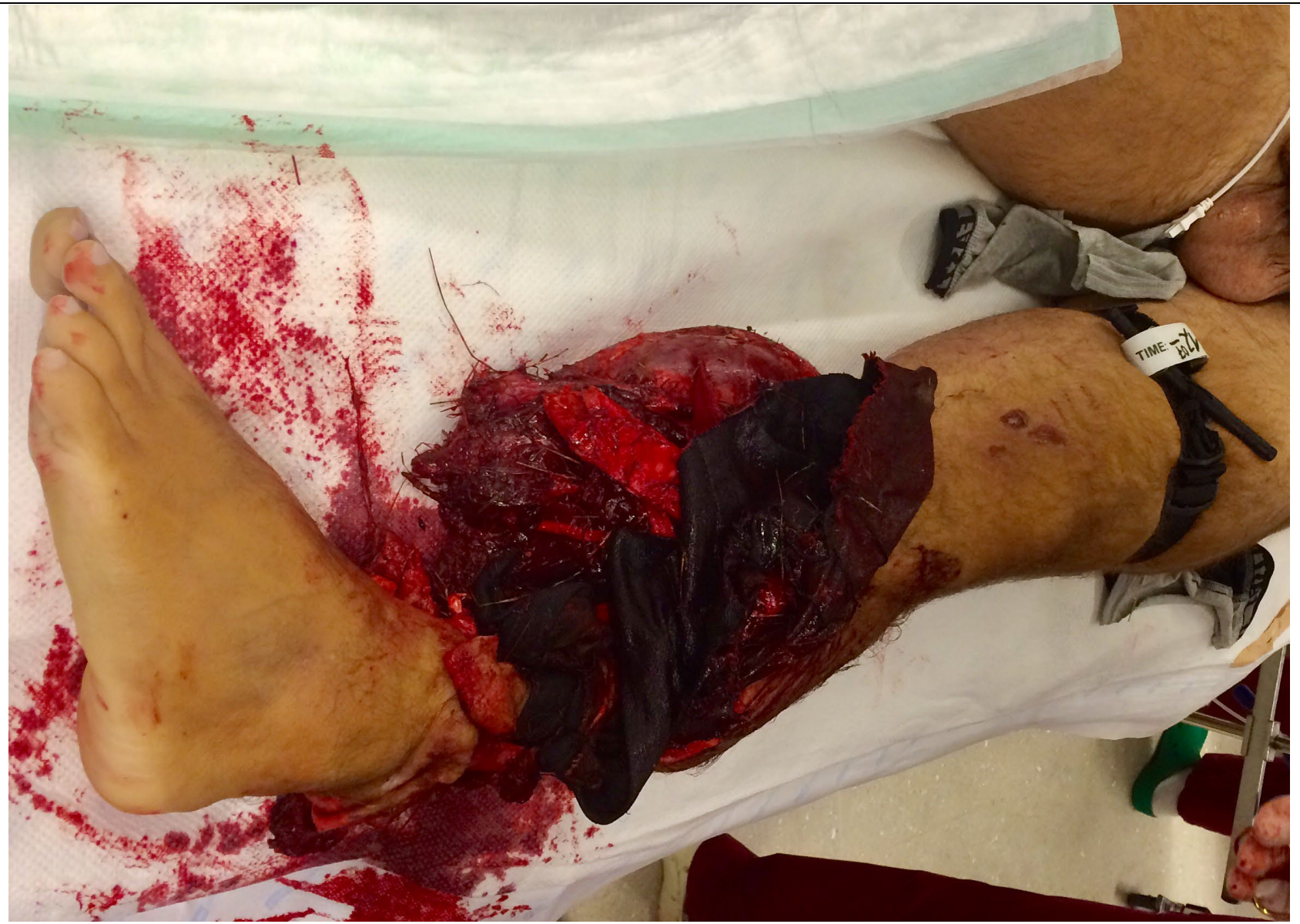
etwa 3¼ Knebelumdrehungen

weitestgehend problemlos
wenn ≤2h; deutlich
↑Komplikationen bei >4h
Joarder M et al. Injury 2023

Weitere wichtige Punkte:

- Nur wenn eine Kompression der Wunde nicht ausreicht oder in der gegebenen Situation nicht praktikabel ist
- Initial bis zum Pulsverlust distal, danach **stetige Re-Evaluation**
- Zeitpunkt dokumentieren
- **Nie** die mit Tourniquet versorgte Extremität **zudecken**
- medikamentöse **Analgesie**

Tourniquet



mit freundlicher Genehmigung von PD Dr. B. Hossfeld, Ulm

Rethinking limb tourniquet conversion in the prehospital environment.

Holcomb JB et al. J Trauma Acute Care Surg 2023

life-saving standard of care, especially when used as soon as possible after injury

ABER: up to 49% of military and 53% of civilian extremity tourniquets may (in hindsight) not have been necessary

- < 2 hours has proven safe
- < 6 hours should have TC or TR attempted
- > 6 h increased need for limb amputation

tourniquet conversion (TC) → Umwandlung in Druckverband mit Hämostyptikum

tourniquet replacement (TR) → Ersatz eines „high & tight"-Tourniquet durch ein neues Tourniquet in unmittelbarer Nähe der lebensbedrohlichen Blutung (pulsatieler / konstanter Fluss, durchtränkter Verband / Kleidung, Blut-"Laache" auf Boden, Amputation)

« tourniquet conversion (TC) »	« tourniquet replacement (TR) »	Tourniquet BELASSEN
Wunde zugänglich für Druckverband & Hämostyptikum **UND** 1. kein Schock **UND** 2. Wunde gut sichtbar (neue Blutung?) **UND** 3. keine Amputation ⇒ **immer, wenn < 2h**	wenn • initiales Tourniquet nicht wirksam • neue Lokalisation / neuer Druck notwendig → Neuanlage möglichst distal (Handbreit proximal der Wunde) ⇒ **immer, wenn < 2h**	wenn • (drohende) Amputation • gescheiterter TC-Versuch • > 6 h

Wissenschaftlicher Arbeitskreis Notfallmedizin
Arbeitsgruppe „Taktische Medizin“

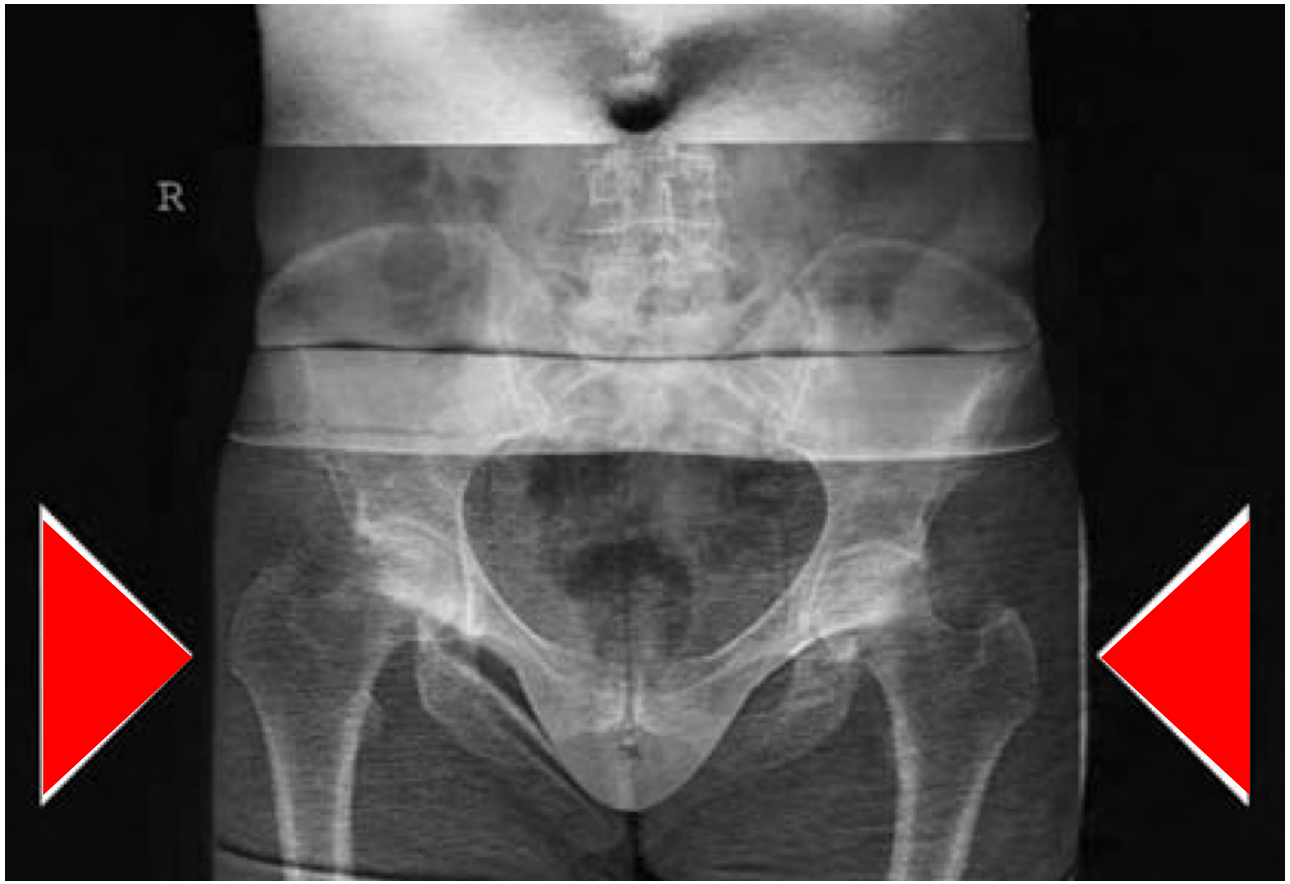
Prähospitale Strategien zur Minimierung des Blutverlustes.

Josse F et al. Anästh Intensivmed 2020

Schematische Darstellung der korrekten Anlagehöhe einer Beckenschlinge exakt auf Höhe der Trochanteres majores.

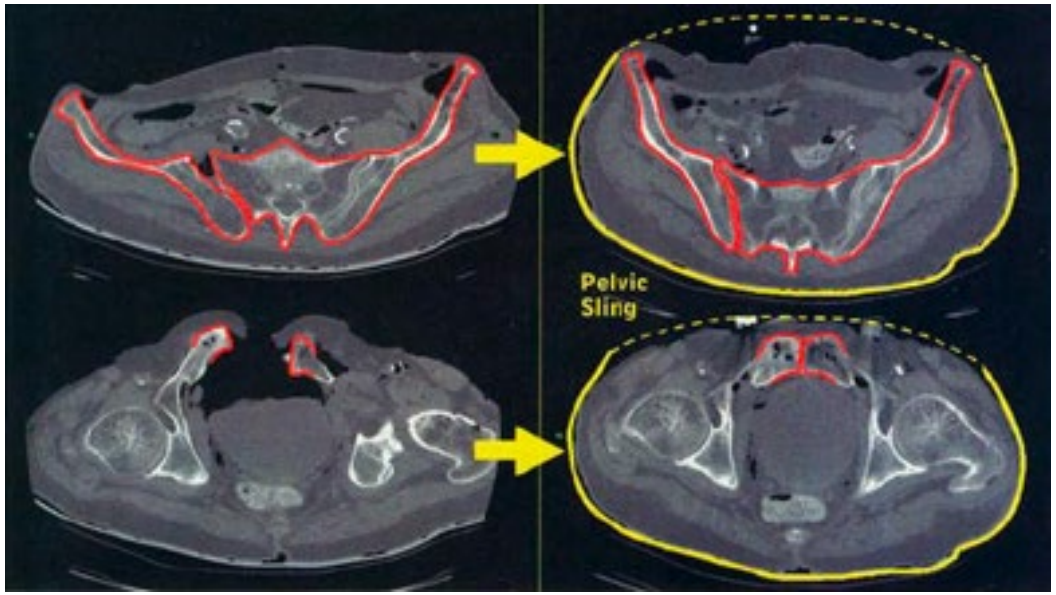
Quelle: S. Thierbach.

„Trochanter-Schlinge“



externe Blutstillung

„Beckenschlinge“



Letalität (n=104): 33,3 % vs. 19,1 %

Esmer E et al. Unfallchir 2015

- pelvine Massenblutung selten, aber vital bedrohlich
- ext. Stabilisierung kann nur bei **„open-book-fracture“** effektiv sein
- Kompression kann Weichteilschäden verursachen
- einmalige Prüfung der Stabilität
- Hämodynamische Instabilität muss in die Indikation miteinbezogen werden !

Roessler MS et al. Notfall Rettungsmed 2021

Die Rahmenbedingungen?

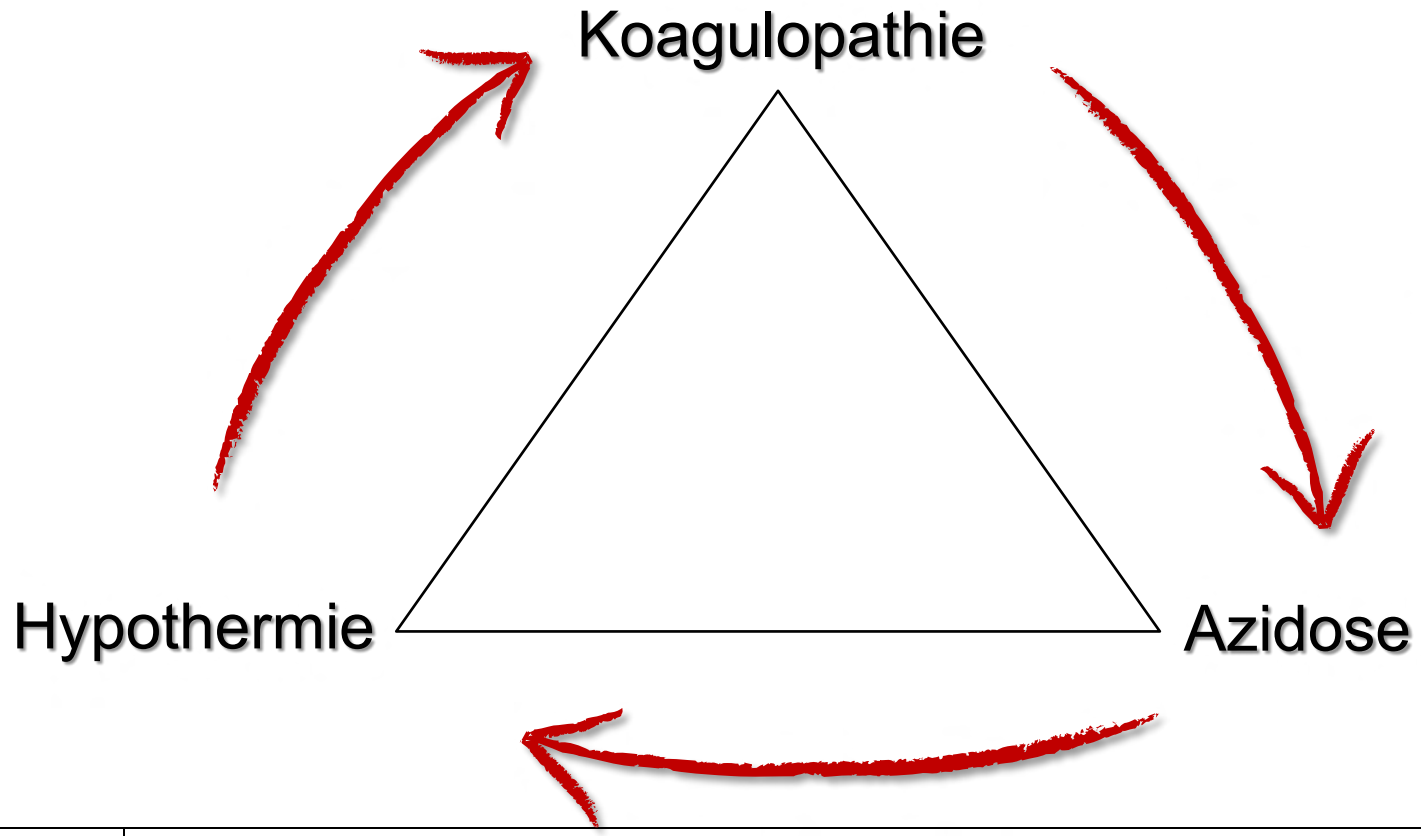
Rahmenbedingungen der Gerinnung
Azidose + Hypothermie

"The **lethal triad** of coagulopathy, hypothermia, and acidosis"

Moore EE eta l. Am J Surg 1996

"The trauma **triad of death**: hypothermia, acidosis, and coagulopathy"

Mikhail J. AACN Clin Issues 1999



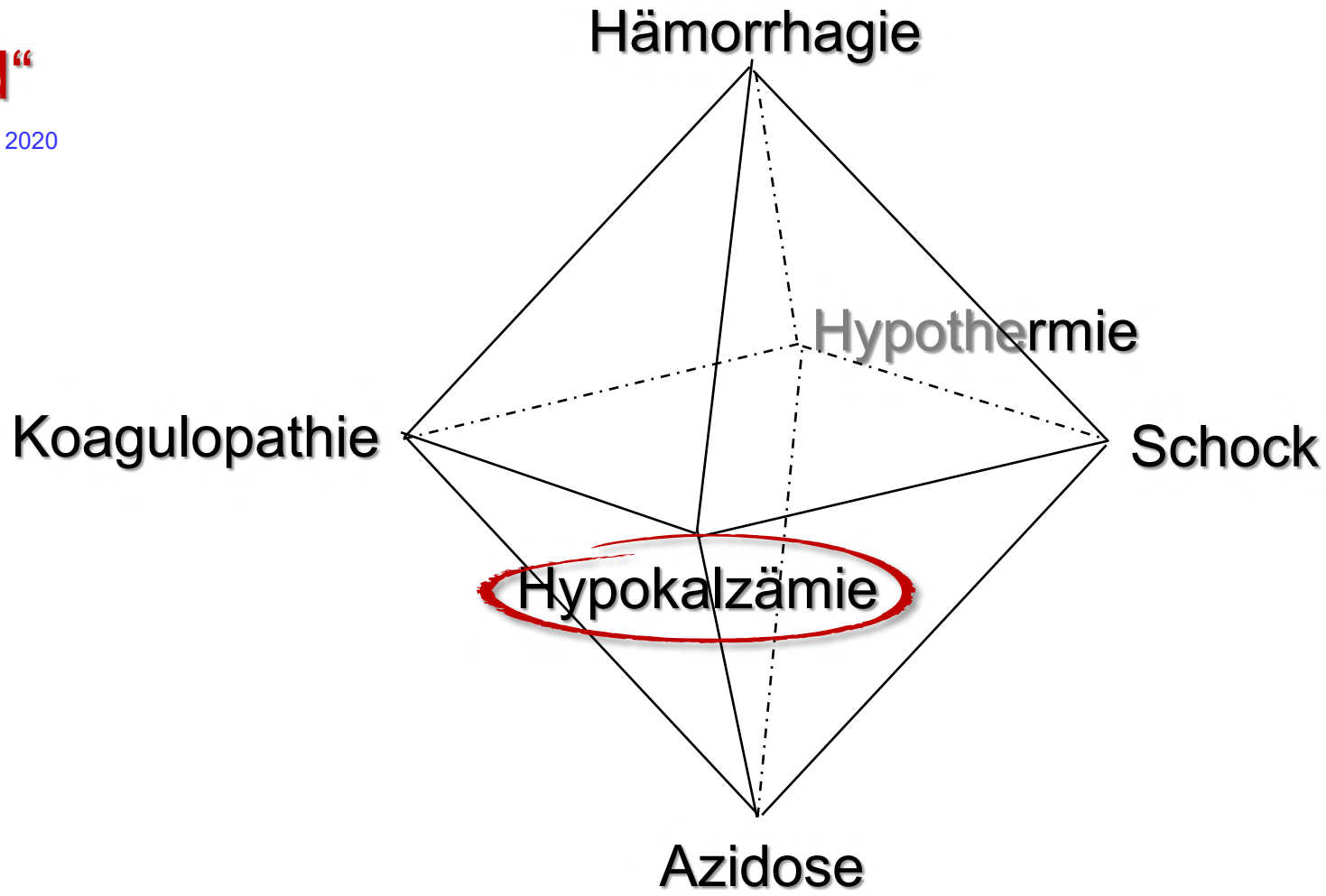
"bloody vicious cycle of hemorrhagic shock"

Kashuk JL et al. J Trauma 1982

Rahmenbedingungen der Gerinnung
Ca^{2+}

“death diamond“

Ditzel RM Jr et al. J Trauma Acute Care Surg 2020

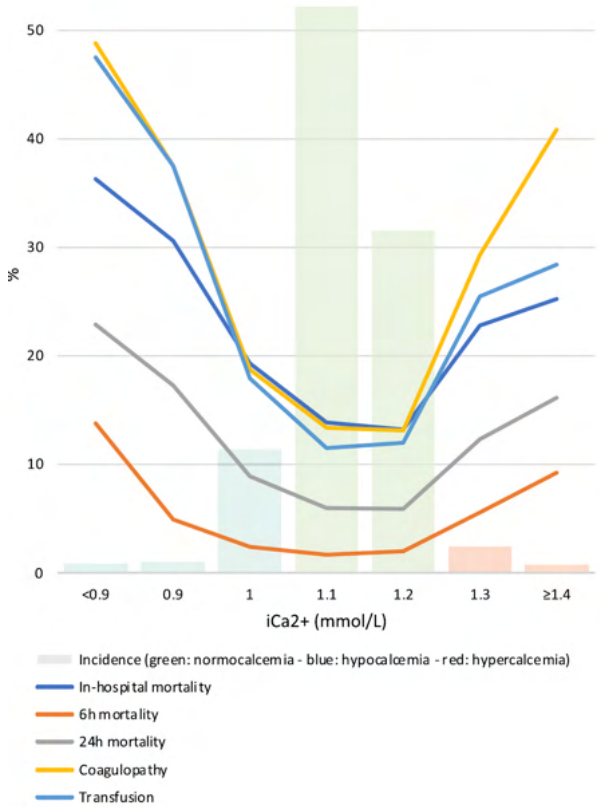


Rahmenbedingungen der Gerinnung
prähospitales Ca^{2+}

Trauma-induced disturbances in ionized calcium levels correlate parabolically with coagulopathy, transfusion, and mortality: a multicentre cohort analysis from the TraumaRegister DGU®.

Helsloot D et al. Crit Care 2023

TraumaRegister DGU®; 30,183 adult major trauma patients (AIS ≥3); values on admission to ED: **13.2% hypocalcemia** (<1.10 mmol/l) and **3.2% hypercalcemia** (≥1.30 mmol/l), most pat. (83.6%) normocalcemic



mortality at 6 h:

- **Ca_i^{2+} <0.90 mmol/L** OR 2.69, 95% CI 1.67–4.34; P<0.001,
- **Ca_i^{2+} 1.30–1.39 mmol/L** OR 1.56, 95% CI 1.04–2.32, P=0.030
- **Ca_i^{2+} ≥1.40 mmol/L** OR 2.87, 95% CI 1.57–5.26; P<0.001

mortality at 24 h:

- **Ca_i^{2+} 1.00–1.09 mmol/L** OR 1.25, 95% CI 1.05–1.48; P = 0.0011

In-hospital mortality:

- **Ca_i^{2+} 1.00–1.09 mmol/L** OR 1.29, 95% CI 1.13–1.47; P < 0.001

Ca_i^{2+} <0.90 mmol/L → 36.3% in-hospital mortality (highest mortality),
48.8% coagulopathy,
47.5% transfusion

Icons made by https://www.infoDiagram.com/

Hypocalcaemia upon arrival (HUA) in trauma patients who did and did not receive prehospital blood products: a systematic review and meta-analysis.

Rushton TJ et al. Eur J Trauma Emerg Surg 2024

meta-analysis, PRISMA guidelines; trauma pat. with ISS ≥15; 14 studies; until 31 March 2023; mean ISS 27;

mean Ca_i^{2+} [mmol/L] on arrival to ED:

- **prehospital blood** (4 studies, 426 pat.)**:** 1.10, 95% CI 0.94–1.26
- **no prehospital blood** (12 studies, 1661 pat.)**:** 1.07, 95% CI 1.01–1.14
- **complete group** (16 studies, 2087 pat.)**:** 1.08, 95% CI 1.02–1.13

mean difference in Ca_i^{2+} [mmol/L] on arrival to ED:

- **prehospital blood vs. no blood** (3 studies, 278 pat. vs. 283 pat.)**:** -0.03, 95% CI -0.04 to -0.03

"… hypocalcaemia is a **common metabolic disturbance in the trauma patient**, outside of blood transfusion …"

"… whilst blood products do play a role in the pathogenesis of hypocalcaemia in this population, it is not the sole cause …"

"… lack of consistency in the existing literature concerning the definition of hypocalcaemia in trauma…."

prähospitale Laborwerte?

Trauma und Laborwerte?

Nur ein Beispiel von vielen Firmen, die POC-"hand held"-Geräte anbieten !!

i-STAT handheld® (Abbott)

Point-of-care laboratory testing to obtain

- hemoglobin,
- base deficit,
- lactate, and potentially
- international normalized ratio (INR;

  currently in validation due to vibratory environment)

used in helicopter EMS at Mayo Clinic, Rochester, Minnesota, USA

Jenkins D et al. Shock 2014

prähospital: Tranexamsäure (TXA)?

Systemic hemostatic agents initiated in trauma patients in the pre-hospital setting: a systematic review.

Biffi A et al. Eur J Trauma Emerg Surg 2023

systematic review; according to **PRISMA**, **GRADE** and **NICE**; five RCT on TXA: CRASH-2 (11 publications), CRASH-3 (2 publications), TXA trial (2 publications), STAAMP, and TAMPITI; no eligible study on the prehospital use of fibrinogen concentrates, recombinant activated coagulation factor VII, prothrombin complex concentrates

- **statistically significant** difference including **clinical relevance** between TXA and placebo for **overall mortality at 24 h**:
  RR = 0.83, 95% CI = 0.74–0.95; two studies (STAAMP, CRASH-2), 21,030 patients
  ⇒ 8 fewer deaths per 1.000 at 24 h

- statistically but **not clinically significant** reduction at **1 month** in the TXA group:
  RR = 0.93, 95% CI = 0.88–0.97; five studies (CRASH-2, CRASH-3, TXA, STAAMP, TAMPITI), 34,873 patients
  ⇒ 12 fewer deaths per 1.000 at 1 month

Effekt von prähospitaler TXA ist vorhanden, aber im Promillebereich

- **no reduction in overall mortality at 1 month** by TXA in patients with
  - **TBI**: RR = 0.96, 95% CI = 0.89–1.03; two studies (CRASH-3, TXA), 13,703 participants or
  - **TBI and significant hemorrhage**: RR = 0.72; 95% CI = 0.49–1.05, three studies, 587 participants

Prehospital Tranexamic Acid for Severe Trauma.

PATCH-trauma

Gruen RL et al. NEJM 2023

international, double-blind, randomized, placebo-controlled trial in 15 emergency medical services in Australia, New Zealand, and Germany; 1310 pat.: 661x TXA (1g prehospitally within 3h + 1g/8h in hospital) vs. 646x saline additionally to standard therapy (~35% RBC, ~4% plasma); at high risk of coagulopathy (COAST score ≥3); median ISS: TXA 29 (18-41) vs. Placebo 29 (17-38); >90% blunt trauma; 24.1% had laboratory evidence of early coagulopathy;

- favorable functional outcome (a GOS-E level of ≥5) after 6 month: TXA 53.7% vs. Placebo 53.3%
  (absolute difference 0,2%, 95%CI -5,6 to 6,0; risk ratio [RR] 1.0; 95%CI 0.90-1.12, p=0.95)
  - … **for AIS head >2**: TXA 35.4% vs. Placebo 38.2% (RR 0.93; 95%CI 0.73-1.18)
  - … **for AIS head <2**: TXA 70.2% vs. Placebo 66.1% (RR 1.06; 95%CI 0.96-1.18)

"… no significant between group difference …"

"… the effect of TXA on early death and death due to bleeding was consistent with … CRASH-2 trial, …"

- mortality:
  - at **24h**: TXA 9.7% vs. Placebo 14.1% (RR 0.69; 95%CI 0.51-0.94)
  - at **28d**: TXA 17.3% vs. Placebo 21.8% (RR 0.79; 95%CI 0.63-0.99)
  - at **6 month**: TXA 19.0% vs. Placebo 22.9% (RR 0.83; 95%CI 0.67-1.03)

"… every 100 patients …4 extra patients alive at 6 months; however, approximately 4 extra patients … having severe disability…."

- one or more vascular occlusive events: TXA 23.6% vs. Placebo 19.7% (RR 1.20; 95%CI 0.97-1.48)

"… little evidence? that tranexamic acid increased the risk of such events…"

Tranexamsäure kann ggf. Leben retten

Kommentar zu

Prehospital Tranexamic Acid for Severe Trauma.

PATCH-trauma

Gruen RL et al. NEJM 2023

- **Daten des "primary outcome" fehlten** für **13%** der Patienten, v.a. wegen Verlust bei der Nachverfolgung
- **Protokollabweichungen:** 32.7% in TXA-Gruppe vs. 37.0% in Placebo-Gruppe
  - 17% der Patienten, die der Placebo-Gruppe zugeordnet waren, erhielten TXA
  - 21% der Patienten, die der TXA-Gruppe zugeordnet waren, erhielten keine 2. Dosis
  - 15.8% der TXA-Gruppe und 16.5% der Placebo-Gruppe erhielten „open-label" TXA im Krankenhaus

Shakur-Still H et al. NEJM 2023; Holcomb JB. THOR 2024

Prehospital tranexamic acid in trauma patients: a systematic review and meta-analysis of randomized controlled trials.

Acharya P et al. Front Med (Lausanne) 2023

meta-analysis of 3 prehospital RCT: STAAMP, ROC-TXA, PATCH-Trauma;

- favorable functional outcome (a GOS-E level of ≥5) after 6 month (2 RCT): no significant difference in survival with a favorable functional outcome at 6 months (RR 1.00, 95% CI 0.93–1.09, I^2 = 0%);

- mortality:

  - at **24h**: prehospital TXA **reduced the risk of 24-h mortality** (RR 0.73, 95% CI 0.56–0.96, I^2 = 0%);
  - at **28d** (3 RCT): prehospital TXA **reduced the risk of 1-month mortality** (RR 0.82, 95% CI 0.69–0.97; I^2 = 0%).
  - **bleeding / TBI**: no significant difference in the risk of mortality due to **bleeding** (RR 0.74, 95% CI 0.43–1.29, I^2 = 12%) and **TBI** (RR 0.87, 95% CI 0.69–1.10, I^2 = 0);

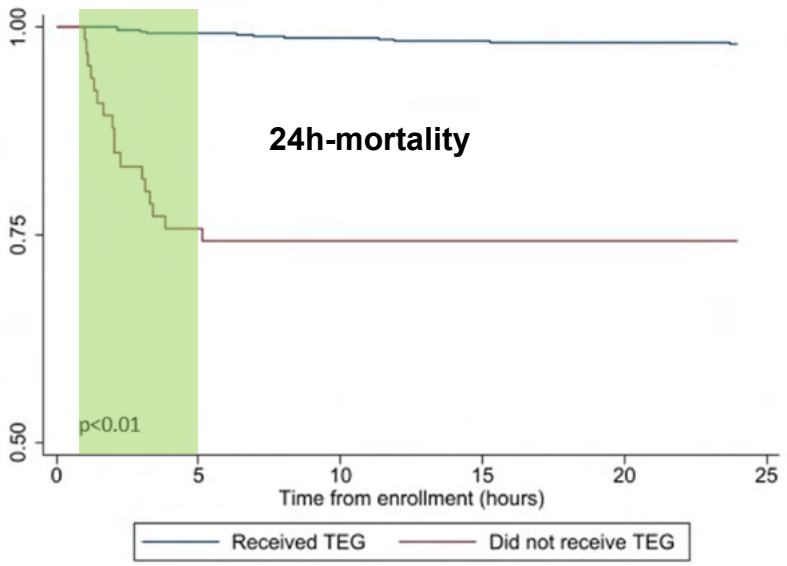
- side effects: no significant difference in the incidence of seizures (RR 1.14, 95% CI 0.59–2.20, I^2 = 0%) and thromboembolic events (RR 1.04, 95% CI 0.72–1.49, I^2 = 62%); **BUT**

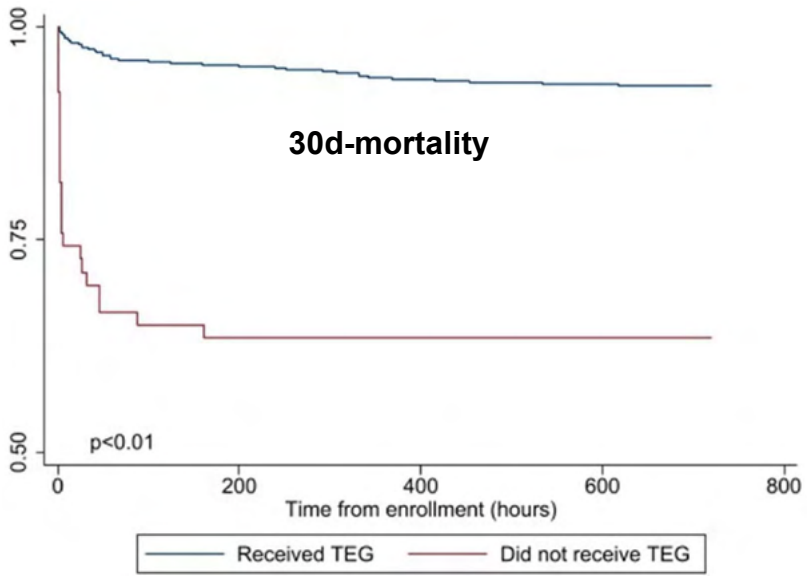
increased risk of infection or sepsis (RR 1.17, 95% CI 1.03–1.33, I^2 = 0%);

Missingness matters: a secondary analysis of thromboelastography measurements from a recent prehospital randomized tranexamic acid clinical trial. STAAMP

Donohue JK et al. Trauma Surg Acute Care Open 2024

Comparison of STAAMP data for pat. receiving TEG (YES-TEG) vs. not (NO-TEG) to characterize injury-related differences and identify subgroups with a significant amount of missing TEG data





"… it is **in the severe prehospital shock subgroup** where TEG improvements were demonstrated and TXA treatment was associated with a significant reduction in 30-day mortality in the primary STAAMP analysis. The concomitant demonstration of a TXA survival benefit and a reduction of LY30 is novel in the setting of traumatic injury. … **the administration of TXA and its impact on TEG parameters and survival is dependent on specific characteristics of traumatic injury**."

"… TXA administration **in patients with severe shock** is independently associated with a lower LY30. Importantly, the reduction in LY30 found is consistent with TXA's hypothesized mechanism of action."

blutungsbedingter Schock = definitive Indikation für TXA

Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury

Resuscitation Outcomes Consortium -Tranexamic Acid for Traumatic Brain Injury (ROC-TXA)

Rowell SE et al. JAMA 2020

multicenter, double-blinded, randomized clinical trial at 20 trauma centers and 39 emergency medical services agencies in the US and Canada; n=966; mean 42 y; 74% male; mean GCS 8; within 2 h of injury: out-off-hospital 1 g TXA + 1 g TXA/8h (n=312) vs. out-of-hospital 2 g TXA + Placebo/8h (n=345) vs. Placebo + Placebo/8h (n=309); median estimated time from injury to out-of-hospital study drug 40 to 43 min

primary outcome (GOSE >4)

- no significantly improvement of 6-month neurologic outcome as measured by the Glasgow Outcome Scale-Extended (65% TXA vs. 62% placebo; difference, 3.5%; [90% 1-sided confidence limit for benefit, −0.9%]; P=0.16; [97.5%1-sided confidence limit for harm, 10.2%]; P=0.84)

secondary outcome:

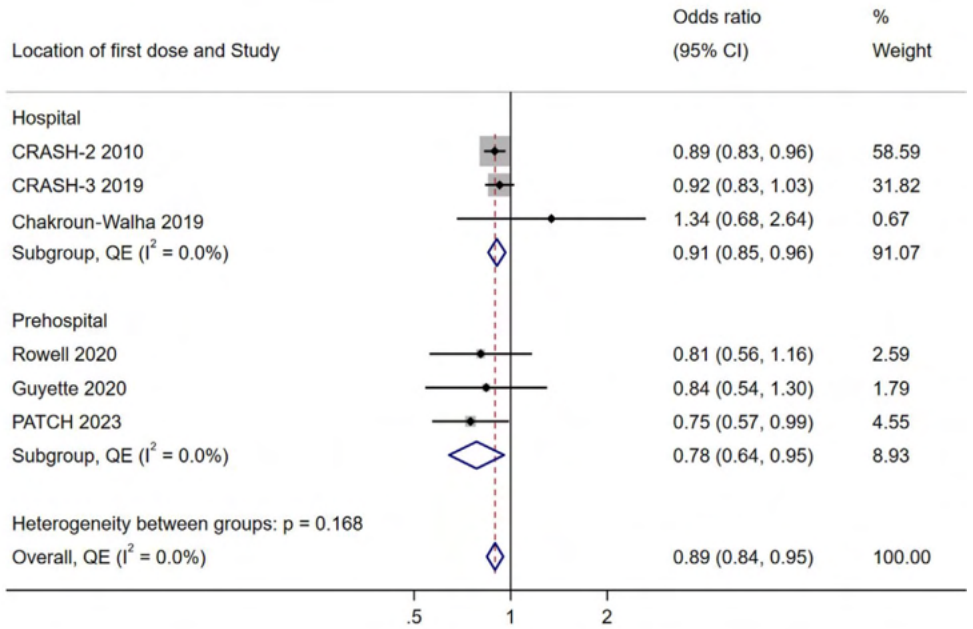
secondary analysis of **patients with ICH on CT**: 28d mortality lower in the 2-g TXA bolus group (17%) compared with the other two groups (1-g bolus/1-g infusion 26%, placebo 27%) Rowell SE et al. JTACS 2024

- no statistically significant difference in 28-day mortality (14% TXA vs. 17% placebo; adjusted difference, -2.9% 95%CI -7.9% to 2.1%; P=0.26)
- no statistically significant difference in progression of intracranial hemorrhage (16%vs 20%; difference, −5.4%; [95%CI, −12.8% to 2.1%]; P=0.16).

- thrombotic events: bolus only 9%; bolus maintenance 4%; placebo 10%
- seizures: pat. without ICH 6%; bolus only 5%; bolus maintenance 0%; placebo 2%

Tranexamic Acid for Traumatic Injury in the Emergency Setting: A Systematic Review and Bias-Adjusted Meta-Analysis of Randomized Controlled Trials.

Fouche PF et al. Ann Emerg Med 2024



7 RCT

The odds of death for **in-hospital** trials are 9% less for TXA compared to placebo (OR 0.91, 95% CI, 0.85 to 0.96).

⇒ **NTT: 70 patients** (95% CI 42 to 159)

The odds of death for **out-of-hospital** trials are 22% less for TXA compared to placebo (OR 0.78, 95% CI 0.64 to 0.95)

⇒ **NTT: 33 patients** (95% CI 20 to 148)

"… benefits of TXA were more pronounced when the primary pathological finding was **hemorrhage accompanied by clinical signs of shock**. … in cases of **systemic trauma** than in cases of traumatic brain injury …"

Prehospital tranexamic acid is associated with a survival benefit without an increase in complications: results of two harmonized randomized clinical trials.

Mazzei M et al. J Trauma Acute Care Surg 2024

harmonized secondary analysis of STAAMP (n=903) and ROC-TXA (n=841); 1744 pat.; overall mortality 11.2%; median ISS16 (IQR: 5-26);

- **multivariable Cox analysis**:
  - TXA independently associated with a **lower risk of 28-day mortality** (HR 0.72, 95% CI 0.54 – 0.96, p=0.03)
  - independent 22% lower risk of mortality **for every gram** of prehospital TXA administered (HR 0.78, 95% CI 0.63 – 0.96, p=0.02)
  - dose-response relationship between increasing TXA dose and decreased red cell transfusion at 24 hours
  - no independent association of prehospital TXA administration on VTE (OR: 1.10, 95% CI 0.66 – 1.86, p=0.71), seizure (OR: 1.08, 95% CI 0.54 – 2.20, p=0.82) or stroke (OR: 0.64, 95% CI 0.31 – 1.32, p=0.23)
  - no association between prehospital TXA **dose** with VTE (OR: 1.14, 95% CI 0.78 – 1.66, p=0.51), seizure (OR: 1.44, 95% CI 0.90 – 2.32, p=0.13) or stroke (OR: 0.97, 95% CI 0.62 – 1.53, p=0.91)

"… utilization of TXA as close to the time of injury as possible …"

Effectiveness and safety of prehospital tranexamic acid in patients with trauma: an updated systematic review and meta-analysis with trial sequential analysis.

Chen HY et al. BMC Emerg Med 2024

meta-analysis; PRISMA, PICO; up to July 1, 2023; 11 studies (2 RCT, 9 cohort: n=5304 TXA vs. 5955 controls); majority blunt trauma; ISS range 16-41;

28–30-day mortality (11 studies; TXA: n=5,303 vs. Control: n=5,957)

- *all*: **no effect** (OR, 0.97; 95%CI, 0.83–1.14; P=0.710; I^2=67.1%)
- *RCTs*: benefit (OR, 0.80; 95%CI, 0.66–0.97; P=0.024; I^2=0%)
- *cohorts*: no effect (OR, 1.02; 95%CI, 0.86–1.22; P=0.815; I^2=66.4%)

"… results were unstable … strong evidence …"

24-hours mortality (9 studies; TXA: n=4,123 vs. Control: n=4,341)

- *all*: **benefit** (OR, 0.82; 95%CI, 0.71–0.94; P=0.004; I^2=46.3%)
- *RCTs*: **benefit** (OR, 0.71; 95%CI, 0.52–0.96; P=0.027; I^2=0%)
- *cohorts*: **benefit** (OR, 0.85; 95%CI, 0.72–0.99; P=0.035; I^2=59.2%)

"… results were stable … strong evidence …"

thromboembolic events (9 studies; TXA: n=4,303 vs. Control: n=4,337)

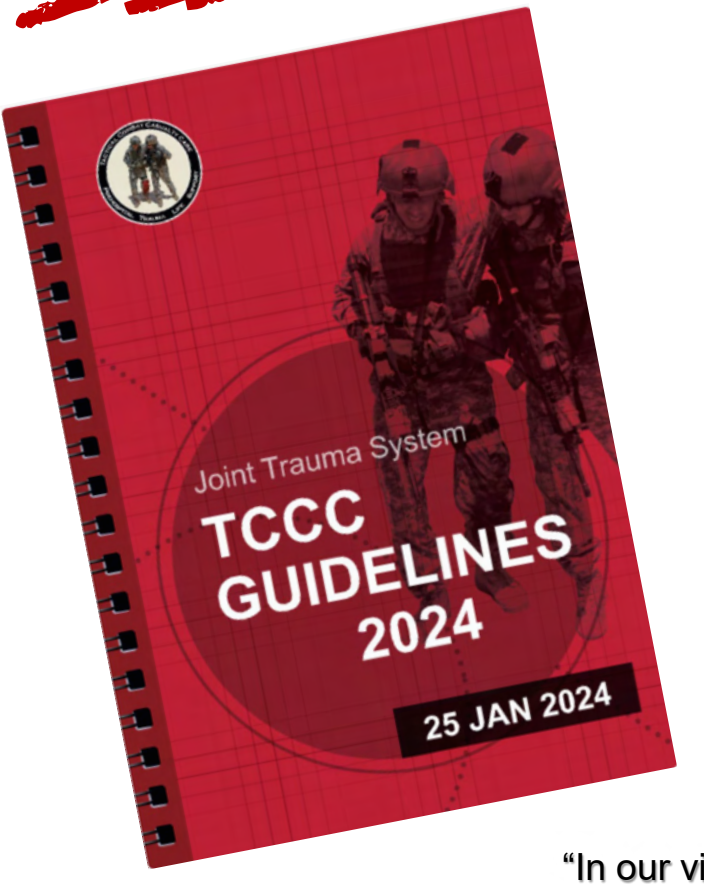
- *all*: **19% higher TE-rate** (OR, 1,22; 95%CI, 1,03–1.44; P=0.019; I^2=30.9%)
- *RCTs*: **significantly more TE** (OR, 1.33; 95%CI, 1.04–1.70; P=0.022; I^2=10.1%)
- *cohorts*: **more TE, but not significant** (OR, 1.13; 95%CI, 0.90–1.42; P=0.140; I^2=37.8%)

ARDS and MODS (4 and 5 studies)

- *all*: **no difference**

"… early (within 24 h) benefits … used with caution …

Militär



Tranexamic Acid (TXA)

- If a casualty **will likely need a blood transfusion** (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)

OR

"An inability to follow commands, which represents a GCS motor score of 5 or less, is an efficient way to determine the threshold for TXA administration in the prehospital setting."
Drew B et al. J Spec Oper Med 2020

- If the casualty has signs or symptoms of significant TBI or has altered mental status associated with blast injury or blunt trauma"

Administer **2 gm of tranexamic acid** via slow IV or IO push as soon as possible but NOT later than 3 hours after injury.

Since 2020: 2g, but bolus only, no continuous infusion

Ist das sinnvoll ??
(nach Datenlage eher nicht ...)

"In our view, there is a clear benefit in taking oral TXA now **for SOF operators** due to their specific characteristics."
Cazes N et al. JTACS 2024

prähospitale Blutprodukte?

Die juristischen, organisatorischen und logistische Regelungen für prähospitale Blutprodukte sind **identisch** mit denen der innerklinischen Transfusion.

klinische Zeichen eines hämorrhagischen Schocks

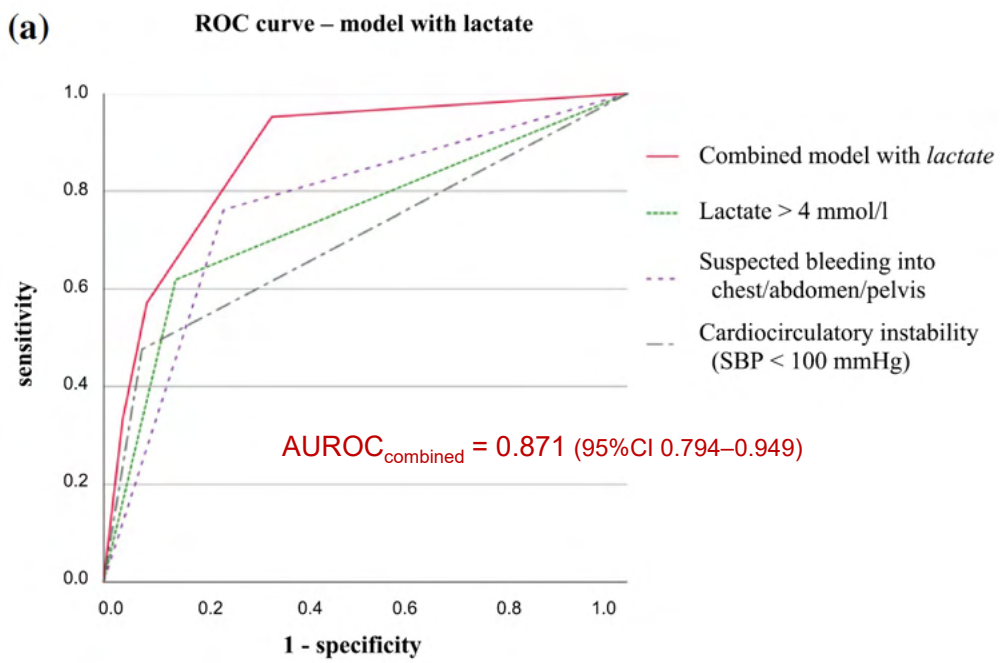
1. verschwitzt (sweaty)
2. blass (pallor / pale)
3. keine Venenfüllung (collapsed veins)
4. niedriges / fallendes etCO_2 (Low or falling end-tidal CO_2)
5. Hypotension
6. Atemnot (Air hunger)
7. nicht normale Herzfrequenz (abnormal heart rate, either high or low)
8. verwirrt (altered mental status)

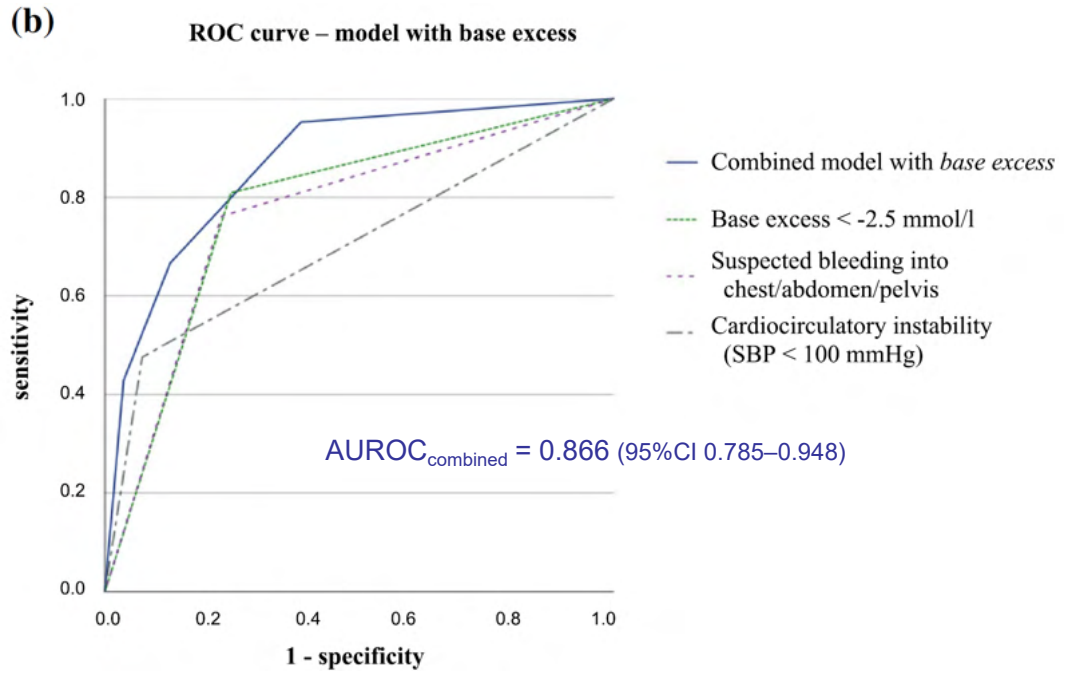
https://www.crisis-medicine.com/prehospital-blood-administration-and-the-hateful-eight/

Prehospital predictors of the need for transfusion in patients with major trauma.

Gaessler H et al. Eur J Trauma Emerg Surg 2022

part of the PREDICT study (Prehospital Evaluation and Detection of Induced Coagulopathy in Trauma); Christoph 22, BwK Ulm; 130 patients; mean ISS 22.1 ± 16.8 (median 18; range, 3–75); 28-day mortality was 6.9%; a prospective follow-up study currently being conducted (TICDETECT)





prähospital: Laktat > 4 mmol/l + BE < -2,5 mmol/l + vermutete Blutung in Brust / Bauch / Becken + RRsyst < 100 mmHg

Plasma prähospital: COMBAT

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial (COMBAT).

Moore HB et al. Lancet 2018

single center Denver, Colorado, USA; primary ground transport; 125 pat.; <30 min till hospital; ~50% blunt trauma; ~200 ml crystalloid;

24h mortality: 12% (plasma) vs. 10% (control), p=0.68

28d mortality: 15% (plasma) vs. 10% (control), p=0.37

multiple organ failure: 6% (plasma) vs. 2% (control), p=0.37

⇒ kein Effekt durch prähospitales Plasma (tendenziell sogar höhere Sterblichkeit und MOV)

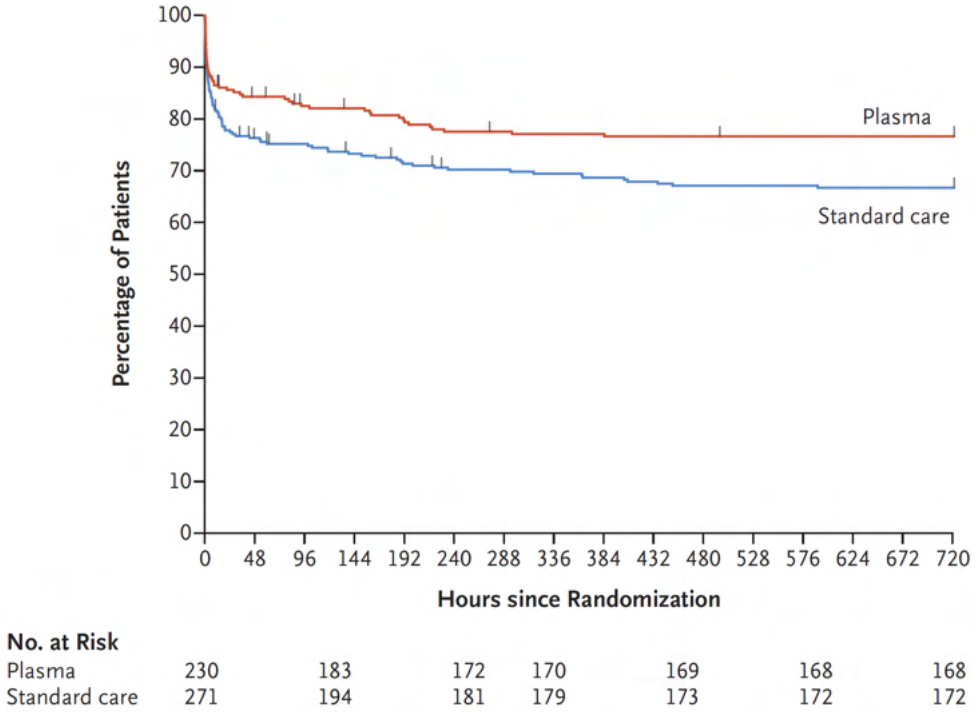
ABER: 68% of pat. received <250 mL plasma

Duchesne J et al. Acad Emerg Med 2024

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock (PAMPer).

Sperry JL et al. NEJM 2018

multicenter, USA; helicopter; primary + secondary transport; 501 pat.; <45 min till hospital; >80% blunt trauma; 500-900 ml crystalloid;



24h mortality: 13.9% (plasma) vs. 22.1% (control), p=0.02

30d mortality: 23.2% vs. 33.0%, p=0.03

in-hospital mortality: 22.2% vs. 32.5%, p=0.01

multiple organ failure: 63.0% vs. 57.6%, p=0.23

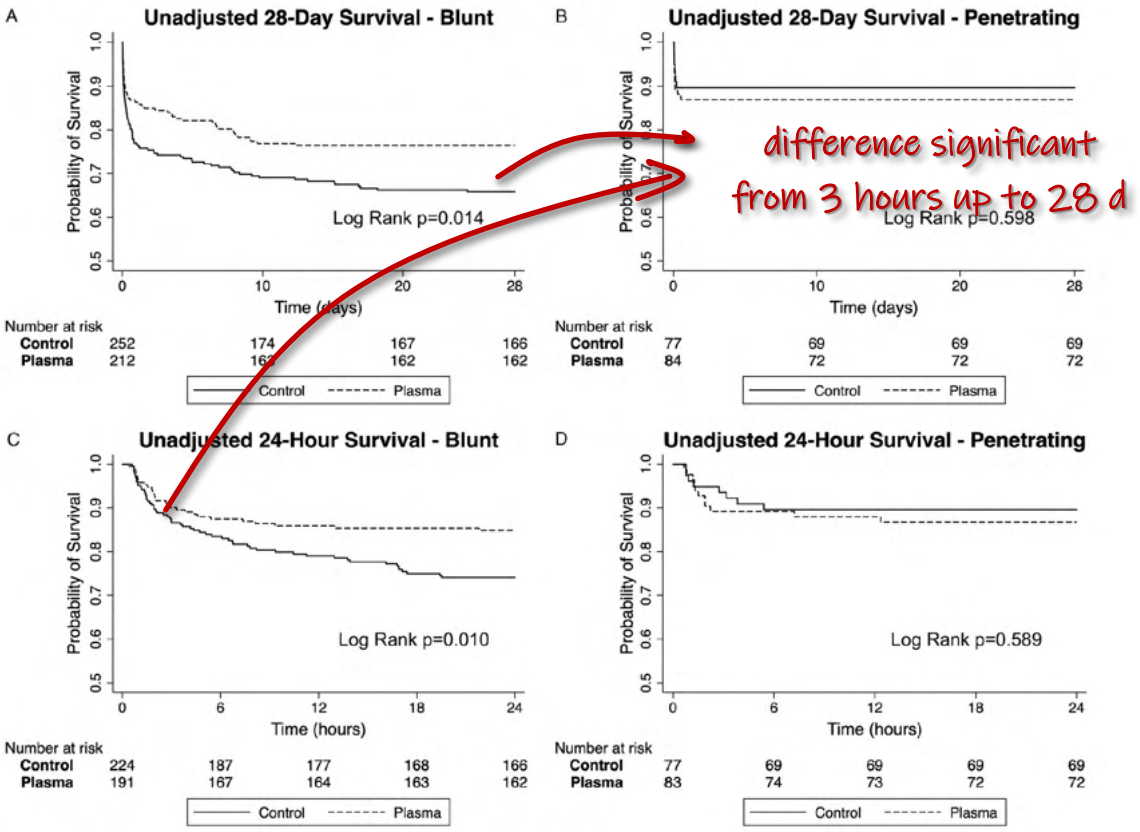
NTT 10
Cannon JW. NEJM 2018

⇒ signifikanter Überlebensvorteil durch prähospitales Plasma (aber auch mehr MOV)

Prehospital plasma in injured patients is associated with survival principally in blunt injury: Results from two randomized prehospital plasma trials.

Reitz KM et al. Trauma Acute Care Surg 2020

predefined secondary analysis of COMBAT Moore HB et al. Lancet 2018 and PAMPer Sperry JL et al. NEJM 2018; 626 patients; median ISS 22 (IQR, 12–34); mean prehospital SBP 80 mm Hg (80 ± 31 mm Hg); median GCS 6 (IQR, 3–15); overall mortality 24.8%.



prehospital plasma ⇒ 

"… underpowered to rule out an effect of prehospital plasma in penetrating injury…."

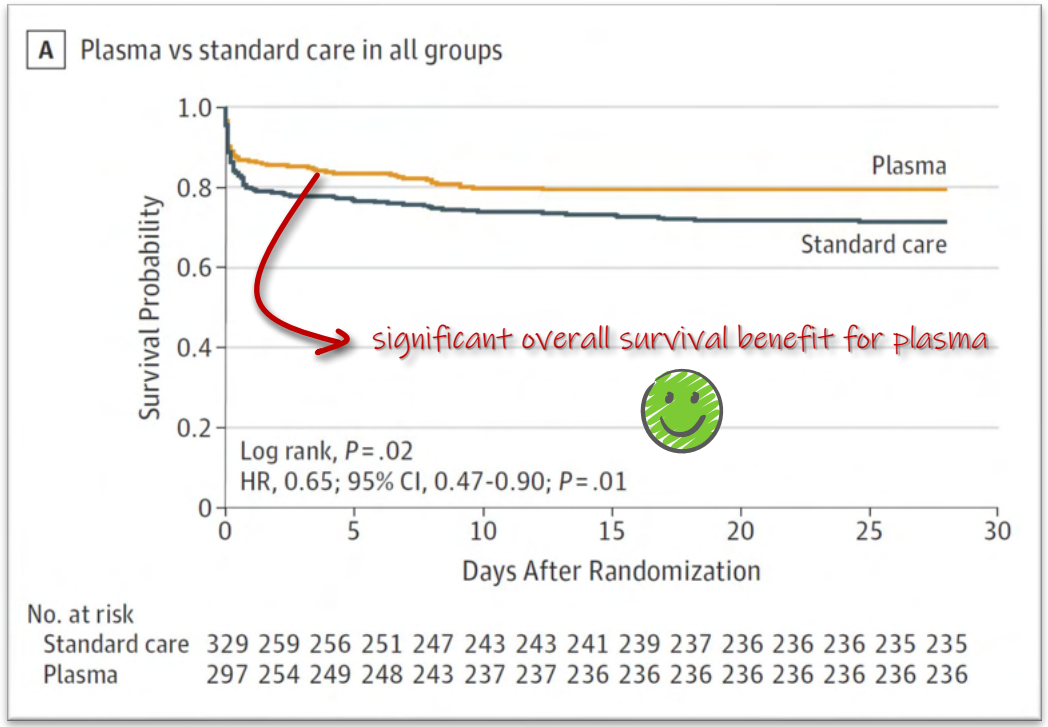
- **all patients** (prehospital plasma vs standard therapy): significantly lower 24-hour (13.5% vs. 20.1%; p = 0.028) and 28-day mortality rates (20.9% vs. 28.6%; p = 0.026)

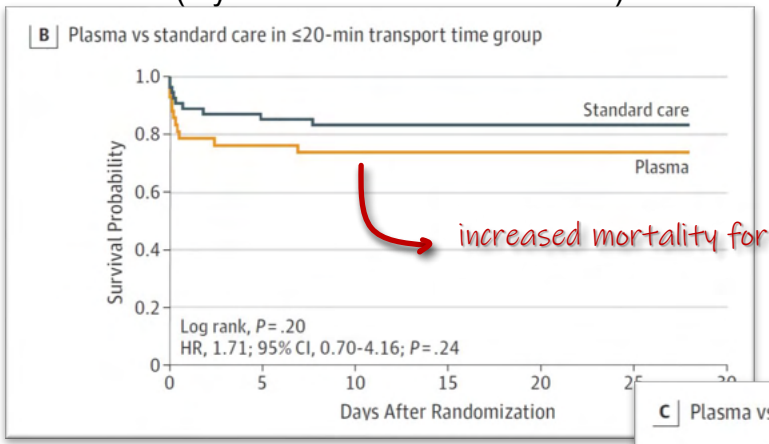
- **blunt vs. penetrating**: **in the blunt injured subgroup** → 
  - survival benefit at 24 hours (HR, 0.59; 95% confidence interval [CI], 0.370–0.947; p = 0.029) and at 28 days (HR, 0.68; 95% CI, 0.472–0.965; p = 0.031)
  - 24% reduction in the risk of total blood transfusion (incident risk ratio [IRR], 0.76)
  - significant risk reductions for RBC and platelet transfusion (IRR, 0.77, 0.52, respectively)

Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes.

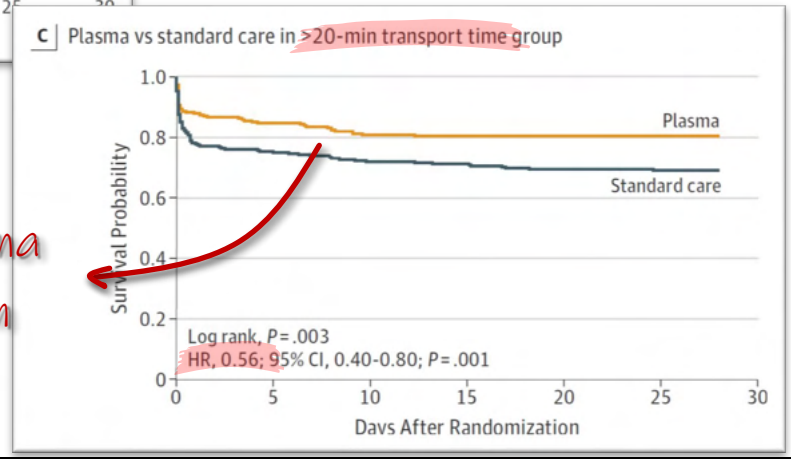
Pusateri AE et al. JAMA Surg 2020

post-hoc-analysis of COMBAT Moore HB et al. Lancet 2018 (no survival improvement) and PAMPer Sperry JL et al. NEJM 2018 (nearly 30% relative [10% absolute for 24 h-mortality] reduction in mortality with prehospital plasma transfusion); 626 pat. with trauma and hemorrhagic shock (median ISS 22 [12-34]) received prehospital plasma (2 U of FFP ~250 ml each) vs. standard care (crystalloid-based resuscitation)





increased survival for plasma if transport time >20 min



Icons made by https://www.infoDiagram.com/

Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL).

Crombie N et al. Lancet Haematol 2022

multicentre, allocation concealed, open-label, parallel group, RCT; 4 UK centers (physician + paramedic); trauma-related haemorrhagic shock and hypotension (SBP <90 mm Hg or absence of palpable radial pulse); either alternating up to two units each of PRBC and LyoPlas* (n=209) or up to 4 units of 250 mL of 0.9% sodium chloride (n=223), identical in external appearance; terminated early after 93%; 62% road traffic collision; ISS 36 (IQR 25-50); before randomization, 430 mL crystalloid and 90% TXA

* prehospital 60% of the patients received 2 U pRBC and 40% received 2 U Lyoplas (unpublished data); mean volume of Lyoplas transfused was 266 ml, or only 3.8 ml/kg in a 70 kg patient.
Yazer MH et al. Transfusion 2022

Weite CI + kalkulierte Anzahl nicht erreicht ⇒ „underpowered" Jänig C et al. J Clin Med 2023

- no difference in **primary outcome** (composite of episode mortality or impaired lactate clearance, or both): RBC-LyoPlas 64% vs. NaCl 65% (adjusted risk difference –0.025% [95% CI –9.0 to 9.0], p=0.996).
- no difference in **any secondary outcome** (all-cause mortality within 3 h and 30 days, prehospital timings, type and volume of fluid administered, vital signs, venous lactate concentration, haemoglobin concentration, ...)
- no difference in **any subgroup** (intervention delivery site, transport (air vs ground), initial lactate concentration (≤2.2 mmol/L vs >2.2 mmol/L), time to hospital arrival from injury (≤1 h vs >1 h), mode of injury (blunt vs penetrating vs crush), volume, ...)

"… The implication is that the logistical and financial costs of bringing blood product resuscitation forward from hospital to the prehospital domain **might not be routinely justified** **within the context of a modern major trauma network**."

EK + LyoPlas prähospital: RePHILL

Kommentar zu

Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL).

Crombie N et al. Lancet Haematol 2022

- unfortunate composite outcome: mortality & lactate clearance ⇒ Laktat-Clearance als Outcome nicht validiert (somit keine binäre Entscheidung möglich)
- a-priori sample size estimate for primary outcome: baseline composite incidence 20% in the 0.9% sodium chloride group decreased to 10% in the PRBC–LyoPlas group ⇒ erwartete relative Mortalitätsreduktion von 50% ist höchst unwahrscheinlich (bei CRASH-2 waren es relativ ~10% [absolut: 14,5% TXA vs. 16,0% Placebo])
- high mortality rate: RBC-LyoPlas 43% vs. 45% NaCl (adjusted risk ratio 0.97 [95% CI 0.78–1.20]; p=0.75) PAMPer: 23.3%
  ⇒ Wenn fast die Hälfte der Patienten sterben, kann ein Unterschied in „mortality" (64% vs. 65%) kaum erreicht werden.
- 7% (adjusted average difference 95% CI –15 to 1; p=0.08) absolute reduction of 3 h mortality (16 vs 22%; adjusted risk ratio 0.75, 95% CI 0.50 to 1.13; p=0.17) and 4% (95% CI –13 to 6; p=0.44) absolute reduction of 30- day mortality (42% vs 45%; adjusted risk ratio 0.94, 95% CI 0.76–1.17; p=0.59)
  ⇒ positives Ergebnis (CRASH-2: absolut 1,5%), aber statistisch nicht signifikant
- small overall transfusion requirements: averaged 1.57 units (443 mL) of pRBC + 1.25 units of plasma (266 mL) vs. 638 mL of NaCl, followed by averaged 4.5 units of RBC in the first 24 h after admission.
  ⇒ Bei medianem ISS 36 (IQR 25-50) und medianem NISS 43 (IQR 34-57) sehr überraschend

EK + Plasma prähospital

Association of red blood cells and plasma transfusion versus red blood cell transfusion only with survival for treatment of major traumatic hemorrhage in prehospital setting in England: a multicenter study.

Tucker H et al. Crit Care 2023

prospectively collected data; six prehospital services in England (2018–2020); prehospital transfusion for traumatic hemorrhage: **RBC** alone (each ~ 250 mL; n=223; median 2 (IQR 2;4) units) vs. RBC + thawed plasma (each ~ 250 mL) / Lyoplas (each 200 mL) (**RBC+P**, n=391; median 1 (0;1) + 1 (0;1) units) vs. leukocyte-depleted red cell and plasma (**RCP**, each 470 mL; n=295; median 2 (1;2) units); median ISS 30-33; time from injury to hospital 79-97 min;

median 2x 250 = 500 mL

median 2x 470 = 940 mL

median 250+250 or 200 = 500 mL

compared to **RBC** alone:

lower odds of death at 24-h

- **RCP:** aOR 0.69 (95%CI: 0.52; 0.92)
  - for penetrating injury: aOR 0.39 (95%CI: 0.20; 0.76)
- **RBC+P:** aOR 0.60 (95%CI: 0.32; 1.13)
  - for penetrating injury: aOR 0.22 (95%CI: 0.10; 0.53)

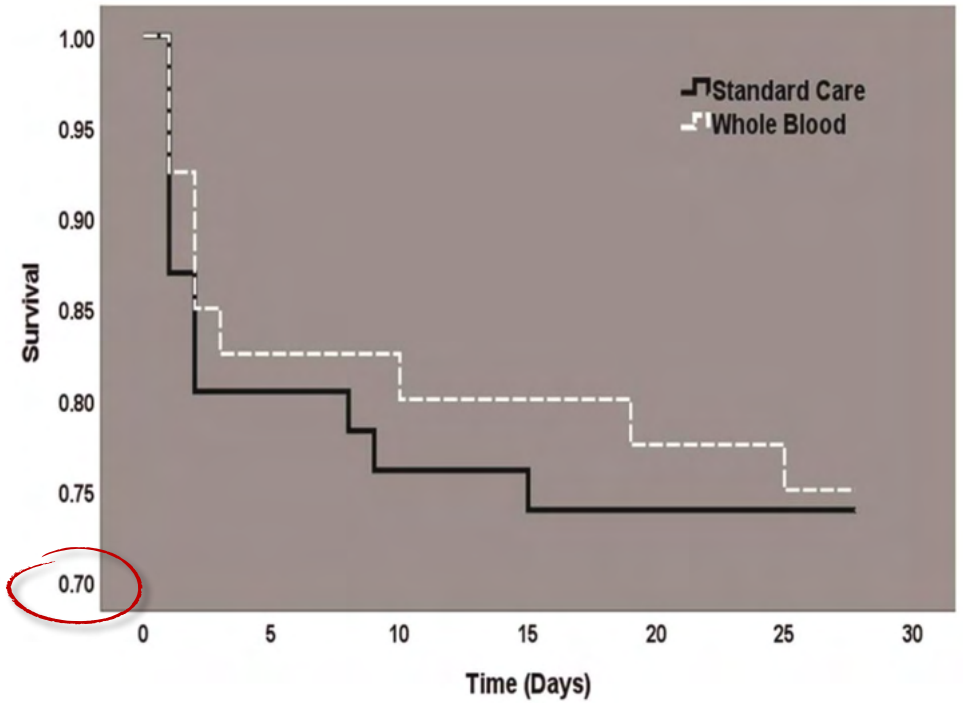
"… plasma is also an ideal volume expander in the intravascular space … has a homeostatic effect on endothelial function and innate immune system activation …"

EK plus Plasma vorteilhaft, besonders bei penetrierendem Trauma

Prehospital low titer group O whole blood is feasible and safe: Results of a prospective randomized pilot trial. (PPOWER)

Guyette FX et al. J Trauma Acute Care Surg 2022

single-center (Pittsburgh, Pennsylvania, USA), prospective, cluster randomized, prehospital through in-hospital whole blood pilot trial; 86 air-medical pat. at risk of hemorrhage (SBP ≤90 mm Hg and HR ≥108 bpm or SBP ≤70 mm Hg); prehospital LTOWB (n = 40) vs. standard care (n = 46; including up to 2 U RBC); halted early at 77% enrollment.



- no statistical mortality benefit at 28 days (LTWOB 25.0% vs. standard 26.1%, difference -1.1%; p = 0.91).
- no significant differences in the rate of early mortality (3 hours, 6 hours, or 24 hours)

Prähospitale RCTs

	COMBAT	PAMPer	PREHO-PLYO	RePHILL	PPOWER
Einschlusskriterien	SBP ≤70 mmHg oder SBP 71-90 mmHg + HF ≥108/min	SBP ≤70 mmHg oder SBP <90 mmHg + HF ≥108/min	SBP <70 mmHg oder SI ≥1,1	SBP <90 mmHg oder nicht-tastbarer Radialis-Puls	SBP ≤90 mmHg + HF ≥108/min oder SBP ≤70 mmHg
Eingeschlossene Patienten (n)	125 („as-treated“): Plasma: 65 vs. NaCl: 60	501: Plasma: 230 vs. Standard: 271	150 („intention-to-treat“): Plasma: 68 vs. NaCl: 66	432: EK+lyPlas: 209 vs. NaCl: 223	86: LT0WB: 40 vs. EK: 46
Primärer Endpunkt	28d-Sterblichkeit	30d-Sterblichkeit	INR bei Krankenhausaufnahme	Composite aus Sterblichkeit und Laktat-Clearance	Machbarkeit und 28d-Sterblichkeit
Transport	Bodengebunden	Luftgestützt	Bodengebunden	Boden- (~60%) und Luft- (~40%) gebunden	Luftgestützt
Studienmedikation	2x FFP vs. NaCl	2x „thawed plasma“ vs. Kristalloid bzw. EK	≤4x lyPlas vs. NaCl	abwechselnd ≤2 EK und 2x lyPlas vs. ≤4x NaCl	≤2x LT0WB vs. ≤2x EK
Zeitdauer von Unfall bis zur klinischen Behandlung (Min.)	28 (22-34) vs. 24 (19-31)	42 (34-53) vs. 40 (33-51)	median 26 (6-37) nach Ankunft am Unfallort	26 (±16) vs. 25 (±17)	k.A.
Stumpfes Trauma (%)	46 vs. 53	81 vs. 83	58 vs. 60	78 vs. 80	85 vs. 84,8
Prähospital EK-Transfusion	nein	26% vs. 42% (13 von 27 Stationen)	nein	ja	ja
Schädel-Hirn-Trauma (%)	~22,5	~45,5	13,2 vs. 10,6	48 vs. 47	k.A.
Kristalloide (mL)	150 vs. 250	500 vs. 900	700 [475-1000] vs. 700 (475-1000)	vor Randomisierung: 422 vs. 437	prähospital k.A.
Verletzungsschwere	NISS: 27,0 (10,0-41,0) und 51% >25 vs. 27,0 (11,5-36,0) und 57% >25	ISS: 22 (14-33) vs. 21 (12-29)	ISS: 29 (12-48) vs. 25 (9-41)	ISS: 36 (25–49) vs. 36 (25–50) NISS: 43 (34–57) vs. 48 (34–57)	ISS: 13 (8,5–22) vs. 17 (9–25)
Tranexamsäure (%)	≤6h: 9 vs. 13	k.A.	83,8 vs. 90,9	87 vs. 92	k.A.
Behandlungsergebnis **24-h Mortalität (%)** **28-/30-d Mortalität (%)**	 12 vs. 10 15 vs. 10	 13,9 vs. 22,1 22,2 vs. 32,5	 13,2 vs. 9,1 17,6 vs. 15,2	 16 vs. 22 42 vs. 45	 15 vs. 17,4 25 vs. 26,1

prähospitale Blutprodukte: möglicher Bedarf

Jährlich in Deutschland zwischen 300 und 1800 Traumata als potentielle Empfänger

	USA: National Emergency Medical Services Information System (NEMSIS) 2019 database (trauma activations: n=3,700,000) Hashmi ZG et al. Transfusion 2022	TraumaRegister DGU® 2021 (n=22,106) (Basisdatensatz; primär versorgt; Deutschland; „missing data“ ~15%)		
		lebensgefährlich verletzt MAIS3+ (n=17,771; 80.4%)	**ISS ≥16** (n=11,009; 49.8%)	**Polytrauma** (Berlin Def.) (n=2,244; 10.2%)
SBP <90 mmHg	89,391 (2.4%) [0.9% of estimated number of whole blood units collected]	907 (6.0%)	764 (8.0%)	477 (25.8%)
SBP <90 mmHg and / or HR >120/min	901,346 (24.3%) [9.2%] motor vehicle collision: 242,800 (6.5%)	1781 (11.4%)	1390 (14.5%)	727 (36.9%)
SBP <90 mmHg and HR >108/min; or SBP <70 mmHg	54,160 (1.4%) [0.6%]	551 (3.6%)	488 (5.1%)	332 (17.4%)
Shock Index ≥1	300,475 (8.1%) [3.1%]	1472 (10.1%)	1152 (13.0%)	578 (34.6%)

Cave: ~50% aller prähospitalen Transfusion bei nicht-traumatologischen Blutungen

Jenkins D et al. Shock 2014; Sunde GA et al. J Trauma Acute Care Surg 2015; Thiels CA et al. World J Surg 2016; Mena-Munoz J et al. Prehospital Emergency Care 2016; Cassignol A et al. Vox Sang 2020

modifiziert nach Maegele M et al. Dtsch Arztebl 2023

Neues Register in Planung!

Unter dem Dach der **Bundesvereinigung der Arbeitsgemeinschaften Notärzte Deutschlands (BAND) e.V.**

BAND e.V.

BiNAR
Blut im Notarztdienst Register

Für alle Rettungsmittel, die Blutprodukte mitführen.
Start: 01. Januar 2025
Kontakt: binar@band-online.de

ADAC Luftrettung gGmbH

Bundesamt für Bevölkerungsschutz
und Katastrophenhilfe - Luftrettung

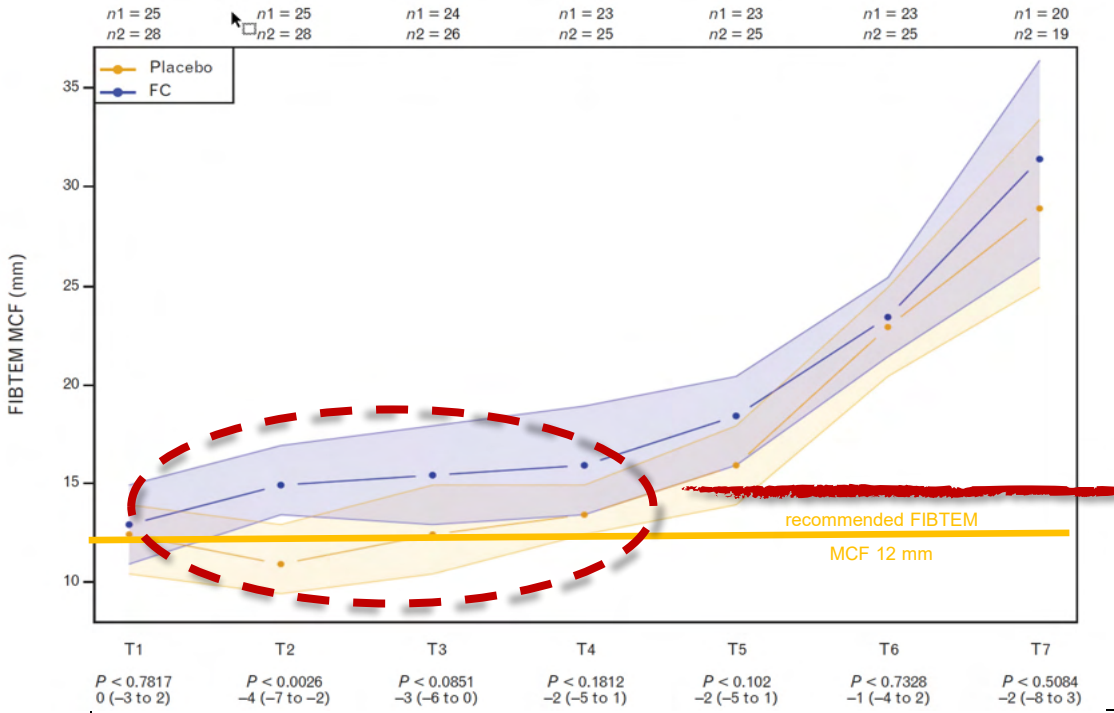
DRF Luftrettung

DRF Stiftung Luftrettung gemeinnützige AG

Efficacy of prehospital administration of fibrinogen concentrate in trauma patients bleeding or presumed to bleed (FlinTIC).

Ziegler B et al. Eur J Anaesthesiol 2021

multi-centered, prospective, randomised, placebo-controlled, double-blinded, international clinical trial in 12 Helicopter Emergency Medical Services (HEMS) and Emergency Doctors' vehicles (NEF or NAW) and four trauma centres in Austria, Germany and Czech Republic between 2011 and 2015; 53 evaluable trauma patients (median ISS Placebo group 16 [16-34] vs. Fib Group 25 [16-34]) with major bleeding and in need of volume therapy (28 x fibrinogen concentrate [3g for 30-60 kg, 4.5g for 60-90 kg, 6g for >90kg] and 25 x placebo); **primary outcome: clot stability** as reflected by maximum clot firmness in the **FIBTEM** assay (FIBTEM MCF) before and after administration of the study drug.



The median between-group difference in the change in FIBTEM MCF was 5 [3 to 7] mm (P<0.0001).

"Early prehospital administration of fibrinogen concentrate **prevented a decrease in median fibrinogen plasma concentration below the critical threshold of 2.0 g l $^{-1}$** that was observed in the control group."

Blut-Transport durch Drohnen

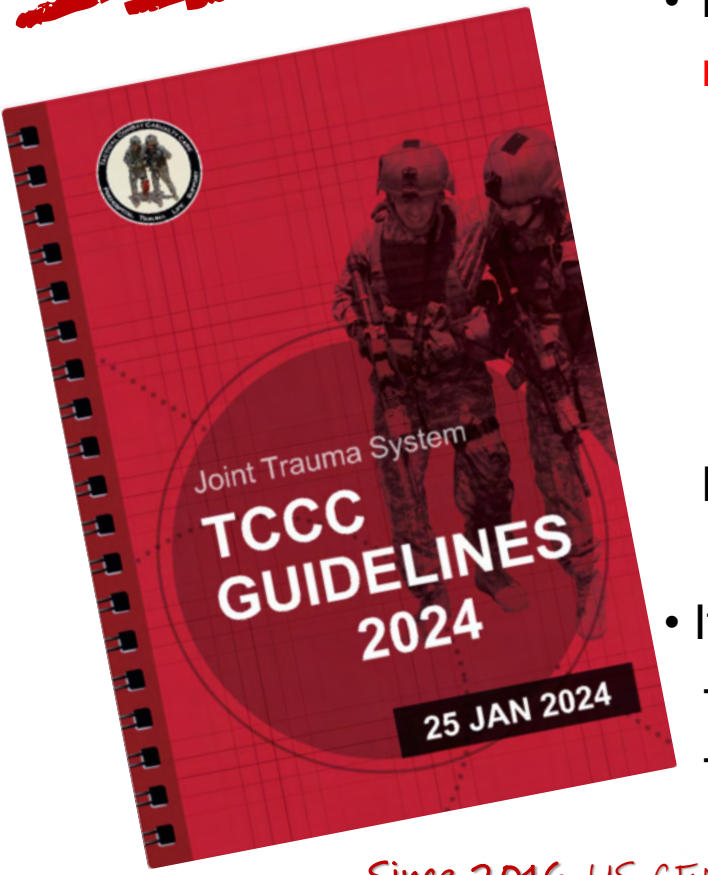
prähospitale Blutprodukte: Beim Militär eindeutig!

Militär

Fluid Resuscitation

- Assess for hemorrhagic shock (altered mental status in the absence of brain injury and/or weak or absent **radial pulse**).
- The resuscitation fluids of choice for casualties in hemorrhagic shock, listed from most to least preferred, are:
  (1) Cold stored low titer O whole blood
  (2) Pre-screened low titer O fresh whole blood
  (3) Plasma, red blood cells (RBCs) and platelets in a 1:1:1 ratio
  (4) Plasma and RBCs in a 1:1 ratio
  (5) Plasma or RBCs alone

  NOTE: Hypothermia prevention measures [Section 7] should be initiated while fluid resuscitation is being accomplished.
- If not in shock:
  - No IV fluids are immediately necessary.
  - Fluids by mouth are permissible if the casualty is conscious and can swallow.



Since 2016, US CENTCOM Clinical Operating Procedure (CCOP) for use of blood products during tactical evacuation

Was ist prähospital sinnvoll?

bei starker Blutung:

Stufenschema

- **Kompression**
- **Druckverband**
- **Tourniquet**

Hämostyptika

bei lebensbedrohlichen Blutungen u./o. im Schock:

prähospital Tranexamsäure

initial 1 g (15 mg/kg);
vermutlich nicht bei isoliertem SHT und GI-Blutung

Um diese Patienten geht es!!

bei lebensbedrohlichen Blutungen u./o. im Schock:

prähospital Gerinnungsfaktoren

Fibrinogen, ggf. PPSB
(bei Schock: PPSB anstatt Plasma?)

bei lebensbedrohlichen Blutungen u./o. im Schock:

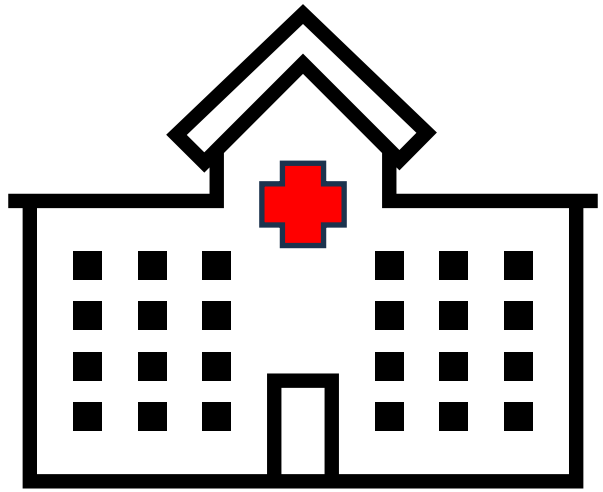
prähospital Erythrozytenkonzentrate

prähospital Plasma

1. Logistik! (Blutbank, größeres Krankenhaus)

2. Bedarf im eigenen Rettungsdienst (≤4%)?

Was ist innerklinisch?



TR-DGU® 2023: Schockraum / OP-Phase

Jahresbericht 2024

Zeitpunkt B: Schockraum / OP-Phase	TR-DGU 2023		TR-DGU 10 Jahre	
Primär versorgte Patienten (n) (%-Anteil vom Basiskollektiv)	28.718 (92 %)		293.047 (91 %)	
Blutung und Transfusion	**MW** ± SA*/ %	n	**MW** ± SA*/ %	n
Vorbestehende Gerinnungsstörung	**22,8 %**	5.770	**20,7 %**	41.412
Systolischer Blutdruck ≤ 90 mmHg	**7,0 %**	1.855	**7,3 %**	19.963
Medikamentöse Hämostase-Therapie **	**24,3 %**	4.207	**20,8 %**	29.566
Gabe von Tranexamsäure **	**15,8 %**	3.875	**15,2 %**	23.047
ROTEM **	**11,0 %**	1.725	**10,5 %**	13.247
Patienten mit Bluttransfusionen	**8,3 %**	2.389	**7,4 %**	21.806
Anzahl EK, falls transfundiert	**4,7** ± 5,3	2.389	**4,9** ± 5,9	21.806
Anzahl FFP, falls transfundiert	**2,8** ± 4,8	2.389	**3,0** ± 5,4	21.806
Therapie im Schockraum	%	n	%	n
Herzmassage **	**2,3 %**	597	**2,0 %**	4.298
Thoraxdrainage **	**9,7 %**	2.556	**8,4 %**	18.071
Endotracheale Intubation **	**8,4 %**	2.159	**11,5 %**	21.047
Initiale Laborwerte	**MW** ± SA*	n	**MW** ± SA*	n
Base Excess [mmol/l]	**-1,6** ± 5,0	23.818	**-1,6** ± 4,7	232.235
Hämoglobin [g/dl]	**13,0** ± 2,2	27.753	**13,2** ± 2,2	282.437
INR	**1,1** ± 0,4	26.433	**1,2** ± 0,5	272.005
TPZ (Quick) [%]	**88,0** ± 20,7	25.791	**88,2** ± 21,3	264.998
Temperatur [C°] **	**36,3** ± 1,0	18.015	**36,2** ± 1,1	118.122

jeder 4.-5. Patient

jeder 12. Patient

* ITS = Intensivtherapie-Station; SR = Schockraum; MW = Mittelwert; SA = Standardabweichung

** nicht verfügbar im QM-Datensatz V2015

Die Grundlagen?

Chirurgische Blutung

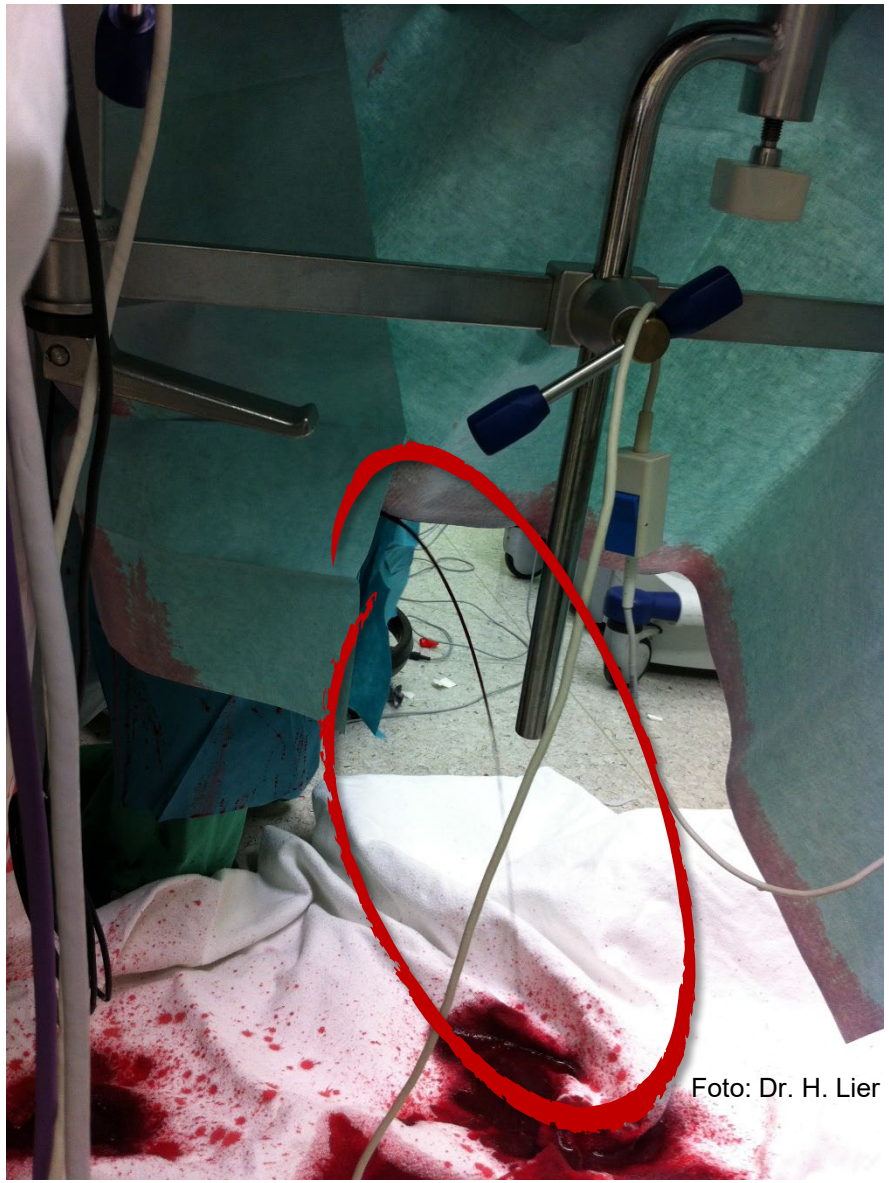


Foto: Dr. H. Lier

Die Erfahrung des Operateurs ist der entscheidende Faktor bezüglich des perioperativen Blutverlustes.

Wilcox CF et al. Am J Obstet Gynecol 1959

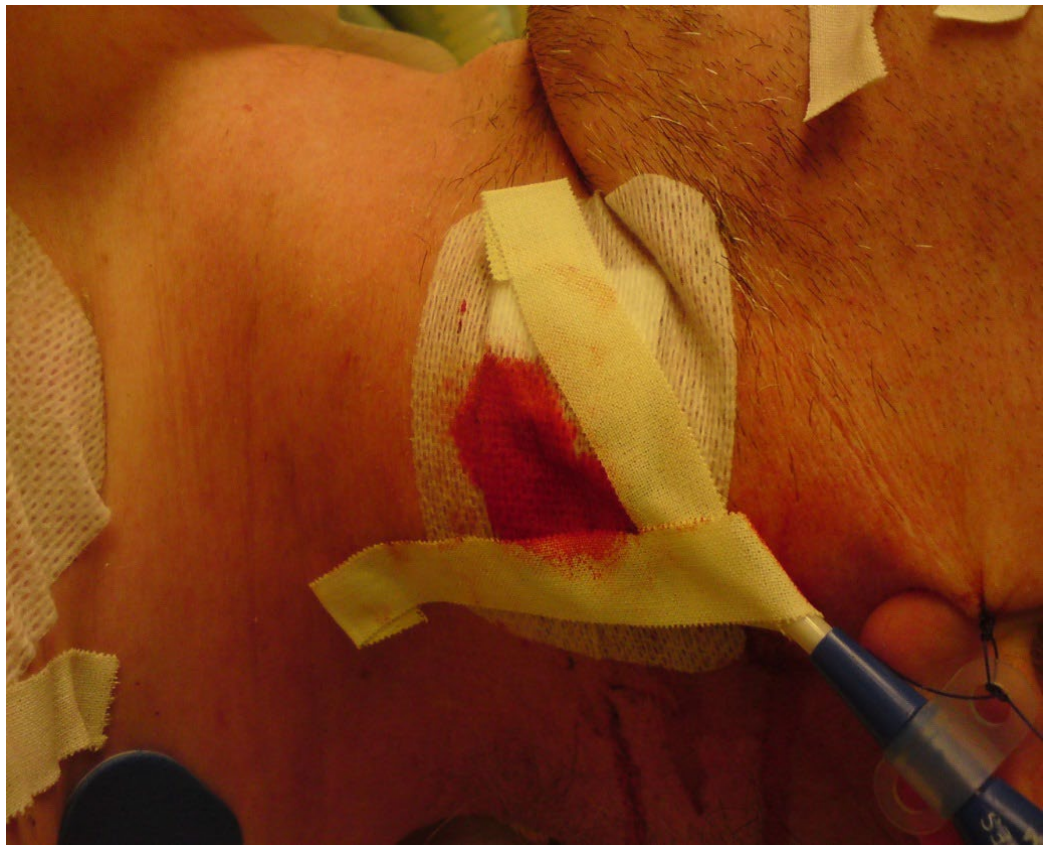
Eine chirurgische Blutung kann nicht hämostaseologisch gestillt werden!

Charbit J et al. Vox Sang 2016

visuelle Diagnose einer Koagulopathie

nicht-chirurgische, diffuse Blutungen aus Schleimhaut, Serosa und Wundflächen

Typisch ist auch das Auftreten von Blutungen aus den Einstichstellen intravasaler Katheter und Blutungen aus liegenden Blasenkathetern oder Magensonden.



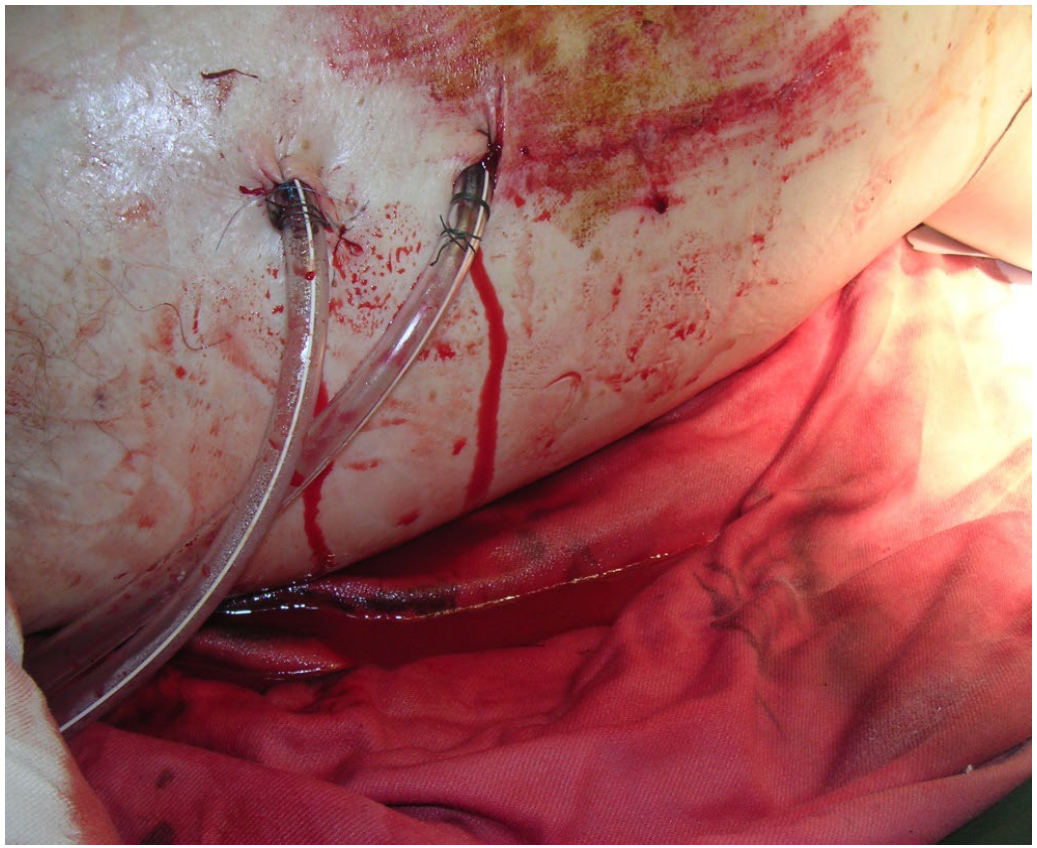
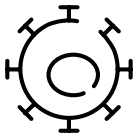


Foto: Dr. H. Lier

Definition

Hemmkörper  Medikamente  oder andere Ursachen 

Koagulopathie

= Störung des „Organsystems Gerinnung“

INR >1,5* häufig als Hinweis genutzt, aber nicht „evidence-based“

? *INR 1,2 oder 1,3 oder 1,5 oder 1,6 ?

Peng HT et al. Transfusion 2021

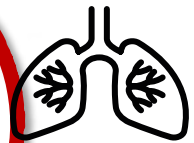
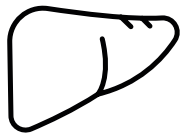
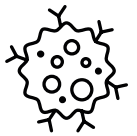
~~tPA~~-Freisetzung aus WEIBEL-PALADE-Körperchen des Endothels durch **Hypoxie** u./o. **Hypoperfusion** (↓Scheerkräfte; ↑Adrenalin, ↑Vasopressin)

Kolev K et al Br J Haematol 2016; Bunch CM et al. Front Physiol 2023; Chalkias A. Int J Mol Sci 2023

zellulärer O_2-Mangel

Sawamura A et al. Thromb Res 2009; Schwameis M et al. Crit Care Med 2015

OP an / Verletzung von :

 Pulmo
 Pankreas
 Plazenta
 Prostata
 Gehirn
 Leber
 Tumor

„4P“

evtl. Hyperfibrinolyse?

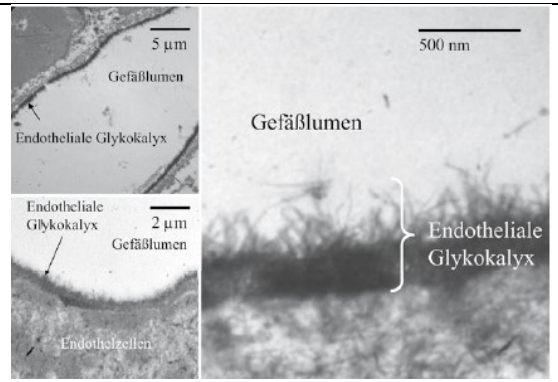
Übrigens: Knochen / Gelenke sind hier nicht erwähnt, weil nicht betroffen.

Verletzungsschwere ↔ Koagulopathie

Level of shock is correlated with level of coagulopathy and inflammation.

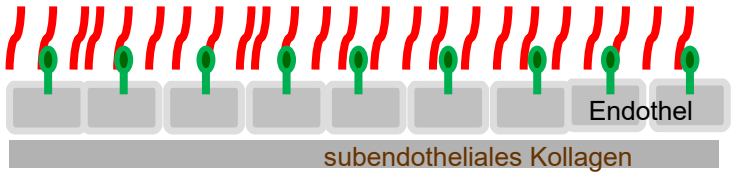
Brohi K et al. J Trauma 2003
MacLeod JBA et al. J Trauma 2003
Maegele M et al. Injury 2007
Hess JR et al. J Trauma 2008

Glykokalyx / Syndecan-1



Endothel:

- einschichtige Begrenzung der luminalen Seite aller Gefäße
- Gesamtgewicht 1 kg
- Gesamtfläche bei Erwachsenen von 4000-7000 m^2



Proteoglykane / Glykoproteine:

- verankern Glykokalyx am Endothel
- häufigste Proteoglykan: Syndecan-1
- Kernprotein mit langen Glykosaminoglykan (GAG, v.a.)-Seitenketten, v.a. aus Hyaloronan [Hyaluronsäure] und Heparansulfat (50-90%)
- bilden ein Netzwerk, in dem lösliche Moleküle (z.B. Albumin) gebunden werden

endotheliale Glykokalyx:

- negativ geladene, antiadhäsive, antikoagulatorische Schicht
- bedeckt und schützt das Endothel → „vascular barrier function“
- abhängig vom Gefäßdurch-messer 0,2-4,5 µm dick
- enthält beim Erwachsenen etwa 1 Liter nicht-zirkulierendes Plasma, d.h. etwa 25% des intravaskulären Volumen
- beeinflusst Blutviskosität / Hkt in Mikrozirkulation
- enthält Bindungsstellen für ATIII, TFPI (tissue factor pathway inhibitor), Thrombomodulin

Glykokalyxschaden als universelles Zeichen für Hypoxie / Reperfusion

"Glycocalyx shedding and endothelial cell injury were estimated to occur at approximately 5 and 8 min after injury, respectively."

⇒ "on-scene phenomenon"

Naumann DN et al. Shock 2018

Freisetzung von u.a. Syndecan-1, lösliches Thrombomodulin (sTM), Heparan-Sulfat und Hyaluronan.

Cusack R et al. Biomedicines 2022

Der Glykokalyxschaden ist aber nicht „Polytrauma-spezifisch", sondern Ischämie-bedingt und ein Trigger für lokale und systemische Freisetzung inflammatorischer Mediatoren.

Bogner-Flatz V et al. Mediators of Inflammation 2019

Ischämie-bedingte ~~HypER~~fibrinolyse bei u.a. Polytrauma und „out-of-hospital cardiac arrest"

Zipperle J et al. J Clin Med 2022

aber ~~Hypo~~fibrinolyse bei u.a. Sepsis

Bunch CM et al. Front Physiol 2023

gestörte Mikrozirkulation → zelluläre Hypoxie → SHock-INduced Endotheliopathy (SHINE) ↔ Multiorganversagen

Cusack R et al. Biomedicines 2022

Vielzahl möglicher Ursachen:
Trauma, Sepsis, „post cardiac arrest", PPH, Massivblutungen, Vergiftungen, Verbrennungen, hämatologische Malignome

Bunch CM et al. Front Physiol 2023

tPA-Freisetzung aus WEIBEL-PALADE-Körperchen als Reaktion auf
- Hypoxie u./o.
- Hypoperfusion (red. Scheerkräfte)

Kolev K et al. Br J Haematol 2016; Bunch CM et al. Front Physiol 2023

Enzephalopathie
akutes Nierenversagen
akutes Lungenversagen
akutes Leberversagen
Koagulopathie

"occult hypoperfusion"

Dutton RP. Br J Anaesth 2012

"The main finding of this study is that the sublingual microcirculation is impaired for at least 72 hours, despite restoration of macrocirculation after surgical and/or radiological hemostasis in traumatic hemorrhagic shock patients. **The restoration of macrovascular hemodynamics was not associated with restoration of microvascular hemodynamics**. …"

Tachon G et al. Crit Care Med 2014

"The application of permissive hypotension should not tolerate

shock-related acidosis."

Fenger-Eriksen C et al. Trends Anaesth Crit Care 2019

in Notaufnahme

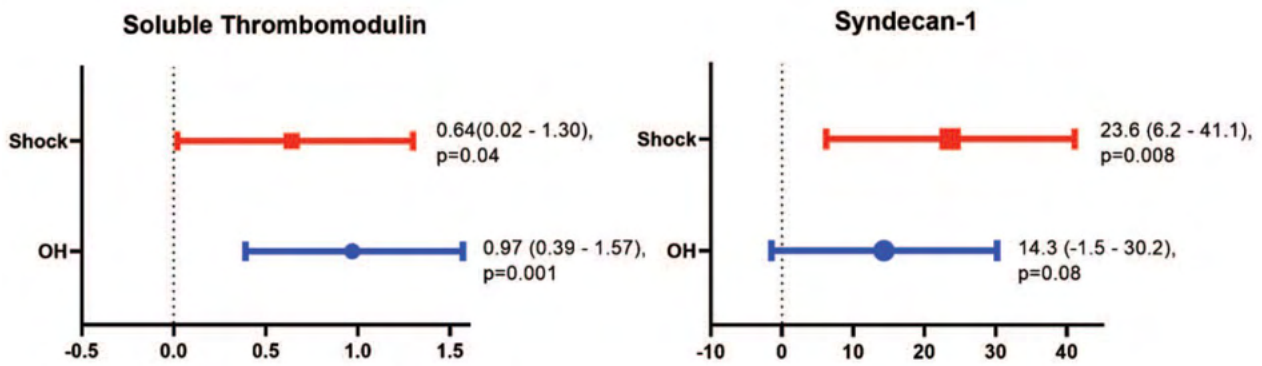
Shock-Induced Endothelial Dysfunction is Present in Patients With Occult Hypoperfusion After Trauma.

Kregel HR et al. Shock 2022

single center study: Houston, TX, USA; 520 patients requiring highest-level trauma activation (2012–2016); evidence of Shock-induced endothelial dysfunction, evidenced by elevated **soluble thrombomodulin (sTM)** and **syndecan-1 (Syn-1)**

Shock (n=134; ISS 20 [12-29]): systolic blood pressure (SBP) < 90 mmHg or heart rate (HR) ≥ 120 bpm.

Occult Hypoperfusion (n=183; ISS 21 [13-29]): SBP ≥ 90 mmHg, HR < 120 bpm, and base excess (BE) ≤ -3

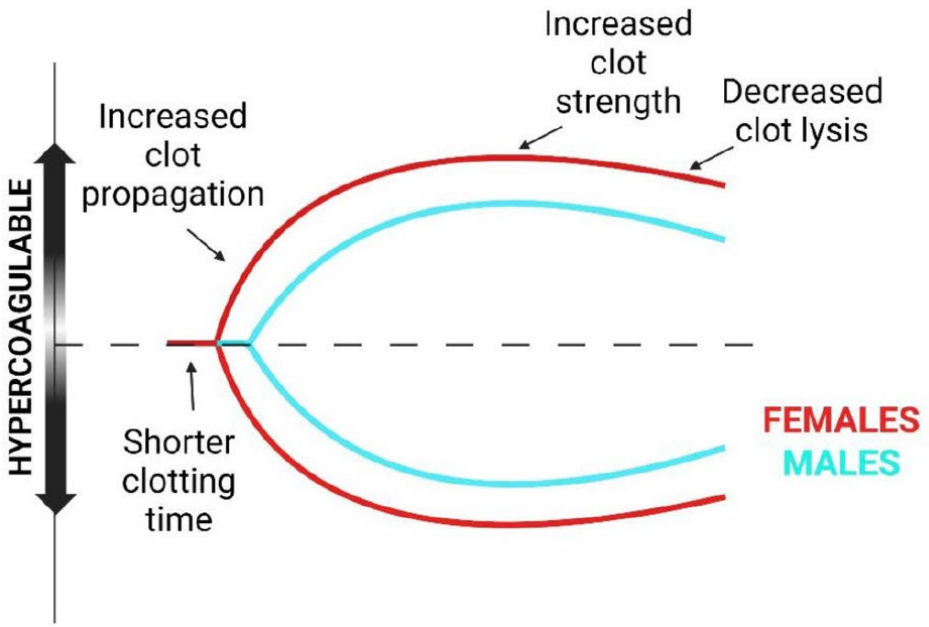


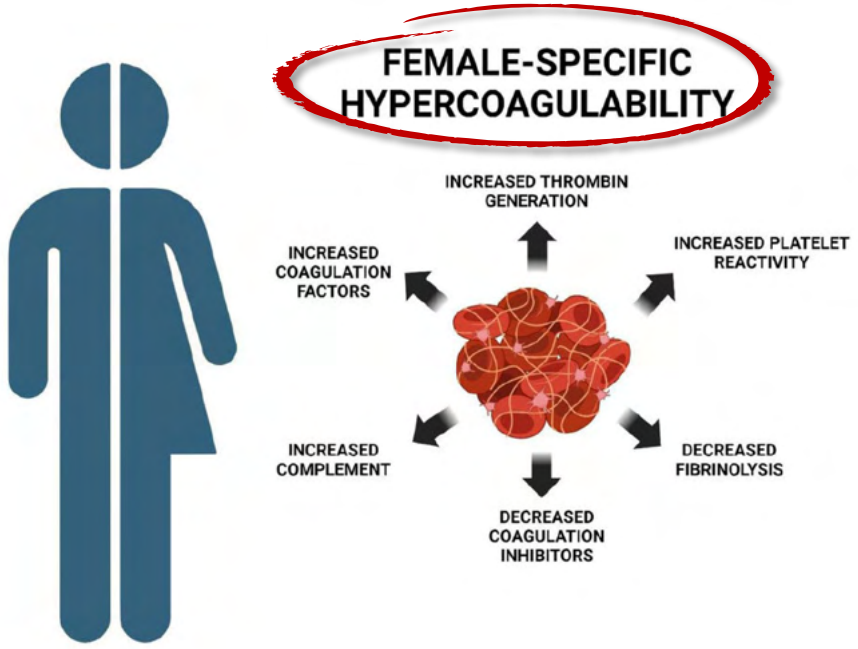
“**Conclusions**: Arrival OH was associated with elevated sTM and Syn-1, indicating endothelial dysfunction.”

BE / Laktat als Zeichen für zellulären Sauerstoff-Mangel, ggf. schon bei „ausreichendem“ Kreislauf !!

Sex dimorphisms in coagulation: Implications in trauma-induced coagulopathy and trauma resuscitation.

Coleman JR et al. Am J Hematol 2024





ABER: >45. Lebensjahr → ↑Fibrinolyse (↑Plasmin-Antiplasmin-Komplexe, ↓α2-Antiplasmin, ↓FII, ↓FX) ⇒

independent relationship between female sex, age 55 years or older, and increased mortality

Dujardin RWG et al. J Trauma Acute Care Surg 2024

Rahmenbedingungen der Gerinnung

frühzeitige und wiederholte Messung

Kietaibl S et al. Eur J Anaesthesiol 2023
Rossaint R et al. Crit Care 2023

„Gerinnung“

- Körperkerntemperatur ≥ 34°C (möglichst Normothermie)
- pH-Wert ≥7,2
- ionisierte Ca^{2+}-Konzentration >0,9 mmol/l (möglichst Normokalzämie)

BGA & Temp.

„Perfusion“

- BE [1,2] (Basenüberschuss) >-6 mmol/l
- Laktat [2] <4 mmol/l
- arteriell-zentralvenöse Differenz des pCO_2 („pCO_2 gap“) <6 mmHg

[1] Cave: BE bis -3 mmol/l ist physiologisch in Schwangerschaft (renal kompensierte, respiratorische Alkalose) Surbek D et al. Arch Gynecol Obstet 2020
[2] Cave bei erhöhtem Blutalkohol Gustafson ML et al. Am J Emerg Med 2015

BGA und Temperatur als einfachstes „Gerinnungs“- Monitoring !!

modifiziert nach Lier H et al. Notaufnahme up2date 2019

Rahmenbedingungen der Gerinnung

FIV = Ca^{2+}

Kalzium im Körper:

biologisch aktiv, Normwert: Ca_i^{2+} ~1,2 mmol/l

- freie Ionen (ionisiert) → 50%
- Protein-gebunden → 40%
- Komplex-gebunden→ 10%

kritisch ab Ca_i^{2+} ≤0,9 mmol/l
Lier H et al. J Trauma 2008

Ursachen für **Hypokalzämie**:

- intrazellulärer Fluss durch Schock
- ischämische Reperfusion

} ↑Laktat bewirkt linearen ↓Ca_i^{2+} (Vivien B et al. Crit Care Med 2005)

- Bindung an Lactat
- Bindung an Citrat → in ALLEN Blutprodukten, am meisten Citrat ist in FFP
- ↓Mg^+ → paralleler intrazellulärer Einfluss von Mg^+ und Ca^{2+}
- Bindung an Phosphate → Chelatbildung
- ↓Parathormon → proinflammator. Zytokine (IL-6) und DAMPs (damage-associated molecular proteins)

Folgen einer **Hypokalzämie**:

- Hypotension
  - ↓kardiale Kontraktilität
  - ↓Kontraktion glatter Gefäßmuskulatur

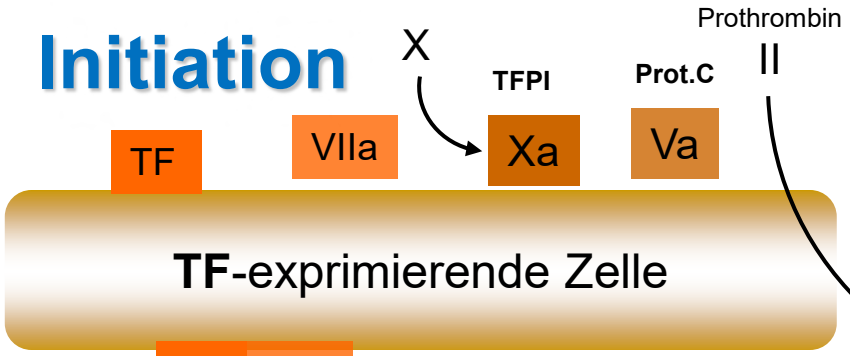
} wenn Ca_i^{2+} <0,9 mmol/l

  - Endotheliopathie → Auflösung intrazellulärer „junctions"
- Koagulopathie
  - ↓Fibrinpolymerisation
  - ↓Plättchen-Aktivierung und –Aggregation
  - ↓Faktorenaktivität

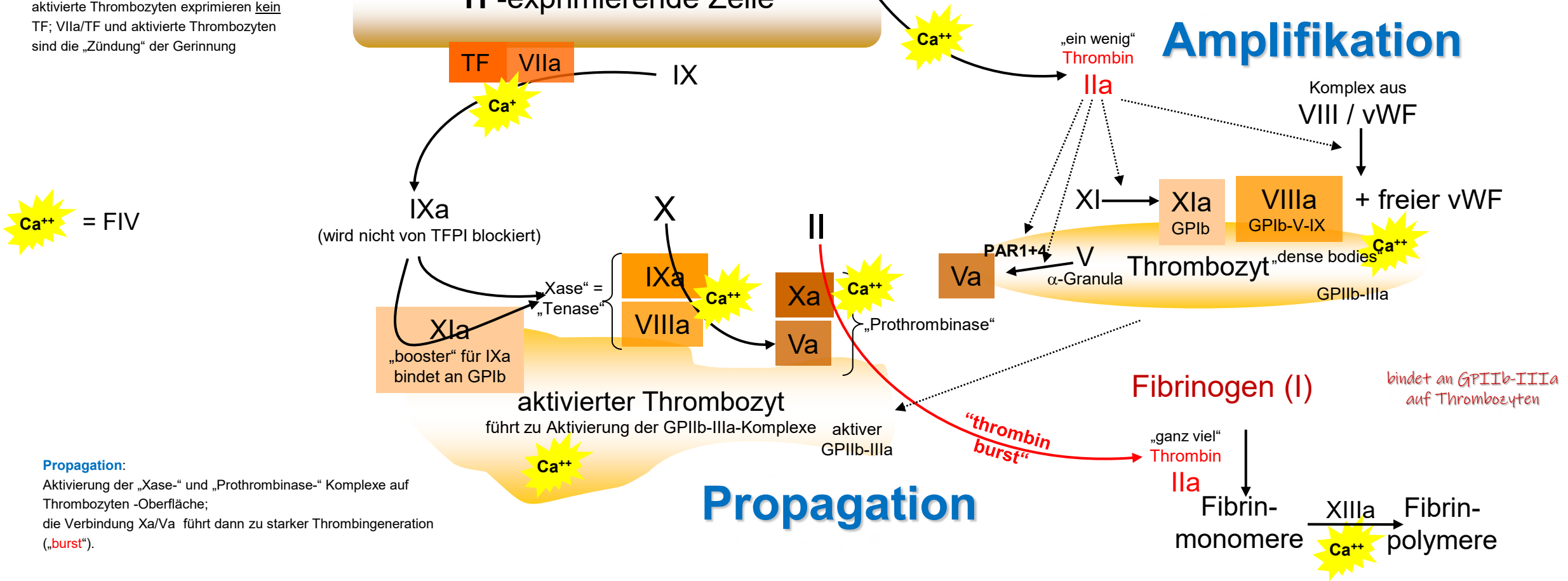
deBot M et al. Transfusion 2022; Rushton TJ et al. Eur J Trauma Emerg Surg 2024

Zellbasiertes Modell

Initiation:
TF (tissue factor = Gewebefaktor) ist physiologischer Initiator der Gerinnung; integrales Membranprotein; auf vielen *extra*vaskulären Zellen unter „normalen“ Bedingungen, bei Entzündung auch auf Monozyten und Endothelzellen; nicht-aktivierte Thrombozyten exprimieren kein TF; VIIa/TF und aktivierte Thrombozyten sind die „Zündung“ der Gerinnung



Amplifikation:
Aktivierung der Thrombozyten durch Kontakt mit subendothelialen Zellen; geringe Mengen von II=Thrombin, das von TF-exprimierenden Zellen gebildet wurde, verstärken die Thrombozyten -Adhäsion, aktivieren die Thrombozyten vollständig und aktivieren V+VIII+XI.



Propagation:
Aktivierung der „Xase-“ und „Prothrombinase-“ Komplexe auf Thrombozyten -Oberfläche;
die Verbindung Xa/Va führt dann zu starker Thrombingeneration („burst“).

modifiziert nach Hoffman M. Thromb Haemost 2001

BE und outcome

Renaissance of base deficit for the initial assessment of trauma patients: a base deficit based classification for hypovolemic shock developed on data from 16,305 patients derived from the TraumaRegister DGU®.

Mutschler M et al. Crit Care 2013

	Class I	Class II	Class III	Class IV
Shock	No shock	Mild	Moderate	Severe
Base deficit at admission, mmol/L	≤ 2	> 2.0 to 6.0	> 6.0 to 10.0	> 10.0
Need for blood products	Watch	Consider	Act	Be prepared for massive transfusion

Steigende „class I-IV" korreliert mit abnehmendem Aufnahme-Hb, abnehmender Aufnahme-INR, steigendem ISS, steigender Sterblichkeit und steigendem Transfusionsbedarf.

European Trauma 6th ed. Rossaint R et al. Crit Care 2023

We *recommend* blood lactate as a sensitive test to estimate and monitor the extent of bleeding and tissue hypoperfusion; in the absence of lactate measurements, base deficit may represent a suitable alternative.

(Rec. 10; **1B**)

"… these two variables do not strictly correlate with each other in severely injured patients and lactate levels more specifically reflect the degree of tissue hypoperfusion."

average ABG **pH ≤7.15**: AUROC 0.958 (95% CI 0.925 to 0.979, p<0.0001) **for mortality**.

Katirai A et al. Am J Emerg Med 2018

"BE, lactate and pH are independent predictors of mortality"

Table 3 ROC curve analyses

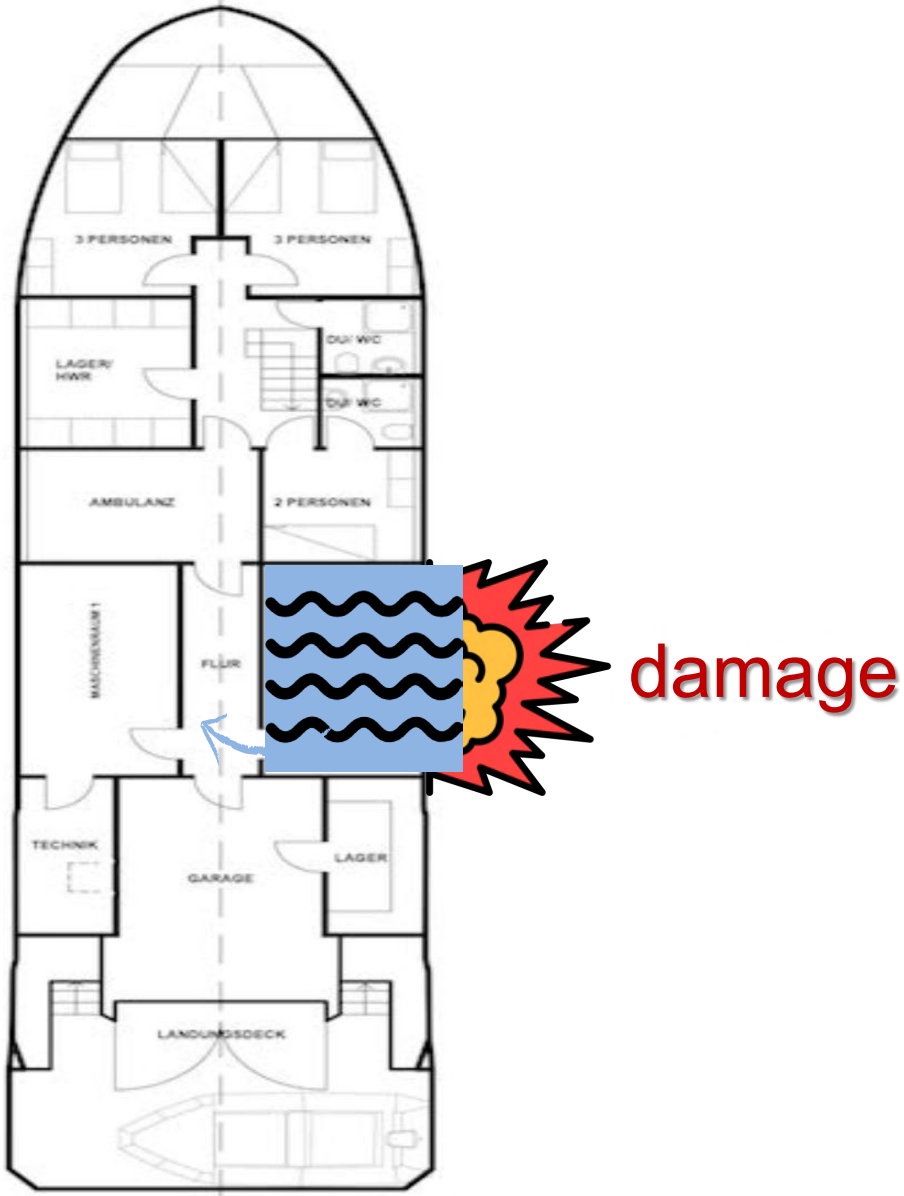
Variable	AUC	SE	95%CI	threshold values	sensitivity	95%CI	specificity	95%CI	positive likelihood ratios	95%CI	negative likelihood ratios	95%CI
BE[a]	0.693	0.0143	0.675–0.712	≤ −4.6	59.19	54.7–63.6	71.84	69.8–73.8	2.10	1.9–2.3	0.57	0.5–0.6
Lactate[b]	0.715	0.0132	0.697–0.733	> 2.42	69.49	65.2–73.5	60.74	58.5–62.9	1.77	1.6–1.9	0.50	0.4–0.6
pH[c]	0.670	0.0149	0.651–0.689	≤7.24	41.82	37.4–46.3	87.00	85.4–88.5	3.22	2.8–3.8	0.67	0.6–0.7

"true positives"

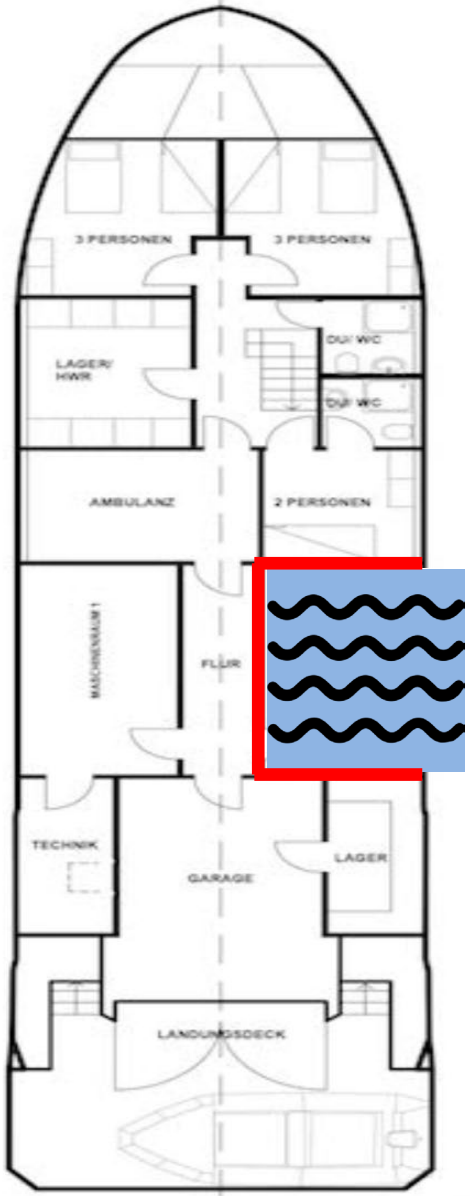
Qi J et al. BMC EmergMed 2021

„damage control“ und „permissive Hypotonie“?

„Damage Control“



damage



damage control

Maßnahmen, die ergriffen werden, um Verluste oder Schäden zu minimieren oder zu begrenzen.

ATLS-Klassifikation

		stabil (I)	grenzwertig (II)	instabil (III)	moribund (IV)
Schock	syst. Blutdruck	≥100	≥80-<100	≥60-<80	≤60
	EK in 2h	≤2	3-≤8	9-15	≥16
	Laktat [mmol/l]	≤2,2	>2,2-≤2,5	>2,5-≤4	>4
	BE [mmo/l]	0- -2	-2 - -6	-6 - -10	≥≥-10
	ATLS-Schock	I (BV <15%)	I-II (BV <30%)	III-IV (BV 30-40%)	IV (BV >40%)
	Urin [ml/h]	↔	↔	↓	↓↓
Gerinnung	Thrombozyten [10^3/µl]	>110	>90-≤110	>70-≤90	≤70
Temperatur	Temperatur [°C]	>34	>33-≤34	>30-≤33	≤30
Verletzung	Lunge (PaO_2 / FiO_2)	>350	300-350	200-300	<200
	Thorax (AIS)	0,1 oder 2	3	4	5
	Abdomen (Moore)	0,1 oder 2	3	4	5
	Becken (AO)	kein	A	B	C oder crush

ETC

DCR

„damage control resuscitation“ bei hämorrhagischem Schock

schnellst-möglicher Therapiebeginn	**6th Europ. Trauma (ET) 2023**: **1B** (Recom. 1)
1. „permissive Hypotension“	**S3-LL „Polytrauma“ 2023**: **GoR B** („sollte“; Empfehlg. 2.4.4) **6th ET 2023**: **1B** (Recom. 13)
2. (Wieder-)Erwärmung	**S3-LL „Polytrauma“ 2023**: **GoR B** („sollte“, Empfehlg. 2.4.8) **6th ET 2023**: **1C** (Recom. 18) **ESAIC 2023**: (G2)
3. Azidoseausgleich	**S3-LL „Polytrauma“ 2023**: **GoR B** („sollte“, Empfehlg. 2.4.9) **6th ET 2023**: **1B** (Recom. 10, Text) **ESAIC 2023**: (G2)
4. „haemostatic resuscitation“ Blut (-komponenten), Faktoren, Ratio, VET	siehe dort

permissive Hypotension
Fazit

- bei aktiver Blutung **UND** bis zur chirurgischen Blutstillung
- Blutdruck niedriger als normal **ABER** ausreichende Perfusion auf zellulärer Ebene
- CPP = MAP-ICP
  cerebral perfusion pressure (CPP) → Soll: >60 mmHg
  intracranial pressure (ICP) → Soll: <20 mmHg
- restriktive Flüssigkeitsgabe, ggf. Noradrenalin
- regelmäßige Kontrolle mittels BGA (alle 20-60 Min.)

2018: Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: A systematic review and meta-analysis of randomized controlled trials.

Tran A et al. J Trauma Acute Care Surg 2018

Der Artikel hat einen sehr spannenden letzten Satz:

"The ideal blood pressure target for such a strategy remains unclear."

MAP = 65 mmHg ?

tastbarer Radialispuls ?

RR_{sys} = 90 mmHg oder 100 mmHg ?

bei anamnestischer Hypertension?

„damage control resuscitation“

Welches Volumenersatzmittel ?

(isotone) kristalline Lösungen

initiale Flüssigkeitstherapie

S3-LL „Polytrauma“ 2023: GoR A („soll“; Text der Empfehlg. 1.3.7);
6. ET 2023: („0.9% sodium chloride [“limited to a maximum of 1-1.5L”] or balanced crystalloid“) **1B** (Recom. 15);
ESAIC 2023: 1B (Recom.15)

keine / wenig Kolloide

S3-LL „Polytrauma“ 2023: „soll verzichtet werden“ (Text der Empfehlg. 1.3.8);
6. ET 2023: „be restricted“ **1C** (Recom. 15);
ESAIC 2023: „The crystalloid–colloid debate in peri-operative care has not been settled.” (Text der Recom.15)

HAES: **EMA:** kontraindiziert bei Sepsis, Verbrennung, kritisch Kranke EMA PRAC 11.Oct 2013

HAES: **BfArM:** Therapie des akuten Blutverlustes; Programm für den kontrollierten Zugang BfArM 21.Nov 2023

~~hypertone Kochsalzlösung*~~

bei Verdacht auf stark erhöhten intrakraniellen Druck / Herniation

S3-LL „Polytrauma“ 2023: GoR 0 („kann“; Empfehlg. 1.6.5 und 2.10.9);

* 2023 **Meta-Analyse**, 6 RCT: keine Wirkung auf neurol. Outcome, LOS oder Sterblichkeitt; negativer Effekt durch ↑Na^+

Bernhardt K et al. Neurocrit Care 2023

Die Tranexamsäure?

Tranexamsäure ist …

… ein **Antifibrinolytikum** (d.h., es verhindert die vorzeitige und verstärkte Auflösung eines bereits gebildeten Gerinnsels).

Tranexamsäure ist …

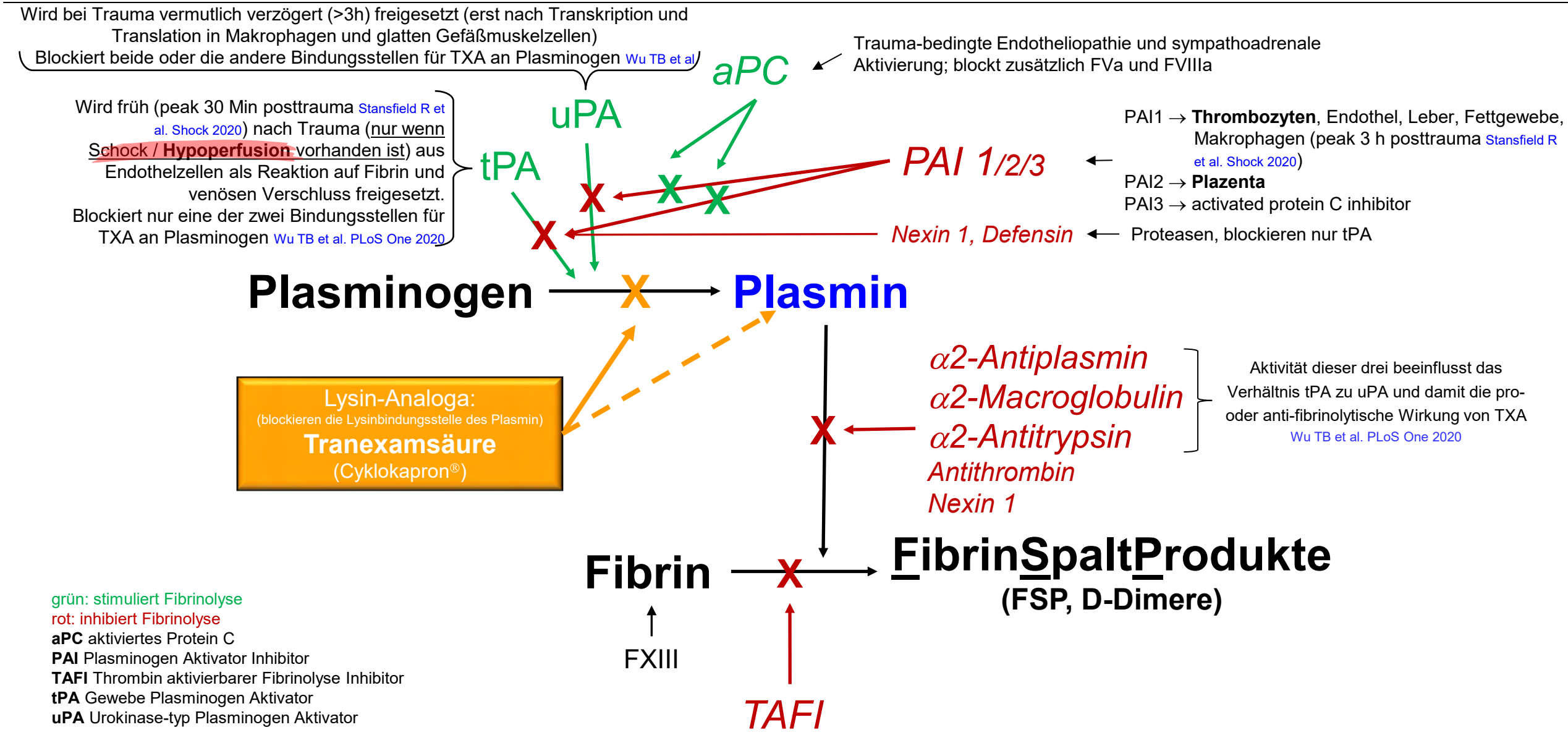
… **kein Antihämorrhagikum** (d.h., es bildet keine Gerinnsel).

Tranexamsäure ist …

… **kein universelles „Gerinnungswundermittel“**,

auch wenn es hämostaseologisch ggf. supportiv bei *koagulopathischen* Blutungen benutzt werden kann.

Tranexamsäure
Wirkung



grün: stimuliert Fibrinolyse
rot: inhibiert Fibrinolyse
aPC aktiviertes Protein C
PAI Plasminogen Aktivator Inhibitor
TAFI Thrombin aktivierbarer Fibrinolyse Inhibitor
tPA Gewebe Plasminogen Aktivator
uPA Urokinase-typ Plasminogen Aktivator

modifiziert nach Lier H et al. Anesth Analg 2019

Tranexamsäure

Dosierung?

CRASH und Folgende benutzen

1g Bolus gefolgt von 1g Infusion über 8 Stunden

basierend auf

Cochrane Database Syst Rev. 2007

"This review updates previous estimates of the efficacy of aprotinin, tranexamic acid, and epsilon aminocaproic acid in reducing perioperative allogeneic blood transfusion in elective surgery."

53 (of 211) trials that studied the efficacy of TXA
29 involved cardiac surgery
21 involved orthopaedic surgery
2 involved liver surgery
1 trial involved vascular surgery

- elektiv, keine Notfälle
- keine PPH
- kein Polytrauma
- keine intrakranielle Pathologien

TXA ist keine inerte Substanz!!

RCT, 25 cardiac surgery patients with CPB, 2x 2,5 g TXA

- effective inhibition of fibrinolysis at a concentration of 10 µg/mL
- TXA-induced lysis inhibition was detectable up to 96 h
- interindividual differences in lytic response (renal impairment)
- small differences in renal function had great effects

Kammerer T et al. Transfus Med Hemother 2021

RCT, 42 elective orthopaedic surgery patients, 1 g TXA

- fibrinolytic inhibition increased up to 48 h after application

Groene P et al. Transfus Med Hemother 2021

Case-report, dialysis-dependent cardiac surgery patient with CPB, 1 g TXA

- significant fibrinolysis inhibition: 5-15 µg/mL
- after 42 h ongoing extensive inhibition of fibrinolysis ("fibrinolytic shutdown") despite 6 h intermittent hemodialysis (IHD)
- after 6 h intermittent hemodialysis on post-OP day 1, TXA plasma concentration remained therapeutical (6.9 µg/mL)

Yoshii R et al. AA Pract 2023

Trauma und Fibrinolyse

Reaktion des Körpers auf (schwere)Trauma:

HypERfibrinolyse*	schnelle, anhaltende und überschießende Aktivierung	frühe: Häufigkeit ~20% Sterblichkeit >40%
„normale“ Fibrinolyse	kurzfristigen Aktivierung der Fibrinolyse, die dann schnell reduziert wird	Häufigkeit <20% Sterblichkeit <5%
„fibrinolytic shutdown“* HypOfibrinolyse*	niedrige fibrinolytischer Aktivität nach initialer Aktivierung niedrige fibrinolytischer Aktivität ohne initiale Aktivierung	späte: Häufigkeit >60% Sterblichkeit ~20%

* nicht Polytrauma-spezifisch!!!

Tranexamsäure kann ggf. Leben retten

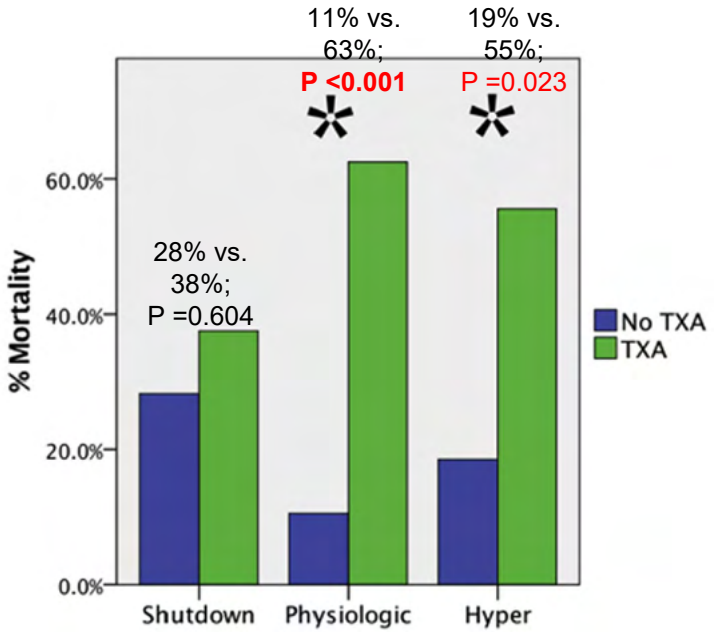
Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis

IFOM-2021/22: Evidenzgrad 2b

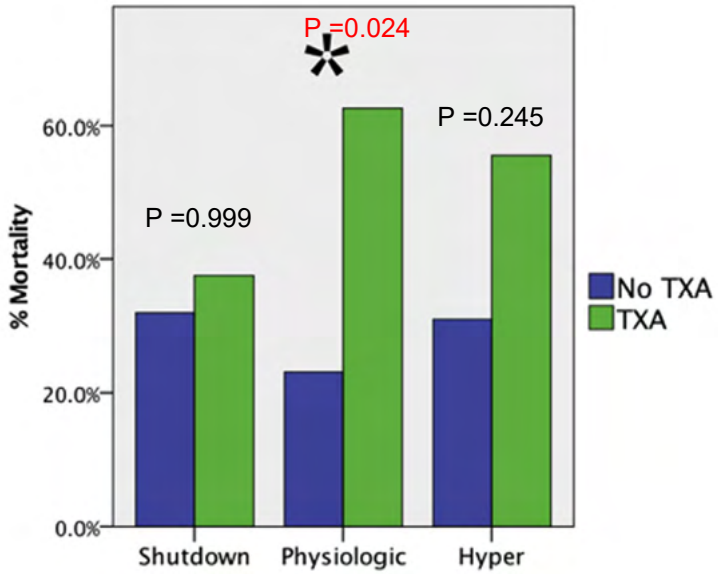
Moore HB et al. J Surg Res 2017

prospective; Denver, Colorado; 232 patients, 33% penetrating injuries, median NISS 33 (22-47), 19% massive transfusion, overall mortality rate 20%. 11% received TXA,

"TXA administration was associated with a higher new injury severity score (49 versus 28; P < 0.001), massive transfusion rate (69% versus 12%; P < 0.001), and mortality (52% versus 17%; P < 0.001)."



TXA effect on **mortality** between phenotypes.
* P <0.05



TXA effect on **mortality** between phenotypes in patients **requiring blood product** resuscitation.* P <0.05

Das heißt:
① TXA führt nicht immer zu einem Überlebensvorteil.
② TXA ist zumindest bei physiologischer Lyse schädlich (und bei Shutdown nicht hilfreich).

Temporal Transitions in Fibrinolysis after Trauma: Adverse Outcome Is Principally Related to Late Hypofibrinolysis.

Rossetto A et al. Anesthesiology 2022

secondary analysis of previously collected data from trauma patients enrolled into an ongoing prospective cohort study (ACIT-2); ROTEM on admission and at 24 h: maximum lysis <5% (low) vs. 5 to 15% (normal) vs. > 15% (high); 731 patients: 432 (5%) no TXA, 299 (41%) TXA

- Two different cohorts with low-maximum lysis at 24 h were identified: (1) severe brain injury and (2) admission shock and hemorrhage.
- Multiple organ dysfunction syndrome was greatest in those with low-maximum lysis on admission and at 24 h, and
- late mortality was four times higher than in patients who remained normal during the first 24 h (7 of 42 [17%] vs. 9 of 223 [4%]; P = 0.029).
- Patients that transitioned to or remained in low-maximum lysis had increased odds of organ dysfunction (5.43 [95% CI, 1.43 to 20.61] and 4.85 [95% CI,1.83 to 12.83], respectively).
- Tranexamic acid abolished ROTEM hyperfibrinolysis (high) on admission, increased the frequency of persistent low-maximum lysis (67 of 195 [34%]) vs. 8 of 79 [10%]; P = 0.002), and was associated with reduced early mortality (28 of 195 [14%] vs. 23 of 79 [29%]; P = 0.015).

"… to **bleeding trauma patients** for whom the **major hemorrhage protocol is activated** in the presence of **low systolic blood pressure less than 90 mmHg** and **suspected active hemorrhage**."

Tranexamsäure
Wirksamkeit

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (**CRASH-2**): a randomised, placebo-controlled trial.

Es wurde nicht aktiv nach thromboembolischen Komplikationen gesucht

CRASH-2 trial collaborators. Lancet 2010

20.211 Patienten, 369 thrombo-embolische Komplikationen ??
"… vascular occlusive events … we cannot exclude the possibility of some increase in risk … we might have under-reported the frequency of these events."

10.060 vs.10.067 Patienten

NNT = 67 (gesamt) bzw. 125 (blutungsbedingt)

absolute mortality risk reduction = 1,5% (gesamt) / 0,8% (blutungsbedingt)

65% insgesamt und 55% der Todesfälle in der ersten Stunde waren NICHT blutungsbedingt!!

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (**MATTERs**) Study.

Morrison JJ et al. Arch Surg 2012

293 / 896 Patienten

NNT = 15

absolute mortality risk reduction = 6,5%

Bei Massivtransfusion:

NNT = 7

absolute mortality risk reduction = 13,7%

"The higher rate of DVT and PTE in the TXA group* should be taken in the context of a higher injury burden, which is associated with thrombotic events."

*9-fach (0.3% vs. 2.7%) erhöhte Rate an Lungenembolien und 12-fach (0.2% vs. 2.4%) erhöhte Rate an tiefen Venenthrombosen

Tab.1 und Gruen RL et al. Med J Austr 2013

modifiziert nach Lier H et al. Anesth Analg 2019

Precision medicine: clinical tolerance to hyperfibrinolysis differs by shock and injury severity.

Vigneshwar NG al. Ann Surg 2022

multi-centered, prospective, 3 urban level 1 trauma centers (Colorado, USA); ≥1 RBC within 10h of admission; influence of ISS (<26, 26-50, >50) and shock severity (SBP] upon admission: >90, 60-90, <60 mmHg) on massive transfusion (MT), defined as >10 RBC units or death within 6 hours postinjury

	Center 1 n=332	Center 2 N=893	Center 3 N=922
Hyperfibrinolysis Cutoffs, LY30 [%]			
All patients	11.5	5.0	7.0
By admission SBP [mmHg]			
>90	13.9	5.1	8.7
70-90	7.7	2.9	7.0
<70	2.5	2.2	3.7
By ISS			
<26	11.5	5.0	7.0
26-50	2.6	5.1	1.8
>50	2.5	1.0	1.9

"… the optimal LY30 threshold predictive for MT decreases with worsening hypotension and increasing Injury Severity Score, suggesting that **anti-fibrinolytics should be initiated early in severely injured/hypotensive patients**, while more latitude is allowed among those with less severe injuries and higher SBP."

"Rather than setting a strict threshold for HF for all patients, we recommend **a more patient-centric approach**, aligned with the modern trend towards **personalized, precision medicine**. More severely injured patients can only tolerate low levels of fibrinolysis, while conversely, a less severely injured patient with mild hypotension may tolerate higher levels of clot lysis."

Je schwerer der Schock & je höher der ISS, desto stärker die Hyperfibrinolyse !!

Icons made by https://www.infoDiagram.com/ und https://www.istockphoto.com/

Tranexamsäure, Statistik und Interpretation

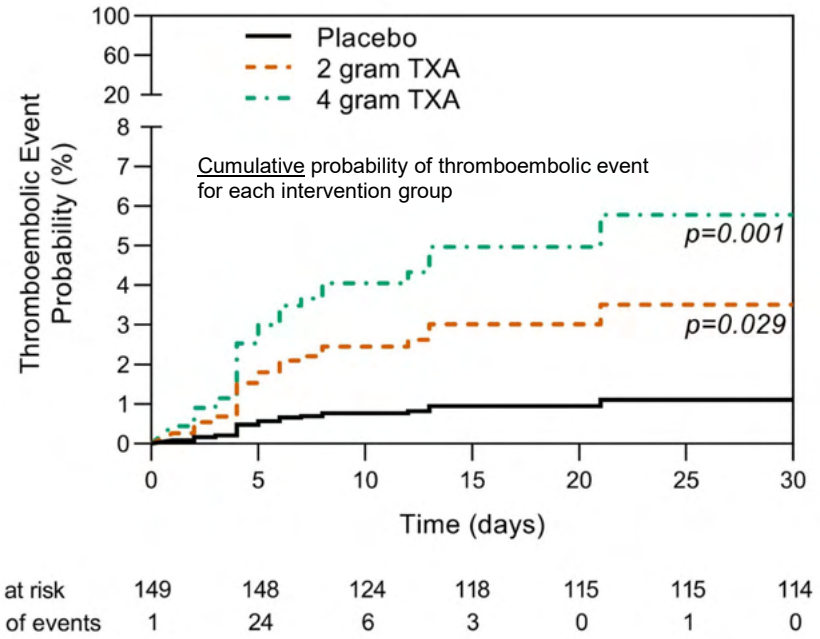
study	result	quote
PATCH-trauma Gruen RL et al. NEJM 2023	**prehospital and any vascular occlusive event**: TXA 23.6% vs. Placebo 19.7% (RR 1.20; 95%CI 0.97-1.48)	"little evidence that tranexamic acid increased the risk of such events" ?
Hmidan Simsam M et al. Injury 2023	**trauma + ≥2g and thromboembolic events**: OR 1.33, 95% CI 0.86 to 2.04	"uncertain effect on thromboembolic events" ?
TICH-NOAC Polymeris AA et al. Stroke 2023	**intracerebral haemorrhage and major thromboembolic complications**: TXA 13% vs. 6% placebo (aOR 1.86; 95% CI, 0.37 to 9.50)	"no major safety concerns" ?
Xiong Y et al. PLoS One 2023	**subarachnoid haemorrhage and DVT**: OR 1.08, 95%CI 0.51 to 2.30 **subarachnoid haemorrhage and stroke / TIA**: OR 1.20, 95%CI 0.83 to 1.72 **traumatic brain injury and pulmonary embolism:** OR 1.22, 95%CI 0.45 to 3.27	"without increasing the incidence of ischemic events" ?
Augustinus S et al. Eur J Trauma Emerg Surg 2023	**hip hemiarthroplasty and pulmonary embolism**: RR 1.10, 95% CI 0.45–2.68	"No differences in the occurrence of … PE were seen." ?

Tranexamsäure kann ggf. Leben retten

The risk of thromboembolic events with early intravenous 2- and 4-g bolus dosing of tranexamic acid compared to placebo in patients with severe traumatic bleeding: A secondary analysis of a randomized, double-blind, placebo-controlled, single-center trial.

Spinella PC et al. Transfusion 2022

secondary analysis of a single center (St. Louis, Missouri), double-blinded, randomized controlled trial (**TAMPITI**) comparing placebo to placebo (n=50), a 2 g (n=49) or 4 g (n=50) intravenous TXA bolus dose in trauma patients with severe injury; median ISS 19-22; 80% penetrating injury; first blood sample ~60 min after trauma;



thromboembolic events: placebo 12.0% vs. 2g TXA 26.5% vs. 4 g TXA 32.0%

Thromboembolic event predictor	HR (95% CI)	P
4-g TXA versus placebo	5.33 (1.94–14.63)	0.001
2-g TXA versus placebo	3.20 (1.12–9.11)	0.029

"Active screening for thromboembolism may account for our ability to detect a TXA dose-dependent relationship with the risk of TE, although 80% of TEs identified were symptomatic."

Use of Tranexamic Acid With Resuscitative Endovascular Balloon Occlusion of the Aorta is Associated With Higher Distal Embolism Rates: Results From the American Association of Surgery for Trauma Aortic Occlusion and Resuscitation for Trauma and Acute Care Surgery Trial.

Shaw J et al. Am Surg 2023

Aortic Occlusion and Resuscitation for Trauma and Acute Care Surgery (AORTA) database; TXA use in the setting of high- (HP) and low-profile (LP) introducer sheaths for resuscitative endovascular balloon occlusion of the aorta (REBOA); 574 patients, 212 received TXA;

TXA use was associated with a higher rate of distal embolism in both groups (OR = 2.92; P = .021).

“For patients receiving TXA, REBOA placement should be accompanied by strict protocols for immediate diagnosis and treatment of thrombotic complications. … larger trials …”

Tranexamic Acid in Upper Gastrointestinal Bleeding is Associated With Venous and Arterial Thromboembolic Events.

Fowler C et al. Crit Care Explor 2024

retrospective cohort study; 2,016,763 patients diagnosed with hematemesis or melena; propensity score matching (PSM) for demographic and comorbidity data

Outcome Variables	TXA	Non-TXA	absolute risk difference (95%CI)	p	OR (95%CI)
starting cohorts					
n	9,644	1,940,058			
CVA (%)	341 (3.5)	28,554 (1.5)	0.020 (0.017–0.024)	< 0.001	**2.4** (2.2–2.7)
MI (%)	322 (3.3)	26,161 (1.3)	0.020 (0.016–0.023)	< 0.001	**2.5** (2.2–2.8)
DVT (%)	589 (6.0)	34,766 (1.8)	0.043 (0.038–0.047)	< 0.001	**3.5** (3.2–3.8)
PE (%)	243 (2.5)	18,567 (1.0)	0.015 (0.012–0.018)	< 0.001	**2.6** (2.3–3.0)
Post-PSM cohorts					
n	9,644	9,644			
CVA (%)	340 (3.5)	219 (2.3)	0.013 (0.008–0.017)	< 0.001	**1.6** (1.3–1.9)
MI (%)	322 (3.3)	225 (2.3)	0.010 (0.005–0.015)	< 0.001	**1.4** (1.2–1.7)
DVT (%)	588 (6.1)	285 (3.0)	0.031 (0.026–0.037)	< 0.001	**2.1** (1.8–2.5)
PE (%)	243 (2.5)	133 (1.4)	0.011 (0.008–0.015)	< 0.001	**1.8** (1.5–2.3)
Post-PSM cohorts, first ever diagnosis of this event					
n	9,644	9,644			
CVA (%)	67 (0.9)	31 (0.4)	0.005 (0.003–0.007)	< 0.001	**2.4** (1.5–3.6)
MI (%)	76 (1.0)	44 (0.5)	0.004 (0.002–0.007)	0.001	**1.9** (1.3–2.7)
DVT (%)	193 (2.5)	77 (0.9)	0.016 (0.012–0.020)	< 0.001	**2.8** (2.1–3.6)
PE (%)	84 (1.0)	22 (0.2)	0.007 (0.005–0.010)	< 0.001	**4.0** (2.5–6.5)

CVA = cerebrovascular accident, DVT = deep venous thrombosis, MI = myocardial infarction, PE = pulmonary embolism

- significant association between the administration of tranexamic acid in UGIB patients and the development of VTE
- significant association between tranexamic acid use and arterial thromboembolic events

"In the 3rd group with patients having the first ever diagnosis of this event, following tranexamic acid use, these events were **twice to four times as likely**."

A comparative analysis of tranexamic acid dosing strategies in traumatic major hemorrhage.

Gunn F et al. J Trauma Acute Care Surg 2024

subanalysis of perpetual, single-center observational cohort study from an urban Level I UK trauma center (prospectively collected **ACIT-II** data); 525 pat. with MHP activation; TXA: 1g bolus (single bolus; n=317, 60%) vs. 1g bolus + 1g infusion (bolus + infusion; n=80, 15%) **vs. 1g bolus + 1g bolus or 2g bolus** (n=128, 25%); "bolus + infusion" had more females (17% vs 34% vs 16%), higher ISS (25 vs. 29 vs. 25), higher blunt injuries (61% vs. 74% vs. 45%) and lower admission fibrinogen (1.8 g/L vs. 1.6 g/L vs. 1.8 g/L); no routine screening for VTE

mortality (single bolus vs. bolus + inf. vs. double bolus):

- 28d: 21% in all groups (p>0.99) → **no** significant difference
- 24h: 10% vs. 6% vs. 11% (p=0.51) → **no** significant difference

  multivariable regression: OR 1.32 (95%CI 0.60–2.92) vs. 1 vs. OR 0.89 (95%CI 0.35–2.26) → **not independently related** to the TXA dosing regimen

MODS (single bolus vs. bolus + inf. vs. double bolus):

64% vs. 84% vs. 63% (p=0.002) → significant difference

multivariable regression: OR 0.97 (95%CI 0.34–2.80) vs. 1 vs. OR 0.72 (95%CI 0.22–2.36) → **not independently related** to the TXA dosing regimen

overall VTE (single bolus vs. bolus + inf. vs. double bolus):

4% vs. 8% vs. 7% (p=0.31) → **no** significant difference

multivariable regression: OR 0.75 (95%CI 0.26–2.18) vs. 1 vs. OR 1.07 (95%CI 0.33–3.47) → **not independently related** to the TXA dosing regimen

"… **no differences in mortality or adverse events** between a single bolus and double bolus strategy when compared with the CRASH-2 trial dosing protocol (1 g bolus plus 1 g infusion). … **a single, 1 g bolus may have equivalent antifibrinolytic efficacy compared with other dosing regimens of TXA**, and clinically is significant given that ROTEM hyperfibrinolysis is associated with higher mortality."

Tranexamsäure kann ggf. Leben retten

Efficacy of high dose tranexamic acid (TXA) for hemorrhage: A systematic review and meta-analysis.

Hmidan Simsam M et al. Injury 2023

systematic review of RCT and observational cohort studies until July 27, 2022; **GRADE**; standard dose (≤ 1 g) TXA vs. high dose IV TXA (≥2 g or ≥30 mg/kg as a single bolus); 20 studies with a combined total of 12,523 patients;

high dose IV TXA (≥2 g or ≥30 mg/kg as a single bolus)

- probably decreases transfusion requirements (OR 0.86, 95% confidence interval [CI] 0.76 to 0.97, moderate certainty)

- possibly no effect on blood loss (mean difference [MD] 43.31 ml less, 95% CI 135.53 to 48.90 ml less, low certainty)

das ist eindeutig ...

- uncertain? effect on thromboembolic events (OR 1.33, 95% CI 0.86 to 2.04, very low certainty)

- uncertain effect on mortality (OR 0.70, 95% CI 0.37 to 1.32, very low certainty)

Tranexamsäure

Schlussfolgerung (1)

Was wir aktuell wissen:

Bei

lebensbedrohlicher Blutung u./o. Schock

ist

möglichst frühzeitig und innerhalb von 3 Stunden

1 gr (15 mg/kgKG) Tranexamsäure langsam i.v.

hochwirksam und lebensrettend

!!!

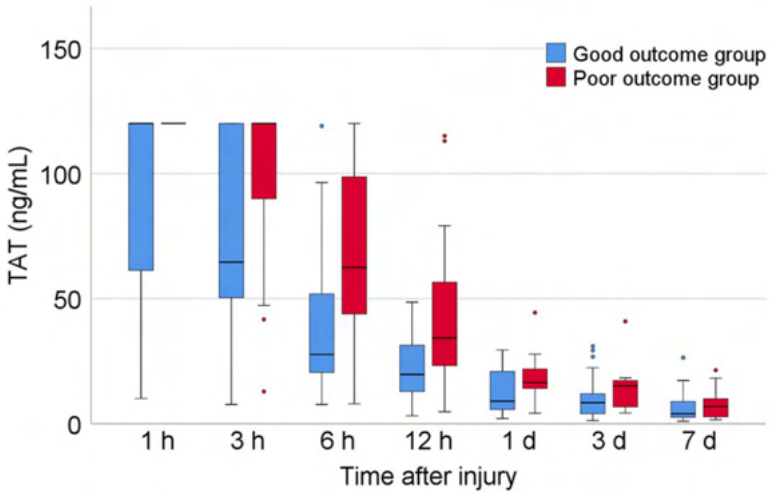
TXA & SHT / ICB / SAB?

Hyperfibrinolysis and fibrinolysis shutdown in patients with traumatic brain injury.

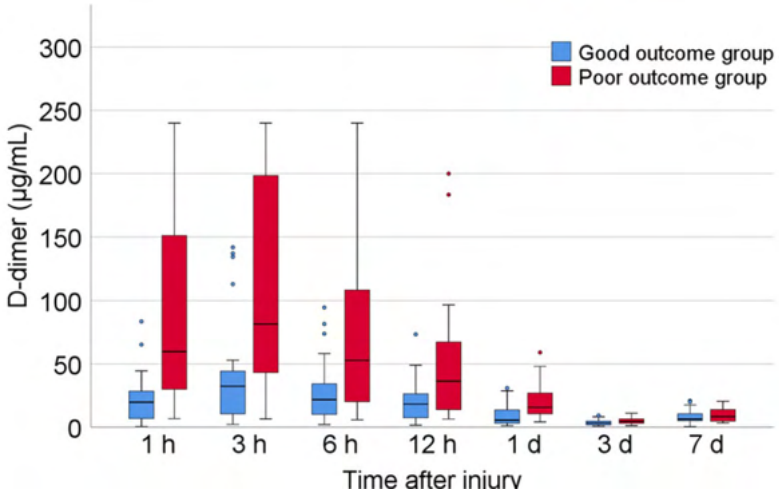
Nakae R et al. Sci Rep 2022

retrospective, single-center; 61 pat. with isolated TBI with intracranial AIS ≥ 3 and extracranial AIS < 3

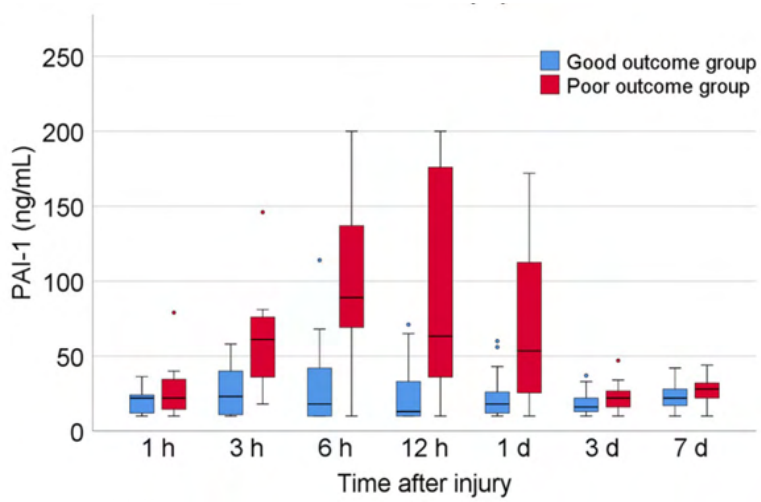
"The plasma levels of TAT, D-dimer, and PAI-1 were higher in the poor outcome group … from the time of admission to 7 days after injury … (all p < 0.001)."



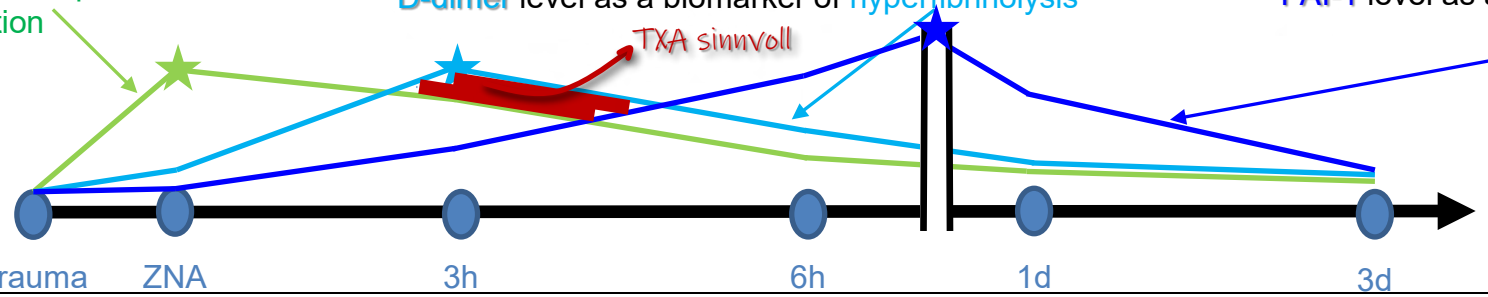
TAT level as a biomarker of fibrin production / hypercoagulation



D-dimer level as a biomarker of hyperfibrinolysis



PAI-1 level as a biomarker of shutdown



Erhebliche Überschneidungen! Unklare Lage!!

SHT und Fibrinolyse-Phänotypen

Patients with TBI were found to have a higher rate of **fibrinolytic shutdown** compared those without TBI.

Meizoso JP et al. J Trauma Acute Care Surg 2022* (25% vs. 18%; p<0,0001); Favors L et al. Am J Surg 2024* (68.7% vs. 63.5%, p=0.054); Durbin S et al. J Trauma Acute Care Surg 2024* (65.3%);

*einmalige Blutabnahme bei Aufnahme

unterschiedliche Aussagen bezüglich einer Korrelation zur	TEG™ Ly30	Sterblichkeit
Meizoso JP et al. J Trauma Acute Care Surg 2022	✓	
Favors L et al. Am J Surg 2024	✓	
Durbin S et al. J Trauma Acute Care Surg 2024	✗	✗

Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (**TICH-NOAC**): A Multicenter, Randomized, Placebo-Controlled, Phase 2 Trial.

Polymeris AA et al. Stroke 2023

double-blind, randomized, placebo-controlled trial at 6 Swiss stroke centers; presence of haematoma expansion on follow-up imaging at 24 (±3) hours, defined as intracerebral hematoma volume increase by at least 33% or 6 mL from baseline; 63 (of 109 calculated) pat. taking any NOAC with last intake ≤48h and randomized ≤15h of symptom onset; TXA (1g bolus + 1g/8h; n=32) vs. placebo (n=31); follow-up 90 days; premature trial discontinuation due to exhausted funding;

- **presence of HE on follow-up imaging**: TXA 38% vs. 45% placebo (aOR, 0.63; 95% CI, 0.22 to 1.,82; p=0.40)
- **suggestion of positive effects**:
  - onset-to-treatment time ≤6 hours
  - intraventricular hemorrhage extension, GCS ≤12, and systolic blood pressure ≤170 mm Hg.
- **no evidence of interaction with**:
  - 4fPCC treatment (2/3 of patients received additional PCC)
  - NOAC plasma level or time from last intake.

"imprecise estimates with wide CIs due to small participant numbers"

"no evidence that TXA limits HE nor that it improves clinical outcomes by 90 days"

- **major thromboembolic events within 90 d**: TXA 13% vs. 6% placebo (aOR,1.86; 95% CI, 0.37 to 9.50; p=0.45)
- **any serious adverse events** (including major thromboembolic events, seizures, and death collected up to 90 days and any serious adverse events collected up to day 7): TXA 75% vs. 65% placebo (aOR,1.43; 95% CI, 0.45 to 4.47; p=0.54)

"no major safety concerns" ↔ "higher rate of adverse events in the TXA arm merits further investigation in future larger trials"

Stopping Intracerebral Haemorrhage with Tranexamic Acid for Hyperacute onset Presentation including Mobile Stroke Units

Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2 h of symptom onset (STOP-MSU): an international, double-blind, randomised, phase 2 trial.

Yassi N et al Lancet Neurol 2024

investigator-led, parallel group, double-blind, randomised, placebo-controlled, phase 2 trial conducted at 25 sites in Australia, Finland, New Zealand, Taiwan, and Viet Nam, including 24 hospital sites and one mobile stroke unit; acute spontaneous ICH treated **within 2 h of stroke onset**; 1g TXA over 10 min + 1g TXA over 8h (n=103) vs. normal saline over 10 min + normal saline over 8h (n=98)

- no difference in haematoma growth: placebo 37/97 (38%) vs. TXA 43/101 (43%) (OR 1·31 [95% CI 0·72 to 2·40], p=0·37)
- no difference in absolute haematoma growth [mL]: placebo 1·2 (–0·2 to 7·6; n=91) vs. 1·2 (0·1 to 9·3; n=99)
- no difference in mRS score at 90 days: placebo 4 (2 to 5) vs. TXA 3 (2 to 5) (OR 0·83 [95% CI 0·60 to 1·14])
- no difference in death
  - by 90 d: placebo 15/98 (15%) vs. TXA 19/103 (18%) (OR 1·61 [0·65–3·98])
  - by 7 d: placebo 8/98 (8%) vs. TXA 8/103 (8%) (OR 1·08 [0·35–3·35])
- no difference in major thromboembolic events: placebo 1/98 (1%) vs. TXA 3/103 (3%)

OR größer als 1, d.h. TXA eher schlechter

sic !

Icons made by https://www.infoDiagram.com/ und https://www.istockphoto.com/

Efficacy and safety of tranexamic acid in acute traumatic brain injury: A meta-analysis of randomized controlled trials.

Zhang M et al. Am J Emerg Med 2024

11,299 patients from11 RCT up to September 31, 2023.

TXA had **no effect on**

- mortality (RR 0.93 [0.86, 1.00], p=0.06; I^2: 0%, p=0.79),
- poor clinical outcomes (RR 0.92 [0.78, 1.09], p=0.34; I^2: 0%, p=0.40),
- adverse events (RR 0.94 [0.83, 1.07], p=0.34; I^2: 48%, p=0.10),
- vascular occlusive events (RR 0.85 [0.68, 1.06], p= 0.16; I^2: 32%, p = 0.22),
- pulmonary embolism (RR 0.76 [0.47, 1.22], p =0.26; I^2: 0%, p = 0.83),
- seizure (RR 1.11 [0.92, 1.35], p = 0.27; I^2: 0%, p = 0.49) and
- hemorrhagic complications (RR 0.78 [0.55, 1.09], p = 0.14; I^2: 0%, p = 0.42).

"… the lack of reduction in mortality and the poor clinical outcomes …"

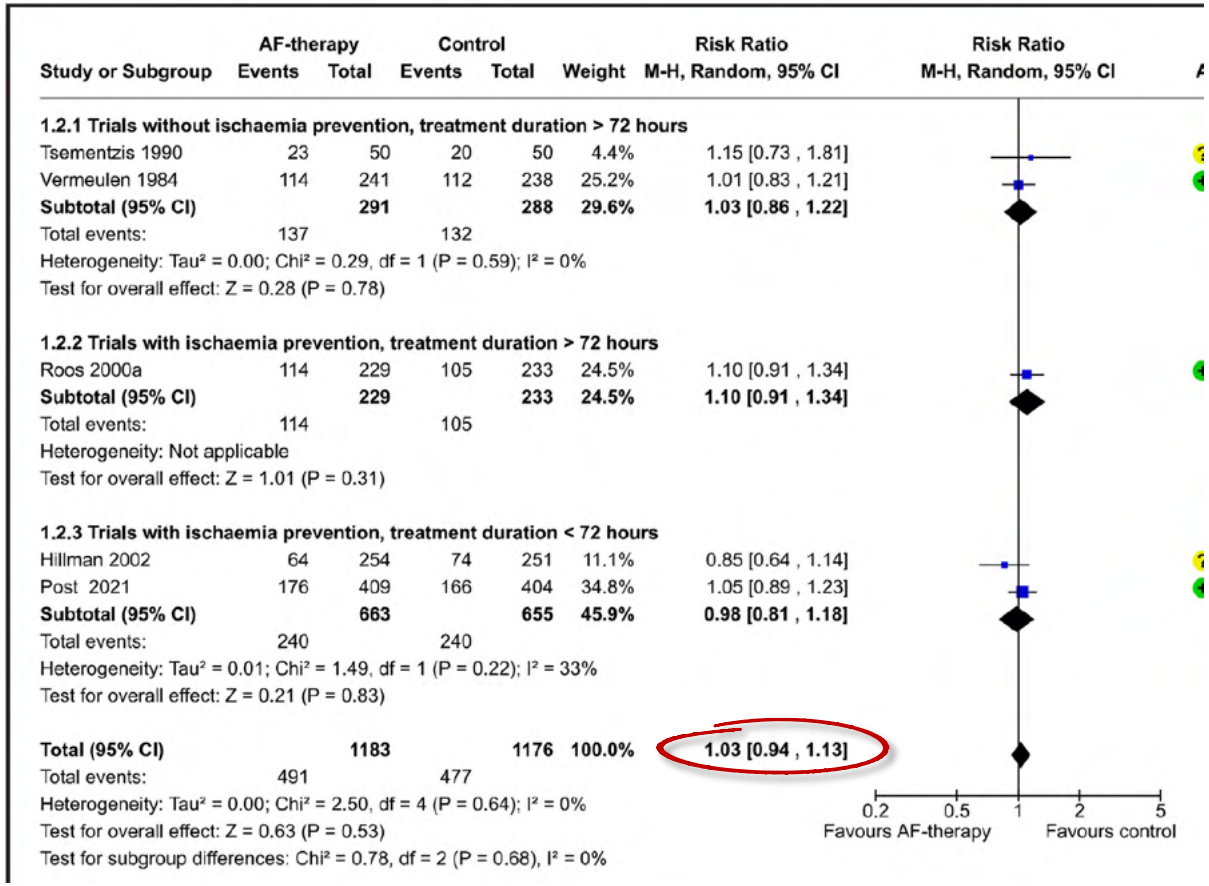
TXA **might reduce**

- the rate of hemorrhagic expansion (RR 0.83 [0.70, 0.99], p = 0.03; I^2: 18%, p = 0.29) and
- mean hemorrhage volume (SMD −0.39 [−0.60, −0.18], p <0.001; I^2: 44%, p=0.13)

Antifibrinolytic Therapy for Aneurysmal Subarachnoid Hemorrhage: An Update of a Cochrane Systematic Review.

Germans MR et al Stroke 2024

update of Cochrane review; 11 trials involving 2717 participants



Study or Subgroup	AF-therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Trials without ischaemia prevention, treatment duration > 72 hours						
Tsementzis 1990	23	50	20	50	4.4%	1.15 [0.73 , 1.81]
Vermeulen 1984	114	241	112	238	25.2%	1.01 [0.83 , 1.21]
Subtotal (95% CI)		**291**		**288**	**29.6%**	**1.03 [0.86 , 1.22]**
Total events:	137		132			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.2.2 Trials with ischaemia prevention, treatment duration > 72 hours						
Roos 2000a	114	229	105	233	24.5%	1.10 [0.91 , 1.34]
Subtotal (95% CI)		**229**		**233**	**24.5%**	**1.10 [0.91 , 1.34]**
Total events:	114		105			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.2.3 Trials with ischaemia prevention, treatment duration < 72 hours						
Hillman 2002	64	254	74	251	11.1%	0.85 [0.64 , 1.14]
Post 2021	176	409	166	404	34.8%	1.05 [0.89 , 1.23]
Subtotal (95% CI)		**663**		**655**	**45.9%**	**0.98 [0.81 , 1.18]**
Total events:	240		240			
Heterogeneity: Tau² = 0.01; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Total (95% CI)		**1183**		**1176**	**100.0%**	**1.03 [0.94 , 1.13]**
Total events:	491		477			
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 4 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 0.78, df = 2 (P = 0.68), I² = 0%						

Risk Ratio M-H, Random, 95% CI

0.2 0.5 1 2 5

Favours AF-therapy Favours control

"The current evidence does **not support the routine use of antifibrinolytic drugs in the treatment of people with aneurysmal subarachnoid hemorrhage**.
It is unlikely, that future trials will change this conclusion."

Tranexamsäure & ICB

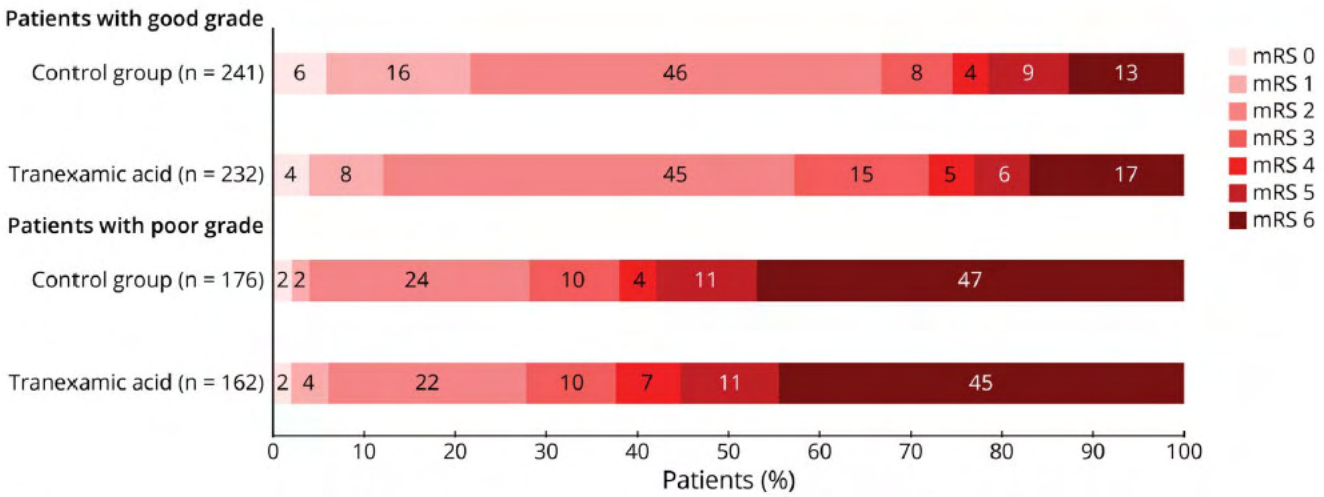
Übersicht RCTs

	setting	haematoma growth	absolute haematoma growth	thromboembolism
STOP-AUST	CT within **4.5h** of symptoms	placebo 26/50 (52%) vs. TXA 22/50 (44%)	median: placebo 3.4 ml (0.0-16.0) vs. TXA 1.9 ml (0.2-9.5)	placebo 2/50 (4%) vs. TXA 1/50 (2%)
STOP-MSU	CT within **2h** of symptoms	placebo 37/97 (38%) vs. TXA 43/101 (43%)	median: placebo 1.2 ml (–0.2 to 7.6) vs. TXA 1.2 ml (0.1 to 9.3) at 24h	placebo 1/98 (1%) vs. TXA 3/103 (3%)
TICH-2	CT within **8h** of symptoms	placebo 304/1058 (29%) vs. TXA 265/1054 (25%)	mean: placebo 4.9 ml (SD 16.0) vs. TXA 3.72 ml (SD 15.9) at 24h	placebo 37/1164 (3%) vs. TXA 39/1161 (3%)
TICH-NOAC	CT within **12h** of symptoms	placebo 14/31 (45%) vs. TXA 12/32 (38%)	median: placebo 1.8 ml (0.1-8.7) vs. TXA 3.3 ml (0.6-8.8)	placebo 6% vs. TXA 13% (aOR 1.86; 95% CI 0.37-9.50)
TRAIGE	CT within **8h** of symptoms	placebo 34/82 (41%) vs. TXA 36/89 (40%)	mean: placebo 7.6 ml (SD 15.6) vs. TXA 6.6 ml (SD 16.5) at 24h	placebo 1/82 (1.3%) vs. TXA 1/89 (1.2%)

Ultra-Early and Short-Term Tranexamic Acid Treatment in Patients With Good- and Poor-Grade Aneurysmal Subarachnoid Hemorrhage.

Tjerkstra MA et al Neurology 2024

post hoc subgroup analysis of ULTRA; ultra-early (immediately after SAH diagnosis and within 24 hours of ictus) and short-term (until aneurysm treatment or maximally 24 hours) TXA in addition to usual care vs. usual care only; categorized into good-grade (WFNS I-III; n=473: 232x TXA vs. 241x standard) and poor-grade (WFNS IV-V; n=338: 162x TXA vs. 176x standard) aSAH (based on the Glasgow coma scale score and presence or absence of motor impairment on admission); **modified Rankin scale**: 0 no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance, but is unable to performall previous activities), 3moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death



good-Grade aSAH: TXA-group had

- **worse clinical outcome** (OR 0.67, 95% CI 0.48–0.94)
- **less often excellent clinical outcome** (133/232, 58% vs 161/241, 67%; aOR 0.67, 95% CI 0.46–0.97)
- **higher occurrence of hydrocephalus** (138/232, 60% vs.121/241, 50%; OR 1.46, 95% CI 1.01–2.10)

poor-Grade aSAH:

- no significant differences between the TXA and usual care groups (OR: 1.04, 95% CI 0.70–1.55)

"This post hoc subgroup analysis provides another important argument **against the use of TXA** treatment in patients with aSAH, by showing worse clinical outcomes in patients with good-grade aSAH treated with TXA and no clinical benefit of TXA in patients with poor-grade aSAH, compared with patients treated with usual care."

Tranexamsäure

Schlussfolgerung (2)

Bei (isolierter) Blutung im Kopf ist Tranexamsäure eher **nicht** indiziert.

Bei polytraumatisierten Patienten mit **lebensbedrohlicher Blutung u./o. Schock,** die **auch** ein SHT haben,

ist 1 gr (15 mg/kgKG) Tranexamsäure langsam i.v. **hochwirksam** und **lebensrettend.**

"There are no magic bullets when it comes to drugs for stopping bleeding."

M. Schreiber 2010

Tranexamsäure
Zusammenfassung

- Tranexamsäure ist wichtige **Teilkomponente** eines blutsparenden Gesamtkonzeptes.

- **Indikation:** (individualisiert [bei V.a. Hyperfibrinolyse] und nicht flächendeckend!)
  - schwer, d.h. lebensbedrohlich blutende Patienten;
  - optimalerweise bevor es zu einem Schock kommt und innerhalb von 3 Stunden nach Trauma,
  - wenn die Blutung nicht durch Kompression u./o. Tourniquet kontrollierbar ist.

- Eine weitere TXA-Gabe sollte innerklinisch erst bei Nachweis oder zumindest dem hochgradigen Verdacht einer (anhaltenden) **Hyperfibrinolyse** und bei Patienten im **Schock** Duque P et al. Anesth Analg 2020 erfolgen.

Die Blutkomponenten?

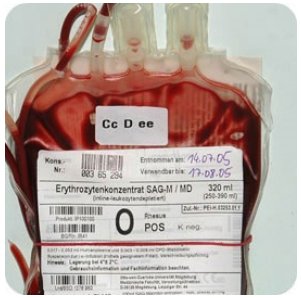
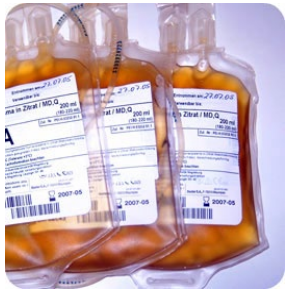
Bluttransfusionen

- In der Regel wird **ein Transfusionsbesteck** (DIN 58360) mit einer Porengröße von 170 – 230 µm **für alle Blutkomponenten** (EK, Plasma und TK) verwendet.

- Transfusionsbestecke werden maximal 6 Stunden genutzt
  (Anmerkung: das entspricht etwa 3 EK bei regulärer Transfusionszeit von 2 Stunden, im OP wird i.d.R. deutlich schneller transfundiert, also nach 3-4 EK ggf. Besteck wechseln)

- Das Anwärmen von Erythrozytenkonzentraten (max. 37°C) bleibt auf spezielle Indikationen, z.B. Massivtransfusionen, Transfusionen bei Neugeborenen, Transfusionen bei Patienten mit Kälteantikörpern, unterkühlten Patienten, Patienten, die auf Kältereiz mit einem Vasospasmus reagieren, beschränkt.
  (Anmerkung: im OP werden **alle Blutprodukte** (EK, Plasma und TK) i.d.R. über Wärmesysteme infundiert)

Bluttransfusionen im OP / auf ICU

	Wärme (-systeme)	Druckinfusion (-systeme)
	✓	✓
	✓	✓
	✓	✗

Die Blutkomponenten?

1. Erythrozytenkonzentrate

4.10.3.1 Erythrozytenkonzentrate

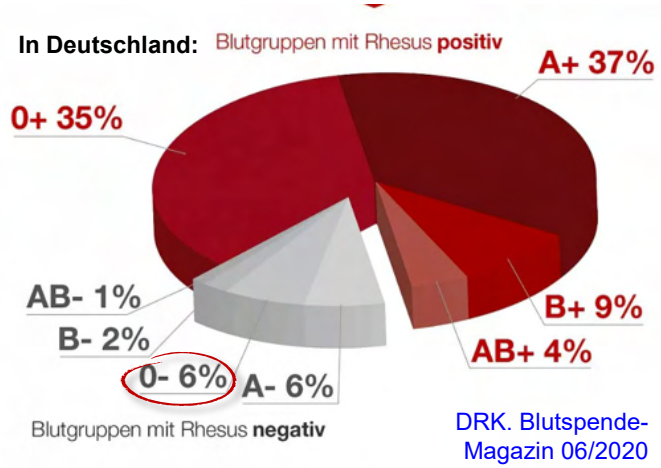
vitale Indikation

„Erythrozytenkonzentrate werden **AB0-gleich** transfundiert. In Ausnahmefällen können auch AB0-ungleiche, sog. „majorkompatible“ Präparate transfundiert werden (s. Tab. 4.10.3.1). Die Ausnahmen sind zu dokumentieren.“

Patient	Kompatible EK
A	A oder 0
B	B oder 0
AB	AB, A, B oder 0
0	0

Bei RhD-negativen Mädchen sowie RhD-negativen gebärfähigen Frauen ist die Transfusion von RhD-positiven Erythrozytenkonzentraten (mit Ausnahme von lebensbedrohlichen Situationen) unbedingt zu vermeiden.

Cave: ungekreuzte EK



DRK. Blutspende-Magazin 06/2020

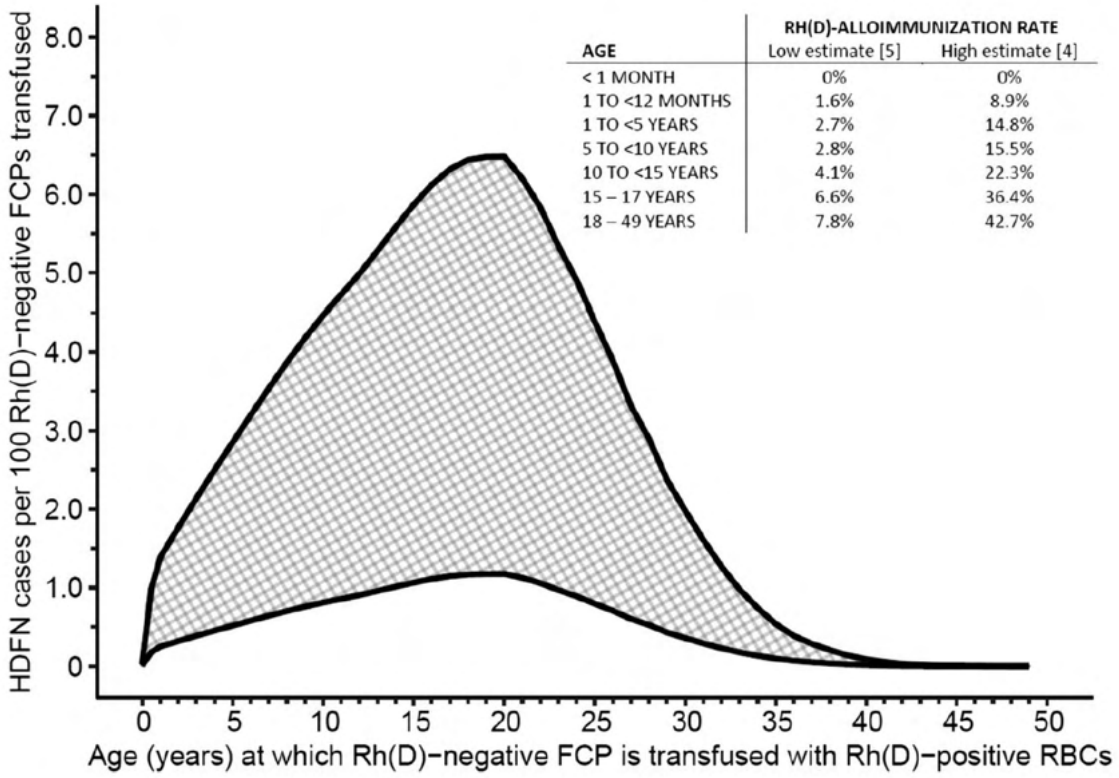
seit 2005 gilt wegen des Mangels an „0 Rh neg.“:

„Solange das Ergebnis der AB0-Blutgruppenbestimmung des Empfängers nicht vorliegt, sind zur Erstversorgung Erythrozytenkonzentrate der Blutgruppe 0 zu verwenden.“ BÄK. Richtlinie Hämotherapie 2023 (Kapitel 4.10.5 Notfalltransfusion)

„Bei RhD-negativen Mädchen sowie RhD-negativen gebärfähigen Frauen ist die Transfusion von RhD-positiven Erythrozytenkonzentraten (mit Ausnahme von lebensbedrohlichen Situationen) unbedingt zu vermeiden.“ BÄK. Richtlinie Hämotherapie 2023 (Kapitel 4.10.3.1 Erythrozytenonzentrate)

Not as “D”eadly as once thought – the risk of D-alloimmunization and hemolytic disease of the fetus and newborn following RhD-positive transfusion in trauma.

Yazer MH et al. Hematology 2023



AGE	RH(D)-ALLOIMMUNIZATION RATE Low estimate [5]	High estimate [4]
< 1 MONTH	0%	0%
1 TO <12 MONTHS	1.6%	8.9%
1 TO <5 YEARS	2.7%	14.8%
5 TO <10 YEARS	2.8%	15.5%
10 TO <15 YEARS	4.1%	22.3%
15 – 17 YEARS	6.6%	36.4%
18 – 49 YEARS	7.8%	42.7%

Estimated risks of overall hemolytic disease of the fetus and newborn (HDFN) for RhD-negative females based on the highest (42.7%) and lowest (7.8%) reported D-alloimmunization.

“ It is worth repeating that if RhD-negative RBCs or LTOWB are available, they should be used for injured FCPs of unknown RhD-type who are in need of an emergency transfusion. However, … a life-saving transfusion should never be withheld for fear of future alloimmunization events even if the unit is RhD-positive. …”

FCP = female of childbearing potential

Erythrozytenkonzentrate
Blutgruppe 0

Blutgruppe „0“ oder A(2) → 25-35% niedrigere vWF- und FVIII-Spiegel Gill JC et al. Blood 1987; deBot M et al. Shock 2022

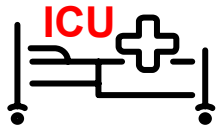
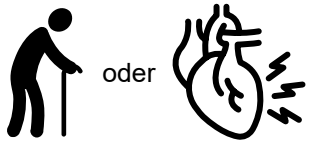
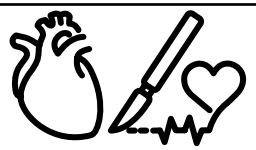
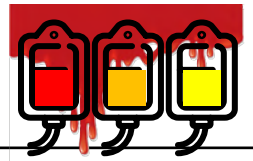
- geringeres Thromboserisiko (verstärkte Empfindlichkeit für Proteolyse durch ADAMTS13; veränderte Wechselwirkung des Gruppe 0 vWF mit Thrombozyten) Ward SE et al. Blood 2020

- höhere Mortalität bei
  - Trauma Takayama W et al. Crit Care 2018
- höherer Blutverlust bei
  - Trauma deBot M et al. Shock 2022
  - PPH Kahr MK et al. Haemophilia 2018
  - Kaiserschnitt Bade NA et al. J Thromb Thrombolysis 2020

- höhere Rate an
  - Hyperfibrinolyse nach Trauma deBot M et al. Shock 2022
  - blutenden Ulcera Franchini M et al. Crit Rev Clin Lab Sci 2012
  - PPH Drukker L et al. J Thromb Thrombolysis 2016
  - ICB He Q et al. J Stroke Cerebrovasc Dis 2019
  - schlechtem neurolog. Outcome nach SHT Esnault JTACS 2023

- Problem bei ”type O whole blood (LTOWB)” deBot M et al. Shock 2022

Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten. Gesamtnovelle 2020

Patienten	Indikation zur Transfusion	Zielbereich nach Transfusion	Grad
 **hospitalisierte** Patienten ohne manifeste kardiovaskuläre Erkrankungen	<7 g/dl (<4,3 mmol/l) individuell niedriger (2C+, kann)		1A „soll“
 **Intensivpatienten** ohne kardiovaskuläre Erkrankungen und ohne akute, schwere Hämorrhagie	<7 g/dl (<4,3 mmol/l)	7 bis 9 g/dl (4,3 bis 5,6 mmol/l)	1A „soll“
 **orthopäd. / unfallchir. >65 Jahre** <u>oder</u> Patienten mit **erheblichen kardiovaskulären Erkrankungen**	<8 g/dl (<5,0 mmol/l)		1A „soll“
 **herzchirurgische** Patienten, die **nicht akut bluten**	<7,5 g/dl (<4,7 mmol/l)		1A „soll“
 **Massivblutungen**		7 bis 9 g/dl (4,3 bis 5,6 mmol/l)	1**C+** „soll“
 **Früh- und Neugeborene**	siehe Tab. 1.5.1.4.1		2A „sollte“
 Patienten mit **instabiler Herz-Kreislauffunktion** (akutes Koronarsyndrom, akuter Myokardinfarkt, akute Herzinsuffizienz)	? aktuell keine ausreichende Datengrundlage, ggf. Hb >8 g/dl (>5 mmol/l) ?		

Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia. The REALITY Randomized Clinical Trial.

Ducrocq G et al. JAMA 2021

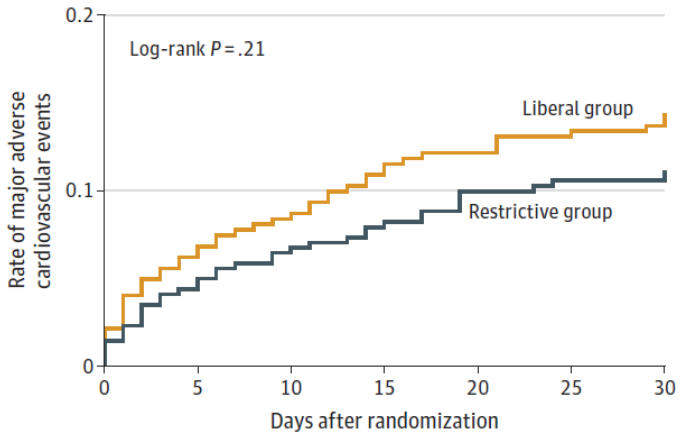
666 patients with AMI (STEMI or NSTEMI; troponin positive) and hemoglobin (Hgb) ≤8 to ≤10 g/dl; **liberal** (for Hgb ≤10 g/dl, goal Hgb >11 g/dl) (n = 342) or a **restrictive** (for Hgb ≤8 g/dl, target Hgb 8-10 g/dl) (n = 324) RBC transfusion strategy; primary outcome: MACE at 30 days; secondary outcome: individual components of the primary outcome.

primary outcome for *restrictive* vs. liberal transfusion strategy, was *11.0%* vs. 14.0% (hazard ratio 0.77, 95% confidence interval 0.50-1.18, p < 0.05 for noninferiority, p = 0.22 for superiority)

- All-cause mortality: *5.6%* vs. 7.7% (p > 0.05)
- Recurrent MI: *2.1%* vs. 3.1%
- Emergency revascularization: *1.5%* vs. 1.9%

secondary outcomes for *restrictive* vs. liberal transfusion strategy:

- Acute kidney injury: *9.7%* vs. 7.1% (p = 0.24)
- Infection: *0%* vs. 1.5% (p = 0.03)
- Acute lung injury: *0.3%* vs. 2.2% (p = 0.03)
- MODS: *0.3%* vs. 0,9%
- Total 30-day hospital costs: *€11,051* vs. €12,572 (p = 0.1)



"Among patients with acute myocardial infarction and anemia, a restrictive compared with a liberal transfusion strategy resulted in a **noninferior rate of MACE after 30 days**. However, the CI included what may be a clinically important harm."

Liberal versus Conservative Transfusion Strategy for Patients with Acute Myocardial Infarction and Anemia: A Systematic Review and Meta-analysis .

Sukhon F et al. Curr Probl Cardiol 2023

meta-analysis of randomized controlled trials; 4 RCT, 2155 patients with liberal transfusion and 2170 with conservative transfusion

liberal transfusion did not significantly reduce

- MI (RR 0.85; 95%CI 0.72 - 1.02, p=0.07),
- death/MI (RR 0.88; 95%CI 0.45 - 1.71, p=0.57),
- all-cause mortality (RR 0.82; 95%CI 0.25 - 2.68, p=0.63),
- stroke (RR 0.89; 95%CI 0.48 - 1.64, p=0.50),
- revascularization (RR 0.93; 95%CI 0.48 - 1.80, p=0.68), or
- heart failure (RR 1.14; 95%CI 0.04 - 28.84, p=0.88).

"Our meta-analysis supports current medical guidelines, **reinforcing the practice of limiting transfusions in acute MI patients to those with an Hb level of 7 or 8 g/dL**. Liberal transfusion strategies did not show improved clinical outcomes."

vielleicht eher 8-9 g/dl

REALITY Ducrocq G et al. JAMA 2021

MINT Carson JL et al. N Engl J Med 2023

Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. MINT

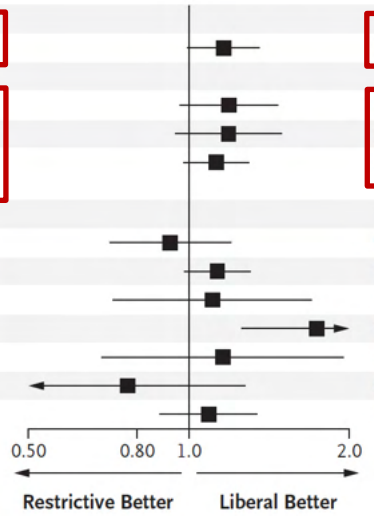
Carson JL et al. N Engl J Med 2023

36% of patients in the MINT study received transfusions before randomization
Braïk R et al. Ann Intensive Care 2024

open-label, randomized trial at 144 sites in the United States, Canada, France, Brazil, New Zealand, and Australia; 3504 adults (≥18 years of age) with ST-segment elevation or non–ST-segment elevation **myocardial infarction**; ~1/3 history of myocardial infarction, per cutaneous coronary intervention, or heart failure, nearly half renal insufficiency; **excluding active bleeding**; **restrictive**: transfusion permitted but not required if Hb <8 g/dL and strongly recommended if Hb <7 g/dL; **liberal**: transfusion until Hb >10 g/dL;

- number of units of RBC: **liberal** 4325 vs. **restrictive** 1237 (**factor 3.5**)
- mean (±SD) number of RBC: **liberal** 2.5±2.3 vs. **restrictive** 0.7±1.6

Outcome	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
Primary outcome			
Myocardial infarction or death	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Secondary outcomes			
Death	173/1749 (9.9)	146/1755 (8.3)	1.19 (0.96–1.47)
Myocardial infarction	149/1749 (8.5)	126/1755 (7.2)	1.19 (0.94–1.49)
Death, myocardial infarction, revascularization, or rehospitalization	342/1749 (19.6)	305/1755 (17.4)	1.13 (0.98–1.29)
Other outcomes			
Heart failure	102/1749 (5.8)	111/1755 (6.3)	0.92 (0.71–1.20)
Death, myocardial infarction, or unstable angina	338/1749 (19.3)	300/1755 (17.1)	1.13 (0.98–1.30)
Unscheduled revascularization	43/1749 (2.5)	39/1755 (2.2)	1.11 (0.72–1.70)
Cardiac death	97/1749 (5.5)	56/1755 (3.2)	1.74 (1.26–2.40)
Stroke	30/1749 (1.7)	26/1755 (1.5)	1.16 (0.69–1.95)
Pulmonary embolism or deep venous thrombosis	26/1749 (1.5)	34/1755 (1.9)	0.77 (0.46–1.27)
Pneumonia or bacteremia	166/1749 (9.5)	153/1755 (8.7)	1.09 (0.88–1.34)



"…we **did not find a significant difference in the incidence of recurrent myocardial infarction or death at 30 days** between patients with acute myocardial infarction and anemia who were assigned to a restrictive transfusion strategy and those who were assigned to a liberal transfusion strategy. … the **95% confidence interval contains values that suggest a clinical benefit for the liberal transfusion strategy** and does not include values that suggest a benefit for the more restrictive transfusion strategy."

Risks of Restrictive Versus Liberal Red Blood Cell Transfusion Strategies in Patients With Cardiovascular Disease: An Updated Meta-Analysis.

Applefeld WN et al. Circ Cardiovasc Qual Outcomes 2024

update of meta-analysis Cortes-Puch I et al. Transfus Med 2018 until November 23, 2023; 14 randomized transfusion trigger trials enrolling subjects with **CVD**, prospectively excluding cardiothoracic surgery trials (including **MINT** Carson JL et al. NEJM 2023); **restrictive**: range, 7–9.7; median, 8 g/dL

mortality

- *liberal arms*: of 3211 subjects with CVD, 334 died (10.4% mortality).
- *restrictive arms*: of 3212 subjects with CVD, 398 died (12.4% mortality)

⇒ **liberal arms had significantly lower risk of death** (relative risk of death, 0.87 [95% CI, 0.76–0.99]; P=0.03; I^2=0%);

ACS

- *liberal arms*: of 2908 subjects with CVD, 244 experienced ACS (8.4%)
- *restrictive arms*: of 2941 subjects with CVD, 309 experienced ACS (10.5%).

⇒ **liberal arms had significantly lower risk of ACS** (relative risk, 0.82 [95% CI, 0.70–0.96]; P=0.01; I^2=0%).;

"… the summary data **support the use of a liberal transfusion threshold** as opposed to a restrictive approach **for patients with CVD**. Physicians must **consider pertinent cardiac comorbidities** and other clinical variables when making decisions about appropriate liberal transfusion thresholds."

⇒ aber kein Vorteil in der Meta-Analysen von Shander A et al. Blood Transfus 2024, Sukhon F et al. Curr Probl Cardiol 2024, Amin AM et al. Coron Artery Dis 2024 und Kiyohara Y et al. J Cardiol 2024

No evidence for liberal transfusion in acute myocardial infarction.

Shander A et al. Blood Transfus 2024

Meta-analysis of 4 RCT with 4,324 participants: 3x pat. with AMI (MINT Carson JL et al. NEJM 2023; REALITY Ducrocq G et al. JAMA 2021; CRIT Cooper HA et al. Am J Cardiol 2011), 1x pat. with AMI, unstable angina, or stable coronary artery disease undergoing cardiac catheterization (Carson et al. Am Heart J 2013)

primary outcome (as defined by each trial's protocol)
- pooled risk ratio 1.00 (95% CI 0.63, 1.59, p=0.99)
- excluding pilot/feasibility trials: pooled risk ratio 1.00 (95% CI 0.68, 1.45, p=0.99, 2 trials [MINT, REALITY], 4,170 participants)

all-cause mortality (all 4 trials)
- pooled risk ratio 1.13 (95% CI 0.67, 1.91, p=0.65) for the conservative compared to the liberal strategy
- excluding pilot/feasibility trials: pooled risk ratio 1.00 (95% CI 0.62, 1.59, p=0.99, 2 trials [MINT, REALITY], 4,170 participants)

cardiovascular mortality (all 4 trials)
- pooled risk ratio 1.34 (95% CI, 0.55, 3.29, p=0.52) for the conservative compared to the liberal strategy
- excluding pilot/feasibility trials: pooled risk ratio 1.05 (95% CI 0.36, 3.04, p=0.92, 2 trials [MINT, REALITY], 4,170 participants)

"The **evidence** that a liberal compared to a conservative transfusion strategy improves outcomes for patients with an AMI and anemia **is inconclusive**. … In the **absence of a clear benefit** from a liberal transfusion strategy, recommending a new hemoglobin threshold of 10 g/dL exposes patients to unnecessary RBC transfusion and therefore some risk without clear evidence of benefit."

ebenfalls kein Vorteil mit den selben Studien bei Sukhon F et al. Curr Probl Cardiol 2024
oder Amin AM et al. Coron Artery Dis 2024
auch kein Vorteil mit 5 RCTs (>80% der Patienten bei Einschluss ein ACS: CRIT, MINT pilot, REALITY, TRICS-AMI, MINT) bei Kiyohara Y et al. J Cardiol 2024
Vs. Vorteil bei Applefeld WN et al. Circ Cardiovasc Qual Outcomes 2024

Liberal versus restrictive transfusion strategies in acute myocardial infarction: a systematic review and comparative frequentist and Bayesian meta-analysis of randomized controlled trials.

Braïk R et al. Ann Intensive Care 2024

Meta-analysis of 4 RCT with 4,324 participants: 3x pat. with AMI (MINT Carson JL et al. NEJM 2023; REALITY Ducrocq G et al. JAMA 2021; CRIT Cooper HA et al. Am J Cardiol 2011), 1x pat. with AMI, unstable angina, or stable coronary artery disease undergoing cardiac catheterization (Carson et al. Am Heart J 2013)

"…, we conclude that liberal transfusion **may** decrease the risk of early mortality or MI, with very low certainty of evidence (GRADE).

For the other secondary outcomes, including recurrent MI, need for revascularization, stroke, and cardiac death, we concluded that liberal transfusion **may or may not** be beneficial, with very low certainty of evidence (GRADE). ...

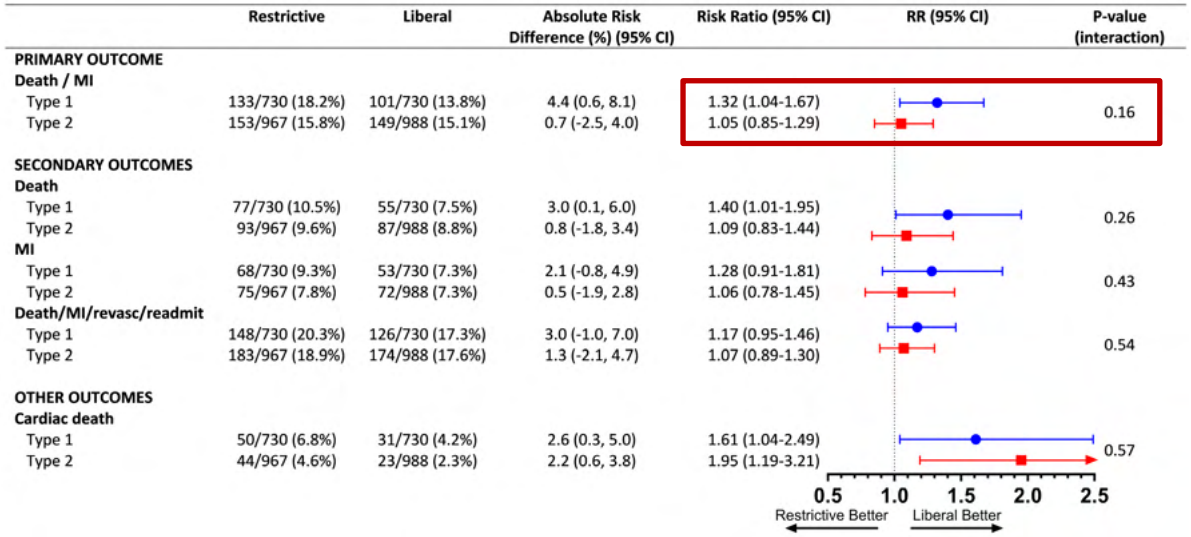
…, patients in the REALITY trial had more revascularizations before randomization than those in the MINT trial. Additionally, 36% of patients in the MINT study received transfusions before randomization, whereas the REALITY study did not allow the inclusion of patients who had received transfusions in the last 30 days.

… the relevance of 30-day mortality is questionable because one of the major issues after an AMI is the development of chronic heart failure."

Restrictive Versus Liberal Transfusion in Patients with Type 1 or Type 2 Myocardial Infarction: A Prespecified Analysis of the Myocardial Ischemia and Transfusion (MINT) Trial.

DeFilippis AP et al. Circulation 2024

type 1 MI (n=1,460; 42%) resulting from a coronary thrombus overlying a disrupted atherosclerotic plaque (rupture or erosion);
type 2 MI (n=1,955; 56%) resulting from a mismatch in myocardial oxygen supply and demand unrelated to atherothrombosis.

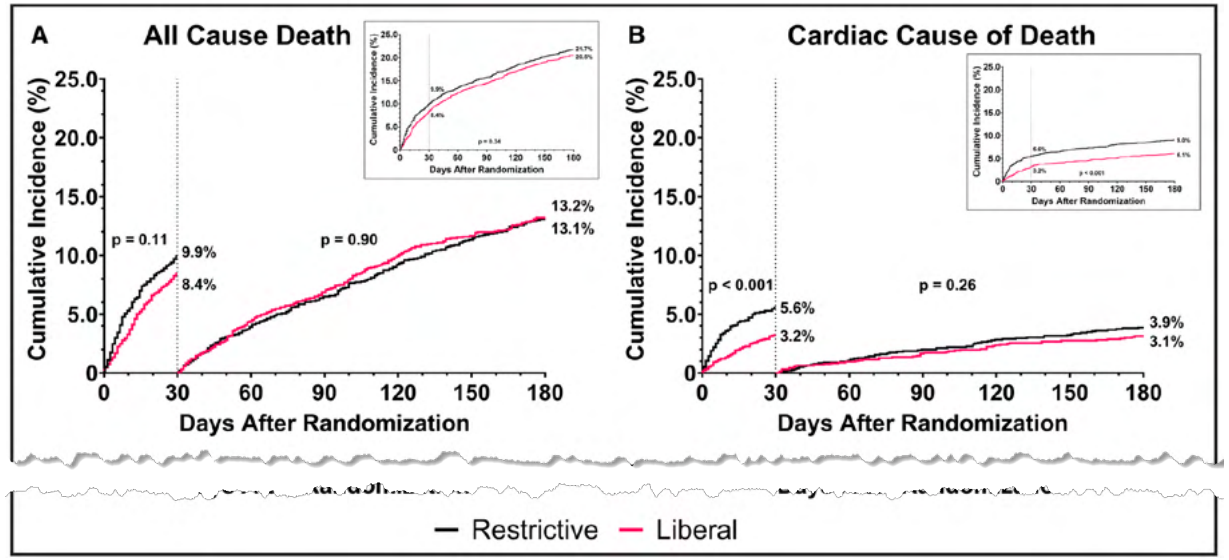


	Restrictive	Liberal	Absolute Risk Difference (%) (95% CI)	Risk Ratio (95% CI)	RR (95% CI)	P-value (interaction)
PRIMARY OUTCOME						
Death / MI						
Type 1	133/730 (18.2%)	101/730 (13.8%)	4.4 (0.6, 8.1)	1.32 (1.04-1.67)		0.16
Type 2	153/967 (15.8%)	149/988 (15.1%)	0.7 (-2.5, 4.0)	1.05 (0.85-1.29)		
SECONDARY OUTCOMES						
Death						
Type 1	77/730 (10.5%)	55/730 (7.5%)	3.0 (0.1, 6.0)	1.40 (1.01-1.95)		0.26
Type 2	93/967 (9.6%)	87/988 (8.8%)	0.8 (-1.8, 3.4)	1.09 (0.83-1.44)		
MI						
Type 1	68/730 (9.3%)	53/730 (7.3%)	2.1 (-0.8, 4.9)	1.28 (0.91-1.81)		0.43
Type 2	75/967 (7.8%)	72/988 (7.3%)	0.5 (-1.9, 2.8)	1.06 (0.78-1.45)		
Death/MI/revasc/readmit						
Type 1	148/730 (20.3%)	126/730 (17.3%)	3.0 (-1.0, 7.0)	1.17 (0.95-1.46)		0.54
Type 2	183/967 (18.9%)	174/988 (17.6%)	1.3 (-2.1, 4.7)	1.07 (0.89-1.30)		
OTHER OUTCOMES						
Cardiac death						
Type 1	50/730 (6.8%)	31/730 (4.2%)	2.6 (0.3, 5.0)	1.61 (1.04-2.49)		0.57
Type 2	44/967 (4.6%)	23/988 (2.3%)	2.2 (0.6, 3.8)	1.95 (1.19-3.21)		

"…However, statistical testing for a differential effect of a restrictive versus liberal transfusion strategy in type 1 versus type 2 MI was **not significant**. Therefore, this pre-specified subgroup analysis **did not provide definitive evidence that a restrictive versus liberal transfusion strategy affected patients with type 1 or type 2 MI differently**. However, given the high likelihood for harm with a restrictive and low likelihood of harm with a liberal transfusion strategy, this **data is supportive of a liberal transfusion strategy in patients with type 1 MI** and anemia, contrary to data in multiple other disease states where a restrictive strategy is preferred."

Restrictive or Liberal Transfusion Strategy in Patients With Acute Myocardial Infarction and Anemia: 6-Month Mortality in the MINT Trial.

Simon T et al. Circulation 2024



Mortality at 30 days

restrictive: 16.9% vs. liberal: 14.5%; (RR, 1.15 [95% CI, 0.99–1.34]; P=0.07)

Mortality at 6 months

restrictive: 21.7% vs. liberal: 20.5% (HR, 1.07 [95% CI, 0.93–1.24]).

Mortality during first 30 days

restrictive: 9.9% vs. liberal: 8.4% (RR, 1.19 [95% CI, 0.96–1.49]).

Mortality beyond 30 days

restrictive: 13.1% vs. liberal: 13.2% (RR, 0.99 [95% CI, 0.81–1.20]).

6-month hazard of cardiac death

restrictive: 9.0% vs. liberal: 6.1%; (HR, 1.52 [95% CI, 1.19–1.94]; P<0.001)

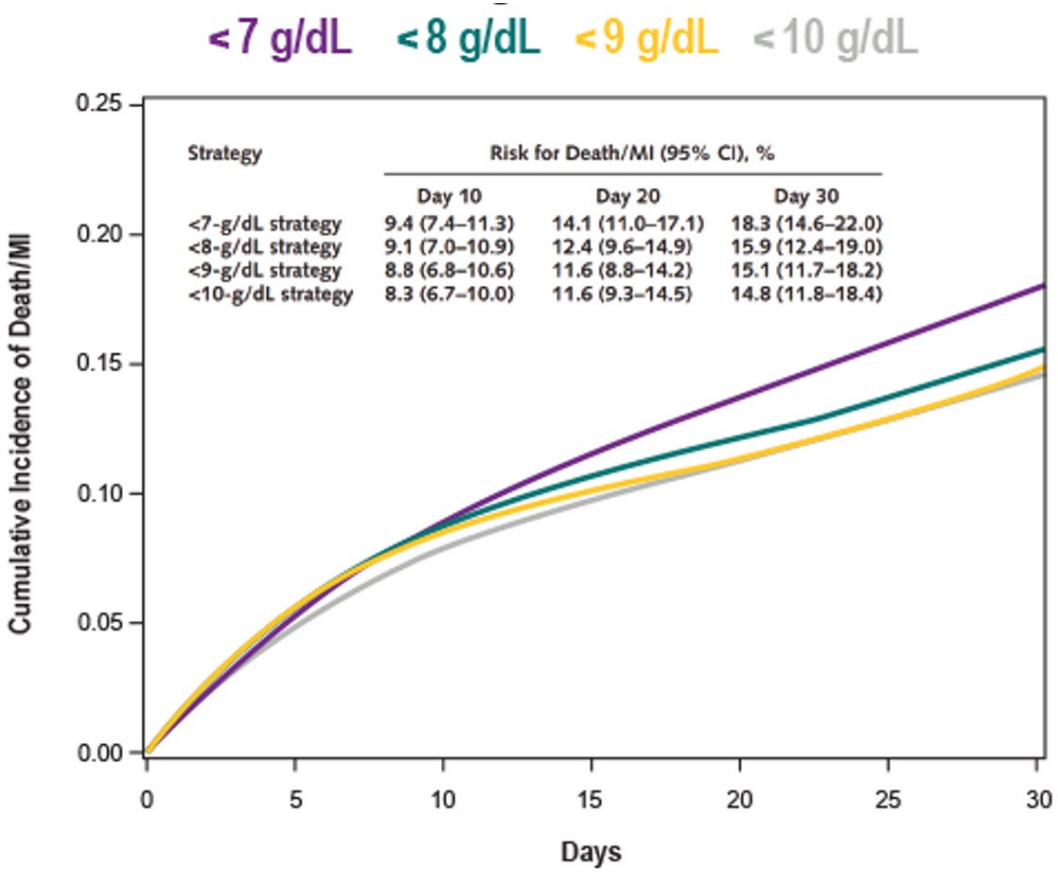
⇒ "52% greater in the restrictive arm, driven mostly by events within 30 days"

"MINT was not designed or powered to detect a difference between transfusion strategies on 6-month death."

Effect of Four Hemoglobin Transfusion Threshold Strategies in Patients With Acute Myocardial Infarction and Anemia. A Target Trial Emulation Using MINT Trial Data.

Portela GT et al. Ann Intern Med 2024

prespecified a secondary analysis of the MINT trial to evaluate effects of 4 different transfusion strategies (hemoglobin thresholds <10, <9, <8, and <7 g/dL) to trigger RBC transfusion on the composite risk for death or recurrent MI through 30 days; fitted weighted pooled logistic regression; n=3492;



"… 95% CIs for the effect estimates were wide and included null values. … The present findings **suggest that transfusion guidelines could consider avoiding hemoglobin triggers of less than 8 g/dL** …The imprecision of these estimates, however, prevents explicit recommendations about individual hemoglobin transfusion thresholds."

Anemia Acuity Effect on Transfusion Strategies in Acute Myocardial Infarction A Secondary Analysis of the MINT Trial.

Carrier FM et al. JAMA Netw Open 2024

prespecified a secondary analysis of the MINT trial; 3144 pat. (mean age 72.3 ±±11.6 years; 54.5% male; 41.6% type 1 MI) in 126 hospitals; effects of acute (acquired during the hospitalization) vs. chronic anemia; **acute anemia**: Hb >13 (♂) / >12 (♀) g/dL at admission AND <10 g/dL at randomization or drop ≥2 g/dL between admission and randomization (**pure hospital-acquired acute anemia;** 10.8%); **median time from admission to randomization: acute 5 (IQR, 3-8) days vs. chronic 2 (IQR, 1-4) days**; median Hb decrease from admission to randomization: 3.6 (IQR, 2.6-5.3) g/dL vs. 0.7 (IQR, 0.2-1.3) g/dL

acute anemia

- 25% higher incidence of death or recurrent MI (RR, 1.25; 95%CI, 1.05-1.48),
- 47% higher incidence of death (RR, 1.47; 95%CI, 1.16-1.86),
- 36% higher incidence of pulmonary complications (RR, 1.36; 95%CI, 1.12-1.66)
- no differences for recurrent MI, heart failure, cardiac death, and major bleeding

restrictive vs. liberal transfusion strategy

- *acute anemia*: RR 1.09 (95%CI, 0.85-1.40)
- *chronic anemia*: RR1.20 (95%CI, 0.97-1.48)

} *P* = .57 for interaction

- *pure hospital-acquired acute anemia*: adj. RR, 0.95; 95%CI, 0.72-1.26

⇒ **no differential effect of the randomized transfusion strategy according to anemia acuity for any 30-day outcome** !!

"… acute anemia was a marker of a more complex and morbid clinical course. … participants with acute anemia at the time of randomization had a higher risk of adverse outcomes at 30 days. … anemia acuity did not appear to explain the potential harm of a restrictive RBC transfusion strategy observed in the MINT trial. In patients with anemia and MI, clinicians should not be guided by the acuity of the anemia in selecting a transfusion strategy."

Haemoglobin values, transfusion practices, and long-term outcomes in critically ill patients with traumatic brain injury: a secondary analysis of CENTER-TBI.

Guglielmi A et al. Crit Care 2024

1231 pat. between ICU-admission and first week; mean ISS on admission 33 (SD 16); 40.7% isolated TBI; daily lowest measurement of haemoglobin; anaemia defined as Hb < 9.5 g/dL; 18.4% received at least one RBC transfusion; median Hb before transfusion was 8.4 (IQR 7.7–8.5) g/dL; **restrictive**: transfusion if Hb <7.5 g/dL; **liberal**: transfusion if Hb 7.5–9.5 g/dL

day 1: mean Hb 12.6 (SD 2.2) g/dL; 9.8% had Hb < 9.5 g/dL; 1.2% < 7.5 g/dL
day 7: mean Hb 9.8 (SD 1.5) g/dL; 47.9% had Hb < 9.5 g/dL; 8.7% < 7.5 g/dL

↑Hb was independently associated with ↓occurrence of unfavourable neurological outcome (GOS-E 1-4: OR 0.78; 95% CI 0.70–0.87)
if Hb 7.5 and 9.5 g/dL: OR 1.61; 95% CI 1.07–2.42
if Hb <7.5 g/dL: OR 2.09; 95% CI 1.15–3.81

↑Hb was independently associated with ↓mortality at 6 months (OR 0.88; 95% CI 0.76–1.00)
if Hb 7.5 and 9.5 g/dL: OR 1.29; 95% CI 0.77–2.16
if Hb <7.5 g/dL: OR 3.21; 95% CI 1.59–6.49

?? ⇒ Hb ≤9.5 g/dl als Indikation zur Transfusion bei SHT ??

"Whether aiming for a higher haemoglobin value improves outcomes in TBI patients remains uncertain."

Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury: HEMOTION

Turgeon AF et al. N Engl J Med 2024

pragmatic, randomized, open-label, blinded-outcome assessment, 34 centers in Canada, UK, France, Brazil; 736 pat. (mean age 48.7±18.9; 72.7% male) with **moderate or severe TBI** (GCS 3-12) and anemia Hb ≤10 g/dL); **liberal** (n=369; transfusions if Hb ≤10 g/dL) vs. **restrictive** (n=367; transfusions if Hb ≤7 g/dL); primary outcome: unfavorable outcome by Glasgow Outcome Scale–Extended (GOS-E **1-4**) at 6 months; some baseline imbalances in groups

mean Hb in ICU: **liberal** 10.8 (IQR 10.3-11.5) g/dL vs. **restrictive** 8.8 (IQR 8.1-9.6) g/dL (median difference, 2.00 g/dL; 95% CI, 1.97 to 2.03); 1516 vs. 307 RBC transfused

unfavorable outcome at 6 months

liberal 68.4% vs. **restrictive** 73.5% (adj. absolute difference 5.4%; 95% CI, −2.9 to 13.7; RR 0.93; 95% CI, 0.83 to 1.04)

mortality at 6 months

liberal 26.8% vs. **restrictive** 26.3% (HR 1.01; 95% CI, 0.76 to 1.35)

venous thromboembolic events

liberal 8.4% vs. **restrictive** 8.4%

ARDS

liberal 3.3% vs. **restrictive** 0.8%

"A liberal transfusion strategy **appeared to be associated** with better scores on several measures of motor function and quality of life among survivors at 6 months."

!? ⇒ Hb 8,5-9 g/dl als Indikation zur Transfusion bei SHT !?

"… a liberal transfusion strategy did **not** reduce the risk of an unfavorable neurologic outcome at 6 months."

"The trial was not designed to assess the noninferiority of a more restrictive transfusion strategy, so the possibility of harm with such a strategy cannot be excluded."

Restrictive vs Liberal Transfusion Strategy in Patients With Acute Brain Injury. The TRAIN Randomized Clinical Trial.

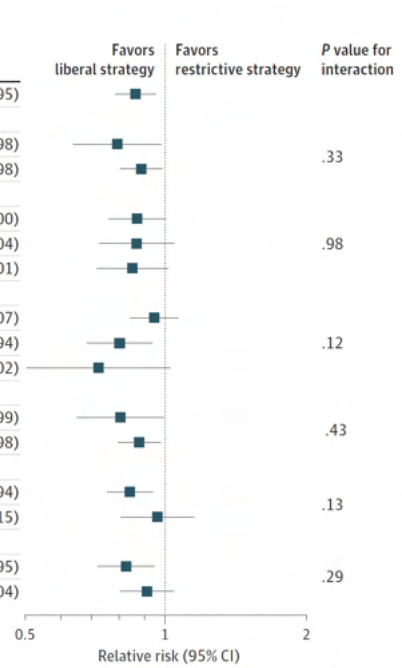
sehr heterogene Gruppe

Taccone FS et al. JAMA 2024

phase 3, parallel-group, investigator-initiated, pragmatic, open-label, outcomeassessor–blinded, randomized, 72 ICUs across 22 countries; 806 pat. (mean age 51; 54% male) with **acute brain injury** (**TBI / SAB / ICH**; GCS ≤13) and anemia Hb ≤9 g/dL) **liberal** (n=393; transfusions if Hb <9 g/dL) vs. **restrictive** (n=413; transfusions if Hb <7 g/dL); primary outcome: unfavorable outcome by Glasgow Outcome Scale–Extended (GOS-E **1-5**) at 6 months; sample size calculation adjusted twice; mean 3 days from ICU admission to randomization

liberal: median of 2 (IQR, 1-3) RBC vs. **restrictive**: median of 0 (IQR, 0-1) RBC; absolute mean difference of 1.0 unit (95%CI, 0.87-1.12 units).

Subgroup	Unfavorable neurological outcome, No./total No. (%)		Absolute difference, % (95% CI)	Relative risk (95% CI)	P value for interaction
	Liberal strategy	Restrictive strategy			
Overall	246/393 (62.6)	300/413 (72.6)	-10.0 (-16.5 to -3.6)	0.86 (0.78 to 0.95)	
Age, y					
<45	62/124 (50.0)	87/137 (63.5)	-13.5 (-25.4 to -1.6)	0.79 (0.63 to 0.98)	.33
≥45	184/269 (68.4)	213/276 (77.2)	-8.8 (-16.2 to -1.3)	0.89 (0.80 to 0.98)	
Type of brain injury					
Traumatic brain injury	138/236 (58.5)	161/239 (67.4)	-8.9 (-17.5 to -0.2)	0.87 (0.76 to 1.00)	
Subarachnoid hemorrhage	57/86 (66.3)	78/102 (76.5)	-10.2 (-23.1 to 2.8)	0.87 (0.72 to 1.04)	.98
Intracerebral hemorrhage	51/71 (71.8)	61/72 (84.7)	-12.9 (-26.3 to 0.5)	0.85 (0.71 to 1.01)	
Glasgow Coma Scale score at randomization					
3 to 5	134/186 (72.0)	147/193 (76.2)	-4.1 (-12.9 to 4.7)	0.95 (0.84 to 1.07)	
6 to 9	85/140 (60.7)	112/147 (76.2)	-15.5 (-26.1 to -4.9)	0.80 (0.68 to 0.94)	.12
10 to 13	27/67 (40.3)	41/73 (56.2)	-15.9 (-32.2 to 0.5)	0.72 (0.50 to 1.02)	
ICP monitoring within first 48 h					
No	60/114 (52.6)	83/126 (65.9)	-13.2 (-25.6 to -0.9)	0.80 (0.65 to 0.99)	.43
Yes	185/277 (66.8)	216/284 (76.1)	-9.3 (-16.7 to -1.8)	0.88 (0.79 to 0.98)	
Salvage therapies for elevated ICP					
No	191/318 (60.1)	235/328 (71.6)	-11.6 (-18.8 to -4.3)	0.84 (0.75 to 0.94)	.13
Yes	55/75 (73.3)	65/85 (76.5)	-3.1 (-16.6 to 10.3)	0.96 (0.80 to 1.15)	
SOFA score[a]					
<8	132/229 (57.6)	166/237 (70.0)	-12.4 (-21.1 to -3.7)	0.82 (0.72 to 0.95)	.29
≥8	111/160 (69.4)	131/172 (76.2)	-6.8 (-16.4 to 2.8)	0.91 (0.80 to 1.04)	



unfavorable outcome at 6 months

liberal 62.6% vs. **restrictive** 72.6% (absolute difference, −10.0% [95% CI, −16.5% to −3.6%]; adj. RR, 0.86 [95%CI,0.79-0.94]; P = .002)

"… significant shift toward a larger proportion of patients distributed in higher GOS-E subscores in the liberal strategy group … (OR, 1.37 [95% CI, 1.07-1.75]; P = .01)."

mortality at 6 months

liberal 20.7% vs. **restrictive** 22.5%

(RR 0.95 [95% CI, 0.74-1.22])

!? ⇒ Hb 9 g/dl als Indikation zur Transfusion bei Gehirnverletzungen !?

perioperativer Hb-Zielbereich [1]

Bei einem aktiv blutenden Patienten ist die Indikation zur Transfusion immer **individuell.**

Hb plus „klinisches Bild"

BÄK Querschnittsleitlinie 2020

? vorher „ganz gesund" PPH Zeugen Jehova ?

ICB / SAB / SHT[3]

akuter Herzinfarkt[2], frühe Sepsis,

die **überwiegende Mehrzahl aller Patienten** inklusive KHK, späte Sepsis & Neonaten[4]

([4] Konserven sollten bei Neonaten ≤5 d alt sein)

Transfusions-Trigger = untere Grenze des jeweiligen Zielbereiches.

Möglichst zu keinem Zeitpunkt soll dieser Bereich verlassen werden; es kann also bei einem anhaltend und massiv blutenden Patienten ggf. bereits vor diesem Bereich eine Transfusion erforderlich sein.

[3] HEMOTION Turgeon AF et al. NEJM 2024; TRAIN Taccone FS et al. JAMA 2024; Guglielmi A et al. Crit Care 2024
[2] REALITY trial JAMA 2021; MINT trial: Carson JL et al. NEJM 2023; Sukhon F et al. Curr Probl Cardiol 2023
[1] ASATF 2006, Scand 2008, SHC BHS 2008, SCCM 2009, AABB 2010, HAS-MOH 2011, AABB 2012, NCCN 2012, ACP 2013, BCSH 2013, SEPAABT 2013, BÄK 2014, Expert Cons. 2014, BSCH 2015, NICE 2015, AAGBI 2016, BCSH 2016, SIAARTI 2019, NICE 2020

Erythrozytenkonzentrate

Für polytraumatisierte Patienten gibt es **keine RCT** bezüglich restiktiver vs. liberaler Transfusionsindikation !!

European Trauma 6th ed. Rossaint R et al. Crit Care 2023

If erythrocyte transfusion is necessary, we *recommend* a target haemoglobin of 70–90 g/L
(Rec. 16; **1C**)

"… the decision to transfuse should not be based on haemoglobin levels alone."

RESTRIC-trial

Hayakawa M et al. J Intensive Care 2023

target hemoglobin levels 7–9 (n=216) vs. 10–12 g/dL (n=195) immediately after arrival at the emergency department; 90% blunt trauma; median ISS 24; a significant non-inferiority of 3% was not observed; **serious miscalculation of sample size requirement** (auch Sprachprobleme? Kosaki Y et al. World J Emerg Surg 2024)

28-day survival rates: (7-9 g/dL) 92.1% and (10-12 g/dL) 91.3%

⇒ "no clinical significance between the two strategies was observed"

Die Blutkomponenten?

2. Therapeutisches Plasma

therapeutisches Plasma

Vier Arten Therapeutischen Plasmas stehen in Deutschland gemäß der Liste des PAUL-EHRLICH-Instituts zur Verfügung:

- Quarantäne-gelagertes Therapeutisches **Einzelspender**-Plasma ohne Behandlung zur Pathogenreduktion (**Q-Plasma**; früher fresh frozen plasma FFP),

individuelle Schwankungen (v.a. bei FI und FVIII); Ziel: 70%ige (FVIII-) Aktivität nach Auftauen.
BÄK. Querschnittleitlinie, Gesamtnovelle 2020

- aus leukozytenreduzierten **Einzelspender**plasmen hergestelltes, zur PathogenReduktion
  - mit Methylenblau / Rotlicht [590 nm] oder
  - mit Amotosalen / UVA [320-400 nm] behandeltes Therapeutisches Plasma (**PR-Plasma**),

Fibrinogen u. FVIII: ↓30%; restl. Faktoren: ↓5%-21%
BÄK. Querschnittleitlinie, Gesamtnovelle 2020

- aus einem **Pool** von Blutgruppen-gleichen, aus leukozytenreduzierten Einzelspenderplasmen hergestelltes, Lyophilisiertes [gefrier-getrocknet] Humanplasma (**LHP**),

FVII und vWF: ↓20-25%;
BÄK. Querschnittleitlinie, Gesamtnovelle 2020

- zur Virusinaktivierung mit Solvens [Tributylphosphat TNBP] / Detergent [Triton-X 100] behandeltes Therapeutisches Plasma (**SD-Plasma**) [**Pool**en von 630 bis 1.520 Einzelspenderplasmen].

↓alle; ↓↓FVIII, a2-Antiplasmin, Prot.S;
BÄK. Querschnittleitlinie, Gesamtnovelle 2020

4.10.3.4 Therapeutisches Plasma

NEU SEIT 2017

„Therapeutisches Plasma wird **AB0-gleich** transfundiert. In Ausnahmefällen kann auch AB0-ungleiches (kompatibles) Plasma transfundiert werden. Eine serologische Verträglichkeitsprobe entfällt."

weiterhin nicht spezifiziert

keine „Kreuzprobe" nötig
→ ob im Blut des Patienten irreguläre Antikörper gegen die zur Transfusion vorgesehenen Spender-Erythrozyten sind

„… mit **Standardfilter** (in der Regel Porengröße 170 bis 230 µm),… spätestens nach 6 Stunden zu wechseln. …"
BÄK, Querschnittsleitlinie, Gesamtnovelle 2020

Patient	Kompatibles Plasma
A	A oder AB
B	B oder AB
AB	AB
0	0, A, B oder AB

NEU 2020!!
„… wenn bei Massivblutungen Plasmavolumen ersetzt werden muss, … mindestens 30 ml/kg … … 30-50 ml/min …“
Plasmavolumen: ca. 40 ml/kg (siehe 7.1.1.7)
BÄK. Querschnittsleitlinie, Gesamtnovelle 2020

Indikation für FFP-Transfusionen (wenn überhaupt):

- Nur bei erwarteten Massivtransfusionen
  (d.h., beim Erwachsenen ab 4-6 EK)

mikrovaskuläre, koagulopathische Blutung [1]

- dann aber frühzeitig,
- viel,

d.h. mindestens 6 FFP für Erwachsene bzw. ≥30 ml/kg BÄK2020 und EK:FFP:TK ~4(-5):4(-5):1* und

- schnell,

d.h. ~50 ml/min BÄK2020 (≈3000 ml/h).

*Anpassung der PROPPR-Daten mit US-Einzelspender-TK an deutsche Pool- bzw. Apherese-TK mit 2x 10^{11} Plättchen

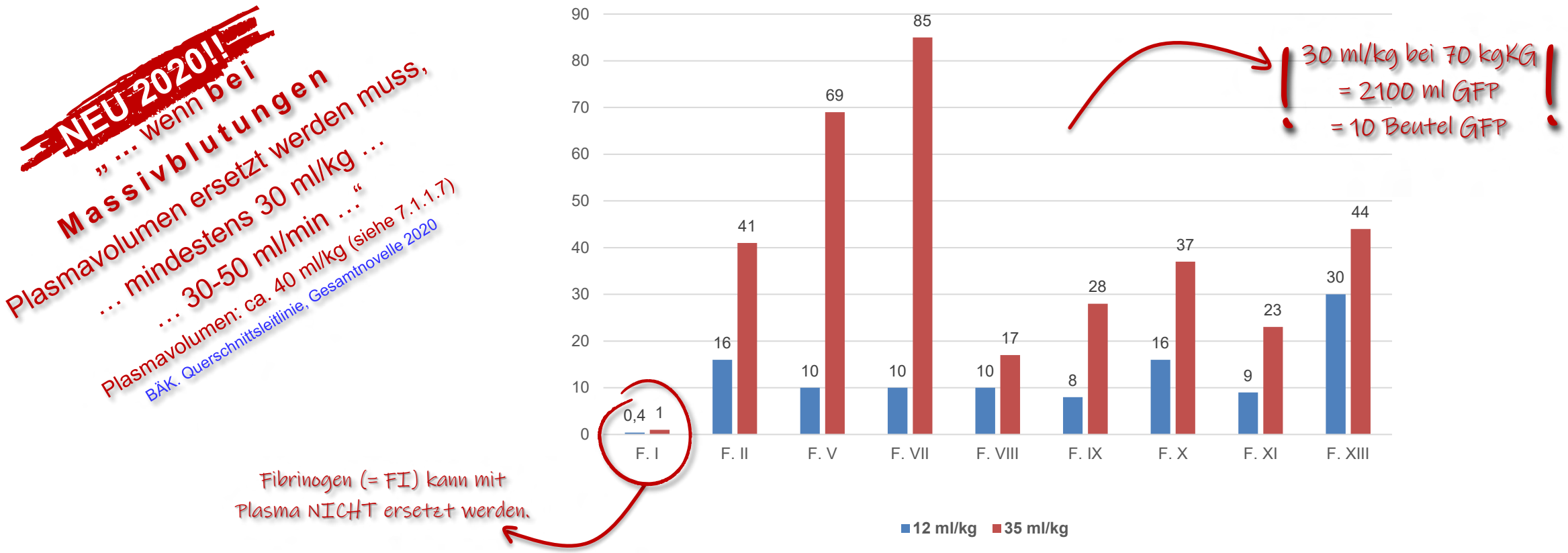
[1] ASATF 2006, Scand 2008, HAS-MOH 2011, SEPAABT 2013, BÄK 2014, BSCH 2015, NICE 2015, AAGBI 2016, NICE 2020

GFP: Wirksamkeit

Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients.

Chowdary P et al. Br J Haematol 2004

critically ill patients; 10 pat. received 12.2 ml/kg vs. 12 pat. received 33.5 ml/kg



NEU 2020!!
„... wenn bei Massivblutungen Plasmavolumen ersetzt werden muss, ... mindestens 30 ml/kg ... ... 30-50 ml/min ...“
Plasmavolumen: ca. 40 ml/kg (siehe 7.1.1.7)
BÄK. Querschnittsleitlinie, Gesamtnovelle 2020

30 ml/kg bei 70 kgKG
= 2100 ml GFP
= 10 Beutel GFP

Fibrinogen (= FI) kann mit Plasma NICHT ersetzt werden.

Icons made by https://www.infoDiagram.com/

"dried plasma"

für präklinisch

Neue Zulassungsstudien für lyophilisiert = gefrier-getrocknet = „freeze-dried" in PLASTIK-Beutel

pre-clinical and Phase 1 clinical trial Hoxworth Blood Center (Cincinnati, OH), Vascular Solutions LLC, and the US Department of Defense. Cancelas JA et al. Transfusion 2022

lyophilisation of apheresis-derived FFPs

lyophilisation of whole blood-derived FFPs

Test parameter	% Change	% Change
PT	7.19	8.52
INR	7.06	8.33
aPTT	5.15	6.41
NAPTT	12.13	7.42
TT	9.60	11.90
Fibrinogen	−6.83	−4.81
Factor II activity	−11.87	−10.19
Factor V activity	−10.05	−14.67
Factor VII activity	−7.15	−10.12
Factor VIII activity	−10.11	−6.85
Factor IX activity	−13.08	−13.50
Factor X activity	−11.65	−14.35
Factor XI activity	−10.94	−4.63
Factor XII activity	−11.37	−15.73
Factor VIIa	−15.12	−5.42
Protein C activity	−6.33	−9.28
Protein S activity	−1.17	−7.48
Plasmin inhibitor	−6.53	−4.48
Plasminogen activity	−4.92	−8.49
Antithrombin	−5.49	−7.07
vWF activity	−7.13	−10.52
vWF antigen	−9.87	−9.13

Im Vergleich zum Ausgangsmaterial FFP führt die Lyophilisierung zu einer Änderung der Aktivität um ±15%!

pre-clinical study Canadian Armed Forces, Canadian Blood Services and Terumo BCT. Sheffield WP et al. Transfusion 2022

lyophilisation of pooled FFPs

Quality parameters	% difference
Coagulation factors	
Factor II (U/ml)	−4.9
Factor V (U/ml)	−9.8
Factor VII (U/ml)	−7.1
Factor VIII (U/ml)	−14.3
Factor IX (U/ml)	−5.2
Factor XI (U/ml)	−2.2
Factor XIII (U/ml)	−6.9
Fibrinogen (g/L)	−3.0
Coagulation- and fibrinolysis-r	
Protein C (U/ml)	−1.6
Protein S (U/ml)	−12.1
Antithrombin (U/ml)	−8.7
α_2-Antiplasmin (U/ml)	−14.3
VWF (U/ml)	−9.1
ADAMTS-13 (U/ml)	−14.3
D-Dimer (µg/ml)	−3.3
TAT (ng/ml)	0.0
Hemostasis screening tests	
PT (s)	+5.9
APTT (s)	+6.9
Complement-related factors	
C3a (ng/ml)	+64
C5a (ng/ml)	+9.0
Physical characteristics	
pH	Not applicable
Osmolality (mmol/kg)	−4.3
Residual moisture (%)	Not applicable

lyophilisation of apheresis FFPs

Quality parameters	% difference
Coagulation factors and coa	
Factor II (U/ml)	−10
Factor V (U/ml)	−8.3
Factor VIII (U/ml)	−18
Fibrinogen (g/L)	−3.3
Protein S (U/ml)	−8.6
Antithrombin (U/ml)	−7.4
Hemostasis screening tests	
PT (s)	+3.1
APTT (s)	+6.6
Complement factors	
C3a (ng/ml)	+18
C5a (ng/ml)	−14

Dried Plasma for Major Trauma: Past, Present, and Future.

Peng HT et al. Life (Basel) 2024

sehr ausführlicher Artikel über die einzelnen Präparate und aktuelle Entwicklungen

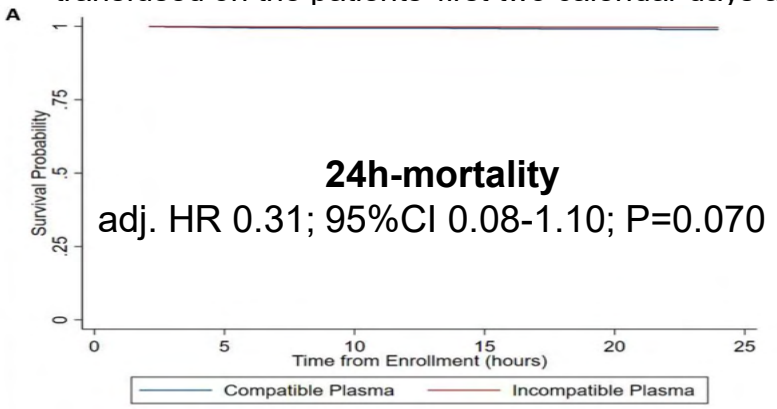
gefrier-getrocknet (freeze-dried): French FDP (FLyP), German FDP (LyoPlas), Canadian FDP (CFDP), South-African Bioplasma FDP

"… dried plasma … effective in managing hemorrhagic shock when administered as close as possible to the time of injury, thereby improving short-term survival within a 6 h window. … several freeze- and spray-dried plasma products under development …"

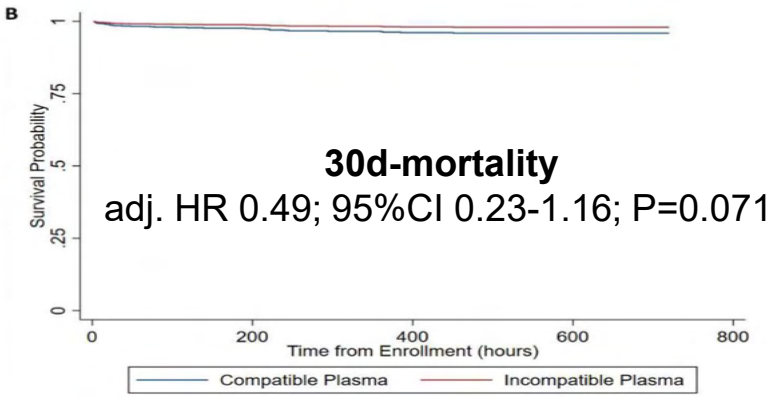
Incompatible plasma transfusion is not associated with increased mortality in civilian trauma patients.

Donohue JK et al. Hematology 2023

single center's (University of Pittsburgh) contributions to three multicenter studies of different trauma resuscitation strategies (PAMPer, PPOWER, SWAT); 347 patients transfused on the patients' first two calendar days after admission (167 patients only compatible plasma vs. 180 patients some incompatible plasma)



24h-mortality
adj. HR 0.31; 95%CI 0.08-1.10; P=0.070



30d-mortality
adj. HR 0.49; 95%CI 0.23-1.16; P=0.071

"… the univariate analysis of 24 h and 30 d mortality as well as hospital and ICU lengths of stay. There was not a significant difference in these parameters between the two groups. …upon controlling for confounders, there was not a difference in survival between the two groups of patients. … receipt of incompatible plasma was not significantly predictive of either mortality endpoint and in fact trended towards being protective from these endpoints."

Die Blutkomponenten?

3. Thrombozytenkonzentrate

Thrombozyten

Thrombozyten***zahl*** ≠ Thrombozyten***funktion***. → aber beide korrelieren (beim Polytrauma) mit Mortalität

Initial bleibt beim Polytrauma die Thrombozyten***zahl*** i.d.R. >100.000/µl, ABER: eine Thrombozyten-***funktion***sstörung ist obligater Bestandteil der Trauma-induzierten Koagulopathie.

Thrombozyten***funktion*** in Standardlabor (quantitative Messung) gar nicht und in viskoelastischen Tests (Messung des thrombozytären Anteils an der globalen Bildung des Gerinnsels) nicht ausreichend abgebildet.

POC-Thrombozyten***funktion***stests mit Messung der Verschlusszeit (z. B. Platelet Function Analyzer PFA100™ / 200™), der Impedanzaggregometrie (z. B. Multiplate™) oder der Lichttransmissionsaggregometrie nach BORN (z.B. VerifyNow™) werden durch niedrige Hkt- u./o. Thrombozytenwerte beeinflusst (↓Sensitivität, ↓Spezifität).

Hkt <25-30% und Thrombozyten <50.000-100.000/µl

Impact of platelet transfusion on outcomes in trauma patients.

Hamada SR et al. Crit Care 2022

Traumabase™ (French trauma registry), retrospective observational analysis; 19,596 patients: 8% severe haemorrhage (≥4 RBC/6h or death from haemorrhage), 3% massive transfusion (≥10 RBC/24h)

- median platelet count: 229 G/l
  - "a biomarker of trauma severity"
- >150 G/l → 18% coagulopathic (INR >1.5), 100-150 G/l → 52% coagulopathic; <100 G/l → 67% coagulopathic
  - "variations of platelet count within "normal ranges" reflect trauma severity"
- for every 50 G/L decrease in platelet count, one more unit of RBC was transfused (95% CI 0.8–1.2, p < 10–3)
- the odds of death increased by 37% for every 50 G/L decrease in platelet count (OR 0.63, 95% CI 0.57–0.70, p < 0.001)
  - "Early platelet transfusion improved survival, when 96% of early platelet transfusion were performed to patients with an admission platelet count > 100 G/L."
- **severe haemorrhage**: early platelet transfusion (within 6 h) was an independent protective factor for 24-h all-cause mortality: OR 0.56, 95% CI 0.38–0.84, *p* = 0.004
  - "These data support platelet transfusion despite normal platelet count."

DDAVP = Desmopressin (Minirin®)

jeweils 0,3 µg/kg („1 Amp (4 µg) pro 10 kgKG“) langsam als Kurzinfusion

Wirkung nach 30-60 Min. für 8-12h; Tachyphylaxie (nach 3-5 Gaben)

„off-label“ indiziert bei

- Thrombozytopathie (= Thrombozyten*funktion*sstörung)
- angeborenes VON WILLEBRAND-Syndrom (Typ 1 und 2 [kontraindiziert bei 2B, nicht wirksam bei 3], jeweils + Tranexamsäure)
- erworbenes VON WILLEBRAND-Syndrom, d.h. infolge von **Hypothermie**, **Azidämie** u./o. **Krankheiten** (kardiovaskulär [Klappenvitien, VSD, ASD], myeloproliferativ, autoimmun), **extrakorporale Zirkulation** (ECMO, HLM, ventricular assist devices) bzw. **Medikamenten** (z.B. ASS, COX-1-Inhibitoren [Ibuprofen, Diclofenac], Antibiotika [Ciprofloxacin, Griseofulvin, Tetracycline], Valproat, Clopidogrel, Ticagrelor, HAES)

DDAVP = Desmopressin (Minirin®)

Desmopressin to reduce periprocedural bleeding and transfusion: a systematic review and meta-analysis.

Wang C et al. Perioper Med (Lond) 2024

63 randomized trials (4163 participants); up to February 1, 2023

need for RBC transfusion (n=1944; 28 studies)
RR 0.95 [0.86, 1.05] → **21 fewer per 1000** (58 fewer to 21 more); p=0.306

total volume of blood loss (n=2037; 35 studies)
→ **0.40 SD lower** (0.56 lower to 0.23 lower); p<0.001

units of RBC transfused (n=1601; 26 studies)
→ **0.55 fewer units** (0.15 fewer to 0.94 fewer); p=0.007

any bleeding (n=202; 2 studies)
RR 0.45 [0.24, 0.84] → **139 fewer per 1000** (192 fewer to 40 fewer); p=0.0012

reoperation due to bleeding (n=1831; 24 studies)
RR 0.75 [0.47, 1.19] → **11 fewer per 1000** (23 fewer to 8 more); p=0.223

myocardial infarction (n=1866; 28 studies)
RR 1.22 [0.75, 1.98] → **5 more per 1000** (6 fewer to 22 more); p=0.429
cardiac surgery (n=1129; 17 studies): RR 1.40 [0.90, 2.47]
non-cardiac surgery (n=53; 9 studies): RR 0.76 [0.27, 2.19]

stroke (n=1399; 20 studies)
RR 1.31 [0.61, 2.84] → **1 more per 1000** (2 fewer to 8 more); p=0.487
cardiac surgery (n=831; 12 studies): RR 1.51 [0.60, 3.85]
non-cardiac surgery (n=406; 7 studies): RR 0.96 [0.22, 4.14]

hypotension (n=1321; 20 studies)
RR 2.15 [1.36, 3.41] → **29 more per 1000** (9 more to 60 more); p=0.001

venous thromboembolism (n=1467; 21 studies)
RR 0.81 [0.38, 1.76] → **2 fewer per 1000** (5 fewer to 6 more); p=0.597

hyponatremia (n=254; 3 studies)
RR 2.02 [0.53, 7.72] → **16 more per 1000** (7 fewer to 105 more); p=0.307

Die Blutkomponenten?

4. Das Verhältnis

Massivtransfusion?
Definitionen

Massivtransfusion „traditionelle Definition“	≥ 10 EK / 24 h Vietnam-Krieg 1971 Miller RD et al. Ann Surg 1971
Massivtransfusion „moderne Definition“ Guerado E et al. Eur J Trauma Emerg Surg 2016	≥ 10 EK / 6 h ≥ 4 EK / 1 h bei Kindern: 40 ml/kg Kamyszek RW et al. J Trauma 2019 Verlust von ≥ 50% des Blutvolumens / 3 h
bedeutsame Blutung „substantial bleeding“ Holcomb JB et al. Prehosp Emerg Care 2015	1. ≥ 1 EK innerhalb von 2 h plus 2. ≥ 5 EK oder blutungsbedingter Tod innerhalb von 4 h
Wiederbelebungs-Intensität * „resuscitation intensity, RI“ Rahbar E et al. J Trauma Acute Care Surg 2013	Anzahl an Einheiten innerhalb von 30 Min nach Aufnahme ≥4 Einheiten = ↑Mortalität (1 Einheit= 1 l Kristalloid, 0,5 l Kolloid, 1 EK, 1 GFP oder 1 Pool-/Apherese-TK)
CAT positiv * „critical administration threshold“ Savage SA et al. J Trauma Acute Care Surg 2013 Savage SA et al. J Trauma Acute Care Surg 2015	≥ 3 EK CAT24h innerhalb irgendeiner Stunde innerhalb von 24 h CAT1h innerhalb der ersten Stunde CAT4h innerhalb einer der ersten 4 Stunden

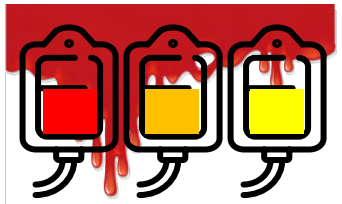
* in comparison:
• CAT+ best sensitivity
• RI4+ better specificity and good PPV and NPV
Meyer DE et al. J Trauma Acute Care Surg 2018

≥4 units:
• 3-fold mortality at 6 h
• 76% increased mortality at 24 h
Rahbar E et al. J Trauma Acute Care Surg 2013

CAT positive:
• 4-fold overall-mortality
Savage SA et al. J Trauma Acute Care Surg 2013

Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten. Gesamtnovelle 2020

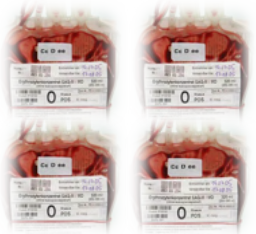
EU dito:
- **ESAIC 2nd update** Kietaibl S et al. EJA 2023 (R16; **2C**)
- **European Trauma 6th ed.** Rossaint R et al. Crit Care 2023 (Rec. 25; **1C**)

 Massivtransfusion	therapeutischem Plasma und EK … frühzeitig … festen Verhältnis von 1:1 bis 1:2	1C „sollte“
	Thrombozyten … frühzeitig … ab 6 EK 1TK; dann: pro 4 EK 1 TK	1B „soll“

EU **ESAIC 2nd update** Kietaibl S et al. EJA 2023 no common recommendation
European Trauma 6th ed. Rossaint R et al. Crit Care 2023 high platelet/pRBC ratio (Rec. 25; **2C**)

das heißt*,

EK : therapeut. Plasma : TK = 4(-5) : 4(-5) : 1



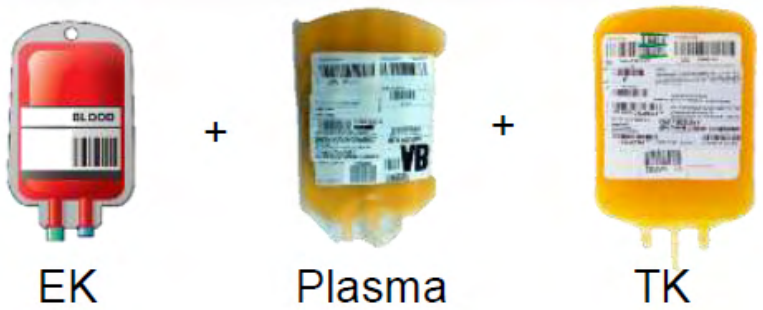
*Anpassung der 1:1:1 - PROPPR-Daten mit Einzelspender-TK an deutsche Pool- bzw. Apherese-TK mit 2x 10^{11} Plättchen

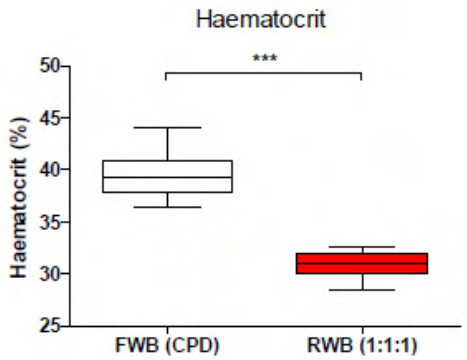
Haemostatic profile of reconstituted blood in a proposed 1:1:1 ratio of packed red blood cells, platelet concentrate and four different plasma preparations.

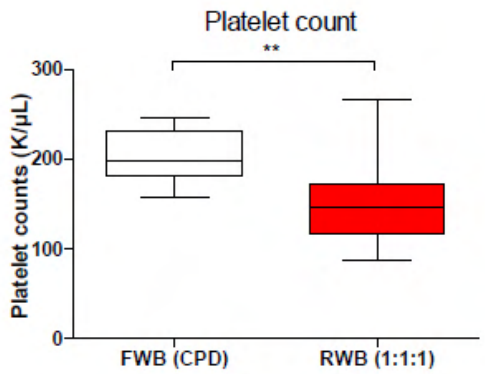
dito: Armand R et al. Transf Med Rev 2003

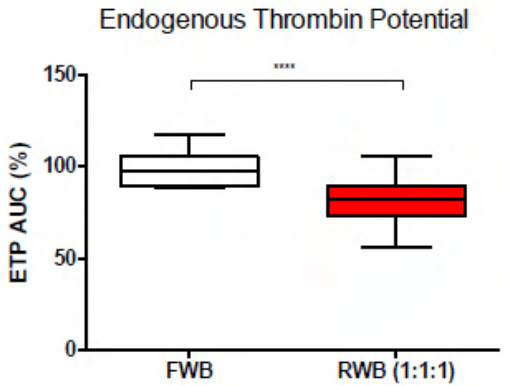
Ponschab M et al. Anaesthesia 2015

! ~1/4 des Inhalts sind Stabilisatoren, Konservierungsmittel, u.ä. !









Gefordert wird …

individualisierter Transfusionstrigger

BÄK. Querschnittsleitlinie, Gesamtnovelle 2020

„personalized, precision medicine“

Vigneshwar NG et al. Ann Surg 2022

Eine individualisierte, „Präzisions-“ Therapie ist bei Nutzung eines Verhältnis-gesteuerten (“ratio-driven“) Algorithmus‘ nicht möglich.

The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition.

Spahn DR et al. Critical Care 2019

"… Only in the absence of rapid near-patient coagulation testing to facilitate goal-directed therapy may initial treatment with blood components in a fixed ratio constitute a reasonable approach. …"

"ratio" vs. "goal-directed" bei Massivtransfusion

4 : 4 : 1

"ratio-driven approach" = "empiric strategy"

initial

d.h., Verhältnis
EK zu Plasma zu TK =
4(bis 5) : 4(bis 5) : 1

"Copenhagen Concept"
Johansson PI. Transfus Apher Sci 2010

"hybrid approach"
Baksaas-Aasen K et al. Ann Surg 2019

Cave:
Bisher kein RCT mit Überlebensvorteil durch dieses Konzept!

Europäische Leitlinien

Kietaibl S et al. Eur J Anaesthesiol 2023 Rec. 16: **2C & 1C**
Rossaint R et al. Crit Care 2023C & 2B Rec. 25: **1C & 2B**; Rec. 26: **1B**

schnellst-möglich

individualized, "goal-directed approach"

d.h., ziel-gerichtet,
auf POC / Labor beruhend

: VET (S3-LL Polytrauma: Empfehlg. 2.4.3 und 2.4.14; GoR A)

: VET, wenn nicht möglich, dann SLT
(6th Europ. Trauma: Rec. 11, 1C und Rec. 26, 1B)

Icons made by https://www.infoDiagram.com/ und https://www.flaticon.com/

Use of Bayesian Statistics to Reanalyze Data From the Pragmatic Randomized Optimal Platelet and Plasma Ratios Trial.

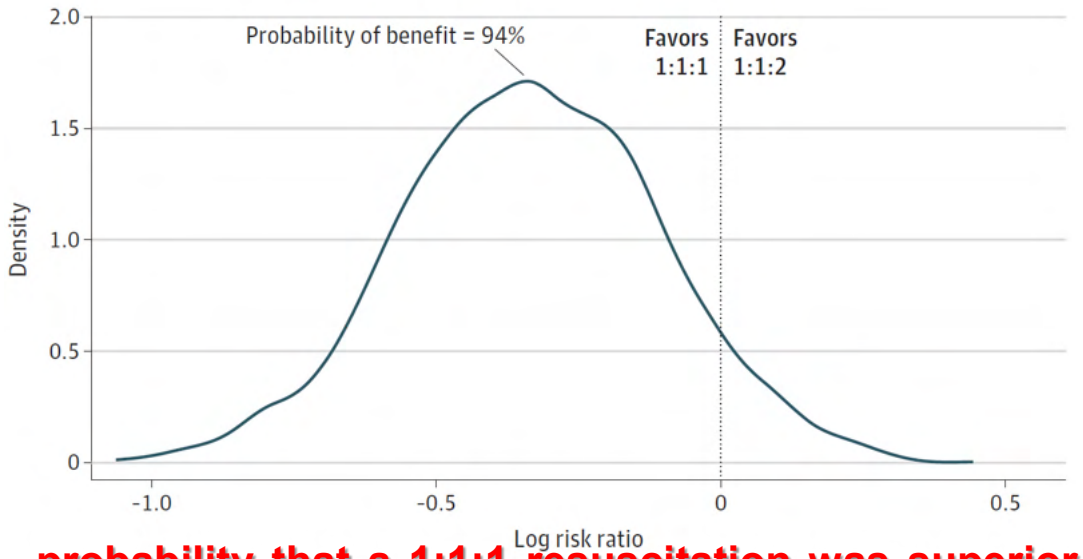
*showed a **non-significant** mortality benefit by 1:1:1 of 4.2% for 24h and 3.7% for 30d

Lammers D et al. JAMA Netw Open 2023

PROPPR* Trial; 680 patients (338 in the 1:1:1 cohort vs 342 in the 1:1:2 cohort); 546 (80.3%) male; median (IQR) age of 34 (24-51) years; median ISS of 26 (IQR 17-41); 330 **(48.5%) with penetrating** injury; 591 **(87.0%) with severe hemorrhage**. original trial: frequentist analysis; here: **bayesian analysis**

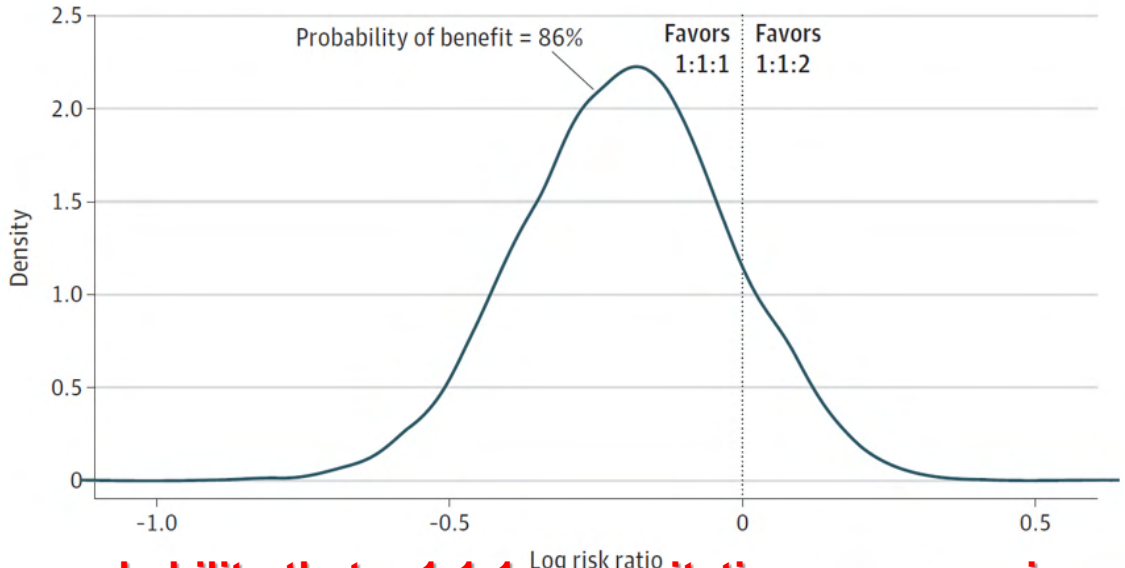
post-hoc analysis; PROPPR data; focus on early mortality benefit (Spinella P et al. JTACS 2021);

Posterior Distribution for **Mortality Difference at 24 Hours**



probability that a 1:1:1 resuscitation was superior to a 1:1:2 strategy with regards to **24-hour mortality** was found to be **93%** (RR, 0.72 [95%CrI, 0.45-1.11])

Posterior Distribution for **Mortality Difference at 30 Days**



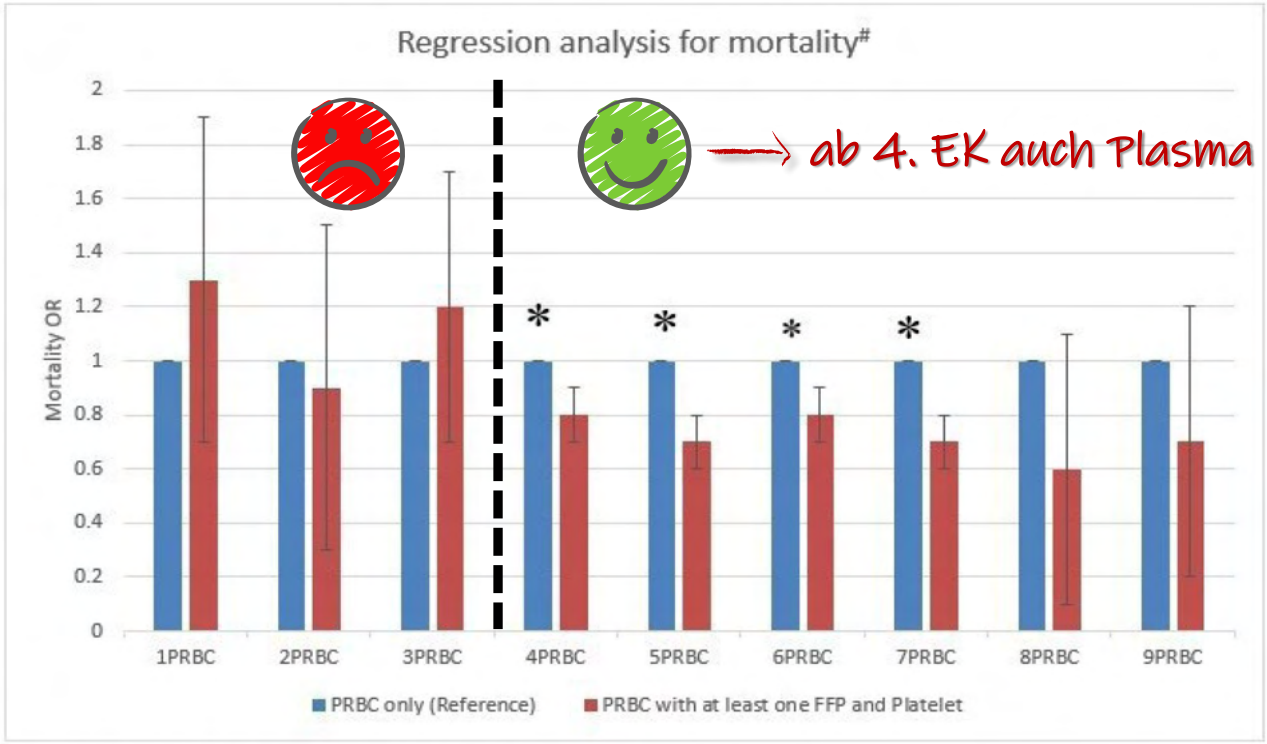
probability that a 1:1:1 resuscitation was superior to a 1:1:2 strategy with regards to **30-days mortality** was found to be **86%** (RR, 0.82 [95%CrI, 0.57-1.16])

Is there a need for fresh frozen plasma and platelet transfusion in trauma patients receiving submassive transfusion?

only about 3% of civilian and 8% of military trauma patients require ≥10 PRBC/24h

Jehan F et al. Trauma Surg Acute Care Open 2024

retrospective cohort study; American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) database 2016-2018; 85 234 patients received **submassive transfusion** (<10 PRBC within the first 24h); **combined resuscitation** (**CR**, Transfusion of PRBCs combined with at least 1 unit of FFP and/or platelets); 84% blunt trauma; median ISS 11 (IQR 9-17)



→ ab 4. EK auch Plasma

* Significant value ($p < 0.05$)
\# Regression analysis controlling for age, gender, race, ISS, body region AIS, ED vitals, GCS, Temperature, anticoagulant use.

in patients receiving **more than 3 units of PRBC**:

- **CR group** had **improved mortality**
  - 4 PRBC group OR: 0.8 (p=0.03),
  - 5 PRBC group OR: 0.7 (p=0.2),
  - 6 PRBC group OR: 0.8 (p=0.04),
  - 7 PRBC group OR: 0.7 (p=0.03),
  - 8 PRBC group OR <1 (p=0.82), and
  - 9 PRBC group OR <1 (p=0.79).

  } almost all patients received at least one FFP/platelet ⇒ type B error
- **CR group** had **lower rate of**
  - **any complications** (15% vs 26%) (p=0.01),
  - **ARDS** (3% vs 5%) (p=0.03), and
  - **AKI** (8% vs 11%) (p=0.02).

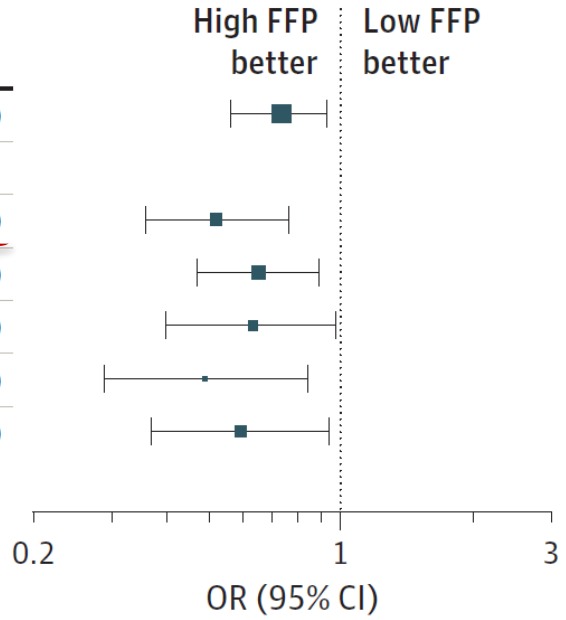
High Fresh Frozen Plasma to Red Blood Cell Ratio and Survival Outcomes in Blunt Trauma.

Fujiwara G et al. JAMA Surg 2024

retrospective cohort; Japan Trauma Data Bank; 1954 pat. with severe blunt trauma but without severe TBI (AIS head >2) who required blood transfusion; **high-FFP** (n=976; FFP to RBC ratio >1) vs. **low-FFP** (n=978; FFP to RBC ratio ≤1); median age 61 (IQR 41-77); 63.6% male; median ISS 25 (IQR 19-32).

median transfusion volume within 24 hours
low-FFP: 8 (IQR 6-16) RBC units and 6 (IQR 4-12) FFP
high-FFP: 8 (IQR 4-14) RBC units and 14 (IQR 8-22) FFP units

Group	OR (95% CI)
Overall cohort	0.73 (0.56-0.93)
Subgroup	
Shock	0.52 (0.36-0.76)
Massive transfusion	0.65 (0.47-0.89)
Thoracic AIS >3	0.63 (0.40-0.97)
Abdominal AIS >3	0.49 (0.29-0.84)
Lower extremity AIS >3	0.59 (0.37-0.94)



"… relationship between the FFP to RBC ratio and in-hospital mortality showed a **dose-response relationship** … in the area where the ratio was lower than **1.5** but suggested a **ceiling effect** at higher ratios **1.0 to 1.5 may be reasonable** …"

ditto: Kojima M et al. J Intensive Care 2022

Gibt es eine Grenze?

Facing futility in hemorrhagic shock: when to say ‘when’ in children and adults.

Cotton BA et al. Trauma Surg Acute Care Open 2024

the STOP criteria or Suspension of Transfusions and Other Procedures

Table 1 Predictors of 100% futility using the Suspension of Transfusions and Other Procedures (STOP) criteria

STOP criteria for 100% futility	PPV	NPV
Arrival SBP ≤50 mm Hg and LY-30 ≥30%	100%	78%
Arrival SBP ≤50 mm Hg and lactate ≥15	100%	77%
Arrival SBP ≤70 mm Hg, lactate ≥15, and LY-30 ≥30%	100%	77%
ROSC and lactate ≥12	100%	78%
ROSC and LY-30 ≥30%	100%	76%
ROSC and field GCS of 3	100%	77%

GCS, Glasgow Coma Scale; LY-30, percent amplitude reduction of the clot at 30 min after maximal amplitude achieved, reflecting the degree of fibrinolysis; NPV, negative predictive value; PPV, positive predictive value; ROSC, return of spontaneous circulation; SBP, systolic blood pressure.

Table 2 Futility cut-off points for children and adolescents

Suspension of Transfusions and Other Procedures criteria for 100% futility	PPV	NPV
Arrival pH ≤7.00 and INR ≥2.0	100%	58%
Arrival base deficit ≥20 and INR ≥2.0	100%	55%
Arrival pH ≤7.05 and LY-30 ≥20%	100%	56%
Arrival base deficit ≥12 and LY-30 ≥20%	100%	70%
TBI and INR ≥2.0	100%	63%
TBI and LY-30 ≥20%	100%	89%

INR, international normalized ratio; LY-30, percent amplitude reduction of the clot at 30 min after maximal amplitude achieved, reflecting the degree of fibrinolysis; NPV, negative predictive value; pH, potential of hydrogen; PPV, positive predictive value; TBI, traumatic brain injury.

“… futility should not be declared based on high transfusion volumes alone. …
fibrinolysis by rapid thrombelastography was a predictor and achieved 100% futility as a single value at 50% or higher.
Consistent with the low platelets, rapid thrombelastography maximal amplitude of 30 mm or less was 100% fatal.”

Rahmenbedingungen der Gerinnung

FIV = Ca^{2+}

Cave:

calcium chloride: 10 mL as a 10% solution contains 270 mg of elemental calcium

calcium gluconate: 10 mL as a 10% solution contains only 90 mg of elemental calcium

Rossaint R et al. Crit Care 2023

Faustregel:

1 g Calcium-Chlorid oder 2,5 g Calcium-Gluconat

alle 5 Beutel EK bzw. Plasma

Wade DJ et al. J Surg Res 2024

↳ .... und regelmäßig BGA-Kontrolle !!

in Deutschland:

Calciumchlorid 5,5% Baxter 20 ml / Ampulle

Calciumgluconat B. Braun 10% Injektionslösung 10 ml / Ampulle

Vollblut („whole blood“) beim Trauma**?**

Whole blood transfusion in the treatment of acute hemorrhage, a systematic review and meta-analysis.

van der Horst RA et al. J Trauma Acute Care Surg 2023

meta-analysis; 44 studies (27 studies **WB±COMP vs. COMP** and 17 studies WB without COMP comparison); publication dates from 2013 to 2023, until January 16, 2023; **20 civilian studies:** retrospective cohort studies (n = 11), prospective cohort studies (n = 7), and RCTs (n = 2).

Mortality (20 civilian studies with WB±COMP vs. COMP):

- **early (≤6h) mortality** (6 studies): OR, 0.65; 95% CI, 0.44–0.96; I^2 = 0%
- **24-hour mortality** (11 studies): OR, 0.71; 95% CI, 0.52–0.98; I^2 = 58%
- **late (28/30d) mortality** (18 studies): OR, 0.97; 95% CI, 0.80–1.18; I^2 = 44%

"Selection and confounding bias were present in almost all studies."

Whole blood resuscitation for injured patients requiring transfusion: A systematic review, meta-analysis, and practice management guideline from the Eastern Association for the Surgery of Trauma.

Meizoso JP et al. J Trauma Acute Care Surg 2024

meta-analysis; 21 civilian studies (WB vs. COMP; only 1 RCT); publication dates from 2013 to 2023, until May 30, 2023; **excluding prehospital** studies.

Mortality (WB vs. COMP):

- **early (≤6h) mortality** (7 studies): OR, 1.03; 95% CI, 0.68–1.56; I^2 = 40%
- **24-hour mortality** (10 studies): OR, 0.78; 95%CI, 0.54–1.12; I^2 = 75%
- **late (28/30d) mortality** (8 studies): OR, 1.16; 95% CI, .97–1.37; I^2 = 0%
- **in-hospital mortality** (10 studies): OR, 0.96; 95% CI, 0.71–1.29; I^2 = 66%

ICU LOS (WB vs. COMP): MD = mean difference

- **ICU-free days** (5 studies): MD, −0.50; 95% CI, −2.18 to 1.19; I^2 = 2%
- **24-hour mortality** (9 studies): MD, −0.35; 95% CI, −1.34 to 0.63; I^2 = 46%

Infectious Complications (WB vs. COMP):

- (8 studies): OR, 0.93; 95% CI, 0.74–1.17; I^2 = 13%)

Transfusion Requirements (WB vs. COMP): MD = mean difference

- **4h RBC transfusions** (6 studies): MD, −1.82; 95% CI, −3.12 to −0.52; I^2 = 93%
- **4h plasma transfusions** (6 studies): MD, −1.47; 95%CI, −2.94 to 0; I^2 = 95%
- **24h RBC transfusions** (14 studies): MD, −1.22; 95% CI, −2.24 to −0.19; I^2 = 90%
- **24h plasma transfusions** (14 studies): MD, −0.68; 95% CI, −1.54 to 0.18; I^2 = 87%
- **24h total transfusions** (14 studies): MD, 0.56; 95% CI, −1.57 to 2.69; I2 = 78%

"… imprecision was considered serious for most outcomes, except the mortality outcomes, where the CIs were noted to be narrow. … the overall quality of evidence was deemed to be very low."

Die Faktorkonzentrate?

Trauma coagulopathy: Insights from the PROCOAG and CRYOSTAT-2 trials. Coagulation factors are not antibiotics.

Gauss T et al. Editorial. Anaesth Crit Care Pain Med 2024

"… factors are only to be substituted **if their deficiency is detected in point-of-care testing** … an **empiric administration** of coagulation factors **does not provide clinical benefit** and may raise the risk of thromboembolic events …"

in Deutschland zugelassene Fibrinogenkonzentrate

	Inhalt	Zusatzstoffe		Dosierung	Zulassung
FibCLOT® LFB 1,5 g	mit 100 ml rekonstituiert mit Aqua enthält ca. 15 mg/ml humanes Fibrinogen	Arginin-Hydrochlorid Isoleucin Lysinhydrochlorid Glycin Natriumcitrat-Dihydrat	Na^+ maximal 46 mg [2 mmol] pro 1 g Fibrinogen	**Erwachsene und Kinder**: 50-60 mg/kg	05. Februar 2016
Fibryga® Octapharma 1 g	mit 50 ml rekonstituiert mit Aqua enthält ca. 20 mg/ml humanes Fibrinogen	L-Argininhydrochlorid Glycin Natriumchlorid Natriumcitrat-Dihydrat	Na^+ bis zu 132 mg [5,8 mmol] pro 1 g Fibrinogen	**Erwachsene**: initial 1 – 2 g; ggf. größere Mengen (4 – 8 g) **Kinder**: 20 – 30 mg/kg	23. Juni 2017
Haemocomplettan® CSL Behring 1 g / 2 g	mit 50 bzw. 100 ml rekonstituiert mit Aqua enthält ca. 20 mg/ml humanes Fibrinogen	Human Albumin L-Argininhydrochlorid Natriumhydroxid (zur Einstellung des pH-Wertes) Natriumchlorid Natriumcitrat	Na^+ bis zu 164 mg [7,1 mmol] pro 1 g Fibrinogen	**Erwachsene**: initial 2 g (bzw. 30 mg/kg), ggf. große Mengen (4 – 8 g) **Kinder**: 20 – 30 mg/kg	22. März 2005

FibCLOT® nur bei kongenitaler, Fibryga® und Haemocomplettan® auch bei erworbener Hypo- oder Afibrinogenämie zugelassen.

"Fibrinogen concentrate preparations have **comparable levels of fibrinogen**, and therefore it is likely that different fibrinogen concentrates have **comparable levels of effectiveness**." Stephan F et al. J Clin Pharmacol 2023

Fibrinogen & ROTEM

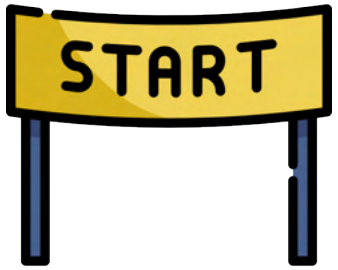
$A5_{FIB}$ < 9 mm ≈ fibrinogen level < 2 g/L

$A5_{FIB}$ ≥ 12 mm ≈ fibrinogen level ≥ 2.5 g/L

$A5_{FIB}$ ≥ 15 mm ≈ fibrinogen level ≥ 3 g/L

Drotarova M et al. Diagnostics (Basel) 2023

FAZIT: Fibrinogen-Substitution



Indikation zur Substitution:

Fibrinogen <1,5-2,0 g/l

bei PPH

Mavrides EAS et al. BJOG 2017
Schlembach D et al. Geburtsh Frauenheilk 2018
Munoz M et al. Blood Transfus 2019
Innerhofer N et al. J Clin Med 2021
Kietaibl S et al. Eur J Anaesthesiol 2023
Rossaint R et al. Crit Care 2023

Ziel der Substitution:

Fibrinogen 2,2-2,5 g/l

Hagamo JS et al. Crit Care 2014
Collins PW et al. Br J Anaesth. 2017
Wu F et al. Shock 2019
Lv K et al. World J Emerg Surg 2020

auch bei PPH

SHT: 2,5-3 g/l ?!

Icons made by https://www.flaticon.com/de/packs/road-bicycle-racing

Hypofibrinogenemic Massive Transfusion Trauma Patients Experience Worse Outcomes.

Parker MJ et al. Am Surg 2023

prospective practice management guideline; a total of 96 out of 130 patients met criteria and underwent MT with a median admission fibrinogen of 170.5 mg/dL

"Hypofibrinogenemic (**<200 mg/dL**) patients demonstrated **greater mortality** than patients with normal levels (50% vs 23.5%, P = .021)."

Fibrinogen: abrechenbar?

https: //www.zusatzentgelt-gerinnungsfaktoren.de

aG-DRG-Version 2024, Zusatzentgelte-Katalog, Anlage 4

ZE2024-138 *Gabe von Fibrinogenkonzentrat*

- Schwellenwert: 2.500 € *
- OPS-Kode 8.810.j; mengenabhängig gestaffelt (Anlage 6 FPV)
- ICD-Kodes aus Liste 2 oder 3 (Anlage 7 FPV)

obligat zu kodierende Ausrufezeichenkodes

⇒ temporäre Blutgerinnungsstörungen zusätzlich ICD: U69.12!

- Das Zulassungsrecht bleibt von der Katalogaufnahme unberührt. Die Kostenträger entscheiden im Einzelfall, ob die Kosten dieser Medikamente übernommen werden.
- Die jeweils zugehörigen ICD-Kodes und -Texte sind in Anlage 7 aufgeführt.
- Für das Jahr 2024 gilt ein Schwellenwert in der Höhe von 2.500 € für den im Rahmen der Behandlung des Patienten für Blutgerinnungsfaktoren angefallenen Betrag. Ab Überschreitung dieses Schwellenwertes ist der gesamte für die Behandlung des Patienten mit Blutgerinnungsfaktoren angefallene Betrag abzurechnen.

*Nach Zulassung weiterer Präparate, d.h. Fibryga® (Octapharma) und FibCLOT® (LFB) zusätzlich zu Haemocomplettan® (CSL Behring)
- deutlicher Preisreduktion pro Gramm, aber
- gleicher Schwellenwert (statt ~8-9 g derzeit ~12-14 g für Erstattung notwendig)

in Deutschland zugelassene PPSB-Präparate

(Inhalt gemäß Fachinformation, Stand: Sept 2020)

hinsichtlich des Faktor-IX-Gehaltes standardisiert (da ursprünglich zur Therapie der Hämophilie B genutzt)
Erdoes G et al. Anaesthesia 2020

		FII [IE/ml]	FVII [IE/ml]	FIX [IE/ml]	FX [IE/ml]	Prot. C [IE/ml]	Prot. S [IE/ml]	Antithrombin [IE/ml]	Heparin [IE/IE]
Beriplex® CSL Behring		20-48	10-25	20-31	22-60	15-45	12-38	0,2-1,5	0,4-2
	Kalina U. 2008	31	16	28	41	-	-	-	-
	Grottke O. 2013	26	16	23	28	23	27	0,56	0,7
	Asmis LM. 2014	31	23	30	40	-	-	0,55	0,25
Cofact® Biotest		14-35	7-20	25	14-35	11-39	1-8	≤0,6	0
	Kalina U. 2008	20	13	23	26	-	-	-	-
	Grottke O. 2013	29	21	22	23	19	14	0,26	<0,05
	Asmis LM. 2014				-	-	-	-	-
Octaplex® Octapharma		14-38	9-24	25	18-30	13-31	12-32	k.A.	0,2-0,5
	Kalina U. 2008	31	16	22	24	-	-	-	-
	Grottke O. 2013	26	19	20	23	19	21	0,06	17,6
	Asmis LM. 2014	33	28	24	30	-	-	0,10	-
Prothromplex® Takeda		24-45	25	30	30	k.A.	k.A.	0,75-1,5	0,2-0,5
	Kalina U. 2008	-	-	-	-	-	-	-	-
	Grottke O. 2013	33	27	20	27	26	26	1,25	14,4
	Asmis LM. 2014	37	37	36	38	-	-	1,68	1,6

k.A. keine Angaben

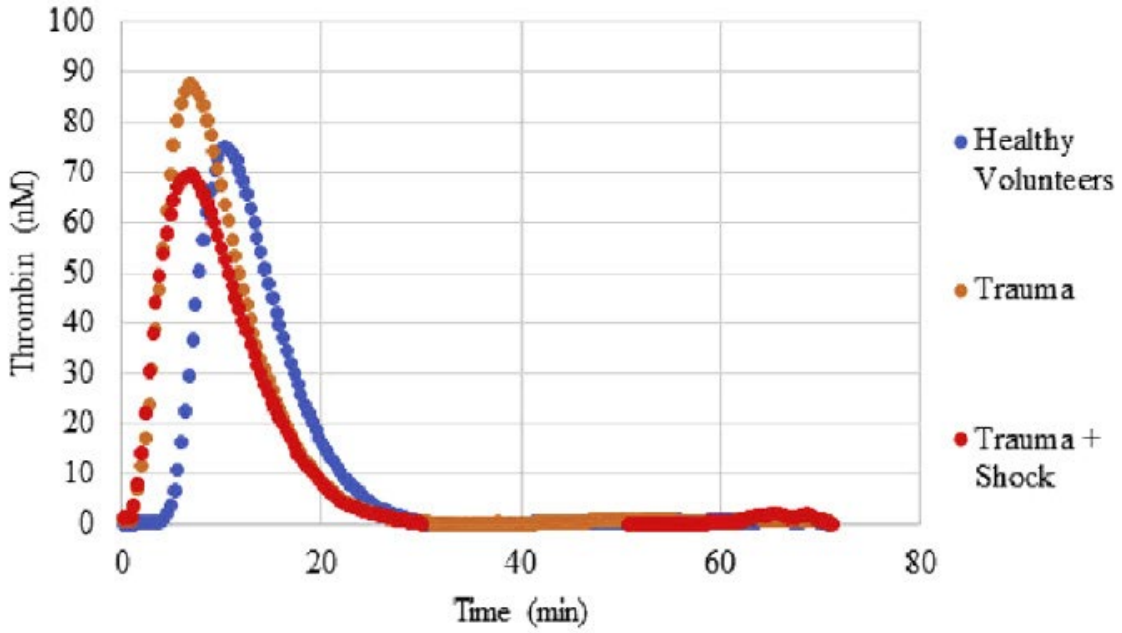
- alle Präparate weisen eine, von den physiologischen Verhältnissen abweichende Zusammensetzung auf
- erhebliche Unterschiede in der enthaltenen Konzentration der Wirkstoffe zwischen den Herstellern
- nur Cofact® (fast) ohne Heparin (→ HIT); vergleichbare Thrombin-Generation Infanger L et al. Anesth Analg 2022

!

Whole Blood Thrombin Generation in Severely Injured Patients Requiring Massive Transfusion.

Coleman JR et al. J Am Coll Surg 2021

Denver, Colorado, USA; Trauma Activation Protocol study; whole blood TG values in healthy volunteers were compared to trauma patients; prototype point-of-care whole blood TG device (ST Genesia™, Stago); 118 trauma-activation patients: 52% blunt trauma; median New Injury Severity Score of 22 (IQR 10 to 34).



healthy: regular thrombin generation (TG), with regular peak thrombin and regular maximum rate of TG.

trauma: robust thrombin generation (TG), with higher peak thrombin and faster maximum rate of TG.

trauma & shock (SBP < 90 mmHg): depressed TG, with significantly lower peak thrombin and slower maximum rate of TG.

bei schockiertem Trauma doch reduzierte Thrombingeneration ⇒ frühzeitig PPSB?

Thromboembolism after treatment with 4-factor prothrombin complex concentrate or plasma for warfarin-related bleeding.

Go AS et al. J Thromb Thrombolysis 2022

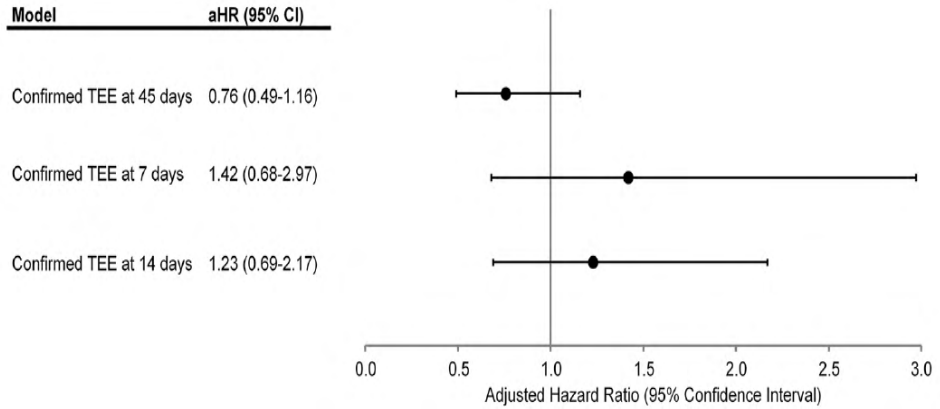
multicenter observational study; California, USA; reversal of warfarin due to major bleeding; matched pairs: 1119 pat. receiving 4F-PCC vs. 1119 pat. receiving plasma; primary outcome: occurrence of arterial or venous thrombembolic event within 45 days;

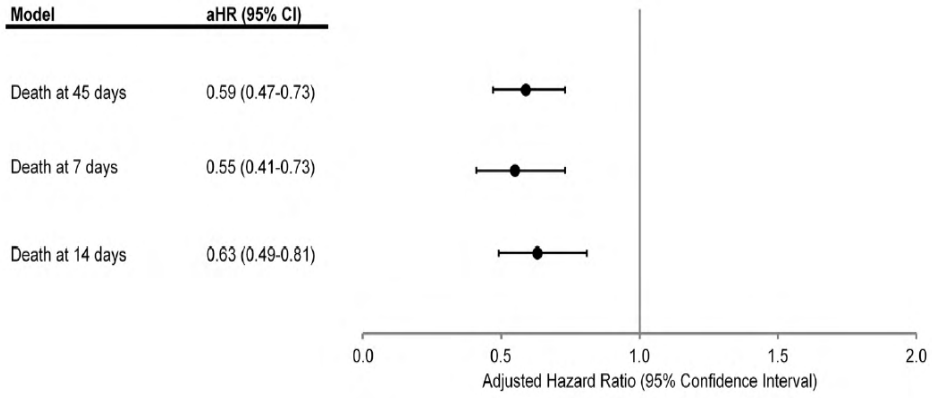
- **overall** risk of **confirmed arterial or venous TEE** after either 4F-PCC or plasma was 4.0% (95% CI 3.3–4.9%)
  - **4F-PCC**: 3.5% (95% CI 2.5–4.7%)
  - **Plasma**: 4.5% (95% CI 3.3–5.9%)

→ no significant difference in the multivariable **risk of TEE** at 45 days post-treatment (aHR 0.92, 95% CI 0.55–1.54).

- no significant difference in the multivariable **risk of all-cause death** (aHR 0.80, 95% CI 0.59–1.10)

erhöhtes ETP heißt nicht zwangsläufig Thromboembolie ?





Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion. The **PROCOAG** Randomized Clinical Trial.

Bouzat P et al. JAMA 2023

Kanokad® (Laboratoire Français du Biomédicament)

double-blind, randomized, placebo-controlled superiority trial; 12 French designated level I trauma centers; 324 patients: 1 mL/kg of 4F-PCC (25 IU of factor IX/kg + FFP; n=164) vs. 1 mL/kg of saline (n=160); 95% received study medication within 1h; median ISS 36 (26-50); 69% expedient hemorrhage control; 59% with prehospital arterial systolic blood pressure <90mmHg; 40% ≥3 RBC in first h; median 6 RBC (4-10);

- **no statistically or clinically significant between-group difference** in median (IQR) total 24-hour blood product consumption (12 [5-19] U in the 4F-PCC group vs 11 [6-19] U in the placebo group; absolute difference, 0.2 U [95% CI, −2.99 to 3.33]; P = .72) or any differences in secondary outcomes

- **higher percentage of thromboembolic events**: 35% vs. 24% absolute difference, 11% [95% CI, 1%-21%]; relative risk, 1.48 [95% CI, 1.04-2.10]; P = 0.03; **PTr >1.2**: 34% vs. 22%, P = 0.06 but **PTr <1.2**: 33% vs. 33%, P = 0.99

- better mortality (not statistically significant):
  - *24h*: 11% vs. 13%; absolute difference −2; 95%CI −9 to 5; P = 0.67
  - *28d*: 17% vs. 21%; absolute difference −3; 95%CI −12 to 5; P = 0.48

- PCC group received less TXA (76% vs. 86%)
- endpoint confounded by **survival bias**
- product used may differ in efficacy from other PCC

Bouzat P et al. Intensive Care Med 2023; Newton H et al. CJEM 2023

"**Conclusion**: … These findings do not support systematic use of 4F-PCC in patients at risk of massive transfusion."

ABER: "… this trial has not sufficient strength to conclusively change the current clinical practice …" Curcio R et al. Intern Emerg Med 2024

PPSB bei Trauma

altersabhängig?

Traumatic coagulopathy in the older patient: analysis of coagulation profiles from the Activation of Coagulation and Inflammation in Trauma-2 (ACIT-2) observational, multicenter study.

Curry NS et al. J Thromb Haemost 2023

multicenter (6 European level 1 trauma centers), prospective, cohort study; 1567 patients: 16-49 y vs. 50-64 y vs. ≥65 y; median ISS 17 (IQR: 9-29); 81% blunt trauma; 20% evidence of shock (BD > −6 mmol/L);

Age-dependent thrombin generation predicts 30-day mortality and symptomatic thromboembolism after multiple trauma.

Lesbo M et al. Sci Rep 2023

retrospective database analysis; Aarhus University Hospital, Denmark; 386 patients: <40 y vs. ≥40 y; >80% blunt trauma; 25% ISS >15; 12% in circulatory shock (SI ≥0.8);

- shock and severity of injury lead to the same pattern of coagulation changes within age groups
- older patients mount a weaker and less dynamic response to trauma than younger patients.
- similar ISS but ↑age:
  - ↑fibrinogen levels (thresholds less sensitive in older patients)
  - ↑thrombin generation (↑PT1 + 2 fragments, ↑TAT, ↓AT)
  - ↑fibrinolysis (↑PAP, ↑tPA [↑endothelial damage], ↑d-dimers, ↑fibrin monomers)
  - ↑consumption of factors
- VHA: ↑CT/R time; ↓MCF/MA; global lytic measures not different

PPSB & ROTEM

nur wenn:

1.) ausreichend Fibrinogen ($A5_{FIB}$ ≥ 9-12 mm)

<u>und</u>:

2.) ↑CT_{EXT} >80 Schöchl H et al. Crit Care 2011 -90 Innerhofer P et al. The Lancet Haematology 2017 sec.

Kietaibl S et al. Eur J Anaesthesiol 2023; Rossaint R et al. Crit Care 2023

PPSB bei Blutung:

- bei Patienten mit lebensbedrohlichen Blutungen u./o. im Schock AWMF- Polytrauma-LL 2023
- ausreichend Fibrinogen*, ABER viskoelastischen Zeichen verzögerter Initiation (↑CT_{EXTEM}) Kietaibl S et al. EJA 2023; Rossaint R et al. Crit Care 2023
  - >80 (1) bzw. >90 (2) Sek.
- initial: 25 IE/kg, bei erhöhtem thromboembolischen Risiko: 12,5 IE/kg Erdoes G et al. Anaesthesia 2021, bei DOAC-Antagonisierung: 25-50 IE/kg Kietaibl S et al. EJA 2023; Rossaint R et al. Crit Care 2023
- für 3 Tage dosisabhängig erhöhtes endogenes Thrombinpotential (ETP) Honickel M et al. Thromb Haemost 2015; Schöchl et al. Crit Care 2014;
- Thromboembolierisiko von 4% BÄK. Querschnittsleitlinie 2020; Go AS et al. J Thromb Thrombolysis 2022 beschrieben (teilweise deutlich höher: 10,5% bei 10 (6-15) IE/kg Uttaro E et al. Transfus Apher Sci 2023; PPSB 35% vs. Placebo 24% → absolute Differenz 11% bei 25 IE/kg + FFP Bouzat P et al. PROCOAG. JAMA 2023)

Icons made by https://www.infoDiagram.com/ und https://www.istockphoto.com/

⇒ IMMER individuelle Nutzen-Risiko-Abwägung!!

*Cave: CT auch von Fibrinogen abhängig

PPSB: abrechenbar?

https: //www.zusatzentgelt-gerinnungsfaktoren.de

aG-DRG-Version 2024, Zusatzentgelte-Katalog, Anlage 5

Gabe von Prothrombinkomplex, parenteral.

- ab 3.500 IE *
- Zusatzentgelt: **ZE30.*ff***; mengenabhängig gestaffelt
- OPS-Kode: **8-812.5***x*

- Bei der Behandlung von Blutern mit Blutgerinnungsfaktoren erfolgt die Abrechnung der Gabe von Prothrombinkomplex über das ZE2024-97 nach Anlage 4 bzw. 6, die gleichzeitige Abrechnung des ZE30 ist ausges.

*relativ hohe Dosis:
- 25 IE/kg Erdoes G et al. Anaesthesia 2020 bei 80 kg = 2000 IE

in Deutschland zugelassene FXIII - Konzentrate

	Inhalt	Zusatzstoffe		Dosierung	Zulassung
Fibrogammin® CSL Behring 250 IE / 1250 IE	62,5 IE/ml (250 IE/4 ml und 1250 IE/20 ml) humanen Blut-gerinnungsfaktor XIII, wenn man es mit 4 bzw. 20 ml Wasser für Injektionszwecke rekonstituiert	Human Albumin Glucosemonohydrat Natriumchlorid NaOH (zur Einstellung des pH-Wertes)	124,4 – 195,4 mg (5,41 – 8,50 mmol) Natrium pro Dosis (40 IE/kg bei durchschnittlich 70 kg), wenn die empfohlene Dosis (2800 IE = 44,8 ml) verabreicht wird	initial 40 IE/kg, 4 ml pro Minute	07. Februar 2005

Catridecacog (NovoThirteen®, NovoNordisk): rekombinante Faktor XIII A-subunit; zugelassen in EU nur für angeborenen Mangel der FXIII A-subunit seit Sept. 2012

First-Line Administration of Fibrinogen Concentrate in the Bleeding Trauma Patient: Searching for Effective Dosages and Optimal Post-Treatment Levels Limiting Massive Transfusion—Further Results of the RETIC Study.

Innerhofer N et al. J Clin Med 2021

preplanned descriptive and exploratory post hoc analyses of the single-center, parallel-group, open-labeled, randomized RETIC-trial; 70 patients (50 Fc as first-line, 20 FC as cross-over rescue): median ISS 35 (29–45)

"… that nearly 30% of trauma patients exhibit FXIII of **less than 60%** on admission, and its **association with blood loss** …"

Acquired Factor XIII Deficiency in Patients with Multiple Trauma.

Hetz M et al. Injury 2023

2-center study with 3 separate cohorts

- **Cohort A** (Dresden, n = 880), **polytraumatized**:
  - initial FXIII activity ≤70%: 12.4%

- **Cohort C** (Dresden, n = 84), **polytraumatized with severe TBI**:
  - initial FXIII activity ≤70%: 17%
  - median FXIII activity 73% (interval, 35-139%; IQR, 59-91%) for poor mid-term outcomes and 94% (interval, 42-177%; IQR, 76-113%) for good outcomes

- **Cohort B** (Berlin, n = 26), **polytraumatized**:
  - mean ISS = 30
  - initial median FXIII activity 87% (IQR 61-98%) → after 7 days: 58% (52-71%)
  - ↓FXIII = ↓time after trauma, ↓PTT, ↓fibrinogen,↑lactate
  - ↑FXIII = ↑Hb
  - substitution to 150% of normal activity → ↑↑$FIBTEM_{MCF}$ & ↓$EXTEM_{ML}$;
  - substitution to 300% of normal activity → ↑↑↑$FIBTEM_{MCF}$ & ↓↓$EXTEM_{ML}$;

"… clinical practice involves the **administration of 1250 IU FXIII with subsequent activity monitoring** in case of a deficiency … Our observations suggest a revision of mass transfusion protocols based on the European guideline for management of major bleeding and coagulopathy following trauma, …"

FXIII & ROTEM

FXIII hat Einfluss auf VET-Parameter (MCF_{FIB}; ML_{EXT})

aber:

derzeit gibt es *keine* geeigneten Cut-offs für VET.

Hinweis im ROTEM:
kontinuierliche Abnahme der MCF + ML_{EXT} > 12%, die sich im Aptem nicht verbesserte
(Cave: schlechte Korrelation zwischen ML_{EXT} und Ausmaß des FXIII-Mangels)
⇒ Konzentration soll im Labor gemessen werden

Hetz M et al. Injury 2023

FXIII bei Blutung:

2022 in deutsch-sprachiger PPH- und Polytrauma-Leitlinie und 2023 sowohl in **ESAIC 2nd update** als auch in **European Trauma 6th ed.** recht ausführlich diskutiert!

- bei Blutverlust >50% des Blutvolumens AWMF- PPH-LL 2022 bzw. einer Aktivität <60% AWMF- Polytrauma-LL 2023; Rossaint R et al. Crit Care 2023
- initial 20 IE/kg bzw. 1250 IE Hetz M et al. Injury 2023

Grenzwert nicht eindeutig; wurde deshalb bei Kietaibl S et al. EJA 2023 gestrichen

Neu ab 2018:

In Anlage 4 des Zusatzentgelte-Katalog:

- **ZE2024-137** *Gabe von rekombinantem aktivierten Faktor VII*
  - Schwellenwert: 20.000 €
  - OPS-Kode 8.810.6; mengenabhängig gestaffelt (Anlage 6 FPV)
  - ICD-Kodes aus Liste 2 oder 3 (Anlage 7 FPV)
- **ZE2024-138** *Gabe von Fibrinogenkonzentrat*
  - Schwellenwert: 2.500 €
  - OPS-Kode 8.810.j; mengenabhängig gestaffelt (Anlage 6 FPV)
  - ICD-Kodes aus Liste 2 oder 3 (Anlage 7 FPV)
- **ZE2024-139** *Gabe von Blutgerinnungsfaktoren*
  - Schwellenwert: 6.000 € als Summe der Faktoren
  - siehe Tabelle rechts; mengenabhängig gestaffelt (Anlage 6 FPV)
  - ICD-Kodes aus Liste 2 oder 3 (Anlage 7 FPV)

⇒

Faktor VII	8.810.7
rekombinanter Faktor VIII plasmatischer Faktor VIII	8.810.8 8.810.9
rekombinanter Faktor IX plasmatischer Faktor IX	8.810.a 8.810.b
Faktor XIII	8.810.e
aktiviertes PPSB = FEIBA	8.810.c
Von-Willebrand-Faktor	8.810.d
humanes Protein C	8.812.9

⇒ temporäre Blutgerinnungsstörungen zusätzlich ICD: U69.12!

obligat zu kodierende Ausrufezeichenkodes

- Ab Überschreitung dieses Schwellenwertes ist der gesamte für die Behandlung des Patienten angefallene Betrag für die Gabe des jeweiligen Medikamentes abzurechnen.
- Für die aufgeführten Leistungen sind **krankenhausindividuelle Entgelte** nach § 6 Abs. 1 Satz 1 des Krankenhausentgeltgesetzes zu vereinbaren, soweit diese als Krankenhausleistungen erbracht werden dürfen.
- Es handelt sich um **unbewertete,** intrabudgetäre **Zusatzentgelte**, d.h. die über dieses Zusatzentgelt vergüteten Leistungen werden aus dem DRG-Budget bereinigt und wirken absenkend auf den Landesbasisfallwert [Umverteilung zwischen Krankenhäusern] → Krankenkassen werden nicht belastet!.
- Die jeweils zugehörigen ICD-Kodes und -Texte sind in Anlage 7 FPV aufgeführt.

Die viskoelastischen Tests?

The Other Side of the Coin: Using Rotational Thromboelastometry to Stop or Avoid Blood Transfusions in Trauma Patients.

Parreira JG et al. Panam J Trauma Crit Care Emerg Surg 2023

retrospective cohort analysis; ROTEM on hospital arrival; "normal ROTEM" (all parameters within normal range; 76.2%) vs. "abnormal ROTEM" (≥1 parameter out of range; 23.8%); 793 adult patients; 80.2% blunt trauma; median ISS 9 (2-19) and 33.9% ISS ≥16

variable	NPV **all patients** (n=793)	NPV **ISS ≥16** (n=80)
any BP	327/345 (94.8%)	67/80 (83.8%)
RBC	327/345 (94.8%)	67/80 (83.8%)
PLS	339/345 (98.3%)	74/80 (92.5%)
PLT	341/345 (98.8%)	77/80 (96.3%)
Cryo	338/345 (98.0%)	74/80 (92.5%)
PL, Pt or CR	336/345 (97.4%)	72/80 (90.0%)
RBC > 9	344/345 (99.7%)	79/80 (98.8%)
RBC > 5	342/345 (99.1%)	77/80 (96.3%)
PLS > 5	344/345 (99.7%)	79/80 (98.8%)
Plat > 2	344/345 (99.7%)	79/80 (98.8%)
Cryo > 2	344/345 (99.7%)	79/80 (98.8%)

Blood product	AUC
Any (at least 1 unit)	0.812
RBC (at least 1 unit)	0.811
CRY (at least one apheresis)	0.890
PLS (at least 1 unit)	0.887
PLT (at least one apheresis)	0.859
RBC (> 9 units) RBC10	0.982
RBC (> 5 units) RBC6	0.921
PLS (> 5 units) PLS6	0.944

normal ROTEM in ~30% of ISS ≥16, which suggests that many such patients may not have an underlying coagulopathy

ROTEM **PPV** was not as strong, indicating that an "Abnormal ROTEM" test was not associated with the transfusion of blood products.

hoher **negativ-prädiktiver Wert (NPV)**

⇒ VET-Algorithmen geben Hinweise, was NICHT notwendig ist !

Thromboelastometry-guided Haemostatic Resuscitation in Severely Injured Patients: A Propensity Score-matched Study.

David JS et al. Crit Care 2023

retrospective analysis of two prospectively populated registries in France; VHA-based versus a CCT-based TIC management; 624 of 7250 patients with ≥1RBC/24h: propensity matched pairs of 250 each;

At 24 h,

- **more patients were alive and free of MT**: ROTEM 75% vs. CCT 52%; p <0.01
- **fewer patients received MT**: 15% vs. 42%, p <0.01
- **overall costs reduced**: 2357 euros [1108-5020] vs. 4092 euros [2510-5916], p <0.001
- **less RBC and FFP**

Überlebensvorteil in RCTs durch VET bei Trauma

survival: VET 36.4% vs. CCA 19.6% (p=0.049).
6h-mortality: VET 7.1% vs. 21.8% CCA group (p=0.032).
haemorrhagic deaths: VET 7.8% vs. CCA 23.4% (p=0.020)
Gonzalez E et al. Ann Surg 2016

mortality: VET 7.1% vs. CCA 10.2% (p=0.017)
OR 0.63 (p=0.04)
Militär
Lammers DT et al. J Trauma Acute Care Surg 2020

Icons made by https://www.flaticon.com

24h-mortality: VET 5% vs. CCA 13% (p=0.006)
30d-mortality: VET 11% vs. CCA 25% (p=0.002)
Cochrane C et al. Diagnostics (Basel) 2020

iTACTIC
24h-survival (**severe TBI**): VET 64% vs. CCA 46%, OR 2.12
Baksaas-Aasen K et al. Intensive Care Med 2021

CCA conventional coagulation assays

Effect of Viscoelastic Testing on Mortality in Bleeding Patients with Severe Trauma: A Meta-Analysis

Klaus Goerlinger[1,2], Marc Maegele[3], Heiko Lier[4], Donat R. Spahn[5]

[1] Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany
[2] Medical Department, TEM Innovations/Werfen PBM, Munich, Germany
[3] Department of Trauma and Orthopedic Surgery, Cologne-Merheim Medical Center (CMMC), University Witten/Herdecke, Cologne, Germany
[4] ASG Anesthesiology and Pain Therapy Medical Care Center, MediaPark Clinic, Cologne, Germany
[5] Prof. Emeritus, University of Zurich, Zurich, Switzerland

BACKGROUND: It is still a matter of debate whether viscoelastic testing-guided bleeding management or a ratio-based transfusion approach is associated with lower mortality in bleeding patients with severe trauma.

METHODS: An Advanced PubMed Search with the search term ((ROTEM[Title/Abstract] OR TEG[Title/Abstract] OR thromboelastometry[Title/Abstract] OR thrombelastography[Title/Abstract] OR viscoelastic[Title/Abstract] OR FIBTEM[Title/Abstract]) AND (trauma[Title/Abstract] OR traumatic[Title/Abstract] OR Injury[Title/Abstract]) AND (mortality[Title/Abstract] OR survival[Title/Abstract])) provided 488 results on March 29, 2024. Twenty-four studies published between 2011 and 2024 reporting mortality in adult and pediatric bleeding trauma patients comparing viscoelastic testing-guided bleeding management with standard of care were included in this meta-analysis [1-24], and further five studies have been identified by other sources and included, too [25-29].

RESULTS: Overall, 29 studies with 11,006 participants and 2,096 events (overall mortality, 19.0%) have been included in this meta-analysis. This included three randomized controlled trials (N=600) and 26 cohort studies (N=10,406). Twenty-seven studies assessed the effect on civilian trauma (N=7467) and two studies on military trauma (N=3539). Twenty-six studies included adult (N=10,007) and three studies pediatric trauma patients (N=999). Seventeen studies used ROTEM (N=5,760), two studies used ROTEM or TEG (N=3,715), and 10 studies used TEG (N=1,531). None of the trauma studies reporting mortality used Quantra. The Risk Ratio for mortality (95% Confidence Interval) was 0.7890 (0.7014; 0.8877) with a P-value of 0.0003 in the random model (Figure). As markers of heterogeneity, Tau2 was 0.0201, Chi2 was 40.34, df was 28, I2 was 30.6% with a P-value of 0.06

CONCLUSIONS: Our meta-analysis demonstrates a significant reduction in mortality by viscoelastic testing (ROTEM/TEG)-guided bleeding management in bleeding patients with severe trauma.

REFERENCES: 1. Schöchl et al. Crit Care. 2011; 2. Tapia et al. J Trauma Acute Care Surg. 2013; 3. Yin et al. J Emerg Surg. 2014; 4. Gonzalez et al. Ann Surg. 2016; 5. Wang et al. J Clin Med Res. 2017; 6. Innerhofer et al. Lancet Haematol. 2017; 7. Stein et al. Anaesthesia. 2017; 8. Prat et al. J Trauma Acute Care Surg. 2017; 9. Aladegbami et al. J Emerg Trauma Shock. 2018; 10. Hota et al. Am Surg. 2019; 11. Guth et al. Anaesth Crit Care Pain Med. 2019; 12. Unruh et al. Am J Surg. 2019; 13. Lammers et al. J Trauma Acute Care Surg. 2020; 14. Rimaitis et al. Med Sci Monit. 2020; 15. Cochrane et al. Diagnostics (Basel). 2020; 16. Dudek et al. Injury. 2020; 17. Baksaas-Aasen et al. Intensive Care Med. 2021; 18. Pernod et al. Turk J Anaesthesiol Reanim. 2021; 19. Barquero Lopez et al. J Trauma Acute Care Surg. 2022; 20. Riehl et al. J Clin Med. 2022; 21. David et al. Crit Care. 2023; 22. Hannington et al. S Afr J Surg. 2023; 23. Salehi et al. World J Emerg Surg. 2023; 24. Liu et al. Transfus Med. 2024; 25. Nienaber et al. Injury. 2011; 26. Lendemans et al. DKOU. 2013; 27. Nardi et al. Crit Care. 2015; 28. Deng et al. J Int Med Res. 2018; 29. Campbell et al. Emerg Med Australas. 2021.

the ANESTESIOLOGY® 2024 annual meeting, PHILADELPHIA, PA, OCTOBER 18-22, 2024: ePoster A2047.

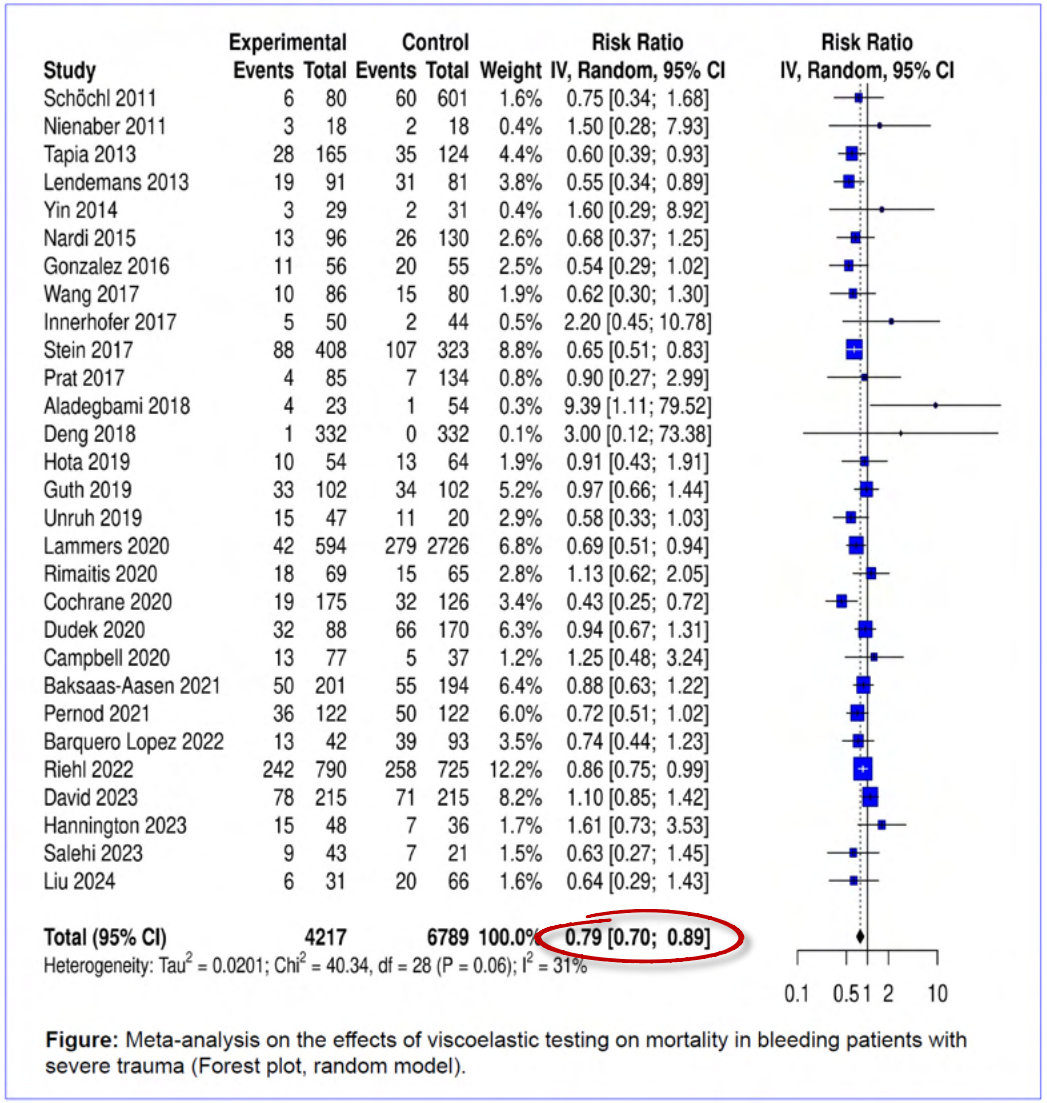


Figure: Meta-analysis on the effects of viscoelastic testing on mortality in bleeding patients with severe trauma (Forest plot, random model).

Effect of Viscoelastic Testing on Mortality in Bleeding Patients with Severe Trauma: A Meta-Analysis.

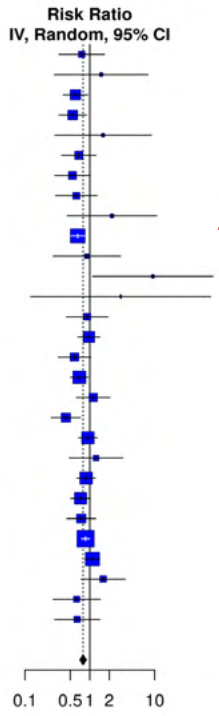
Klaus Goerlinger, Marc Maegele, Heiko Lier, Donat R. Spahn

„ePoster A2047" beim ASA2024

29 studies (3 RCT, 26 cohort studies) with 11,006 participants (overall mortality, 19%)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Schöchl 2011	6	80	60	601	1.6%	0.75 [0.34; 1.68]
Nienaber 2011	3	18	2	18	0.4%	1.50 [0.28; 7.93]
Tapia 2013	28	165	35	124	4.4%	0.60 [0.39; 0.93]
Lendemans 2013	19	91	31	81	3.8%	0.55 [0.34; 0.89]
Yin 2014	3	29	2	31	0.4%	1.60 [0.29; 8.92]
Nardi 2015	13	96	26	130	2.6%	0.68 [0.37; 1.25]
Gonzalez 2016	11	56	20	55	2.5%	0.54 [0.29; 1.02]
Wang 2017	10	86	15	80	1.9%	0.62 [0.30; 1.30]
Innerhofer 2017	5	50	2	44	0.5%	2.20 [0.45; 10.78]
Stein 2017	88	408	107	323	8.8%	0.65 [0.51; 0.83]
Prat 2017	4	85	7	134	0.8%	0.90 [0.27; 2.99]
Aladegbami 2018	4	23	1	54	0.3%	9.39 [1.11; 79.52]
Deng 2018	1	332	0	332	0.1%	3.00 [0.12; 73.38]
Hota 2019	10	54	13	64	1.9%	0.91 [0.43; 1.91]
Guth 2019	33	102	34	102	5.2%	0.97 [0.66; 1.44]
Unruh 2019	15	47	11	20	2.9%	0.58 [0.33; 1.03]
Lammers 2020	42	594	279	2726	6.8%	0.69 [0.51; 0.94]
Rimaitis 2020	18	69	15	65	2.8%	1.13 [0.62; 2.05]
Cochrane 2020	19	175	32	126	3.4%	0.43 [0.25; 0.72]
Dudek 2020	32	88	66	170	6.3%	0.94 [0.67; 1.31]
Campbell 2020	13	77	5	37	1.2%	1.25 [0.48; 3.24]
Baksaas-Aasen 2021	50	201	55	194	6.4%	0.88 [0.63; 1.22]
Pernod 2021	36	122	50	122	6.0%	0.72 [0.51; 1.02]
Barquero Lopez 2022	13	42	39	93	3.5%	0.74 [0.44; 1.23]
Riehl 2022	242	790	258	725	12.2%	0.86 [0.75; 0.99]
David 2023	78	215	71	215	8.2%	1.10 [0.85; 1.42]
Hannington 2023	15	48	7	36	1.7%	1.61 [0.73; 3.53]
Salehi 2023	9	43	7	21	1.5%	0.63 [0.27; 1.45]
Liu 2024	6	31	20	66	1.6%	0.64 [0.29; 1.43]
Total (95% CI)	**4217**		**6789**		**100.0%**	**0.79 [0.70; 0.89]**

Heterogeneity: $Tau^2 = 0.0201$; $Chi^2 = 40.34$, df = 28 (P = 0.06); $I^2 = 31\%$



random effects model

risk ratio 0.79 (0.70; 0.89)

significant reduction in mortality by viscoelastic testing (ROTEM/TEG)-guided bleeding management in bleeding patients with severe trauma

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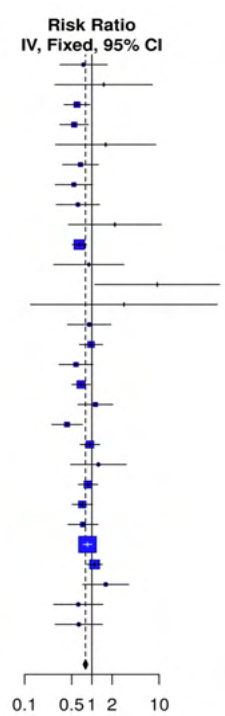
Total (95% CI)	**4217**		**6789**		**100.0%**	**0.80 [0.74; 0.87]**

Heterogeneity: $Tau^2 = 0.0201$; $Chi^2 = 40.34$, df = 28 (P = 0.06); $I^2 = 31\%$



fixed effects model

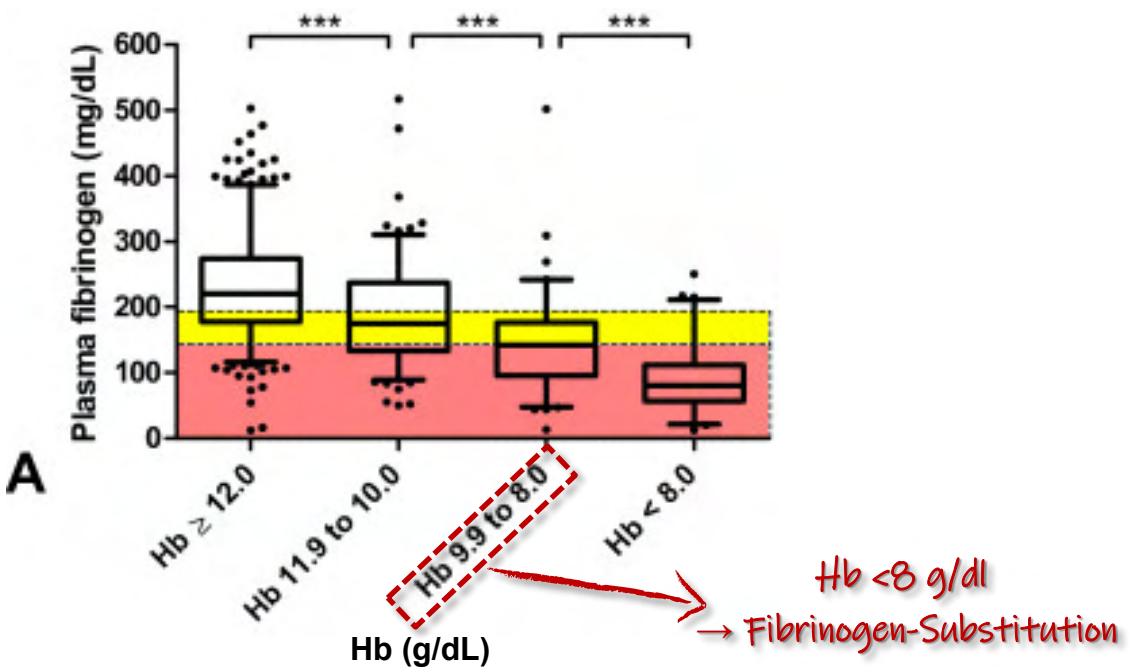
risk ratio 0.80 (0.74; 0.87)

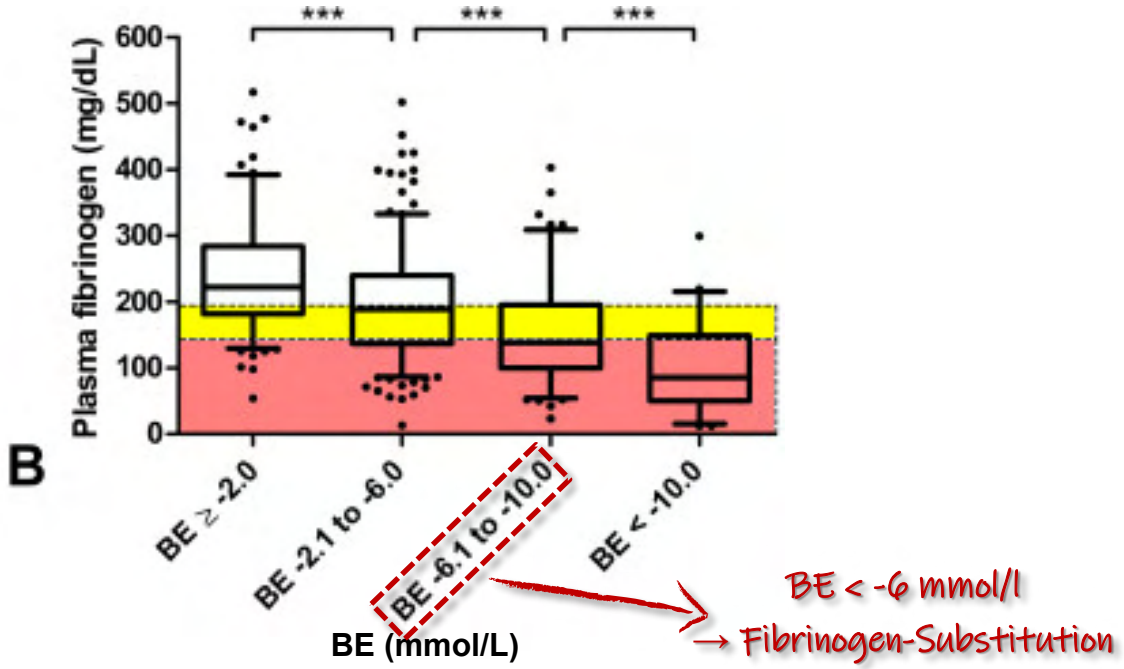
Diagnostik ohne POC / viskoelastische Tests?

Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission.

Schlimp C et al.Crit Care 2013

retrospective; 675 pat. (median ISS 27); admission at emergency department in AUVA Salzburg

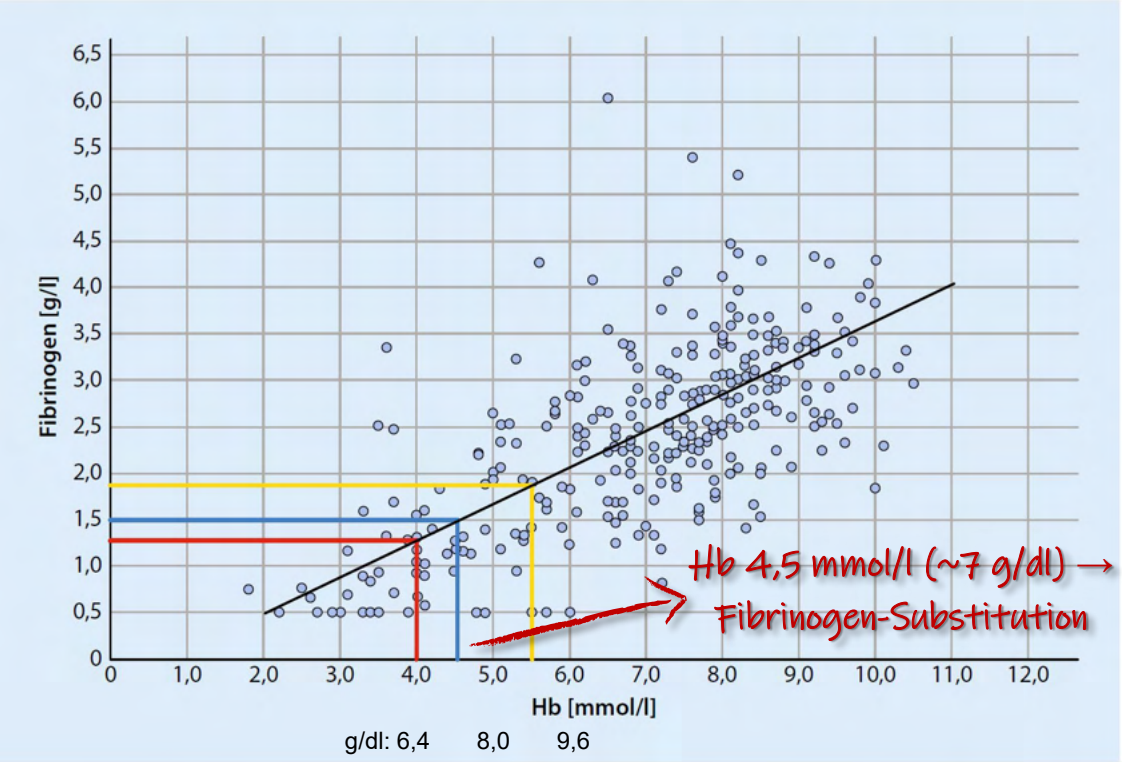




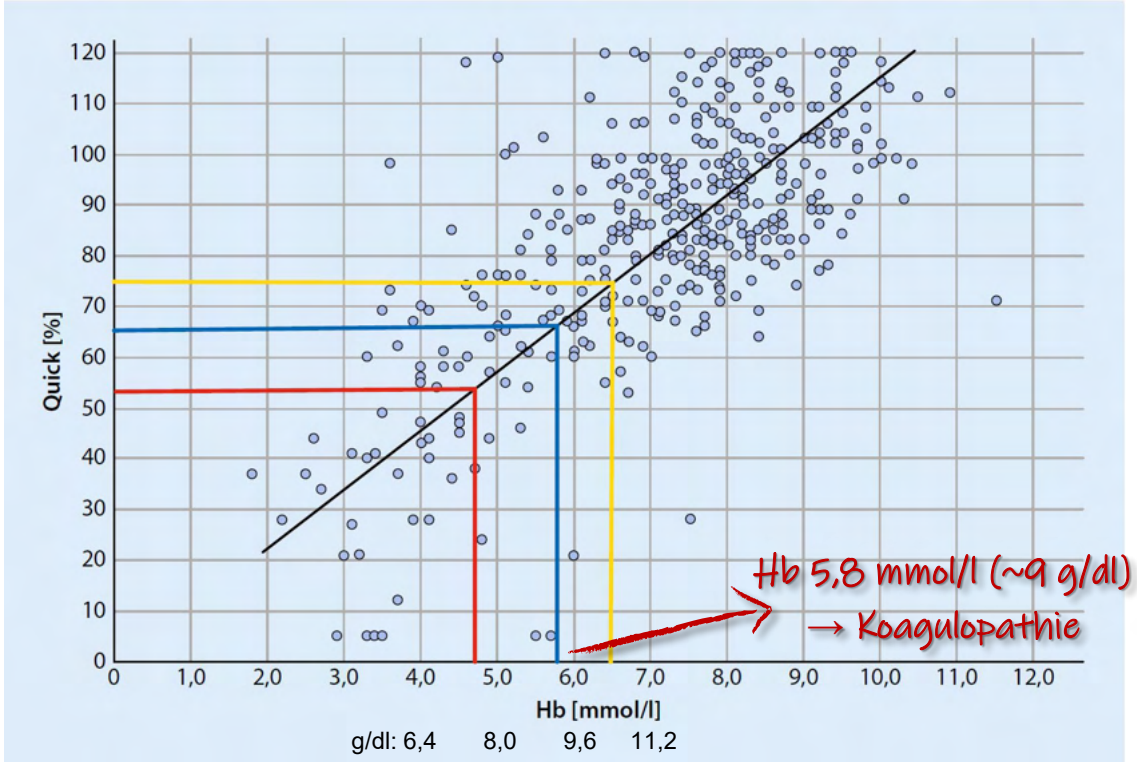
Einfach und praktisch: Gerinnungsmanagement beim Trauma ohne viskoelastische Testverfahren.

Hilbert-Carius P et al. Notfall Rettungsmed 2021

~500 pat.; BG Klinikum Bergmannstrost, Halle

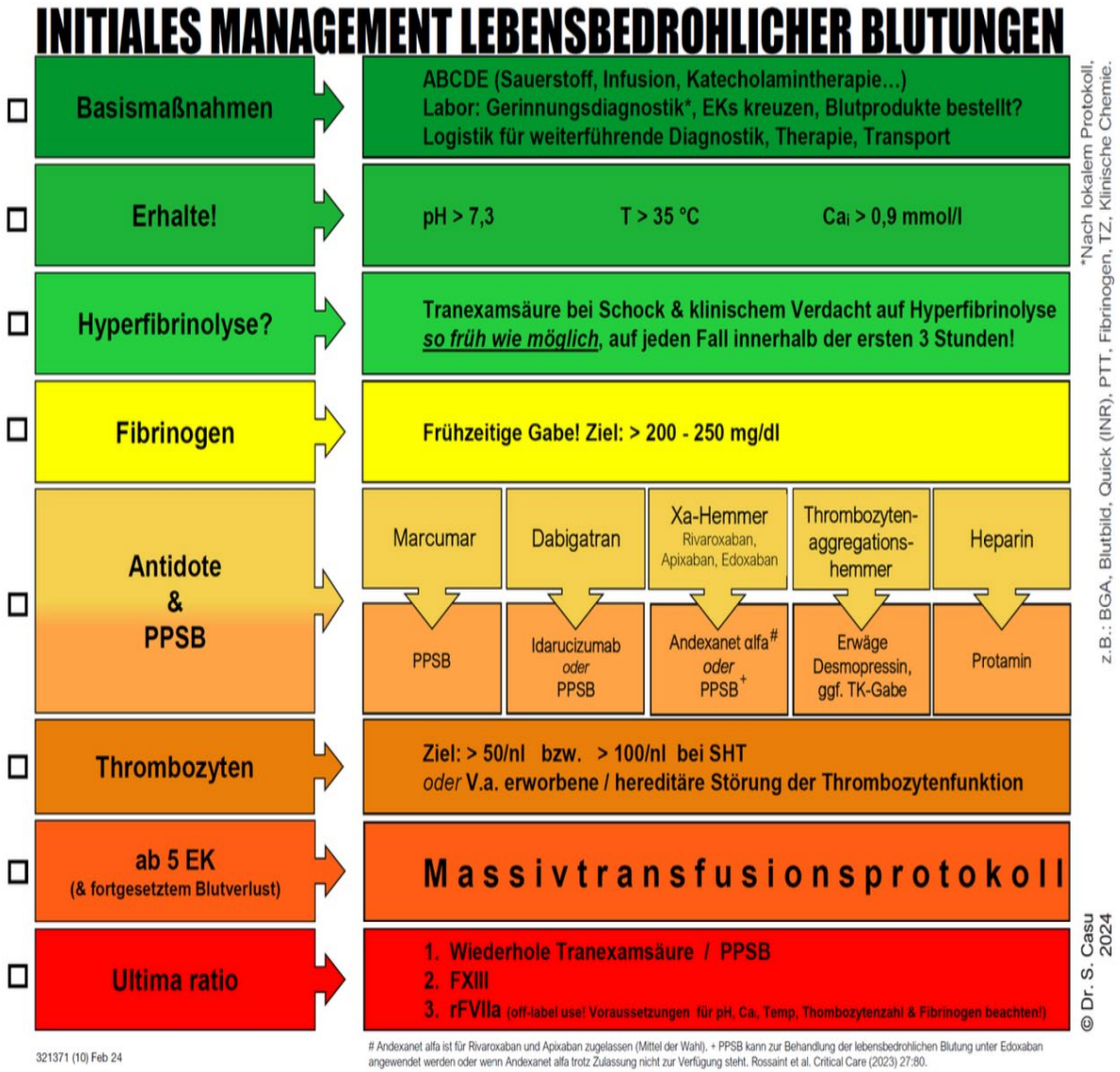


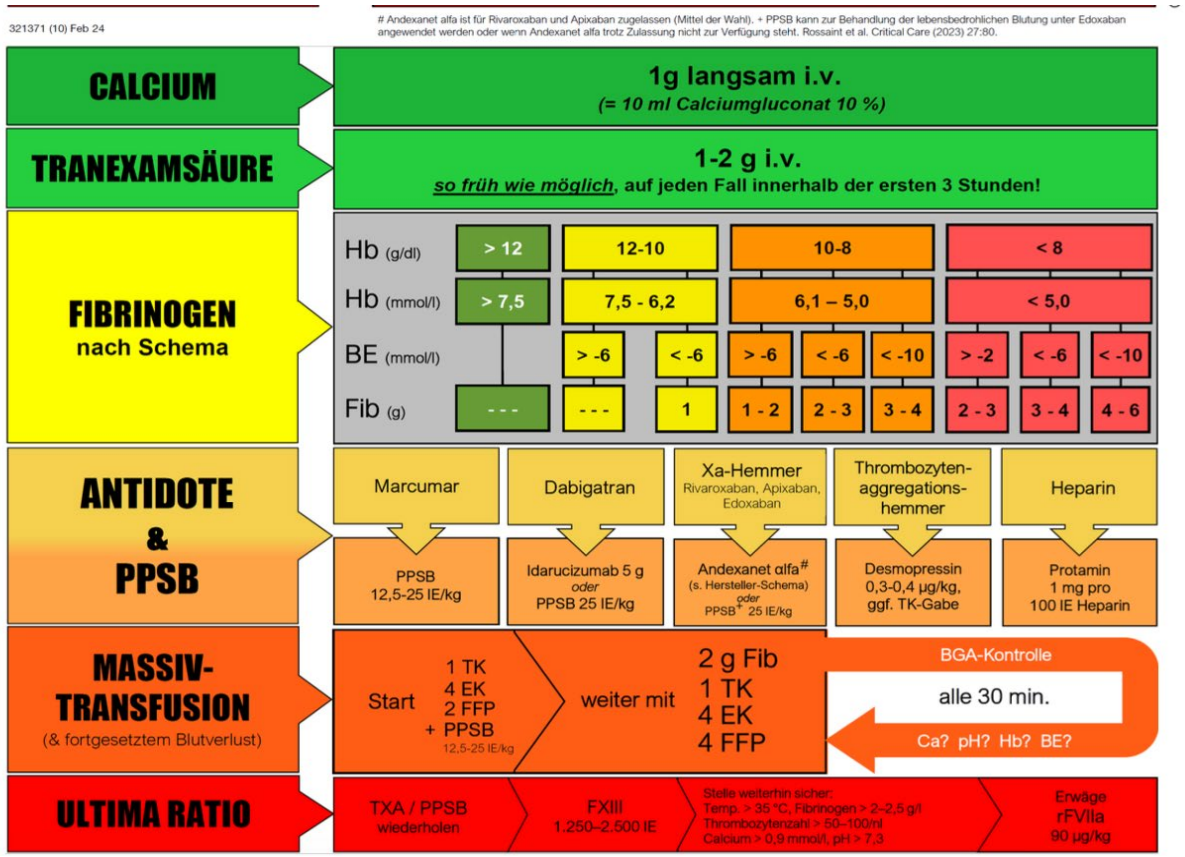
gelbe Linie: „mittlerer“ grenzwertiger Fibrinogenwert mit dazugehörigem Hb-Wert
rote Linie: „mittlerer“ kritischer Fibrinogenwert mit dazugehörigem Hb-Wert
blaue Linie: Fibrinogengrenzwert der aktuellen Leitlinien



gelbe Linie: „mittlerer“ grenzwertiger Quick-Wert mit dazugehörigem Hb-Wert
rote Linie: „mittlerer“ kritischer Quick-Wert mit dazugehörigem Hb-Wert
blaue Linie: ab diesem Quick-Wert ist laut Berliner Polytraumadefinition von einer manifesten Koagulopathie auszugehen

BGA-gesteuert





~~individualisierter Transfusionstrigger~~ BÄK. Querschnittsleitlinie, Gesamtnovelle 2020

~~„personalized, precision medicine“~~ Vigneshwar NG et al. Ann Surg 2022

modifiziert, mit freundlicher Genehmigung von Dr. S. Casu, Hamburg

Ergänzung:
direkte, orale Antikoagulantien (DOAK)?

DOAK
Pharmakokinetik

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)	Phenprocoumon (Marcumar®)
Bioverfügbarkeit:	3-7%	80-100%	50%	~60%	100%
Metabolismus:	~80% renal	~70% renal	~55% fäkal	~50% renal	15% und Metaboliten renal
Proteinbindung:	~35%	~95%	~90%	~55%	~99%
T_{max}:	1,5-3 h	2-3 h	3-4 h	1-2 h	2-3 h
Halbwertszeit:	~13 h	5-13 h	~12 h	~12 h	~6,5 **Tage**
Wechselwirkung	P-Glykoprotein	CYP450-3A4 P-Glykoprotein		P-Glykoprotein	CYP450-2C9 CYP450-3A4

Cave bei DOAK: deutliche inter-individuelle Variabilität bezüglich Pharmakokinetik und -dynamik (genetische Polymorphismen) Raymond J et al. J Pers Med 2021. Deutlich verlängerte Halbwertzeiten v.a. bei Notfallpatienten >70 Jahren Lindhoff-Last E et al. Thromb Haemost 2022.

1.) deutliche interindividuelle Variabilität!!!

	DOAC concentration (ng/ml)					
	Number of samples	Mean (min-max)	CV (%)	Number of samples	Mean (min-max)	CV (%)
	Baseline trough			Baseline peak		
Rivaroxaban 20 mg od	42	43.83 (3–175)	79%	42	298.20 (139–434)	25%
Rivaroxaban 15 mg od	6	50.76 (6–221)	165%	5	253.24 (184–366)	31%
Rivaroxaban 10 mg od	3	14.25 (10–17)	25%	3	171.62 (123–219)	28%
Apixaban 5 mg bid	45	99.92 (20–281)	58%	44	209.30 (71–484)	41%
Apixaban 2.5 mg bid	5	69.38 (27–169)	84%	5	141.29 (86–266)	51%
Dabigatran 150 mg bid	32	89.39 (28–293)	55%	32	214.09 (58–497)	60%
Dabigatran 110 mg bid	19	87.79 (34–213)	60%	19	143.42 (43–286)	46%

CV coefficient of variation

2.) deutliche intraindividuelle Variabilität!!!

	Trough		Peak	
	Number of samples	CV (%)	Number of samples	CV (%)
Rivaroxaban 20 mg od	40	33%	40	17%
Rivaroxaban 15 mg od	5	37%	5	22%
Rivaroxaban 10 mg od	3	92%	3	19%
Apixaban 5 mg bid	43	18%	45	15%
Apixaban 2.5 mg bid	5	21%	5	20%
Dabigatran 150 mg bid	30	18%	30	29%
Dabigatran 110 mg bid	16	23%	16	26%

- follow-up of KIDOAC
- 152 Dutch patients
- switch from VKA to DOAC (51x rivaroxaban, 50x apixaban, 51x dabigatran)
- 73.9 ± 8.4 years
- 63.2% male
- blood sampling on three different days (at day 0, 2 weeks after day 0, and 8 weeks after day 0)

DOAC type and measurement	Number of patients outside range[b] (%)	Outside range ≥2 times (%)
Rivaroxaban, trough levels	36/51 (71%)	18/36 (50%)
Rivaroxaban, peak levels	42/51 (82%)	14/42 (33%)
Apixaban, trough levels	28/50 (56%)	18/28 (64%)
Apixaban, peak levels	35/50 (70%)	18/35 (51%)
Dabigatran, trough levels	29/51 (57%)	16/29 (55%)
Dabigatran, peak levels	33/51 (65%)	15/33 (46%)

[b] 20th and 80th percentile

3.) reichlich Patienten außerhalb des erwarteten Plasmabereiches !!!

Toorop MMA et al. J Thromb Haemost 2022

Bei zeitkritischen Notfallpatienten unter DOAK **immer** Spiegelmessungen!!

Winther-Larsen A et al. Thromb Res 2019
Vandermeulen E et al. Eur J Anaesthesiol 2023
Baker P e al. Br J Haematol 2024

Der Anti-Xa-Spiegel

Messung der Plasmaspiegel von Heparin / -oiden (UFH, LMWH) und Xa-Inhibitoren (**Fondaparinux**, **Rivaroxaban**, **Apixaban**, **Edoxaban**) in der Einheit [IE/ml bzw. ng/ml].

„regulärer" Anti-Xa → auf Heparin geeicht vs. „spezifischer" Anti-Xa→ auf jeweiliges Medikament geeicht

prophylaktisch / „low": 0,1 bis 0,4 IE/ml
therapeutisch / „high": 0,5 bis 1,2 IE/ml

→ unproblematisch:  <0,1 IE/ml und  ≤0,1 IE/ml

Die Thrombinzeit
(TZ, engl.: thrombin time TT)

misst die Umwandlung von Fibrinogen zu Fibrin nach Zugabe von Thrombin (Faktor IIa) zu Citratplasma in der Einheit [**sec**]

Die verdünnte Thrombinzeit
(engl.: diluted thrombin time dTT)

Patientenplasma mit Normalplasma verdünnt (Abzuschwächen der Gerinnungshemmung)

Normwert: 15-35 Sekunden (laborabhängig)

TZ normwertig: kein **Dabigatran**-Effekt auf Gerinnung

TZ deutlich (~10-20-fach) verlängert: therapeutische **Dabigatran**-Konzentration im Plasma

→ TT: qualitative Dabigatran-Bestimmung (ja / nein)

→ dTT: quantitative Dabigatran-Bestimmung (wieviel)

Der DOAK-Plasmaspiegel

✓ <30 ng/ml: unproblematisch

-75 oder -100

⚠ >50 ng/ml (bei starker Blutung): mögliche Indikation zur Antagonisierung

Moster M et al. Curr Anesthesiol Rep 2022; van Es N et al. Eur Heart J 2023

→ gilt für alle DOAK,
aber Datenlage nicht so richtig gut ...

DOAK
Welcher Plasmaspiegel?

Bei der Entscheidung, welcher Plasmaspiegel (50 vs. 75 vs. ≥100 ng/ml) akzeptabel ist, ist von entscheidender Bedeutung, wie eine **mögliche Blutung diagnostizier-** und, vor allem, **therapier-bar** ist!

Kommt der Operateur gut an die Blutung heran?

Ist diese komprimierbar?

Somit ist bei intrakranieller / spinaler / okularer Blutung ganz anders zu entscheiden als bei abdomineller oder muskulärer Blutung.

"watch-and-wait strategy"

Mair A et al. Transfusion 2024

DOAK
Beeinflussung der Wirkung

“replacement”

bei allen DOAK:

PPSB

25-50 IE / kgKG bzw. 2000 IE

nicht zugelassen für DOAK, aber durch Literatur gut abgedeckt

“reversal”

gegen Dabigatran:

Idarucizumab (Praxbind®)

5 g (2 × 2,5 g / 50 ml)

zugelassen für Erwachsene, bei Notfalloperationen / dringenden Eingriffen, bei lebensbedrohlichen bzw. nicht beherrschbaren Blutungen

gegen Xa-Inhibitoren:

Andexanet alfa (Ondexxya®)

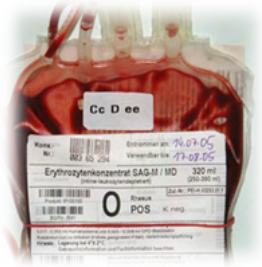
Bolus: 400 bzw. 800 mg [180 ml/h] **plus**
Perfusor: 480 bzw. 960 mg [24-48 ml/h]

zugelassen für Erwachsene, bei lebensbedrohlichen bzw. nicht beherrschbaren Blutungen

Cave: keine Heparinwirkung für ≥24h

Viel gegeben, Alles gut?

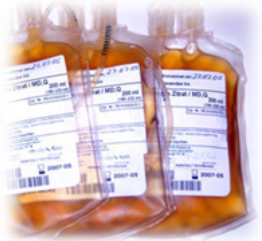
Die Hoffnung und die Theorie!



Erythrozyten

TXA

Fibrinogen

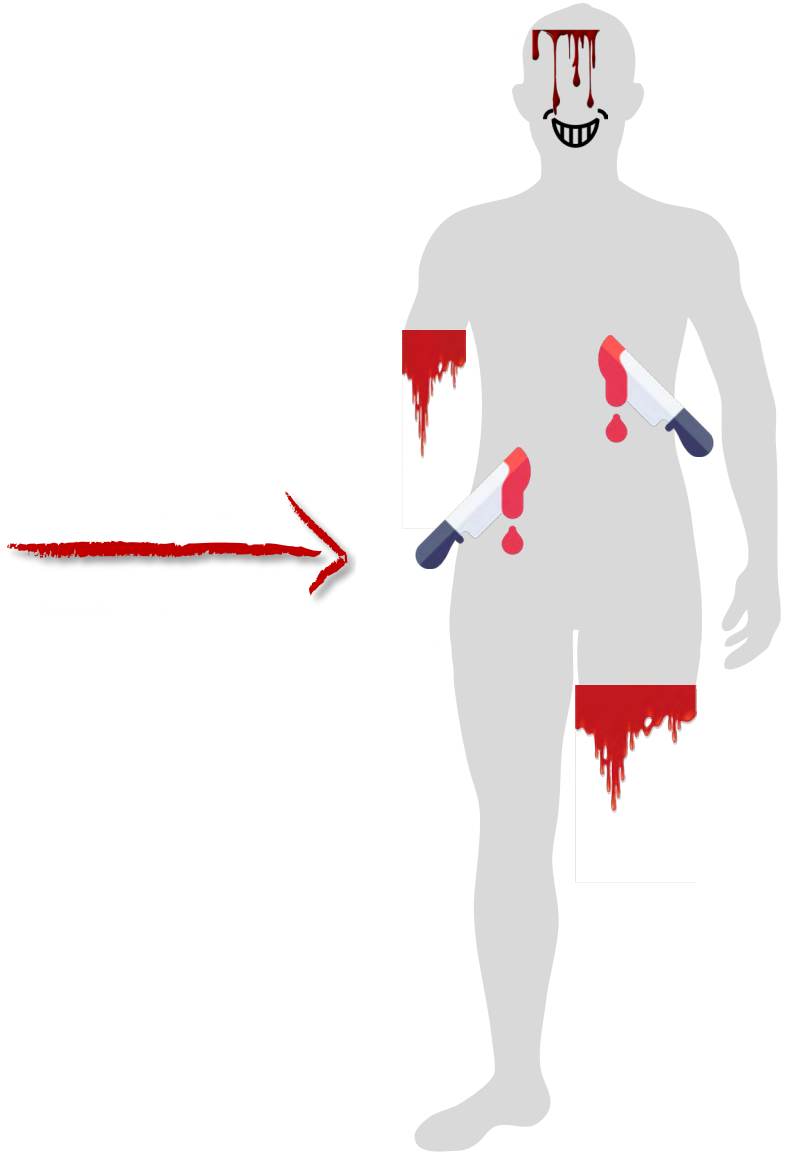


Plasma

PPSB

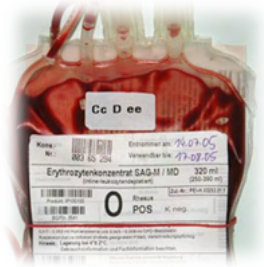
Thrombozyten

FXIII



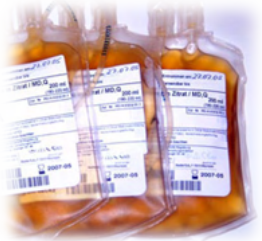
Icons made by https://www.infoDiagram.com/ und https://www.flaticon.com/free-icons

Bei anhaltender / erneuter Blutung fließt (fast) Alles wieder raus!



Erythrozyten

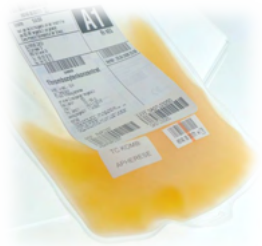
TXA



Plasma

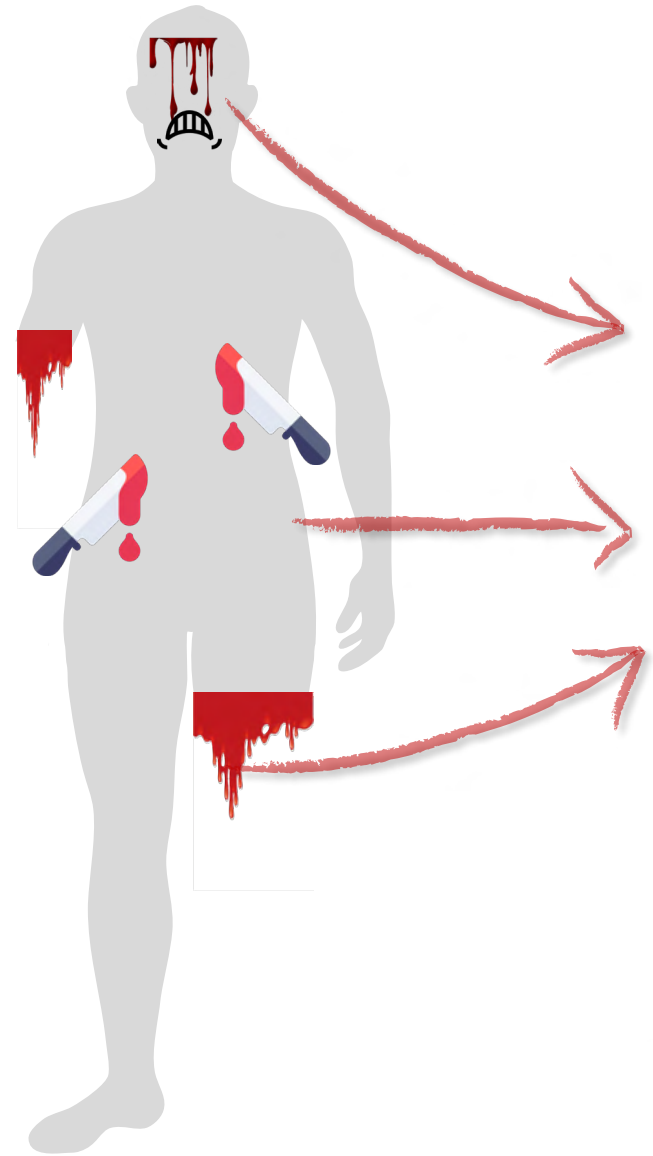
Fibrinogen

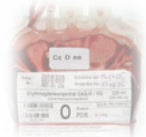
PPSB



Thrombozyten

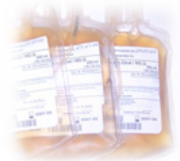
FXIII





Erythrozyten

TXA



Plasma

Fibrinogen

PPSB

Thrombozyten

FXIII

neu / wieder / weiter bluten:
! Blutverlust als Hauptabbauweg der Therapeutika !

Derickson MJ et al. J Trauma Acute Care Surg.2018

Icons made by https://www.infoDiagram.com/ und https://www.flaticon.com/free-icons

Sonst noch was?

Antagonisierung moderner Antithrombotika (GPP)

Cave: Nierenfunktion !!	Zeit bis zur regulären Hämostase nach therapeutischer Dosis (3-5x $t^1/_2$)	Antidot	Bemerkung
Vitamin K-Antagonisten	Phenprocoumon =Marcumar®: 8–10 d Warfarin =Coumadin®: 60–80 h	**Vitamin K** =Konakion® 20 mg i.v. (max. 40 mg/d, Geschwindigkeit etwa 1 mg/min) oder 2-3 mg p.o	Vitamin K =Konakion® i.v.: verzögert wirksam in 12–16 h (Beginn bereits in 2 h) Vitamin K =Konakion® p.o.: verzögert wirksam in 24 h
		PPSB* (initial 25 IE/kg bzw. ($Quick_{Ist}$ - $Quick_{Soll}$) x kg KG)	PPSB i.v. sofort wirksam
Heparin	3–4 h	**Protamin** (25–30 mg): sofort wirksam	1 mg (=100 E) pro 100 anti-Xa -Einheiten, die in den letzten 2–3 h gegeben wurden
LMW Heparine (Certoparin =Mono-Embolex®, Dalteparin =Fragmin®, Enoxaparin =Clexane®, Nadoprarin =Fraxiparin®, Reviparin =Clivarin®, Tinzaparin =Innohep®)	12–24 h	**Protamin** (25–30 mg): sofort partial wirksam	nur partial; 1 mg (=100 E) pro 100 anti-Xa -Einheiten, die in den letzten 8 h gegeben wurden (ggf. 2.Dosis mit 0,5 mg) off-label: **Andexanet alfa** =Ondexxya®
Pentasaccharide / s.c. Xa-Inhibitoren	Fondaparinux =Arixtra® 24–30 h	**probatorisch: rFVIIa** =NovoSeven® (90 µg/kg)	Experimentell off-label: **Andexanet alfa** =Ondexxya®
Orale Xa-Inhibitoren (Rivaroxaban =Xarelto®, Apixaban =Eliquis®) (Edoxaban=Lixiana®)	meist innerhalb von 36 h (→ dann Thromboplastinzeit [TPZ, Quick] normal bzw. fehlender Anti-Xa-Effekt [NMH-Testung])	spezifisches Antidot: **Andexanet alfa** =Ondexxya® (Zulassung nur bei fulminanter Blutung, nicht zur Prophylaxe / Durchführung einer OP; Bolus: 400 bzw. 800 mg [180 ml/h] **plus** Perfusor: 480 bzw. 960 mg [24-48 ml/h]; Rebound nach Absetzen; sehr teuer) **Adjuvantien: DDAVP** =Minirin® (0,3 µg/kg i.v.) **plus Tranexamsäure** (TxA =Cyclokapron®; 1 g oder 15 mg/kg i.v.)**; probatorisch** und bei **Edoxaban: PPSB*** (initial 25(-50) IE/kg i.v. bzw. ($Quick_{Ist}$ - $Quick_{Soll}$) x kg); [ggf. **aktiviertes PPSB** =FEIBA® (50-100 IE/kg i.v.; max. 200 IE/Kg/d) oder **rFVIIa** =NovoSeven® (90-100 µg/kg i.v.)]	**Andexanet alfa** =Ondexxya® bei Edoxaban off-label Aktivkohle (30-50 g) bei Einnahme des Xa-Inhib. <2h experimentell (DDAVP bei erworbenem von Willebrand-Syndrom)
Direkte orale Thrombininhibitoren (Dabigatran =Pradaxa®)	meist innerhalb von 36 h (→ dann Thrombinzeit [TZ] normal bis leicht verlängert)	spezifisches Antidot: **Idarucizumab** =Praxbind®; 2x 2,5 g (Zulassung bei lebensbedrohlichen oder nicht beherrschbaren Blutungskomplikationen sowie bei Notoperationen) **Adjuvantien: DDAVP** =Minirin® (0,3 µg/kg i.v.) **plus Tranexamsäure** (TxA =Cyclokapron®;1 g oder 15 mg/kg i.v.)**; probatorisch: PPSB*** (initial 25(-50) IE/kg i.v., ggf. + 25 IE/kg), [ggf. **aktiviertes PPSB** =FEIBA® (50-100 IE/kg i.v.; max. 200 IE/Kg/d) oder **rFVIIa** =NovoSeven® (90-100 µg/kg i.v.)]	ggf. Dialyse (High-Flux-Filter); Cave: Rebound nach Ende der Dialyse? Aktivkohle (30-50 g) bei Einnahme des IIa-Inhib. <2(-6)h alle experimentell (DDAVP bei erworbenem vonWillebrand-Syndrom)
Aspirin	5–10 d	**DDAVP** =Minirin® (0,3 µg/kg i.v.) und/oder **Thrombozytenkonzentrate** (Ziel: >80.000/µl); wirksam in 15–30 min	abhängig von Klinik
Thienopyridine = ADP-Antagonisten (Clopidogrel =Iscover®=Plavix®, Prasugrel =Efient®)	1–2 d	**Thrombozytenkonzentrate** (Ziel: >80.000/µl), möglichst mit **DDAVP** =Minirin® (0,3 µg/kg i.v.); wirksam in 15–30 min	abhängig von Klinik

modifiziert nach AWMF-S3-LL 187-023 „Polytrauma / Schwerverletztenversorgung“ 2023

Die Thromboseprophylaxe?

Thromboseprophylaxe

2.4.22	**GPP**	Innerhalb von 24 Stunden nach Blutungsstopp soll über Art und Beginn der Thromboseprophylaxe entschieden werden.	bestätigt 2022

gemäß S3-LL: Prophylaxe der venösen Thromboembolie (VTE)

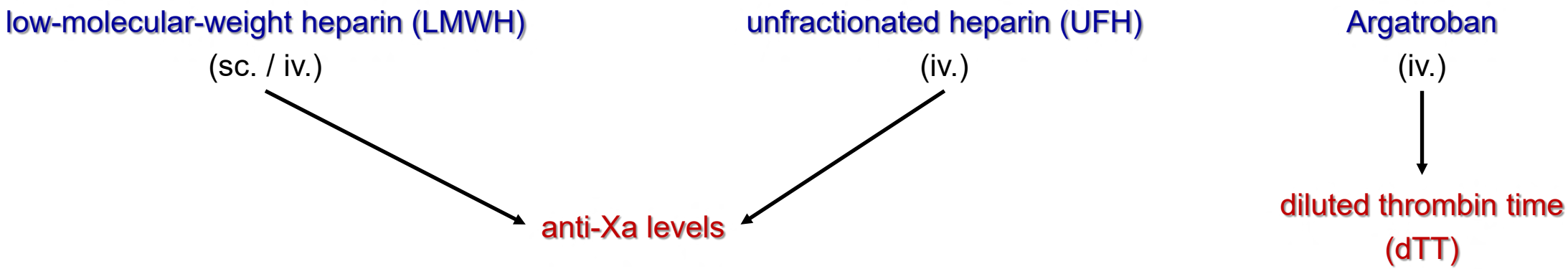
ESAIC 2nd update Kietaibl S et al. EJA 2023 … as early as possible … (R6; **1C**)

European Trauma 6th ed. Rossaint R et al. Crit Care 2023 … within 24 h after bleeding has been controlled … (Rec. 37; **1B**)

Thrombosis prophylaxis following trauma.

Bösch J et al. Curr Opin Anaesthesiol 2024

"In critically ill trauma patients, the monitoring and adjustment of anticoagulant dosages are essential, regardless of whether they are administered subcutaneously or intravenously."



Hemostasis = Love

Everybody talks about it,
nobody understands it.

JH Levy 2000

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