UNIKLINIK KÖLN

Universität zu Köln, Medizinische Fakultät und Uniklinik Köln
Klinik für Anästhesiologie und Operative Intensivmedizin

Gerinnungsmanagement beim Polytrauma

Podcast „pin-up-docs“

30. August 2023

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Interessenskonflikte ?

Bild: https://gracegrapevine.wordpress.com

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Vortragshonorare,
Reisekostenerstattungen o.ä.
erhielt ich von:

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

Die Quellen

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Polytrauma/Schwerverletzten-Behandlung

S3-Leitlinie

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und

Deutsche Arbeitsgemeinschaft Krankenhaus-Einsatzplanung (DAKEP)
Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen e.V. (DGPRÄC)
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Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie e.V. (DGMKG)
Sektion Pflege der Deutsche Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin e.V. (DIVI)

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Critical Care

Online veröffentlicht am 09. März 2023

GUIDELINES **Open Access**

Check for updates

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

Rolf Rossaint[1*], Arash Afshari[2], Bertil Bouillon[3], Vladimir Cerny[4,5], Diana Cimpoesu[6], Nicola Curry[7,8], Jacques Duranteau[9], Daniela Filipescu[10], Oliver Grottke[1], Lars Grønlykke[11], Anatole Harrois[9], Beverley J. Hunt[12], Alexander Kaserer[13], Radko Komadina[14], Mikkel Herold Madsen[2], Marc Maegele[15], Lidia Mora[16], Louis Riddez[17], Carolina S. Romero[18], Charles-Marc Samama[19], Jean-Louis Vincent[20], Sebastian Wiberg[11] and Donat R. Spahn[13]

Klassifizierung von Leitlinien

Leitlinien der Mitgliedsgesellschaften der AWMF werden in drei, auf die Entwicklungsmethodik bezogene Klassen eingeteilt:

S1: von einer Expertengruppe im informellen Konsens erarbeitet (Ergebnis: Empfehlungen)

S2: eine formale Konsensfindung ("S2k") und / oder eine formale "Evidenz"-Recherche ("S2e") hat stattgefunden

Polytrauma

S3: Leitlinie mit allen Elementen einer systematischen Entwicklung (Logik-, Entscheidungs- und "outcome"-Analyse)

Einteilung der Empfehlungsgrade (**Grade of Recommendation, GoR**) gemäß Leitlinienhandbuch der AWMF

Empfehlungsgrad	Beschreibung	Formulierung
A	starke Empfehlung	soll / soll nicht
B	Empfehlung	sollte / sollte nicht
0	Empfehlung offen	kann erwogen werden / kann verzichtet werden

1. Prähospitale Phase

1.1 Stop the Bleed (STB) – Prähospital

1.3 „Gerinnungsmanagement und Volumentherapie“

2. Schockraum-Phase

2.4 „Gerinnungsmanagement und Volumentherapie“

Team des Kapitel 2.4

2. Schockraum-Phase

2.4 „Gerinnungsmanagement und Volumentherapie“

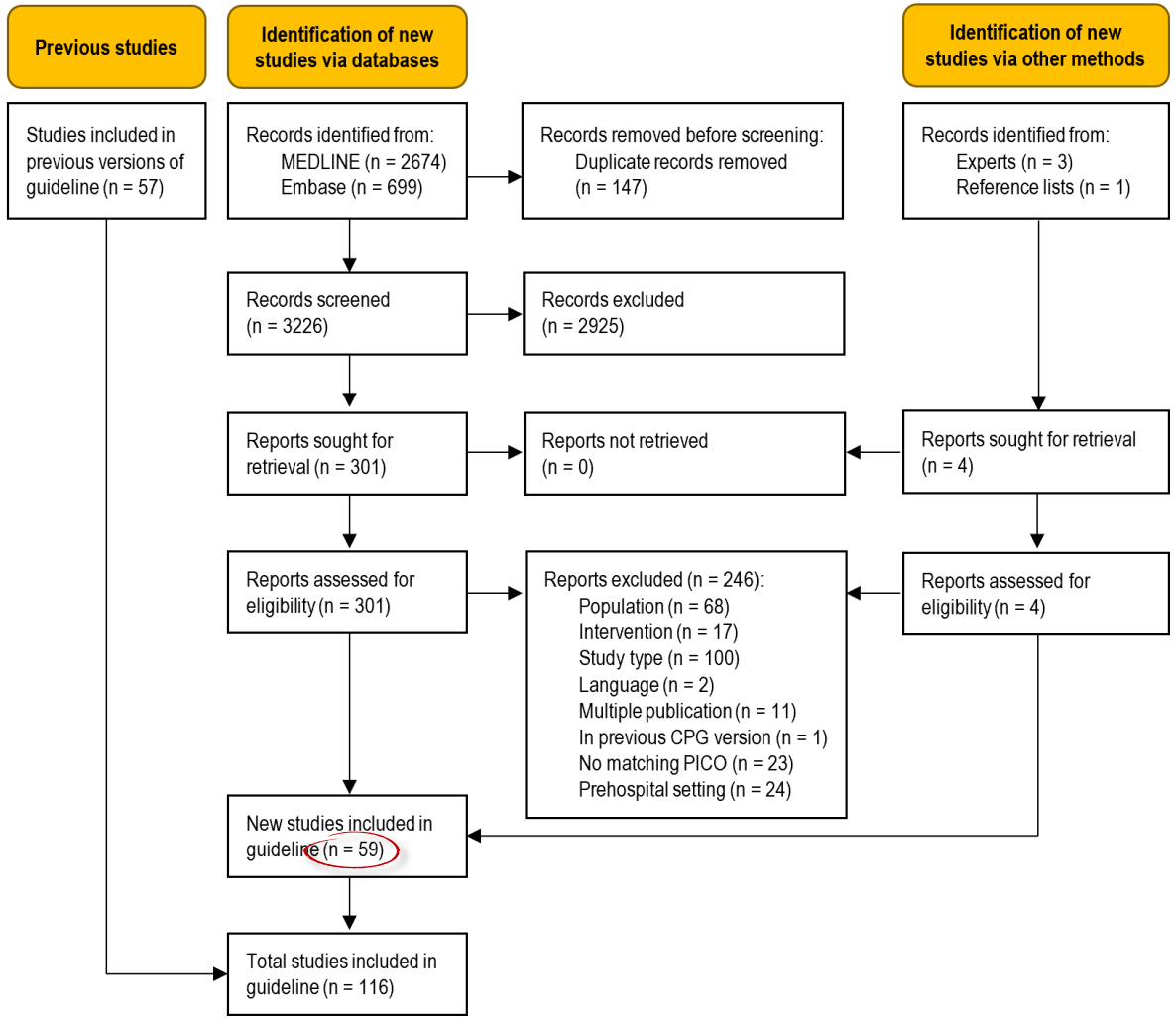
prähospital (1.3): gleicher Titel, anderes Team

Institut für Forschung in der Operativen Medizin (**IFOM**)	• Dr. Käthe **Gooßen** • Charlotte **Kugler**

Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (**DGAI**)	• PD Dr. Peter **Hilbert-Carius**, BG Klinikum Bergmannstrost Halle • Dr. Heiko **Lier**, Uniklinik Köln (*Kapitelverantwortlicher*)
Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (**DGTI**)	• Prof. Dr. Erwin **Strasser**, LMU München
Deutsche Gesellschaft für Unfallchirurgie (**DGU**)	• PD Dr. Björn **Hußmann**, Alfried Krupp Krankenhaus, Essen • Prof. Dr. Marc **Maegele**, Krankenhaus Köln-Merheim

systematische Recherche durch IFOM

Modified PRISMA 2020 flow diagram showing the systematic literature search and selection of studies



⇒ Für Kapitel 2.4 "Gerinnungsmanagement und Volumentherapie" fanden sich (seit 2016) **59** Studien (in Medline und Embase mit Deadline: 07. Mai 2021). (inkl. 1 für Ultraschall bei ZVK)

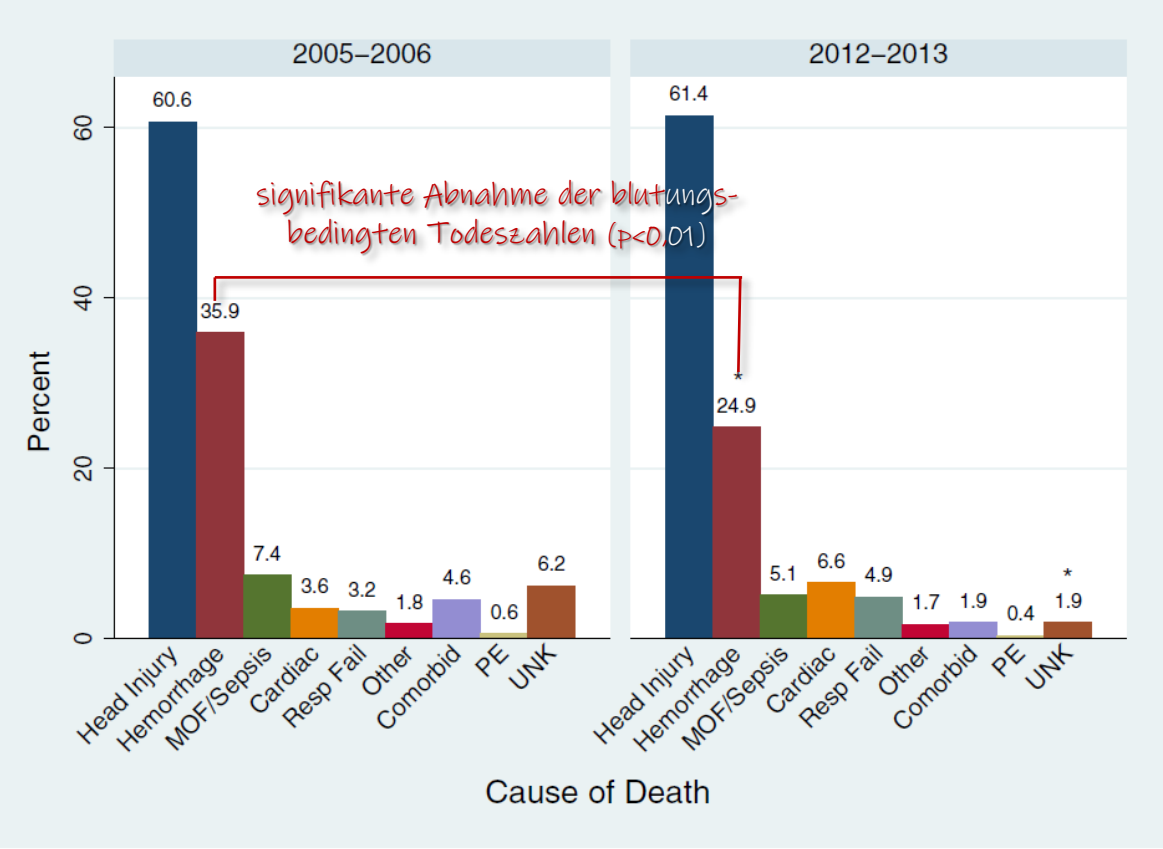
Frage:

Die Problematik?

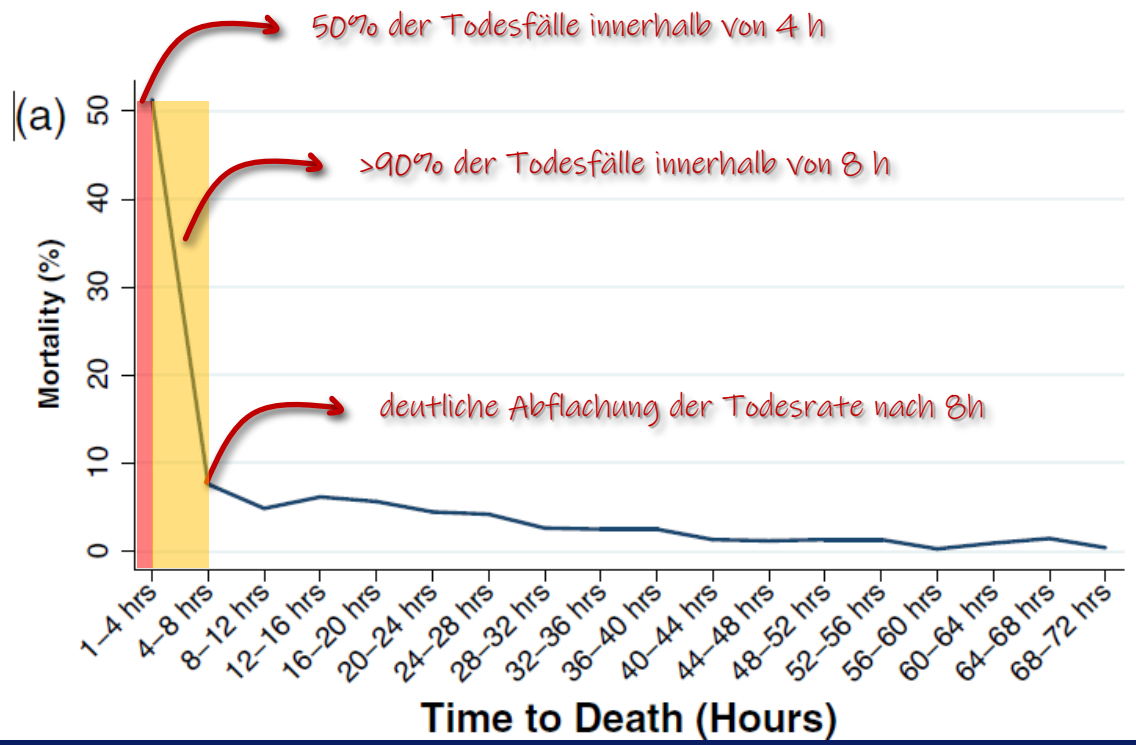
Trends in 1029 trauma deaths at a level 1 trauma center: Impact of a bleeding control bundle of care.

Oyeniyi BT et al. Injury 2017

Memorial Hermann Hospital in Houston, TX; 7080 patients (498 deaths) were examined in 2005–2006, while 8767 patients (531 deaths) were reviewed in 2012–2013; median age increased 6 years;



traumatic brain injury (TBI) and hemorrhage accounted for >91% of all deaths



“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

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** …"

Frage:

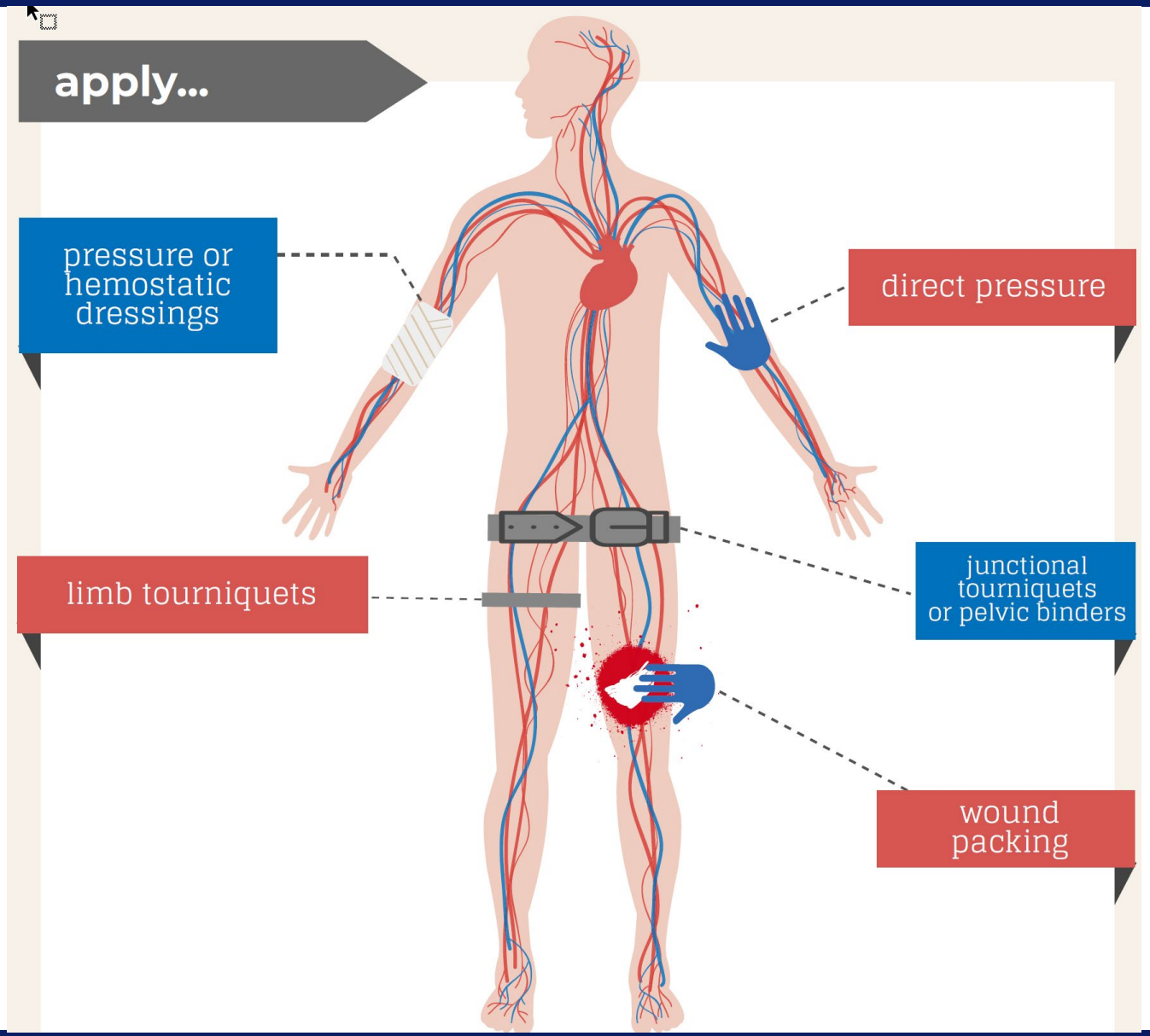
Basismaßnahmen?

externe Blutstillung

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

Joint Trauma System

Clinical Practice Guidelines



https://jts.amedd.army.mil/assets/docs/damage_control/SHORT_DCR_4.pdf

Stufenschema bei aktiven Blutungen

1.1.5	GoR **A** ⇑⇑	Aktive Blutungen der Extremitäten sollen durch folgendes Stufenschema behandelt werden: 1) Manuelle Kompression 2) Kompressionsverband, wenn möglich in Kombination mit einem Hämostyptikum 3) Tourniquet.	modifiziert 2022

Henry R et al. Increased Use of Prehospital Tourniquet and Patient Survival: Los Angeles Countywide Study. J Am Coll Surg 2021 **IFOM-Evidenzgrad 2b**
Taghavi S et al. An Eastern Association for the Surgery of Trauma multicenter trial examining prehospital procedures in penetrating trauma patients. J Trauma Acute Care Surg 2021 **IFOM-Evidenzgrad 2b**
Clasper JC et al. Limb complications following pre-hospital tourniquet use. J R Army Med Corps 2009 **FOM-Evidenzgrad 3b↓**

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**)

externe Blutstillung: präklinische Hämostyptika

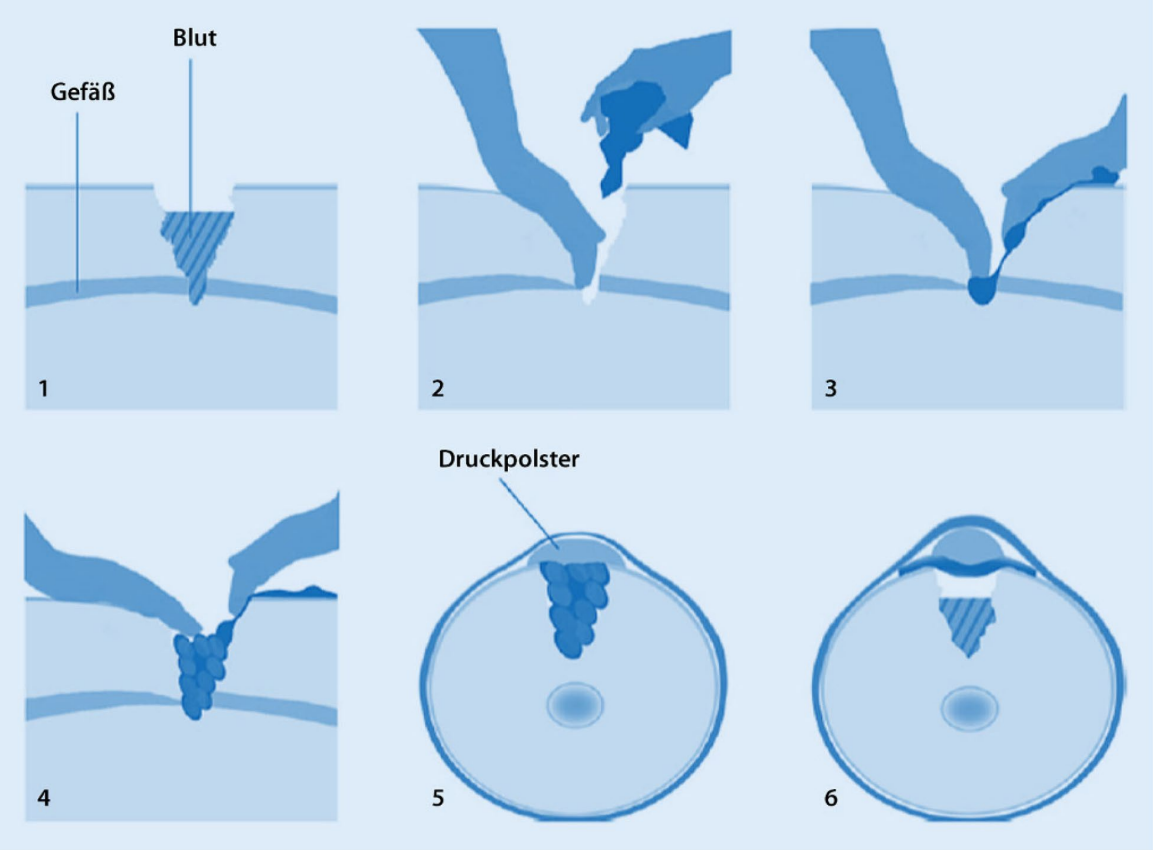
Produkt	Applikation	Wirkung	Nebenwirkung
Zeolith			
QuikClot® (Z-Medica, Wallingford, CT, USA)	Granulat (mikroporöse, kristalline Aluminosilikate aus vulkanischem Gestein)	Konzentration von zellulären Blutbestandteilen wie Thrombozyten und Gerinnungsfaktoren am Ort der Blutung durch Flüssigkeitsresorption Beschleunigung der Gerinnungskaskade durch negative Oberflächenladung des Granulats	exotherme Reaktion (42–140°C)
QuikClot ACS® (Z-Medica Corporation, Wallingford, C,T USA	Granulat in Säckchen verpackt	siehe QuikClot®	
QuikClot ACS+® (Z-Medica Corporation, Wallingford, CT, USA			weniger exotherm als QuikClot®
Kaolin			
Combat Gauze® (Z-Medica Corporation Wallingford, CT, USA)	Verband	Aluminiumsilikat wirkt als Aktivator und Beschleuniger der intrinsischen Blutgerinnungskaskade, selbst bei koagulopathischen und azidotischen Modellen	leichte Endothelschwellung
Chitosan			
Celox® (MedTrade Products Ltd, Cheshire, UK)	Pulver	inertes Polyaminosaccharid aus Chitin; Bildung gelähnlicher Plaque, dann Vasokonstriktion (Auswaschung von NO) und eine schnelle Bereitstellung von Erythrozyten, Thrombozyten und Gerinnungsfaktoren. Verstärkt zudem die Thrombozytenadhäsion und -aggregation am geschädigten Gewebe	Verbringung in den Wundgrund durch Pulverform erschwert
Celox Rapid Gauze® (MedTrade Products Ltd, Cheshire, UK)	Verband mit Celox beschichtet	beste Wirksamkeit; Tamponade/Packing möglich	keine bekannt
ChitoSAM® (SAM Medical Products, Wilsonville, OR, USA)	Wundauflage	besonders weiche Wundauflage aus 100% Chitosan bestehend	
ChitoGauze XRpro® (HemCon Medical Technologies Inc., Portland, OR, USA)	mit Chitosan imprägnierter Wundverband	weich mit Röntgenkontraststreifen	
Zellulose			
z.B. **WoundClot**® (Core Scientific Creations, Westlake Village, California, USA)	Verbandsmull	absorbiert bei Kontakt mit Blut die Flüssigkeit und wird zu einer gallertigen Masse, welche die Viskosität des Blutes erhöht, die Gerinnungsfaktoren aktiviert und sich an die Wundhöhle anpasst	keine bekannt

wirkt auch bei antikoaguliertem Blut




modifiziert nach Lier H et al. Anästhesist 2017 und Josse F et al. AINS 2020

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

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

We *recommend* local compression of open wounds to limit life-threatening bleeding.

(Rec. 2; **1B**)

"Most life-threatening bleeding from open injuries to extremities observed in the civilian setting can be controlled by local compression, either by manual compression or pressure bandages applied to the wounds."

We *recommend* adjunct tourniquet use to stop life-threatening bleeding from open extremity injuries in the pre-surgical setting.

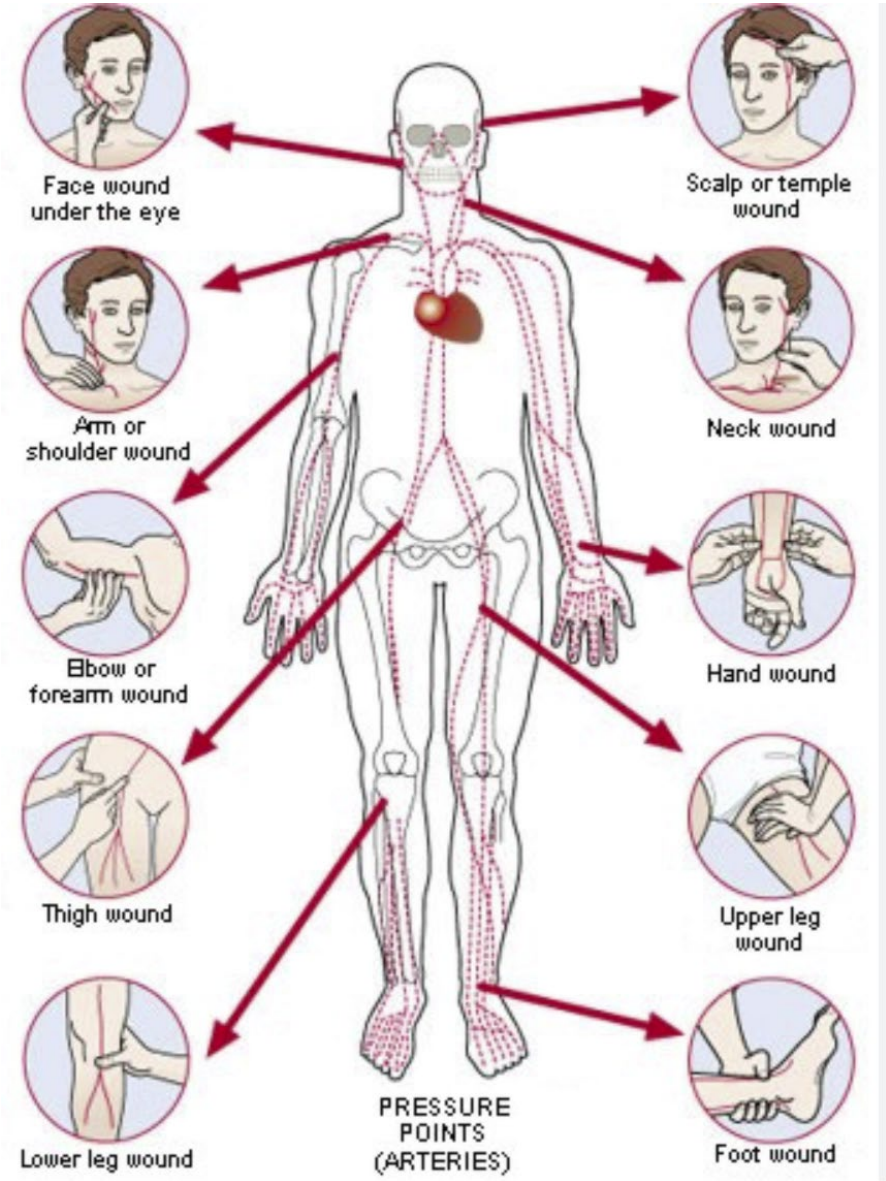
(Rec. 2; **1B**)

"In mangled extremity injuries, penetrating or blast injuries, traumatic amputations and sometimes in more limited extremity injuries, the application of a tourniquet is necessary to achieve complete bleeding control."

We *recommend* the use of topical haemostatic agents in combination with other surgical measures or with packing for venous or moderate arterial bleeding associated with parenchymal injuries.

(Rec. 22; **1B**)

Abdrückpunkte

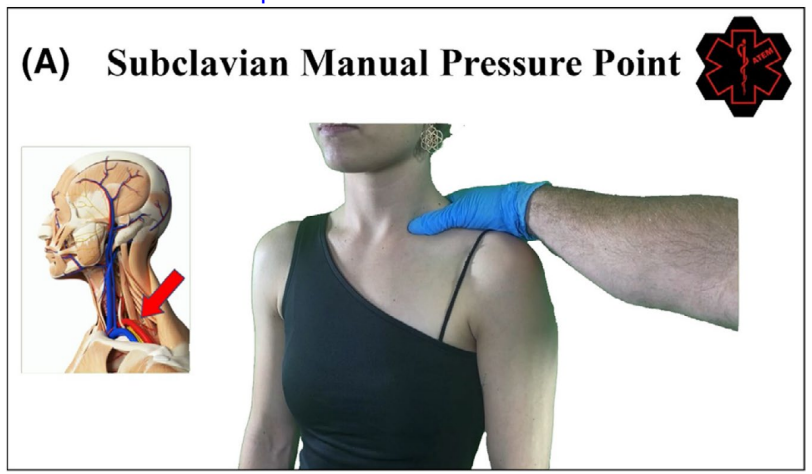


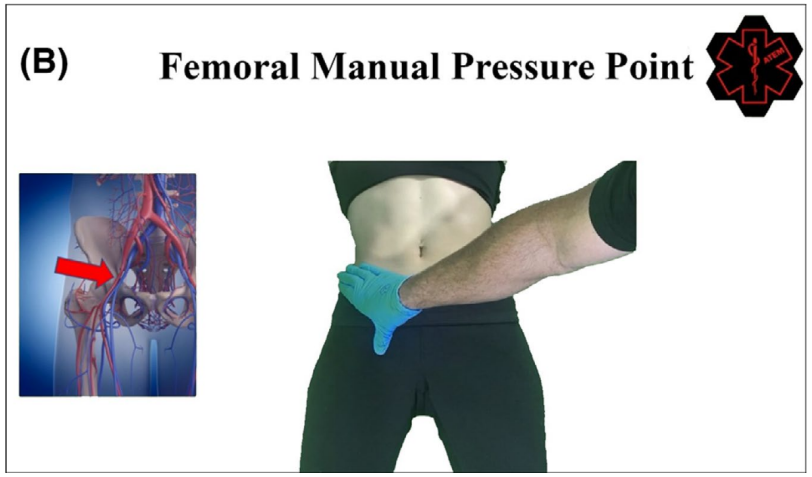
U.S. Navy Training Manual 14191

Abdrückpunkte am Stamm

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

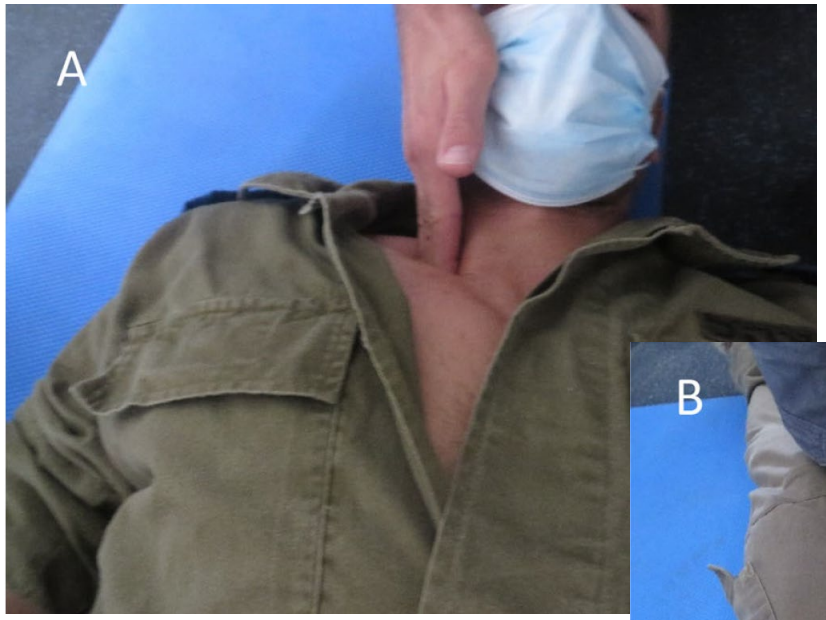
Thompson P et al. Transfusion 2023





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

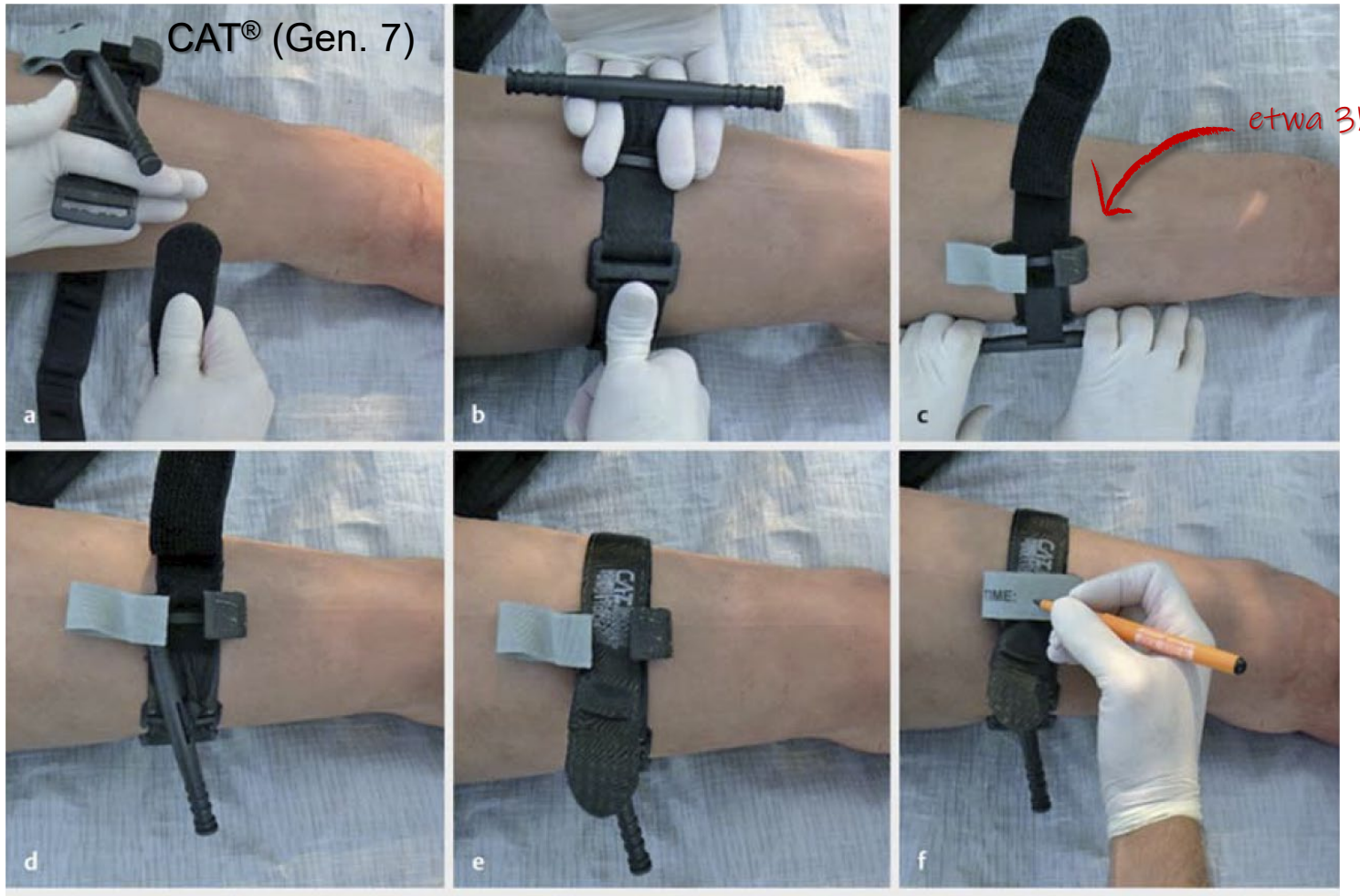
- femoral artery pulse at the femoral crease
- thigh in slight external rotation
- pressure posteriorly using either the metacarpo-phalangeal or the proximal interphalangeal joints against the pelvic bone

externe Blutstillung
Tourniquet

Wissenschaftlicher Arbeitskreis Notfallmedizin
Arbeitsgruppe „Taktische Medizin"

Prähospitale Strategien zur Minimierung des Blutverlustes.

Josse F et al. Anästh Intensivmed 2020



etwa 3¼ Knebelumdrehungen

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**

Frage:

Vorhersagbarkeit?

Schockindex und Überleben

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

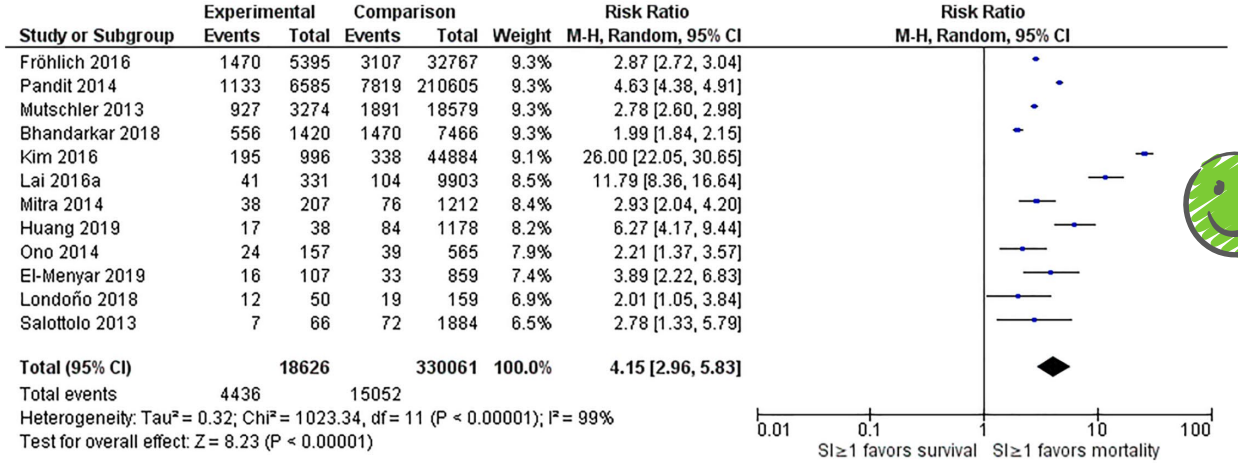
Shock index as a predictor for mortality in trauma patients: a systematic review and meta-analysis

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 …"

Frage:

Die Trauma-Induzierte Koagulopathie?

TIK ist ein komplexes aber eigenständiges Krankheitsbild

"The majority of deaths from traumatic hemorrhage occur within the first three hours of injury."
Tucker H et al. Crit Care 2023

2.4.1	GoR **A** ⇑⇑	Die Trauma-induzierte Koagulopathie ist ein eigenständiges Krankheitsbild mit deutlichem Einfluss auf das Überleben. Aus diesem Grund sollen Gerinnungsdiagnostik und -therapie spätestens im Schockraum ~~begonnen~~ *eingeleitet* werden.	modifiziert 2022
2.4.2	GoR **A** ⇑⇑	Zur Basisdiagnostik von *blutenden* Schwerverletzten sollen frühzeitige und wiederholte Messungen von BGA, Quick (Prothrombinzeit), aPTT, Fibrinogen und Thrombozytenzahl sowie eine Blutgruppenbestimmung erfolgen.	modifiziert 2022

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

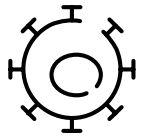
We *recommend* the use of repeated Hb and/or Hct measurements as a laboratory marker for bleeding, as an initial value in the normal range may mask early-phase bleeding.
(Rec. 9; **1B**)

We *recommend* the early and repeated monitoring of haemostasis, using either a traditional laboratory determination such as prothrombin time (PT)/international normalised ratio (INR), Clauss fibrinogen level and platelet count and/or point-of-care (POC) PT/INR and/or a viscoelastic method.
(Rec. 11; **1C**)

Gleichwertigkeit von Standardlabor und POC INR und VET ???

We *recommend* that monitoring and measures to support coagulation be initiated immediately upon hospital admission.
(Rec. 24; **1B**)

Definition

Hemmkörper  Medikamente  oder andere Ursachen 

Koagulopathie

= Störung des „Organsystems Gerinnung“

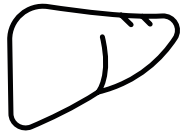
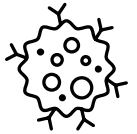
INR >1,5* häufig als Hinweis genutzt, aber nicht „evidence-based“

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

Gewebe-hypoxie
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.

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

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

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

Frage:

Die Rahmenbedingungen?

beachte: Temperatur, pH & Ca^{2+}

2.4.8	GoR **B⇑**	Die Auskühlung des Patienten sollte mit geeigneten Maßnahmen vermieden und Normothermie angestrebt werden.	geprüft 2022
2.4.9	GoR **B⇑**	~~Eine Azidämie sollte vermieden und durch eine geeignete Schocktherapie behandelt werden~~ *Durch eine geeignete und frühzeitige Schocktherapie sollte eine Azidämie vermieden werden*.	modifiziert 2022
2.4.10	GoR **B⇑**	Eine Hypokalzämie < 0,9 mmol/l sollte vermieden und eine Normokalzämie angestrebt werden.	geprüft 2022

(1.3.9; GPP):

1. Vermeidung der weiteren Auskühlung des Patienten (Ziel: Normothermie),
2. geeignete Therapie des hämorrhagischen Schocks(Blutungskontrolle, Volumen- und Gerinnungstherapie) und
3. adäquate Oxygenierung und Ventilation

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

We *recommend* early application of measures to reduce heat loss and warm the hypothermic patient to achieve and maintain normothermia.

(Rec. 18; **1C**)

We *recommend* that ionised calcium levels be monitored and maintained within the normal range following major trauma and especially during massive transfusion.

(Rec. 31; **1C**)

"Acute hypocalcaemia is both a common finding in trauma patients and frequently complicates MT … hypocalcaemia, with ionised Ca^{2+} levels below 0.9 mmol/L or serum total corrected calcium levels of 7.5 mg/dL or lower, should be corrected promptly, …"

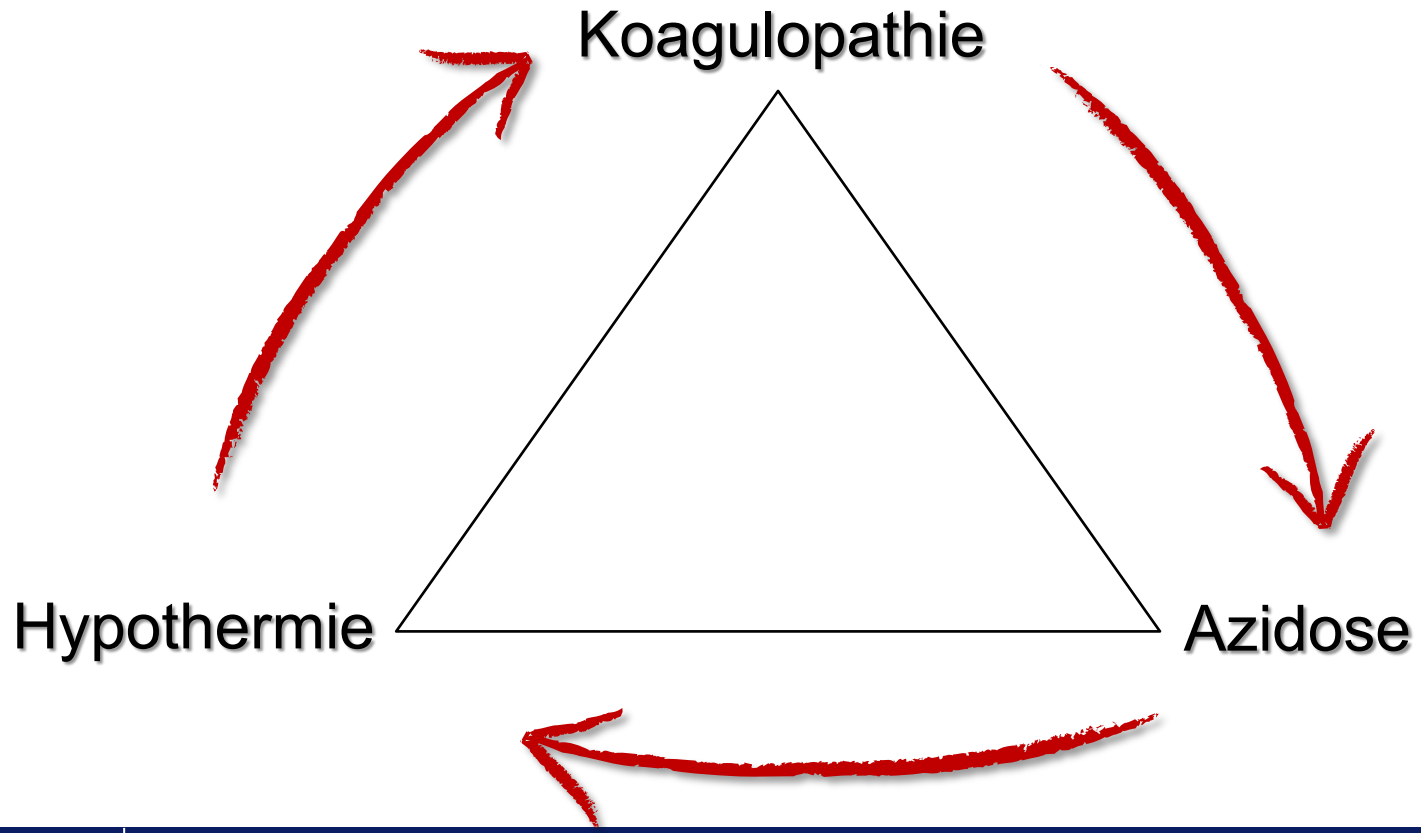
Rahmenbedingungen der Gerinnung
Azidose + Hypothermie

"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



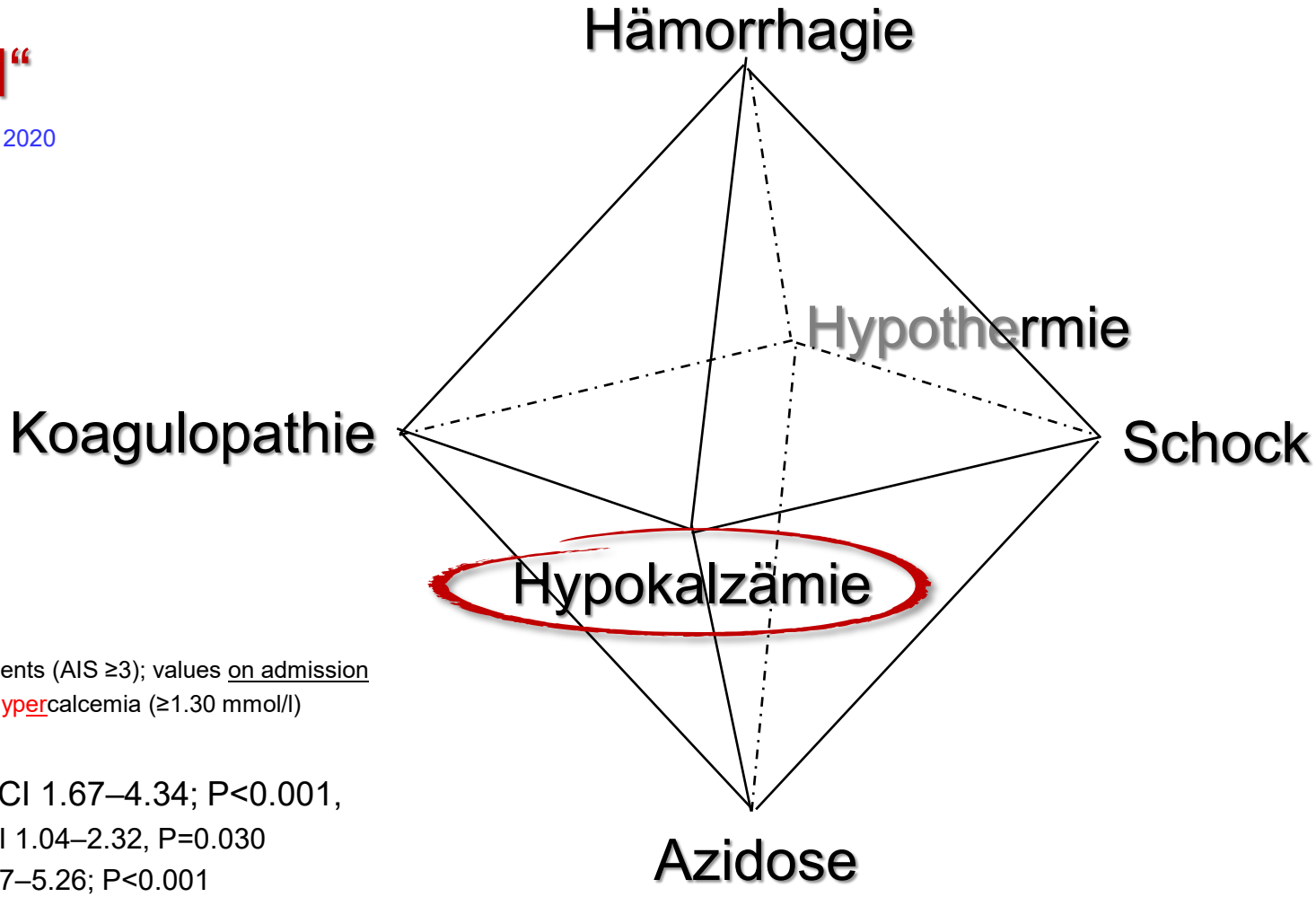
"bloody vicious cycle of hemorrhagic shock"

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



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)

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

Helsloot D et al. Crit Care 2023

European Trauma, 6th edition 2023
blood lactate and base deficit

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

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) Surbeck D et al. Arch Gynecol Obstet 2019
[2] Cave bei erhöhtem Blutalkohol Gustafson ML et al. Am J Emerg Med 2015

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

in Notaufnahme

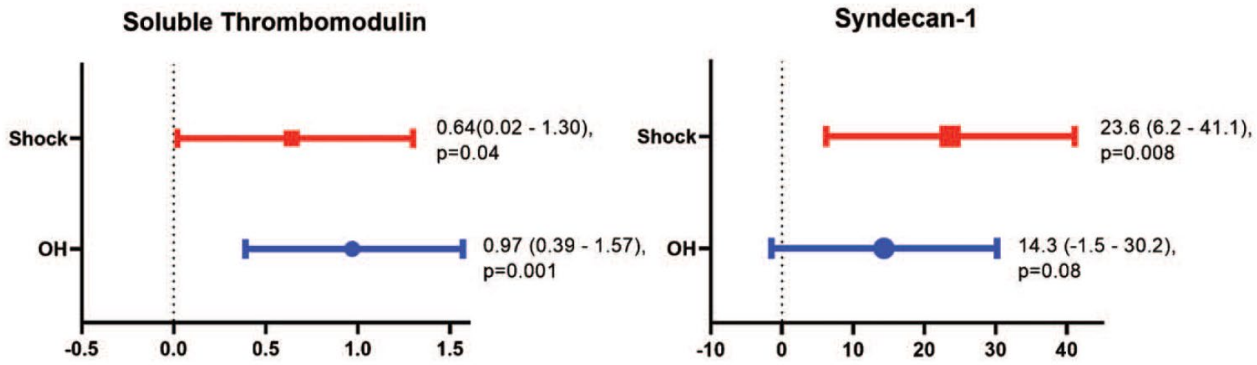
Shock-Induced Endothelial Dysfunction is Present in Patients With Occult Hypoperfusion After Trauma.

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 !!

Frage:

„damage control“
und
„permissive Hypotonie“?

„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

Überlebensvorteil durch permissive Hypotonie

gleiche Zielwerte, „reduzierte" Volumentherapie (1.3.1, GoR B); Vasopressoren titrierend (1.3.6; GPP)

2.4.4	GoR **B⇑**	Bei Patienten, die aktiv bluten, sollte bis zur chirurgischen Blutstillung eine permissive Hypotension (mittlerer arterieller Druck *[MAP]* ~ 65 mmHg, systolischer arterieller Druck ~ 80 mmHg) angestrebt werden.	modifiziert 2022
2.4.5	GoR **B⇑**	*Bei Patienten (ohne kardio-pulmonale Vorerkrankungen) im hämorrhagischen Schock sollte prä-, intra- und früh (3-6 h) -postoperativ eine Flüssigkeitstherapie mit einem Ziel-MAP ~ 65 mmHg erfolgen.* (1)	neu 2022
2.4.6	GoR **B⇑**	Bei der Kombination von hämorrhagischem Schock und Schädel-Hirn-Trauma (GCS < 9) und/oder spinalem Trauma mit neurologischer Symptomatik sollte ~~der~~ *ein* MAP von ~ 85 mmHg ~~betragen~~ *angestrebt werden*.	modifiziert 2022
2.4.7	GoR **A⇑⇑**	*Das Ausmaß und d*ie Behandlung des Schocks soll durch wiederholte Messung von Laktat und/oder Basenüberschuss *überprüft und* gesteuert werden.	modifiziert 2022

bei isoliertem / führenden SHT: RRsys ≥90 mmHg (1.3.2; GoR B)

(1) Gu X et al. Restricted fluid resuscitation improves the prognosis of patients with traumatic hemorrhagic shock. Int J Clin Exp Med 2020;13(7):5319-5327 **IFOM-Evidenzgrad: 1b**
Lu Y et al. Controlled blood pressure elevation and limited fluid resuscitation in the treatment of multiple injuries in combination with shock. Pak J Med Sci 2018;34(5):1120-1124 **IFOM-Evidenzgrad: 1b**

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

In the initial phase following trauma, we *recommend* the use of a restricted volume replacement strategy with a target systolic blood pressure of 80–90 mmHg (mean arterial pressure 50–60 mmHg) until major bleeding has been stopped without clinical evidence of brain injury.
(Rec. 13; **1B**)

dt. S3-LL 2023: MAP ~65 mmHg (Rec. 2.4.4 + 2.4.5)

In patients with severe TBI (GCS ≤ 8), we *recommend* that a mean arterial pressure ≥ 80 mmHg be maintained.
(Rec. 13; **1C**)

dt. S3-LL 2023: MAP ~85 mmHg (Rec. 2.4.6)

prehospital: SBP target ≥110 to <150 mmHg
Lulla A et al. Prehosp Emerg Care 2023

"… the currently available data should be interpreted with caution …"

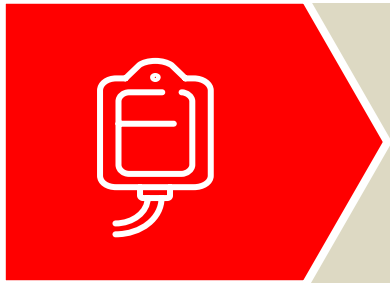
…, we *recommend* … administration of noradrenaline in addition to fluids to maintain target arterial pressure.
(Rec. 14; **1C**)

"… a strategy of restricted volume replacement and permissive hypotension … if these measures fail to achieve the target blood pressure …, transient noradrenaline is recommended to maintain life and tissue perfusion."

We *recommend* … dobutamine in the presence of myocardial dysfunction.
(Rec. 14; **1C**)

„damage control resuscitation“

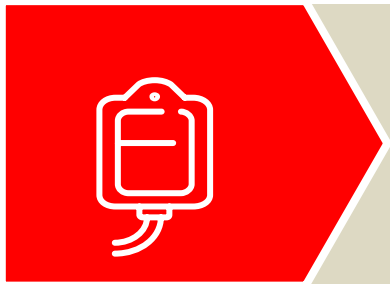
Welches Volumenersatzmittel ?



(isotone) kristalline Lösungen

initiale Flüssigkeitstherapie

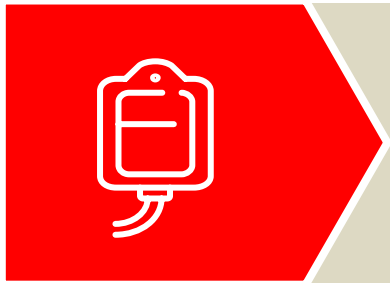
S3-LL „Polytrauma“ 2023: GoR A („soll“; Text der Empfehlg. 1.3.7);
6. ET 2023: („0.9% sodium chloride [“limited to a maximum of 1-1.5L”] or balanced crystalloid“) **1B** (Recom. 15);
ESAIC 2023: 1B (Recom.15)



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)

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



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

2018:

Risks and benefits of hypotensive resuscitation in patients with traumatic hemorrhagic shock: a meta-analysis.

Owattanapanich N et al. Scand J Trauma Resusc Emerg Med 2018

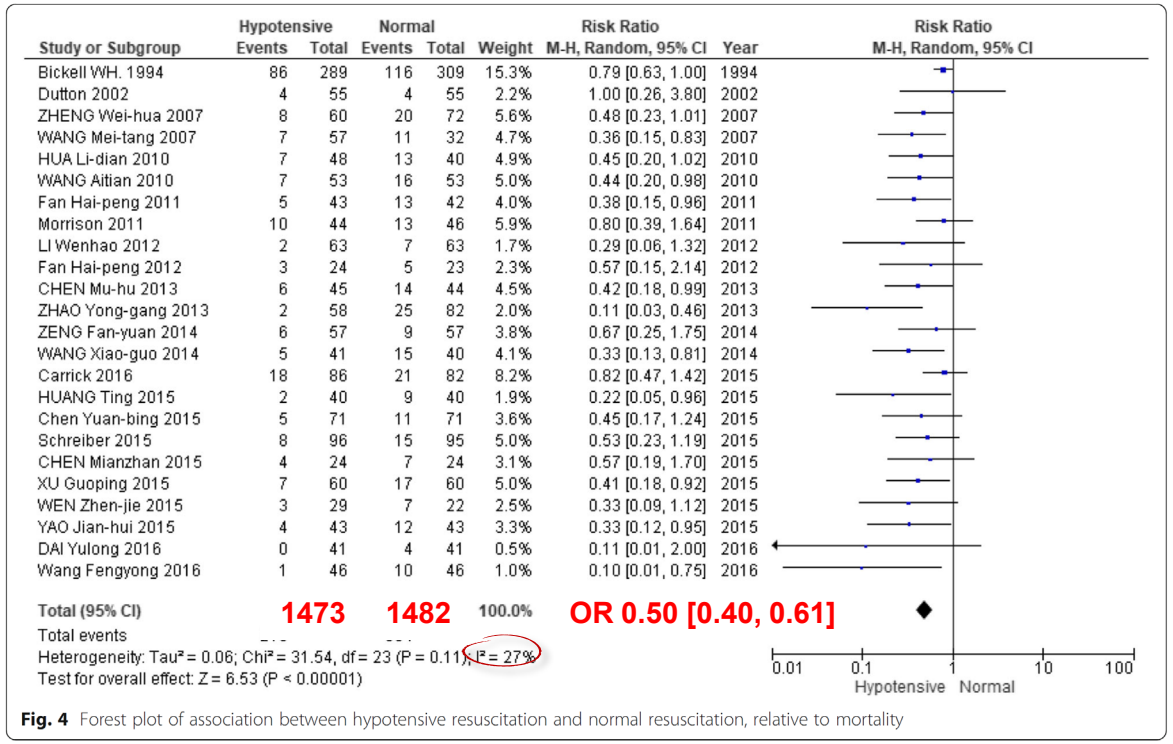


Fig. 4 Forest plot of association between hypotensive resuscitation and normal resuscitation, relative to mortality

Conclusion: This meta-analysis revealed **significant benefits of hypotensive resuscitation** relative to mortality in traumatic hemorrhagic shock patients. It not only reduced the need for blood transfusions and the incidences of ARDS and multiple organ dysfunction, but it caused a non-significant AKI incidence.

significant decrease in mortality
(risk ratio [RR]: 0.50; 95% confidence interval [CI]: 0.40–0.61).

permissive Hypotension

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?

Überlebensvorteil durch permissive Hypotonie

2018: Controlled blood pressure elevation and limited fluid resuscitation in the treatment of multiple injuries in combination with shock.

IFOM-2021/22: Evidenzgrad 1b

Lu Y et al. Pak J Med Sci 2018

Binzhou, Shandong Province, China; prospective study; 164 patients with severe multi-injury induced shock admitted to the ICU; **control** group (n=82): MAP 60-80 mmHg vs. **observation** group (n=82): MAP 40-50 mmHg; age: 21 to 45 years (average 32.3±4.2 years); **Exclusion criteria**: craniocerebral trauma, severe cardiopulmonary and hepatic and renal dysfunction or severe hypertension;

	control	observation	P-value
recovery time	193.5±38.7 min	89.7±25.2 min	
CRP	101.7±12.3 mg/L	132.4±20.6 mg/L	
Hb	84.6±8.3 g/L	102.5±13.0 g/L	P=0.006
death	12.2%	2.4%	P=0.041
ARDS	30.5%	12.2%	P=0.006
MODS	29.3%	12.2%	P=0.027
DIC	17.1%	2.4%	P=0.039

Überlebensvorteil durch permissive Hypotonie

2020:

IFOM-2021/22: Evidenzgrad 1b

Restricted fluid resuscitation improves the prognosis of patients with traumatic hemorrhagic shock.

Gu X et al. Int J Clin Exp Med 2020

Ningbo, Zhejiang Province, China; prospective randomized controlled trial; 160 patients with traumatic hemorrhagic shock (60% traffic injury); **control** group (n=80, ISS 28): 1500–2000 mL NaCl followed by 500 – 1000 mL HES aiming at MAP 60-80 mmHg vs. **experimental** group (n=80, ISS 27): 500–1500 mL NaCl followed by 500 mL HES aiming at MAP 50-60 mmHg; **Exclusion criteria**: Patients who had dysfunction of the vital organs including the liver and kidneys before their admission; patients who were admitted with MODS and ARDS; age: 38.1±8.7 vs. 36.8±7.5

	control	experimental	P-value
MAP after resuscitation	71.1±4.6 mmHg	61.3±3.5 mmHg	P<0.001
lactic acid (before → after)	4.7±1.5 → 2.2±1.0 mmol/L	5.1±1.6 → 3.6±1.1	
BE (before → after)	-10.5±3.7 → -6.5±2.2 mmol/L	-11.3±4.5 → 4.3±1.8 mmol/L	
Hb (before → after)	121.9±14.9 → 92.8±10.7 g/L	123.7±13.8 → 114.5±9.3 g/L	
PLT (before → after)	33.5±9.5 → 38.7±7.2 x10^9/L	34.3±9.2 → 48.7±5.5 x10^9/L	
death	16.3%	6.3%	P=0.045
ARDS	27.5%	12.5%	P=0.018
MODS	22.5%	8.8%	P=0.017

"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

„damage control resuscitation“

(3. Azidoseausgleich)

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.

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.)

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

Frage:

Die Tranexamsäure?

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%

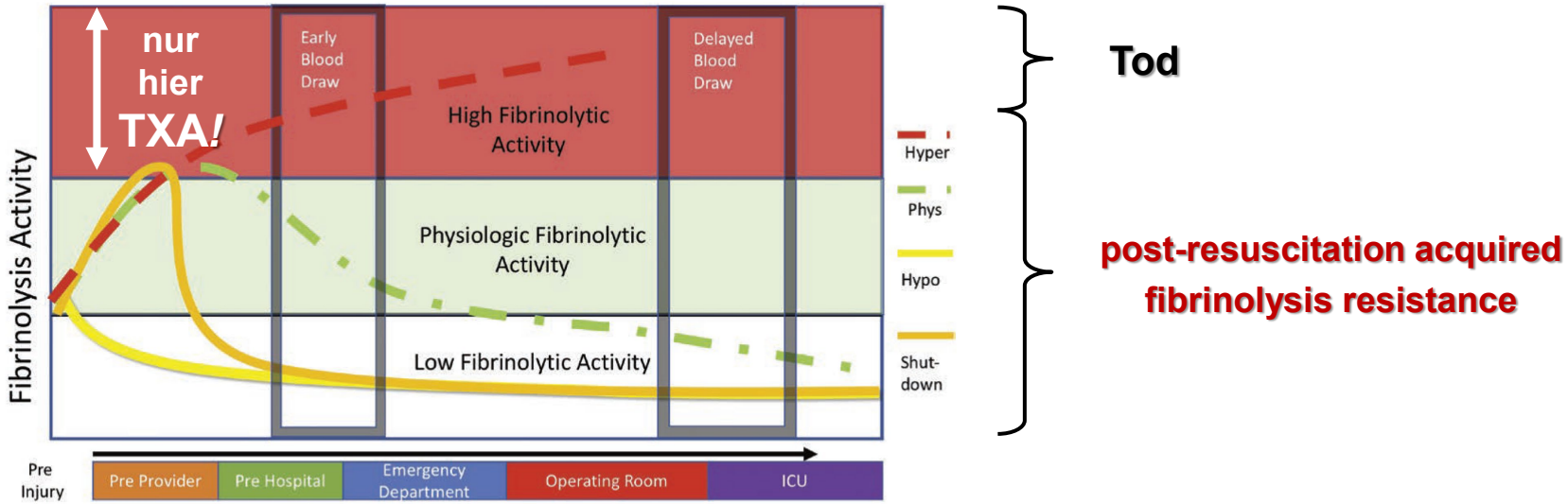
* nicht Polytrauma-spezifisch!!!

Hypofibrinolyse vs. „fibrinolytic shutdown“

Fibrinolysis Shutdown in Trauma: Historical Review and Clinical Implications.

Moore HB et al. Anesth Analg 2019

zeitabhängig**!!**



Hypofibrinolyse	„fibrinolytic shutdown“
aktuell niedrige fibrinolytischer Aktivität ohne Hinweis auf vorherige Aktivierung	aktuell niedrige fibrinolytischer Aktivität nach ehemaliger Aktivierung des fibrinolytischen Systems mit
geschwächte endogene Plasmin-Bildung	ggf. lokale Fibrinolyse an der Verletzung
vielleicht frühe Antikoagulation oder t-PA sinnvoll	Sinnhaftigkeit von Antifibrinolytika unklar

Tranexamsäure kann ggf. Leben retten

gleiche Datengrundlage wie im Schockraum, aber GoR B (1.3.10) statt GoR A (2.4.17)

1.3.10	GoR **B⇑**	Bei Polytraumapatienten mit manifestem oder drohendem hämorrhagischem Schock sollte zügig die Gabe von 1 g Tranexamsäure (TxA) als Bolus über 10 Minuten erfolgen.(1)	neu 2022

(1) Guyette FX et al. Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surg 2020 Oct 5;156(1):11-20. **IFOM-Evidenzgrad: 1b**
Khan M et al. Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. J Trauma Acute Care Surg 2018 Nov;85(5):851-857. **IFOM-Evidenzgrad: 2b**
Roberts I et al. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. Crit Care. 2014 Dec 13;18(6):685. **IFOM-Evidenzgrad: 1b**
Roberts I et al. Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. Trials. 2017 Jan 31;18(1):48. **IFOM-Evidenzgrad: 1b**

Tranexamsäure kann ggf. Leben retten

The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury.

van Wessem KJP et al. Eur J Trauma Emerg Surg 2022

Utrecht, Netherlands; 7.5-year prospective population-based single-center cohort study; polytrauma patients with associated severe TBI (AIS head ≥ 3; excluding AIS head 6 as un-survivable); n=234; 98% blunt trauma; median ISS 33 (27–38); median prehospital time 1:01 (0:57–1:09); 51% (n=120) prehospital TXA (more deranged physiology)

- no difference in mortality between TXA and no-TXA patients (all 24% vs. TXA 27% vs. no TXA 22%; p = 0.45)
- no difference in mortality in patients with SBP ≤ 90 mmHg on arrival (all 34% vs. TXA 43% vs. no TXA 20%; p = 0.18)
- no difference between TXA and mortality between AIS head groups (p = 0.40).
- no difference secondary parameters (ventilator days, LOS, MODS, ARDS, infections, thromboembolism, neurologic outcome)

- TXA was not related to death (prehospital TXA survival 50% vs. deceased 56%; p = 0.40)
- Patients without TXA did as well as TXA patients despite being 11 years older.
- TBI was the cause of death in all AIS head 5 patients compared to 81% in AIS head 4, and 67% in AIS head 3 (p = 0.06).

no beneficial effect of TXA in TBI patients Yutthakasemsunt S et al. BMC Emerg Med 2013; Lawati KA et al. Intensive Care Med 2021; Rowell S et al. JAMA 2020; Mojallal F et al. Med J Islam Repub Iran 2020; Yokobori S et al. J Intensive Care 2020.

negative effect of TXA in TBI patients Bossers SM et al. JAMA Neurol 2021 .

Tranexamsäure kann ggf. Leben retten

Update on Applications and Limitations of Perioperative Tranexamic Acid.

Patel PA et al. Anesth Analg 2022

"This has crystallized in a discussion of prehospital TXA use and appreciation that TXA alone is unlikely to arrest acute traumatic hemorrhage and TIC."

Tranexamsäure kann ggf. Leben retten

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

Tranexamsäure kann ggf. Leben retten

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

Polytraumapatienten mit manifestem oder drohendem hämorrhagischen Schock (1.3.10, GoR B)

Um diese Patienten geht es!!

2.4.17	GoR A⇑⇑	Bei ~~massiv blutenden~~ Patienten mit *lebensbedrohlichen Blutungen u./o. im Schock sowie bei nachgewiesener Hyperfibrinolyse* soll möglichst frühzeitig / *prähospital* die Gabe von 1 g Tranexamsäure (TxA) über 10 Minuten, ggf. gefolgt von einer Infusion von 1 g über 8 Stunden, erfolgen. (1)	modifiziert 2022
2.4.18	GoR B⇑	Mehr als 3 Stunden nach dem Trauma sollte mit der Gabe von Tranexamsäure nicht mehr begonnen werden (außer bei nachgewiesener Hyperfibrinolyse).	geprüft 2022
2.4.19	GoR B⇑	*Da nur bei ~20% der Traumapatienten eine Hyperfibrinolyse auftritt und Tranexamsäure (TxA) bei Fehlen einer Hyperfibrinolyse schädlich ist, sollte TxA nicht automatisch jedem Verletzten appliziert werden.* (2)	neu 2022

(1) Guyette FX et al. Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surg 2020 Oct 5;156(1):11-20. **IFOM-Evidenzgrad: 1b**
Khan M et al. Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. J Trauma Acute Care Surg 2018 Nov;85(5):851-857. **IFOM-Evidenzgrad: 2b**
Roberts I et al. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. Crit Care. 2014 Dec 13;18(6):685. **IFOM-Evidenzgrad: 1b**
Roberts I et al. Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. Trials. 2017 Jan 31;18(1):48. **IFOM-Evidenzgrad: 1b**
(2) Moore HB et al. Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis. J Surg Res. 2017 Dec;220:438-443. **IFOM-Evidenzgrad: 2b**
Spinella PC et al. The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI): A Randomized, Double-Blind, Placebo-Controlled, Single-Center Trial. Front Immunol 2020 Sep 8;11:2085. **IFOM-Evidenzgrad:2b↓**

Tranexamsäure kann ggf. Leben retten

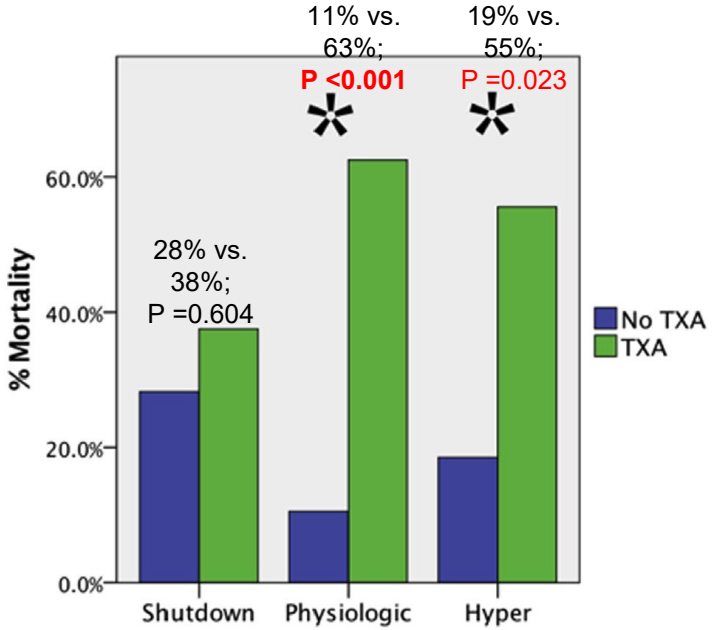
Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis

IFOM-2021/22: Evidenzgrad 2b

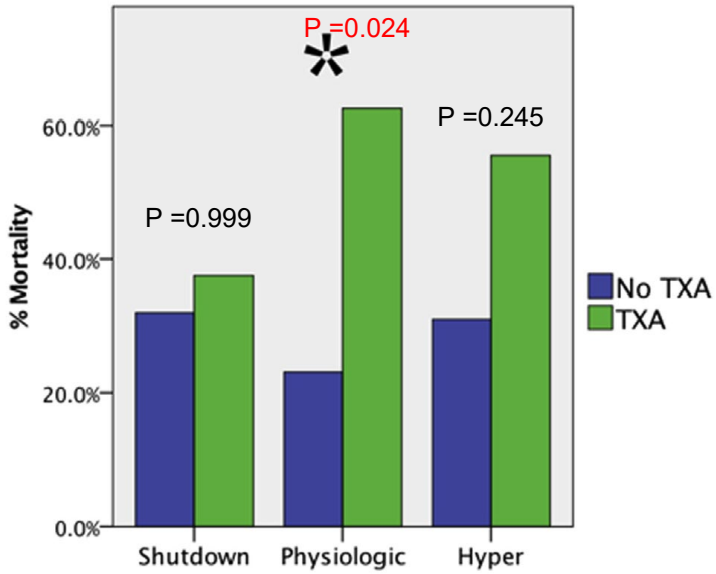
Moore HB et al. J Surg Res 2017

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).

Tranexamsäure kann ggf. Leben retten

The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI).

IFOM-2021/22: Evidenzgrad 2b↓

Spinella PC et al. Front Immunol 2020

single center (St. Louis, Missouri), double-blinded, randomized controlled trial (RCT) 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;

- in patients with primarily penetrating traumatic injuries, 2 and 4 g i.v. bolus dosing of TXA had minimal immunomodulatory and hemostatic effects with respect to leukocyte phenotypes and circulating cytokine levels.
- the immune and hemostatic phenotype induced by traumatic injury greatly outweighs changes in function due to plasmin inhibition by TXA.
- perhaps the phenotypes incurred by trauma are more severe, and outweigh any immune phenotype that would be induced by TXA administration
- immune modulating effects of TXA are most likely highly dependent on disease etiology and timing of TXA administration (pre- or post-insult).
- a difference in the incidence of thromboembolic events (TE, active Duplex screening) between study groups that approached significance (placebo,12.0%; 2 g, 26.5%; 4 g, 32.0%), p = 0.05

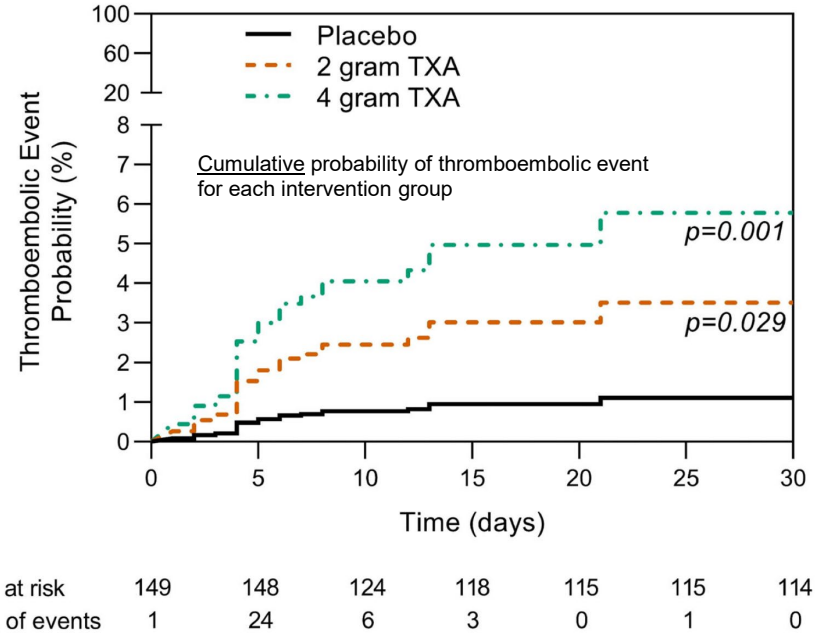
siehe „repeat bolus regime" bei STAAMP
Guyette FX et al. JAMA Surg 2020

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."

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

We *recommend* that tranexamic acid (TXA) be administered to the trauma patient who is bleeding or at risk of significant bleeding as soon as possible, if feasible en route to the hospital, and within 3 h after injury at a loading dose of 1 g infused over 10 min, followed by an i.v. infusion of 1 g over 8 h.
(Rec. 23; **1A**)

We *recommend* that the administration of TXA not await results from a viscoelastic assessment.
(Rec. 23; **1B**)

TXA wird als „**one of the mainstays of therapy for the injured patient at risk of bleeding**" bezeichnet. Im folgenden Text werden dann einige Studien mit positivem Ergebnis genannt, aber auch mehrere RCTs, in denen TXA kein Unterschied zeigte (SHT: Mojallal F et al. Med J Islam Repub Iran 2020; Fakharian E et al World Neurosurg 2018; Rowell SE et al. JAMA 2020; Trauma allgemein: Guyette FX et al. Ann Surg 2021). Trotzdem wird eine glatte 1A-Empfehlung ohne jede Einschränkung gegeben. ???

Tranexamsäure kann ggf. Leben retten

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**."

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."

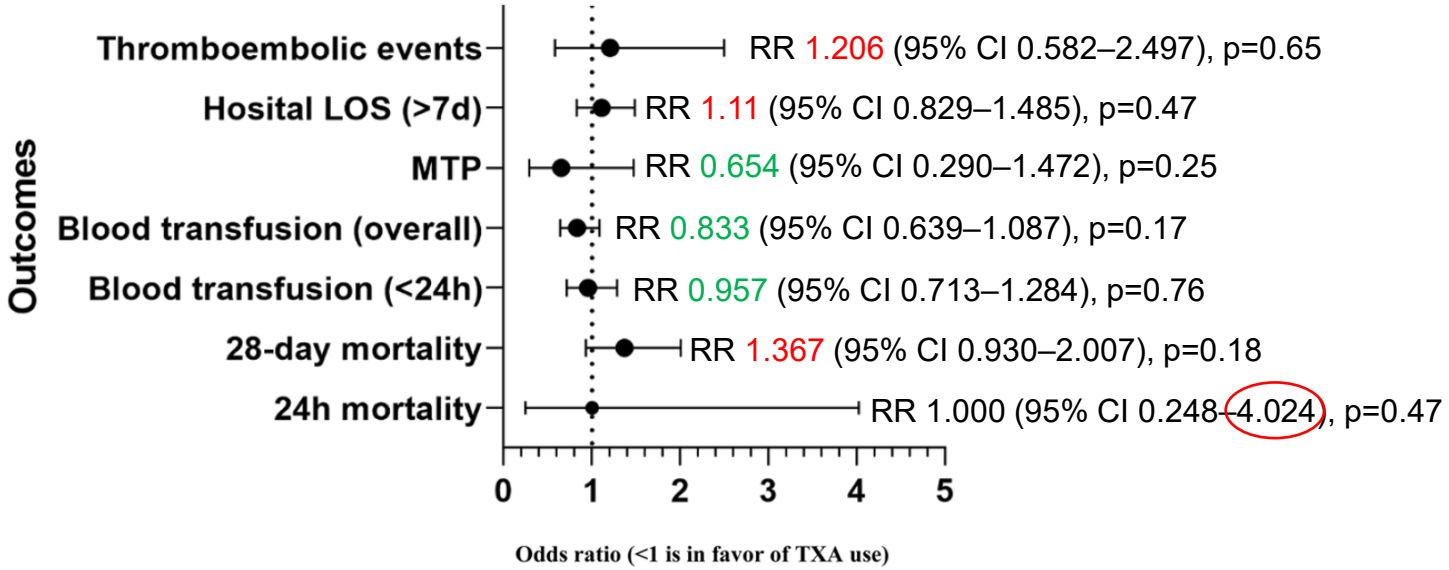
Je schwerer der Schock & je höher der ISS, desto stärker die Hyperfibrinolyse !!

Efficacy and safety of the second in-hospital dose of tranexamic acid after receiving the prehospital dose: double-blind randomized controlled clinical trial in a level 1 trauma center.

El-Menyar A et al. Eur J Trauma Emerg Surg 2022

prospective, double-blind, randomized, placebo-controlled clinical trial, Hamad General Hospital (HGH) in Qatar, between December 2018 and January 2021; > 85% blunt trauma (road traffic injuries and fall from height); prehospital TXA (SBP ≤90 mmHg, HR ≥110 beats per min, or both); 220 patients: second TXA in hospital (n=110) vs. placebo (n=110), blinded; ISS 20; ~40% associated head injury; **primary outcome**: mortality at 24 h (early) and 28 days (late) post-injury; **secondary outcome**: in-hospital thromboembolic complications (PE, deep vein thrombosis), MOF, blood transfusions, massive transfusion protocol activation, and hospital length of stay.

time from injury to prehospital TXA (min): 53.4 (47.1–59.6) vs. 54.2 (47.8–60.6)
time from injury to ED admission (min): 86.4 (79.8–92.9) vs. 86.8 (78.2–95.5)
time from injury to randomization (min): 165.2 (148.7–181.6) vs. 172.4 (160.1–184.7)



- Die **2. Dosis von TXA** hat keinen Einfluss auf das primäre oder sekundäre Outcome. (dito Neeki M et al. Cal-PAT, West J Emerg Med 2017) und ist daher **nicht notwendig** (außer bei nachgewiesener Hyperfibrinolyse).
- Die erhöhte 28d-Mortalität ist v.a. auf schwere SHT zurückzuführen (und statistisch nicht signifikant).
- Die 2. TXA-Gabe führte zu einer erhöhten Rate an Lungenembolie (6.9% vs. 2.9%, p=0.44) und später (sowie tendenziell auch 24h) Sterblichkeit (27.6% vs. 14.3%, p=0.17) → wie alle Ergebnisse statistisch nicht signifikant

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)

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

das ist eindeutig ...

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

The efficacy of tranexamic acid treatment with different time and doses for traumatic brain injury: a systematic review and meta-analysis.

Huang H et al. Thromb J 2022

13 RCT involving 18,675 patients; up to January 31, 2022;

TXA had no effect on

- mortality (RR 0.99; 95% CI 0.92–1.06),
- adverse events (RR 0.93, 95% CI 0.76–1.14),
- severe TBI (GCS 3 - 8) (RR 0.99, 95% CI 0.94–1.05),
- unfavorable Glasgow Outcome Scale (GOS < 4) (RR 0.96, 95% CI 0.82–1.11),
- neurosurgical intervention (RR 1.11, 95% CI 0.89–1.38), or
- rebleeding (RR 0.97, 95% CI 0.82–1.16).

- TXA might reduce the mean hemorrhage volume on subsequent imaging (standardized mean difference, -0.35; 95% CI [-0.62, -0.08]).

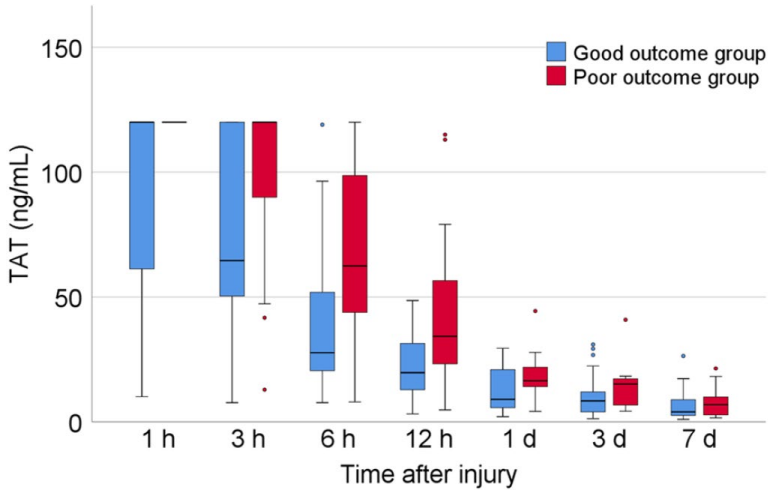
"… the timing of TXA administration is one of the factors affecting the hemostatic effects …"

Hyperfibrinolysis and fibrinolysis shutdown in patients with traumatic brain injury.

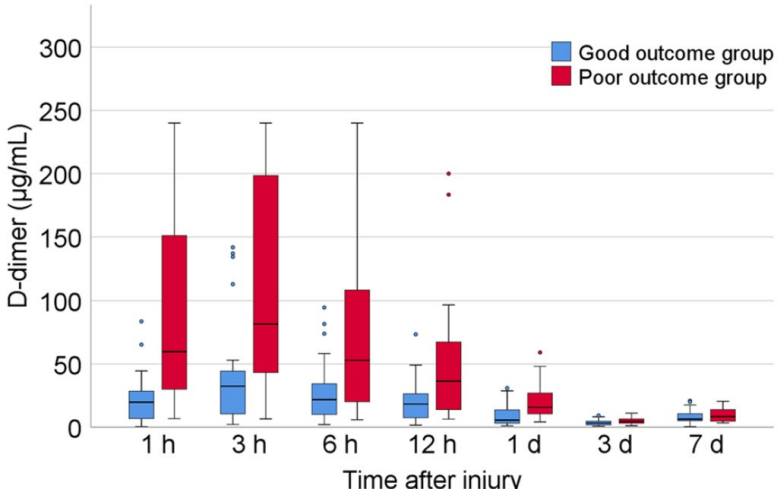
Nakae R et al. Sci Rep 2022

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

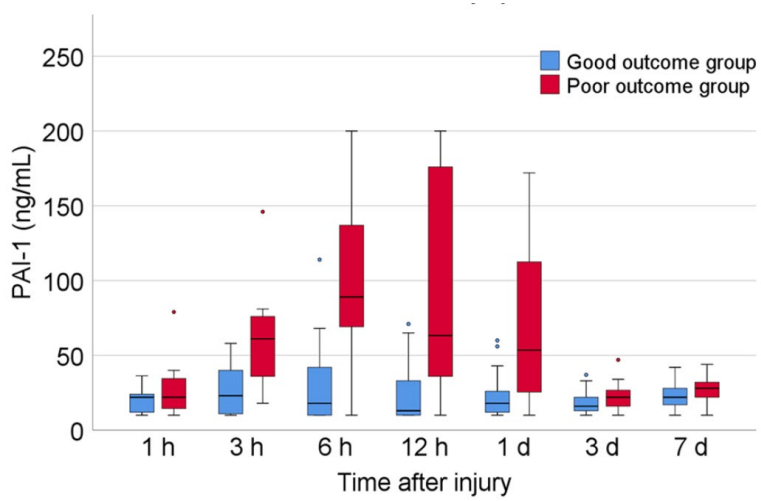
"The plasma levels of TAT, D-dimer, and PAI-1 were higher in the poor outcome group … from the time of admission to 7 days after injury … (all p < 0.001)."



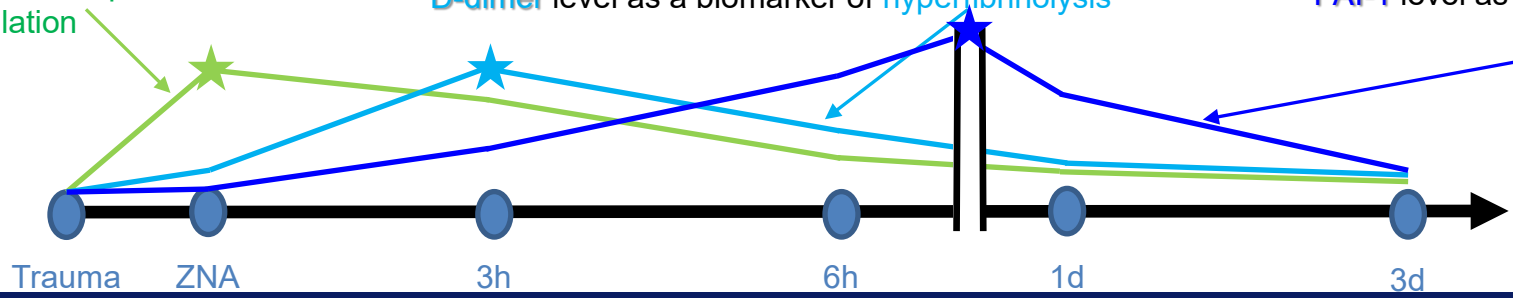
TAT level as a biomarker of fibrin production / hypercoagulation



D-dimer level as a biomarker of hyperfibrinolysis



PAI-1 level as a biomarker of shutdown



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

!!!

Frage:

Die Blutkomponenten?

Prähospitale Blutprodukte

1.3.12	GoR **0**	Bei Polytraumapatienten mit nicht beherrschbarer Blutung kann die Gabe von Erythrozyten- und Plasmakonzentraten (gefrorene Frischplasmakonzentrate oder lyophilisierte Plasmakonzentrate) erwogen werden, sofern die Logistik dieses erlaubt und der Transport in die Zielklinik nicht verzögert wird.	Neu 2022

Gruen DS et al. Association of Prehospital Plasma With Survival in Patients With Traumatic Brain Injury: A Secondary Analysis of the PAMPer Cluster Randomized Clinical Trial. JAMA Netw Open 2020 **IFOM-Evidenzgrad 1b**
Sperry JL et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. N Engl J Med 2018 **IFOM-Evidenzgrad 1b**
Pusater AE et al. Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes: A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials. JAMA Surg 2020 **FOM-Evidenzgrad 2b↓**
Guyette FX et al. Prehospital Blood Product and Crystalloid Resuscitation in the Severely Injured Patient: A Secondary Analysis of the Prehospital Air Medical Plasma Trial. Ann Surg 2021 **IFOM-Evidenzgrad 2b**
Brown JB et al. Pretrauma center red blood cell transfusion is associated with reduced mortality and coagulopathy in severely injured patients with blunt trauma. Ann Surg 2015 **IFOM-Evidenzgrad 3b↓**
Henriksen HH et al. Pre-hospital transfusion of plasma in hemorrhaging trauma patients independently improves hemostatic competence and acidosis. Scand J Trauma Resusc Emerg Med 2016 **FOM-Evidenzgrad 3b↓**

European Trauma, 6th edition 2023
pre-hospital blood product use

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

No clear recommendation or suggestion in favour or against the use of pre-hospital blood products can be provided at this time .

(Rec. 4)

"… a restrictive volume strategy using crystalloid solutions is generally accepted."

EK + LyoPlas prähospital: RePHILL

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

- 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

Prehospital Lyophilized Plasma Transfusion for Trauma-Induced Coagulopathy in Patients at Risk for Hemorrhagic Shock.

Jost D et al. JAMA Netw Open 2022

France; PREHO-PLYO trial; open-label, RCT; physician-staffed ALS teams; severe trauma at high risk for hemorrhagic shock and coagulopathy (SBP <70 mmHg or SI ≥1.1); point-of-care INR (Coaguchek Pro II) followed by transfusing as many as 4 U of plasma (800 mL; n=68; ISS 29 [12-48]) vs.1000 mL of saline (n=66; ISS 25 [9-41]); 59.7% blunt trauma; plasma transfusion started at a median of 26 (IQR, 16-37) minutes after arrival at the point of injury.

INR value at hospital admission: plasma 1.21 (IQR, 1.12-1.49) vs. saline 1.20 (IQR, 1.10-1.39) median difference, −0.01 [IQR, −0.09 to 0.08]; P = 0.88

massive transfusion: plasma 10.3% vs. saline 6.1% RR, 1.78 [95%CI, 0.42-8.68]; P = 0.37

fibrinogen values at hospital arrival: plasma 210 (IQR, 150-250) mg/dL vs. saline 190 (IQR, 150-230) mg/dL P = 0.22

death within 6h: plasma 4.4% vs. saline 3.0% RR 1.48; 95%CI 0.16-18.18; P = 0.67

death within 24h: plasma 13.2% vs. saline 9.1% RR 1.52; 95%CI 0.45-5.53; P = 0.45

28d mortality: plasma 17.6% vs. saline 15.2% RR 1.20; 95%CI 0.43-3.37; P = 0.70

"Allocation to lyophilized plasma was **not associated with reduced INR values**, and the trial yielded **no convincing evidence to support the assumption that prehospital lyophilized plasma is effective for TIC**. These results were **consistent across the explored subgroups**."

prähospital: EK + Plasma?

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 …"

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

mit freundlicher Unterstützung durch Prof. Dr. Rolf Lefering, IFOM, TR-DGU

Neues Register in Planung!

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

BAND e.V.

BiNAR
Blut im Notarztdienst Register

ADAC Luftrettung gGmbH

Bundesamt für Bevölkerungsschutz und Katastrophenhilfe - Luftrettung

DRF Luftrettung

DRF Stiftung Luftrettung gemeinnützige AG

Grundlagen beachten

2.4.11	GoR **B⇑**	Ein ~~spezifisches~~ Massivtransfusions- und Gerinnungstherapieprotokoll sollte *lokal* etabliert sein.	modifiziert 2022
2.4.12	GoR **B⇑**	Bei einem aktiv blutenden Patienten ist die Indikation zur Transfusion individuell nach klinischen Kriterien, dem Verletzungsgrad, dem Ausmaß des Blutverlustes, der Kreislaufsituation und der Oxygenierung zu entscheiden. Nach *hämodynamischer* Stabilisierung sollte eine Normovolämie ~~angestrebt und der Hb-Wert auf~~ *mit einem Ziel-Hb-Wert von* 7–9 g/dl [4,3–5,6 mmol/l] ~~angehoben~~ *angestrebt* werden.	modifiziert 2022
2.4.13	GoR **B⇑**	~~Bei (erwarteten) Massivtransfusionen~~ *Wenn bei Massivblutungen Plasmavolumen ersetzt werden muss,* sollte der Einsatz von ~~FFP~~ *therapeutischem Plasma* möglichst frühzeitig erfolgen~~, ansonsten restriktiv erwogen werden~~. ~40 ml/kg BÄK. Querschnittsleitlinie Gesamtnovelle 2020	modifiziert 2022
2.4.16	GoR **B⇑**	Wird die Gerinnungstherapie bei Massivtransfusion durch die Gabe von ~~FFP~~ *therapeutischem Plasma* durchgeführt, sollte ein Verhältnis von therapeutischem Plasma:EK:TK im Bereich von 4:4:1 angestrebt werden. *Ansonsten sollte die Gabe von therapeutischem Plasma restriktiv erfolgen.*	modifiziert 2022

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

28-day survival rates: 92.1% and 91.3%

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

The Role of Whole Blood Transfusions in Civilian Trauma: A Review of Literature in Military and Civilian Trauma.

Kronstedt S et al. Cureus 2022

literature search using PubMed, Scopus, Cochrane Central, and ClinicalTrials.gov. on randomized control trials, clinical trials, controlled clinical trials, retrospective studies, comparative studies; 19 articles

24h mortality:

Cotton et al. (2013) [21]	WBT vs. BCT	No significant difference	RCT
Shea et al. (2020) [24]	WBT vs. BCT	Improved survival in the WBT group by 23% (HR=0.15; p=0.017)	prospective, observational
Seheult et al. (2018) [25]	WBT vs. BCT	No significant difference (p=0.33)	retrospective
Kemp Bohan et al. (2021) [27]	Arm 1: WBT vs. WBT+BCT	No significant difference between all three cohorts (p=0.45)	retrospective
Kemp Bohan et al. (2021) [27]	Arm 2: BCT vs. WBT+BCT	No significant difference between all three cohorts (p=0.45)	retrospective
Yazer et al. (2021) [29]	WBT vs. BCT	No significant difference	retrospective
Braverman et al. (2021) [30]	WBT vs. no transfusion	No significant difference (p=0.6)	retrospective

30d mortality:

Cotton et al. (2013) [21]	WBT vs. BCT	No significant difference	RCT
Shea et al. (2020) [24]	WBT vs. BCT	Improved survival in the WBT group (p<0.001)	prospective, observational
Yazer et al. (2021) [29]	WBT vs. BCT	No significant difference	retrospective

„Whole Blood“ bei zivilem Trauma

Brill JB et al. ***Impact of Incorporating Whole Blood into Hemorrhagic Shock Resuscitation: Analysis of 1,377 Consecutive Trauma Patients Receiving Emergency Release Uncrossmatched Blood Products***. J Am Coll Surg 2022 Apr 1;234(4):408-418. doi: 10.1097/XCS.0000000000000086.

Houston, TX; prospective observational cohort study; trauma requiring uncrossmatched products in the prehospital or emergency department; 1,377 patients (840 WB vs. 537 COMP); median ISS 27 vs. 20

logistic regression found WB was independently associated with a 4-fold increased survival (OR 4.10, p < 0.001) and 60% reduction in overall transfusions (OR 0.38, 95% CI 0.21-0.70). median 1U WB (1, 2).

Hazelton JP et al. ***Use of Cold-Stored Whole Blood is Associated with Improved Mortality in Hemostatic Resuscitation of Major Bleeding. A Multicenter Study.*** Ann Surg 2022 Oct 1;276(4):579-588. doi: 10.1097/SLA.0000000000005603.

USA, 14-center, prospective observational study of trauma patients who received WB versus BCT in the ED: 1623 [WB: 1180 (74%), BCT: 443(27%)] patients; median ISS 22 vs .21

WB patients were 9% less likely to experience bleeding complications and were 48% less likely to die than BCT patients (P<0.0001). No differences in the rates of acute kidney injury, deep vein thrombosis/pulmonary embolism or pulmonary complications. median 2U WB (1, 2)

Torres CM et al. ***Association of Whole Blood With Survival Among Patients Presenting With Severe Hemorrhage in US and Canadian Adult Civilian Trauma Centers.*** JAMA Surg 2023 May 1;158(5):532-540. doi: 10.1001/jamasurg.2022.6978.

retrospective cohort study, ACS-TQIP; trauma patients with a systolic blood pressure less than 90 mmHg and a shock index greater than 1 who received at least 4 units of red blood cells within the first hour of ED arrival; 2,785 patients: 432 (15.5%) WB-MTP vs. 2353 (84.5%) MTP-only; median ISS 28

WB-MTP was associated with improved survival at 24 hours, 37%lower risk of mortality (HR, 0.63; 95%CI, 0.41-0.96; P = .03). Similarly, the survival benefit associated with WB-MTP remained consistent at 30 days (HR, 0.53; 95%CI, 0.31-0.93; P = .02). median 1U WB (1, 1).

Braverman MA et al. ***The Impact of Prehospital Whole Blood on Hemorrhaging Trauma Patients: A Multi-Center Retrospective Study***. J Trauma Acute Care Surg 2023 Apr 4. doi: 10.1097/TA.0000000000003908. Online ahead of print.

retrospective cohort of 2 trauma centers; transfusion upon arrival to the trauma bay: 171 prehospital WB vs. 1391 non-pWB

pWB patients received fewer pRBC, FFP and PLT units across their LOS but total units and volumes were similar.

Seit Mitte 2022 zeigen **alle** zivilen Trauma-Studien Vorteile bei Vollblut!!

Sperry JL et al. ***Whole Blood Resuscitation and Association with Survival in Injured Patients with an Elevated Probability of Mortality***. J Am Coll Surg 2023 Apr 11. doi: 10.1097/XCS.0000000000000708. Online ahead of print.

prospective, multicenter, observational cohort study of 7 trauma centers; patients at risk of massive transfusion who required both blood transfusion and hemorrhage control procedures: 1,051 patients (624 LT0WB vs. 427 COMP); >70% massive transfusion; >60% penetrating; median ISS 22 (13-30);

After propensity adjustment, no significant 4-hour mortality difference across LTOWB and component patients was found, (RR 0.90, 95%CI 0.59-1.39, p=0.64). No adjusted mortality differences at 24-hours or 28 days. **Patients with an elevated prehospital probability of mortality**: LTOWB resuscitation was independently associated with a 48% lower risk of 4-hour mortality (RR 0.52, 95%CI 0.32-0.87, p=0.01) and a 30% lower risk of 28-day mortality (RR 0.70, 95%CI 0.51-0.96, p=0.03). median number of LTOWB units transfused 2.0 IQR [1.0-3.5].

Guyette FX et al. ***Prehospital low titer group O whole blood is feasible and safe: Results of a prospective randomized pilot trial. PPOWER*** J Trauma Acute Care Surg 2022 May 1;92(5):839-847. doi: 10.1097/TA.0000000000003551.

Pittsburgh, PE; single-center, prospective, cluster randomized, prehospital through in-hospital whole blood pilot trial; prehospital SBP ≤90 mm Hg and HR ≥108 beats per minute or SBP ≤70 mm Hg for patients at risk of hemorrhage: 86 pat (40 pre- + intrahospital LT0WB vs. 46 pre + intrahospital RBC+crystalloid); 36% protocol derivation;

no statistical mortality benefit at 28 days (25.0% vs. 26.1%, p = 0.85). lower red cell transfusion requirements at 24 hours (p < 0.01) and a lower incidence of abnormal thromboelastographic measurements.

Hosseinpour H et al. ***Time to Whole Blood Transfusion in Hemorrhaging Civilian Trauma Patients: There Is Always Room for Improvement***. J Am Coll Surg 2023 Jul 1;237(1):24-34. doi: 10.1097/XCS.0000000000000715

retrospective cohort, ACS-TQIP; 1,952 pat. who received at least 1 unit of WB within the initial 2 hours of ED presentation; mean ISS 17 (10-26)

Transfusion of WB after 30 minutes increased adjusted odds of 24-hour mortality (second 30 minutes: aOR 2.07, p = 0.015; second hour: aOR 2.39, p = 0.010) and in-hospital mortality (second 30 minutes: aOR 1.79, p = 0.025; second hour: aOR 1.98, p = 0.018). Patients with an **admission shock index > 1**, every 30-minute delay in WB transfusion higher odds of24-hour (aOR 1.23, p = 0.019) and in-hospital (aOR 1.18, p = 0.033) mortality. median 2U WB (1, 2)

Ngatuvai M et al. ***Outcomes of Transfusion With Whole Blood, Component Therapy, or Both in Adult Civilian Trauma Patients: A Systematic Review and Meta-Analysis***. J Surg Res 2023 Jul;287:193-201. doi: 10.1016/j.jss.2023.02.010.

16 studies with adult civilian trauma patients transfused with WB versus COMP versus both until March 3rd, 2022

increased risk of 24-h mortality with COMP versus WB + COMP (relative risk: 1.40 [1.10, 1.781) and increased transfusion volumes of red blood cells with COMP versus WB at 6 and 24 h, respectively (-2.26 (-3.82, -0.70); -1.94 (-3.22, -0.65) units).

GFP-Indikation

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 GFP-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 GFP für Erwachsene bzw. ≥30 ml/kg BÄK2020 und GFP:EK: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

Association between perioperative plasma transfusion and in-hospital mortality in patients undergoing surgeries without massive transfusion: A nationwide retrospective cohort study.

Xu X et al. Front Med 2023

China; nationwide retrospective cohort study; 69,319 pat.; excluded patients who received massive transfusion (≥10 U RBC) on the day of surgery and who were diagnosed with coagulopathy at admission (ICD codes); 50.2% received FFP transfusion and 49.8% did not; FFP group received 400 [200, 900] ml FFP

bei 70 kg sind das 5,7 [2,8 bis 12,8] ml/kg

a 100-ml increase in FFP transfusion volume was (after the adjustment of 15 potential confounders) associated with …

- increased odds of in-hospital mortality (OR 1.05, 95%CI 1.04–1.06, p < 0.001),
- increased superficial surgical wound infection (OR 1.03, 95% CI 1.02–1.04, p < 0.001),
- increased nosocomial infection (OR 1.03, 95% CI 1.02–1.04, p < 0.001),
- increased LOS (HR 1.05, 95% CI 1.04–1.07, p<0.001),
- increased ventilation time (OR 1.03, 95% CI 1.03–1.04, p<0.001), and
- increased ARDS (OR 1.03, 95% CI 1.00–1.05, p 0.016).

"… 100-ml increase in FFP transfusion volume was associated with an approximately 5% increased odds of in-hospital mortality…"

"… volume of FFP transfusion is associated with in-hospital mortality, regardless of the units of RBC transfused, and the OR tended to decrease as the units of RBC increased …"

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."

Thrombozyten

Thrombozyten***zahl*** ≠ Thrombozyten***funktion***. → aber beide korrelieren 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.

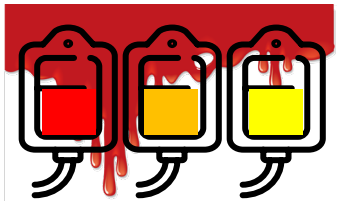
Thrombozyten***funktion*** in Standardlabor (quantitative Messung) gar nicht und in viskoelastischen Tests (Messung des thrombozytären Anteils an der globalen Bildung des Gerinnsels) nicht ausreichend abgebildet.

POC-Thrombozyten***funktion***stests mit Messung der Verschlusszeit (z. B. Platelet Function Analyzer PFA100™ / 200™), der Impedanzaggregometrie (z. B. Multiplate™) oder der Lichttransmissions-aggregometrie 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

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

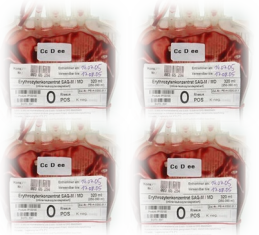
dito:
- **ESAIC 2nd update** Kietaibl S et al. EJA 2023 (R16; **2C**)
- **European Trauma 6th ed.** Rossaint R et al. Crit Care 2023 (Rec. 25; **1C**)

 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“

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

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

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

In the initial management of patients with expected massive haemorrhage, we *recommend* one of the two following strategies:

- Fibrinogen concentrate or cryoprecipitate and pRBC (Rec. 25; **1C**)
- FFP or pathogen-inactivated FFP in a FFP/pRBC ratio of at least 1:2 as needed. (Rec. 25; **1C**)

In addition, we *suggest* a high platelet/pRBC ratio.
(Rec. 25; **2B**)

"… the longer it takes to achieve haemostasis, the more likely high blood product transfusion ratios, including platelets, may be beneficial in terms of both haemostasis and survival."

Balanced blood component resuscitation in trauma: Does it matter equally at different transfusion volumes?

Dorken-Gallastegi A et al. Surgery 2022

retrospective analysis; American College of Surgeons Trauma Quality Improvement Program database; 14,549 patients receiving ≥6 red blood cell, ≥1 platelet, and ≥1 fresh frozen plasma within 4 hours; median age 37 (IQR: 26-54) years; median ISS 29 (I QR: 21-41); 50.9% isolated blunt trauma; RBC:FFP ratio of 1:1 (51.8%) or 2:1 (31.7%) and RBC:PLT ratio of 1:1 (47.6%) or 2:1 (33.5%)

- **4-hour mortality**:
  - **RBC:FFP ratios of ≥4:1** were associated with **significantly higher** risk-adjusted odds of 4-hour mortality
  - for **≥11 RBC**, RBC:FFP ratios of 2:1. 3:1, and ≥ 4:1 were associated with a **significant and gradual increase** in the risk-adjusted odds of 4-hour mortality
  - for **≥11 RBC**, RBC:PLT ratios of 2:1, 3:1. and ≥4:1 were associated with a **gradual and significant increase** in the risk-adjusted odds of 4-hour mortality
- **24-hour mortality**:
  - for **≥11 RBC**, RBC:FFP ratios of 2:1, 3:1, and :c:4:1 were associated with a **significant and gradual increase** in the risk-adjusted odds of 24-hour mortality
  - for **≥11 RBC**, RBC:PLT ratios of 2:1, 3:1. and ≥4:1 were associated with a **gradual and significant increase** in the risk-adjusted odds of 24-hour mortality

→ Je mehr transfundiert wird, desto wichtiger ist die Beachtung des 4:4:1-Verhältnisses.

Balanced resuscitation and earlier mortality endpoints: bayesian post hoc analysis of the PROPPR trial.

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

Lammers D et al. Trauma Surg Acute Care Open 2023

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

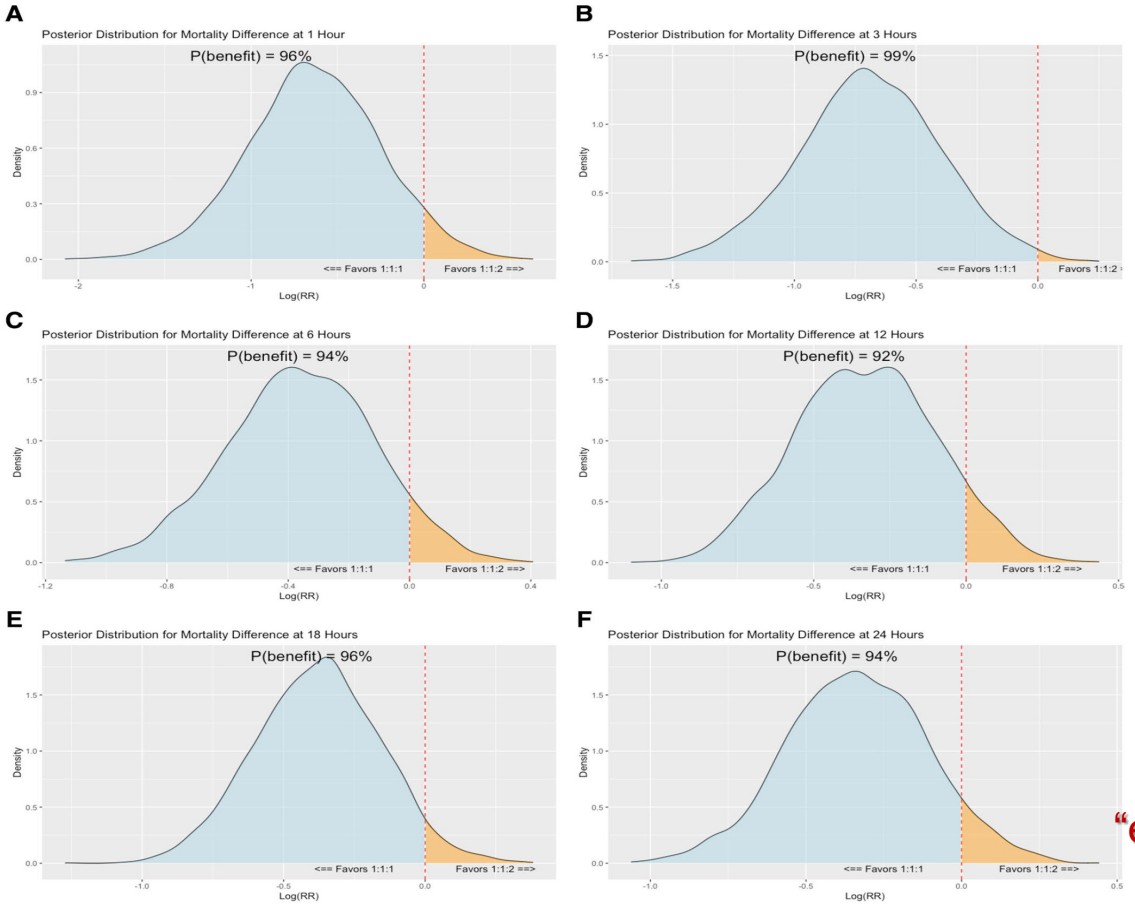


Table 1 Posterior probabilities and BFs favoring the 1:1:1 transfusion strategy

Time period (hour)	P(1:1:1>1:1:2)	BF	Level of evidence*
1	96%	21.2	Strong
3	99%	142	Decisive
6	94%	14.9	Strong
12	92%	11.4	Strong
18	96%	26.4	Strong
24	94%	15.5	Strong

P(1:1:1>1:1:2); posterior probability of balanced transfusion being superior to red cell heavy strategy.
*Based on Jeffery's Scale of Evidence: BFs between 1 and 3 represent anecdotal evidence, 3 and 10 represent substantial evidence, 10 and 30 represent strong evidence, 30 and 100 represent very strong evidence and >100 represent decisive evidence in favor of the alternative hypothesis.
BF, Bayes factor.

"evidence in support that a 1:1:1 resuscitation has a high probability of mortality benefit when compared with a 1:1:2 strategy"

Frage:

Die Faktorkonzentrate?

Faktorenkonzentrate verbessern Überleben

Polytraumapatienten mit nicht beherrschbarer Blutung
„ nach Gabe von Tranexamsäure (1.3.11, GoR 0)

Um diese Patienten geht es!!

2.4.20	~~GoR B~~ GoR A⇑⇑	~~Bei Blutung sollte eine Substitution von Fibrinogen bei thrombelastometrischen Zeichen eines funktionellen Fibrinogendefizites oder Werten von < 1,5 g/l (150 mg/dl) durchgeführt werden.~~ *Bei Patienten mit lebensbedrohlichen Blutungen u./o. im Schock soll zusätzlich die Gabe von Fibrinogen (initial 3-6 g bzw. 30-60 mg/kg) erfolgen.* (1)	neu 2022
2.4.21	GoR B⇑	*Bei Patienten mit lebensbedrohlichen Blutungen u./o. im Schock sollte zusätzlich zur Gabe von Fibrinogen die Gabe von Prothrombinkomplexkonzentrat (PPSB) erfolgen.* (2)	neu 2022

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

(1) Akbari E et al. The effect of fibrinogen concentrate and fresh frozen plasma on the outcome of patients with acute traumatic coagulopathy: A quasi-experimental studyAm J Emerg Med 2018 Nov;36(11):1947-1950. **IFOM-Evidenzgrad:1b**
Innerhofer P et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol 2017 Jun;4(6):e258-e271. **IFOM-Evidenzgrad:1b**
Nascimento B et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. Br J Anaesth 2016 Dec;117(6):775-782. **IFOM-Evidenzgrad:2b↓**
(2) Innerhofer P et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol 2017 Jun;4(6):e258-e271. **IFOM-Evidenzgrad:1b**
Zeeshan M et al. Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: A nationwide propensity-matched analysis. J Trauma Acute Care Surg 2019 Aug;87(2):274-281. **IFOM-Evidenzgrad:2b↓**

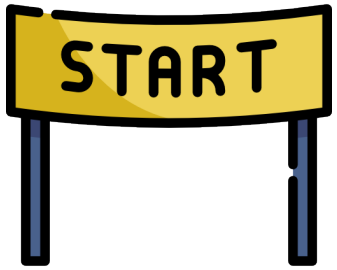
European Trauma 6th ed. Rossaint R et al. Crit Care 2023

We *recommend* treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g/L).
(Rec. 29; **1C**)

We *suggest* an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses should be guided by VEM and laboratory assessment of fibrinogen levels.
(Rec. 29; **2C**)

"Besides early administration of TXA (see recommendation R23) **early fibrinogen administration** (see recommendation R29) is also of key importance, ideally guided by a fibrinogen concentration < 1.5 g/L or viscoelastic evidence of a functional fibrinogen deficiency."

Fibrinogen-Substitution



Indikation zur Substitution:

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

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

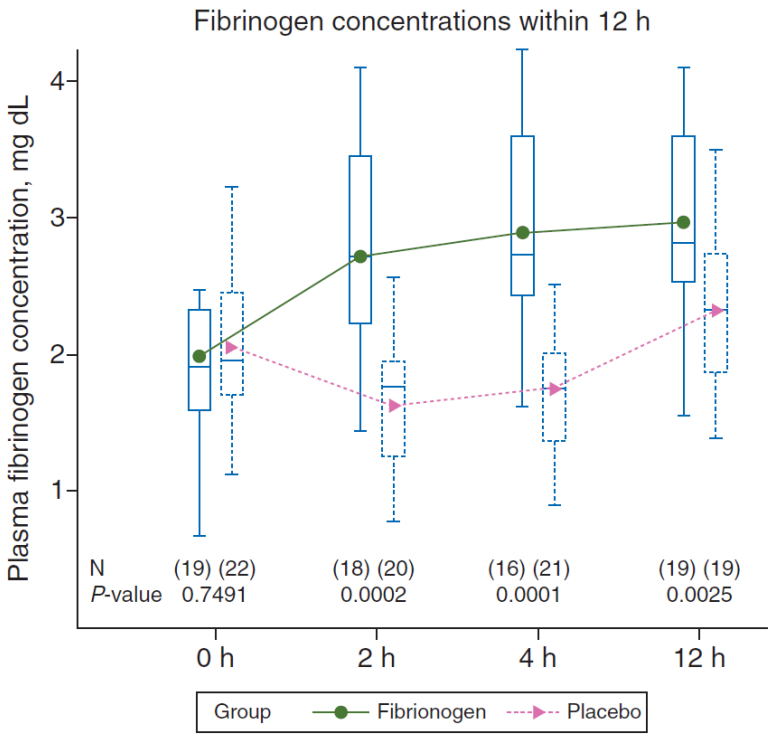
Faktorenkonzentrate verbessern Überleben

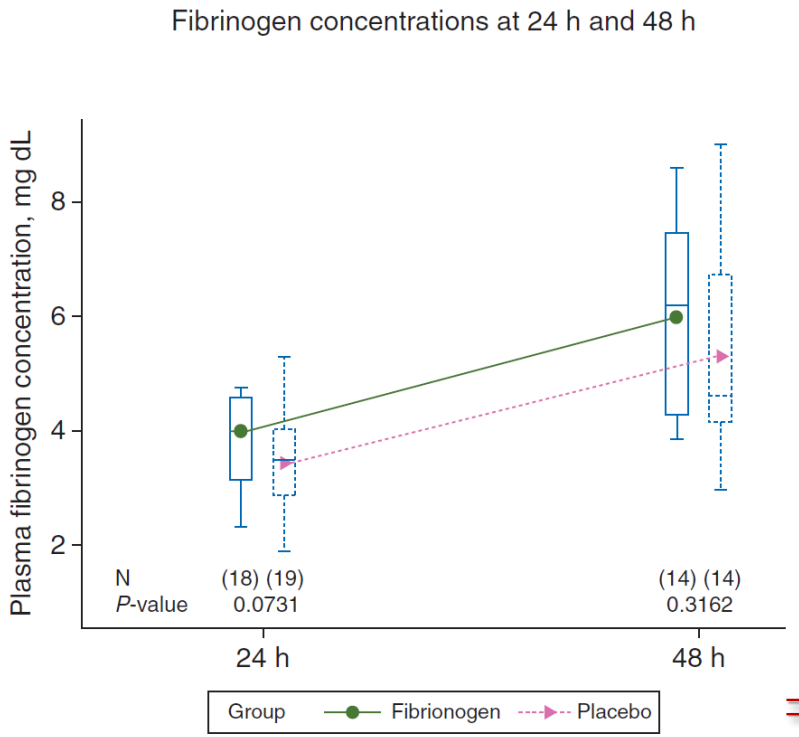
IFOM-2021/22:
Evidenzgrad 2b↓

Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial.

Nascimento B et al. Br J Anaesth 2016

single centre (Toronto, Canada), randomized-controlled, double-blinded, feasibility trial; 50 hypotensive (SAP ≤100mmHg) adult trauma patients requiring uncrossmatched RBC transfusion within 30 min after hospital arrival; 6 g of FC (n=20) vs. placebo (n=24); ISS 25 (19–29) vs. 23 (18–29); TXA 100% vs. 96%





- 96% of patients received the intervention within one h
- Plasma fibrinogen concentrations remained higher in the FC group up to 12h after admission with the largest difference at three h (2.9mg dL^{-1} vs. 1.8mg dL^{-1}; P<0.01)
- no further differences at 24h and 48h
- no statistically significant differences noted between rates of DVT, pulmonary embolism, acute lung injury, acute respiratory distress syndrome, acute kidney injury, multiple organ failure/sepsis, and infection

⇒ kein Hinweis auf Thromboembolie-Risiko

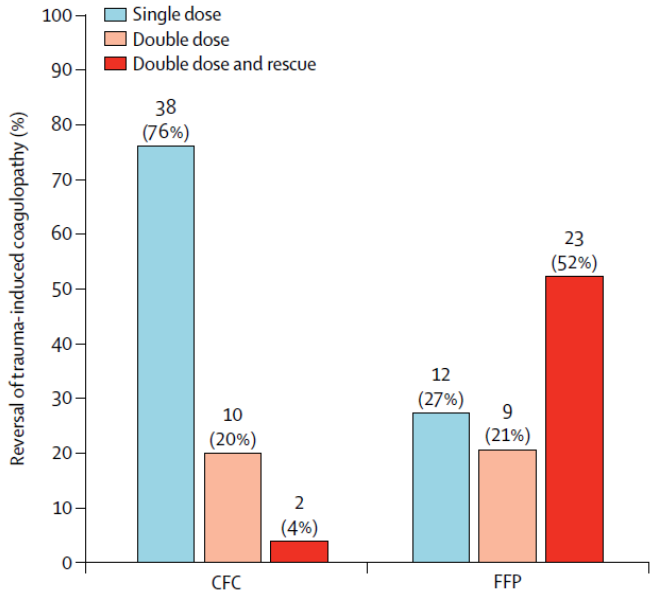
Faktorenkonzentrate verbessern Überleben

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC).

IFOM-2021/22: Evidenzgrad 1b

Innerhofer P et al. Lancet Haematol 2017

University Hospital Innsbruck; prospective, single-centre, parallel group, open-label, randomised study; trauma patients with ISS >15 and substantial haemorrhage; 44 patients FFP-based (15 ml/kg) vs. 50 patients coagulation factor concentrates (CFC)-based (fibrinogen 50 mg/kg **if FibA10 <9mm**, PCC 20 IU/kg **if ExCT >90 s** or PTI <35%, FXIII 20 IU/kg if <60%); terminated early (after 94 pat. [50 CFC vs. 44 FFP]) after pre-planned interim analysis (planned were 2x >100 pat.); ISS CFC 35 (29-42) vs. FFP 30 (24-45)



Percentage of patients with reversal of coagulopathy after either single-dose or double-dose study drug administration during the first therapy loop, and percentage of patients needing double-dose and rescue medication during the first 24 h in the intention-to-treat population

- time until first medication: FFP median 50.5 min vs. CFC median 10 min (estimated difference −40 [95% CI −46 to −33], p<0.0001)
- time until normalization of bleeding: FFP 128 min vs. CFC 22.5 min (estimated difference −97 min [−126 to −60], p<0.0001).
- transfusion of **FFP** is frequently ineffective for correction of the outcome-related pathologies of bleeding, hypofibrinogenaemia, low fibrin polymerisation, and poor clot strength.
- use of **FFP** is associated with enduring coagulopathic bleeding, increased transfusion requirements, and also need for massive transfusion.
- Indication of an increased risk for development of multiple organ failure with first-line use of **FFP**

⇒ Vorteile der Faktorenkonzentrate NUR durch Nutzung von VET !!

Faktorenkonzentrate verbessern Überleben

The effect of fibrinogen concentrate and fresh frozen plasma on the outcome of patients with acute traumatic coagulopathy: A quasi-experimental study.

IFOM-2021/22: Evidenzgrad 1b

Akbari E et al. Am J Emerg Med 2018

retrospective study; 4 hospitals in Iran; 90 patients: blunt trauma in need of RBC & fibrinogen <200 mg/dl; 2 g fibrinogen (n=30; ISS 19.3 ± 4.4; fibr. 106.4 ± 24.6) vs. 2 FFP (n=30; ISS 17.2 ± 3.1; fibr. 120.0±22.4 mg/dl) vs. control (n=30; ISS 19.0 ± 4.3; fibr. 123.2±24.4 mg/dl)

entspricht Dosis bei PAMPer (und COMBAT)
Sperry JL et al. N Engl J Med 2018

fibrinogen group:

- less RBC (p=0.044)
- less iv-fluid (p=0.022)
- less mortality (10.0% vs. 36.7% vs. 36.7%; p=0.022)
- less ICU-admittance (63.3% vs. 93.3% vs. 73.3%; p=0.020)
- less sepsis (16.6% vs. 53.3% vs. 13.3%; p=0.001)
- less MOF (6.7% vs. 26.7% vs. 23.3%; n.s.)

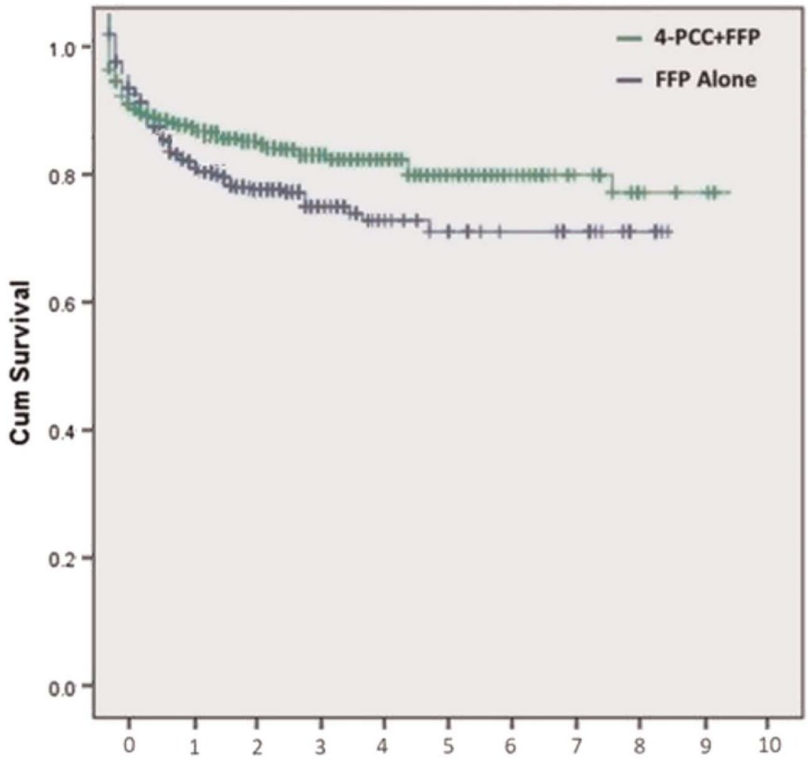
Faktorenkonzentrate verbessern Überleben

Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: A nationwide propensity-matched analysis.

IFOM-2021/22: Evidenzgrad 2b↓

Zeeshan M et al. J Trauma Acute Care Surg 2019

Two-year (2015–2016) analysis of the American College of Surgeons-Trauma Quality Improvement Program (ACS-TQIP) database; propensity score matching for demographics, vitals, injury parameters, comorbidities, and level of trauma centers; adult trauma patients: 4-PCC + FFP (n=234) or FFP alone (n=234); median ISS 27 (20–36); 86% blunt injuries, overall mortality 22.6%



4-PCC + FFP group:

- lower in-hospital mortality (17.5% vs. 27.7%, p = 0.01)
- lower requirement for pRBCs (at 4 h: 3 ± 2 vs. 5 ± 2, p=0.01; at 24 h: 6 ± 4 vs. 10 ± 4, p=0.02) and plasma (at 4 h: 2 ± 1 vs. 4 ± 2, p=0.01; at 24 h: 3 ± 2 vs. 6 ± 3, p=0.01) transfusion
- less likely to develop AKI (2.1% vs. 7.3%, p = 0.01) or ARDS (1.3% vs. 4.7%, p = 0.04)
- shorter hospital LOS (5–days vs. 8 days, p = 0.03)

- for **complete group**: independently associated with improved survival (OR 3.25 [1.78–4.96])
- for **isolated TBI** (n=99): independently associated with higher odds of survival (OR 2.54 [1.88–3.49])

Fibrinogen

Efficacy and safety of fibrinogen administration in acute post-traumatic hypofibrinogenemia in isolated severe traumatic brain injury: A randomized clinical trial.

Sabouri M et al. J Clin Neurosci 2022

single-blinded, multi-centric, randomized clinical trial, RCT; 2 university hospitals, Iran; 71 pat. with isolated severe head injury with on-admission GCS ≤8 + fibrinogen < 200 mg/dl (PT-fibrinogen time) + no extracranial bleeding + no transfusions; median GCS = 5; fibrinogen supplementation (aim: >200 mg/dl; n=36) vs. control (n=35)

- GCS scores higher after 24, 48, and 72 h (median 7 [mean 5.6 ± 2.7] vs. 5 [4.1 ± 2.7]; p = 0.000)
- hematoma expansion was better controlled (22,2% vs. 65.7%; p = 0.000)
- higher Glasgow Outcome Scale –Extended (GOSE) (p = 0.025) → NTT 2.3

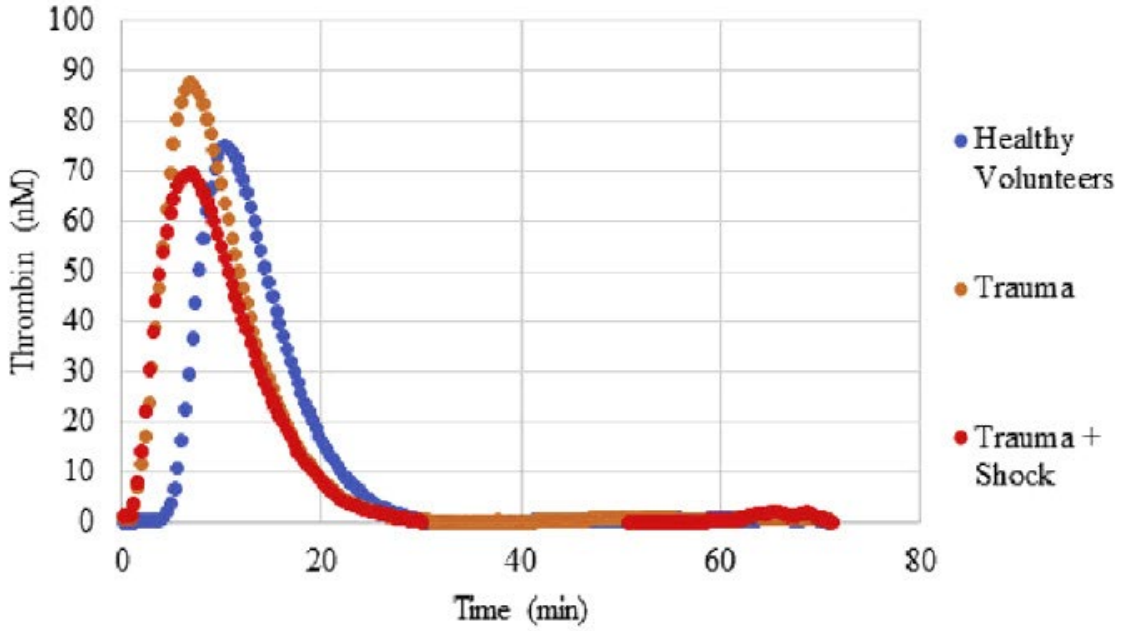
- GCS on discharge: 10.31 ± 5.90 (Median= 14) vs. 7.51 ± 5.91 (Median= 11); p = 0.051
- need for cranial surgery: 66.7% vs. 85.7% (n.s., p = 0.07)
- 90-day mortality: 5.6% vs. 11.4% (n.s., p = 0.51)

bei schwerem SHT mit GCS ≤8 ⇒ Fibrinogen >200 mg/dl

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?

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

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

Go AS et al. J Thromb Thrombolysis 2022

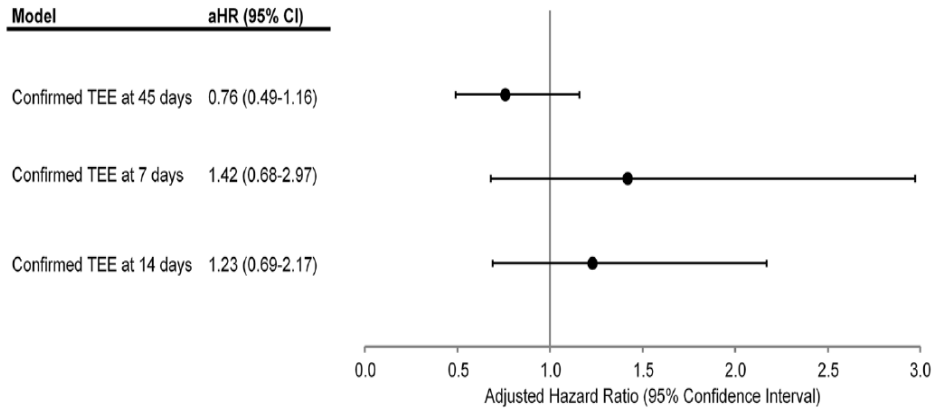
multicenter observational study; California, USA; reversal of warfarin due to major bleeding; matched pairs: 1119 pat. receiving 4F-PCC vs. 1119 pat. receiving plasma; primary outcome: occurrence of arterial or venous thrombembolic event within 45 days;

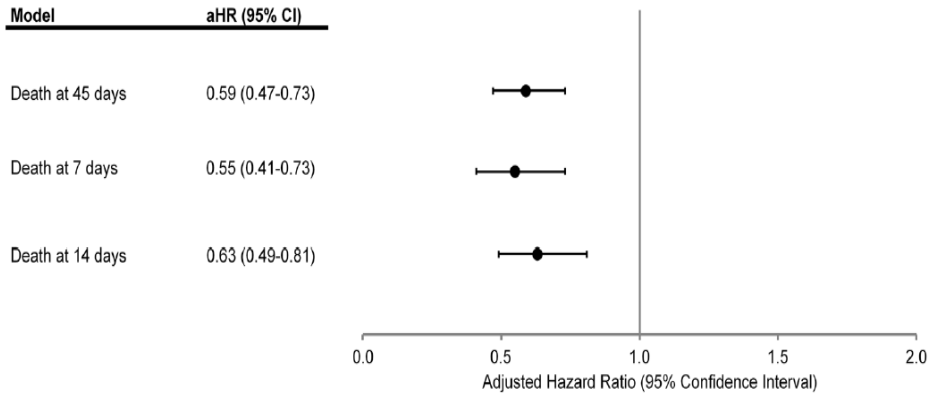
- **overall** risk of **confirmed arterial or venous TEE** after either 4F-PCC or plasma was 4.0% (95% CI 3.3–4.9%)
  - **4F-PCC**: 3.5% (95% CI 2.5–4.7%)
  - **Plasma**: 4.5% (95% CI 3.3–5.9%)

→ 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

- **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

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

PPSB bei Blutung:

- bei Patienten mit lebensbedrohlichen Blutungen u./o. im Schock
  AWMF- Polytrauma-LL 2023
- ausreichend Fibrinogen, aber viskoelastischen Zeichen verzögerter Initiation ($\uparrow CT_{EXTEM}$) 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 je nach Anwendungsbereich von 4% (bis >10% Uttaro E et al. Transfus Apher Sci 2023) beschrieben BÄK. Querschnittsleitlinie 2020

⇒ IMMER individuelle Nutzen-Risiko-Abwägung!!

Weiteres

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!

FXIII:

- 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;

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

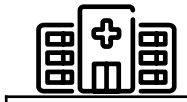
Desmopressin:

- bei (erworbenem) VON WILLEBRAND Syndrom BÄK Querschnittsleitlinie 2020 (Cave: KI bei Typ 2B und 3)
- 0,3 µg/kg als Kurzinfusion;

Frage:

Die viskoelastischen Tests?

Überlebensvorteil durch POC



Schockraum / ZNA

2.4.3	~~GPP~~ GoR A⇑⇑	Im Rahmen der Schockraumversorgung von blutenden Schwerverletzten soll ~~zusätzlich~~ zur Diagnostik und Therapie der Trauma-induzierten Koagulopathie der frühzeitige Einsatz viskoelastischer Testverfahren erfolgen. (1)	modifiziert 2022
2.4.14	GoR A⇑⇑	Die Gerinnungsdiagnostik und -therapie soll über viskoelastische Testverfahren gesteuert werden. (1)	neu 2022
2.4.15	GoR B⇑	Die Gerinnungsdiagnostik und -therapie sollte durch eine Diagnostik der Thrombozytenfunktion ergänzt werden. (2)	neu 2022

OP / ICU

(1) Gonzalez E et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy. Ann Surg. 2016 Jun;263(6):1051-9. **IFOM-Evidenzgrad:1b**
Hagamo JS et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Crit Care 2015 Mar 23;19(1):97. **IFOM-Evidenzgrad:2b**
Moore HB et al.Viscoelastic Tissue Plasminogen Activator Challenge Predicts Massive Transfusion in 15 Minute. J Am Coll Surg 2017 Jul;225(1):138-147. **IFOM-Evidenzgrad:2b**
Peng HT et al. A comparative study of viscoelastic hemostatic assays and conventional coagulation tests in trauma patients receiving fibrinogen concentrate. Clin Chim Acta 2019 Aug;495:253-262. **IFOM-Evidenzgrad:3b↓**
Rizoli S et al. In Trauma, Conventional ROTEM and TEG Results Are Not Interchangeable But Are Similar in Clinical Applicability. Mil Med 2016 May;181(5 Suppl):117-26. **IFOM-Evidenzgrad:3b↓**
Spagnolello O et al. Introduction of a ROTEM protocol for the management of trauma-induced coagulopathy. Trauma (United Kingdom) 2021;23(4):308-321. **IFOM-Evidenzgrad:2b**
(2) Connelly CR et al. Assessment of three point-of-care platelet function assays in adult trauma patients. J Surg Res 2017 May 15;212:260-269. **IFOM-Evidenzgrad:2b**

European Trauma, 6th edition 2023

coagulation monitoring, coagulation support, goal-directed therapy

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

We *recommend* the early and repeated monitoring of haemostasis, using either a traditional laboratoy determination such as prothrombin time (PT)/international normalised ratio (INR), Clauss fibrinogen level and platelet count and/or point-of-care (POC) PT/INR and/or a viscoelastic method.
(Rec. 11; **1C**)

Gleichwertigkeit von Standardlabor und POC INR und VET ???

We *recommend* that monitoring and measures to support coagulation be initiated immediately upon hospital admission.
(Rec. 24; **1B**)

"Early and goal-directed therapeutic intervention improves coagulation …"

We *recommend* that resuscitation measures be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM.
(Rec. 26; **1B**)

"… VEM is highly specific for hyperfibrinolysis, the most lethal and resource-intensive phenotype of fibrinolysis in trauma, and is more sensitive in the detection of coagulopathy than CCAs ... trend towards improved survival in the prespecified subgroup that was coagulopathic (INR > 1.2), which became significant in the subgroup with TBI (iTACTIC) … TEG/ROTEM-guided transfusions were also associated with fewer additional invasive haemostatic interventions …VEM is useful to guide individualised goal-directed coagulation therapy in patients with traumatic coagulopathy (Text Rec. 26) …"

We *recommend* that the routine use of POC platelet function devices for platelet function monitoring in trauma patients on antiplatelet therapy or with suspected platelet dysfunction be avoided.
(Rec. 24; **1B**)

"… diagnostic cut-offs for pathologic platelet dysfunction after traumatic injury have not been established ..."

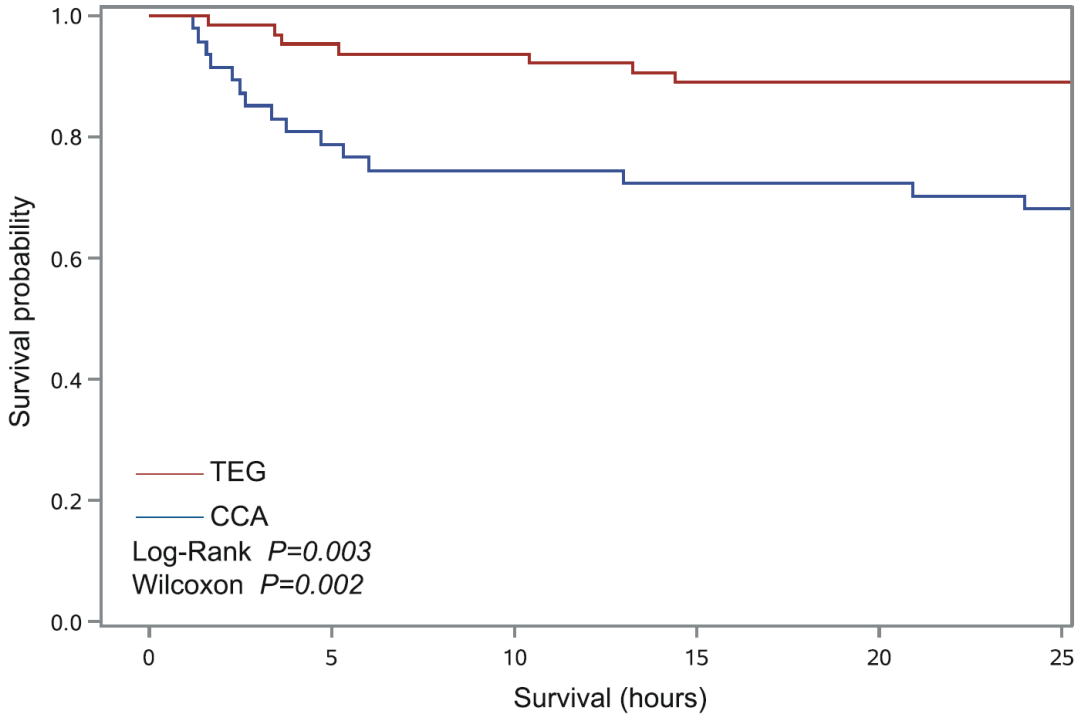
Überlebensvorteil durch POC

IFOM-2021/22: Evidenzgrad 1b

Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy.

Gonzalez E et al. Ann Surg 2016

pragmatic, randomized clinical trial (RCT); Denver, Colorado; upon MTP activation (SBP <70mm Hg or SBP 70–90mm Hg with HR ≥108 beats/min), randomized TEG vs. CCA (i.e., INR, fibrinogen, platelet count); 111 trauma patients (TEG = 56, CCA = 55) ; ISS of 30 (24–43), 67.6% blunt injury mechanism, 18.9% severe TBI



as treated	CCA (n=47)	TEG (n = 64)	P
deaths	40.4%	18.7%	0.011
time to death	3.5 h (2.2-8.3)	11.5 h (4.9-211.0)	0.073
death in first 6 h	23.4%	6.2%	0.010
death > 6h	17.0%	12.5%	0.589
haemorrhagic deaths	23.4%	7.8%	0.020

important limitation:
- clear fluid resuscitation with use of 4 l at 2h, 8 l at 6h and 14 l at 24 h
- very low plasma and PLT to RBC ratio in the initial phase

Überlebensvorteil durch POC

Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study.

IFOM-2021/22: Evidenzgrad 2b

Hagemo JS et al. Crit Care 2015

prospective international multicentre (UK, Denmark, Norway) cohort study as part of the Activation of Coagulation and Inflammation in Trauma study (ACIT) 3, led by the International Trauma Research Network (INTRN)collaboration; ATC defined as laboratory INR >1.2; 808 patients; massive Transfusion 6.1%, ATC 11.0%, ISS in INR >1.2 33 (22) and in MT 29 (16)

Table 4 Optimum thresholds and respective test accuracy parameters for predicting (a) acute traumatic coagulopathy (ATC) defined as INR >1.2 and (b) massive transfusion (MT) (defined as ≥10 units of PRBC)

Test parameter	*Optimum threshold*		*Detection rate*		*False positive rate*		*PPV*		*NPV*	
(a)										
EXTEM CA5	≤37	(34-39)	66.3	(55.1-76.3)	18.8	(15.9-21.9)	29.9	(23.4-37.1)	95.2	(93.2-96.8)
FIBTEM CA5	≤8	(5-8)	67.5	(55.9-77.8)	20.7	(17.7-23.9)	26.9	(20.8-33.8)	95.6	(93.5-97.1)
Fibrinogen	≤1.61	(1.36-1.9)	73.6	(63.0-82.4)	11.5	(9.2-14.1)	45.1	(36.7-53.6)	96.3	(94.5-97.7)
Platelet count	≤199	(128-199)	61.7	(46.4-75.5)	29.9	(26.6-33.4)	11.9	(8.1-16.7)	96.5	(94.6-97.9)
(b)										
EXTEM CA5	≤40	(32-40)	72.7	(57.2-85.0)	31.3	(28.0-34.8)	12.2	(8.5-16.8)	97.7	(96.0-98.8)
FIBTEM CA5	≤9	(6-9)	77.5	(61.5-89.2)	32.8	(29.4-36.4)	11.4	(7.9-15.8)	98.2	(96.6-99.2)
Fibrinogen	≤1.90	(1.39-2.18)	77.8	(62.9-88.8)	29.7	(26.4-30.1)	14.0	(9.9-18.9)	98.1	(96.5-99.1)
INR	≥1.13	(1.0-1.16)	70.2	(55.1-82.7)	19.0	(16.2-22.1)	19.2	(13.6-25.9)	97.7	(96.2-98.7)
Platelet count	≤174	(159-182)	52.8	(41.9-63.5)	14.8	(12.2-17.7)	32.2	(24.7-40.4)	93.1	(90.8-95.0)

INR, international normalized ratio; PRBC, packed red blood cells; PPV, positive predictive value; NPV, negative predictive value; CA5, clot amplitude after 5 minutes.

Überlebensvorteil durch POC

Introduction of a ROTEM protocol for the management of trauma-induced coagulopathy.

IFOM-2021/22: Evidenzgrad 2b

Spagnolello O et al. Trauma 2021

single centre (Edinburgh, Scotland), prospective, observational Emergency Department based study; 57 trauma patients; overall in-hospital mortality 22.8%; 1g TXA prehospital

DIAGNOSIS		A5 in EXTEM		
		≤ 10 mm	11-27 mm	≥ 28 mm
A5 in FIBTEM	≤ 3 mm	Low fibrinogen Low platelets	Low fibrinogen (platelets)	Low fibrinogen
	4-6 mm	Low platelets Low fibrinogen	Low platelets Low fibrinogen	Clot firmness appears ok
	≥ 7 mm	Low platelets	Low platelets	

NEW PROTOCOL BASED ON A5 NOT A10

TREATMENT		A5 in EXTEM		
		≤ 10 mm	11-27 mm	≥ 28 mm
A5 in FIBTEM	≤ 3 mm	8 units FFP (or 4 FFP + 2 pools/10 units cryoprecipitate) + 2 bags platelets	8 units FFP (or 4 FFP + 2 pools/10 units cryoprecipitate) + 1 bag platelets	4 units FFP
	4-6 mm	4 units FFP + 2 bags platelets	4 units FFP + 1 bag platelets	Fibrinogen concentration and platelet count satisfactory*
	≥ 7 mm	2 bags platelets	1 bag platelets	

„Edinburgh ED algorithm“:

Median time from admission to
- CCT result 83 minutes (IQR 60–93)
- ROTEM A5 results 51 minutes (IQR 32-93; p = 0.0006)

RETIC: 50.5 min vs. 10 min
Innerhofer P et al. Lancet Haematol 2017

Trauma-induced coagulopathy (TIC) was identified
- in 24.5% using CCT [1]
- in 38.5% using ROTEM [2] (p = 0.11, n.s.)

[1] INR >1.5; fibrinogen concentration ≤1.5 g/l; platelet count ≤50 or platelet count ≤100 in ongoing bleeding / TBI

[2] iTACTIC protocol: A5 FIBTEM <10 mm, A5 EXTEM - A5 FIBTEM <30 mm, EXTEM CT >80 s

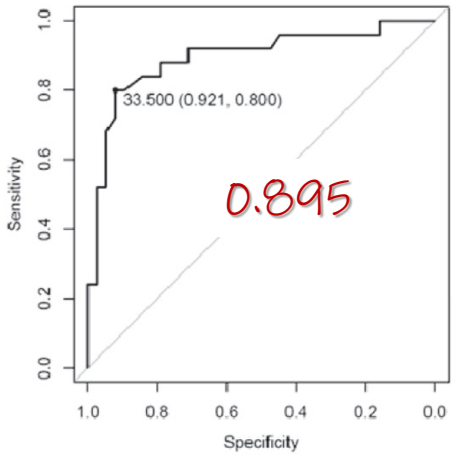
Überlebensvorteil durch POC

IFOM-2021/22: Evidenzgrad 2b

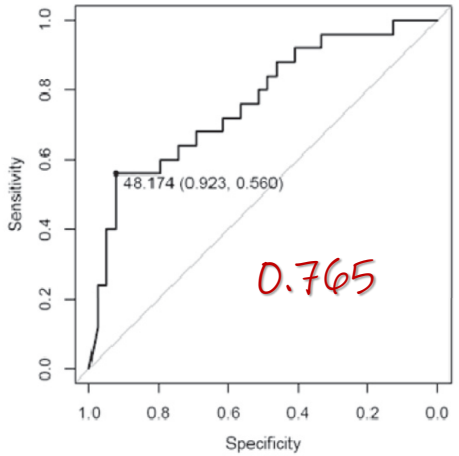
Assessment of three point-of-care platelet function assays in adult trauma patients.

Connelly CR et al. J Surg Res 2017

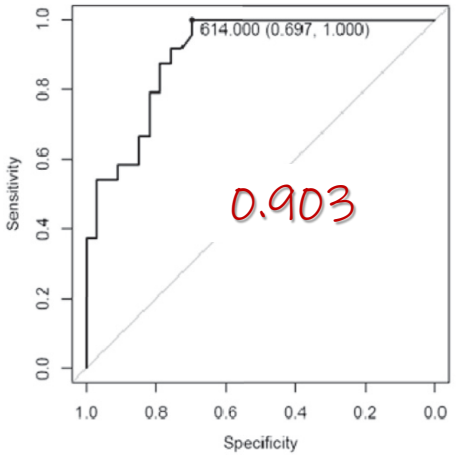
Oregon Health & Science University (Portland, USA); prospective observational study of 64 trauma patients (25 AP and 39 non-AP) at risk for coagulopathy and hemorrhage (GCS <10, SBP <90 mm Hg, intubation, BD >6 mEq/L); blood samples within 1 h of arrival; test for AP medication use (ASA and clopidogrel); 30 patients with platelet dysfunction (Multiplate ASPI AUC <40U) and 33 patients with functional platelets (Multiplate APSI AUC ≥40U)



Multiplate ASPI AUC



TEG-PM AA

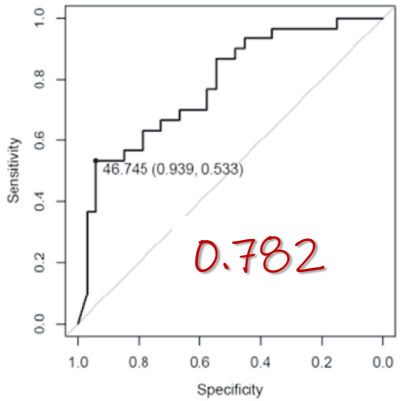


VerifyNow ARU

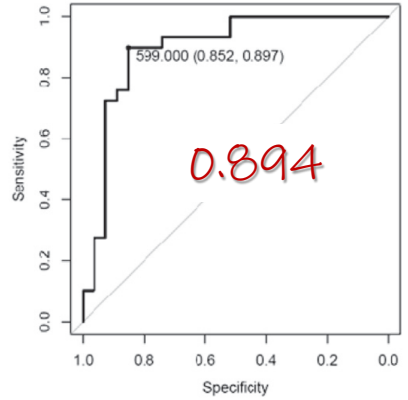
ROC Curves for Detecting Patients on **Any Antiplatelet therapy**

"Multiplate ASPI AUC, TEG-PM AA percent inhibition, and VerifyNow ARU accurately identified AP medication use and platelet dysfunction in trauma patients."

Correlation of TEG-PM and VerifyNow with Multiplate to **Define Platelet Dysfunction**



TEG-PM AA



VerifyNow ARU

Überlebensvorteil durch POC

IFOM-2021/22: Evidenzgrad 1b

Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial.

Baksaas-Aasen K et al. Intensive Care Med 2021

multi-centre, randomized controlled trial (International Trauma Research Network INTRN); empiric MHPs, augmented by either VHA or CCT-guided interventions; 396 patients (VHA n=201, CCT n=195); 2/3 blunt trauma; median ISS 26 vs 26; pre-hospital TXA 94% vs 96%

- no difference in the proportion of patients who were alive and free of massive transfusion
- no differences in other secondary outcomes or serious adverse events

24 h: VHA: 67%, CCT: 64%, OR 1.15, 95% CI 0.76–1.73
28-day: VHA: 25%, CCT: 28%, OR 0.84, 95% CI 0.54–1.31

- **PTr >1.2 at baseline**: (n=102)

24 h: VHA: 57%, CCT: 52%, OR 1.23, 95% CI 0.56–2.69

- **severe TBI** (AIS head ≥4): alive and free of massive transfusion (n=74),

24 h: VHA: 64%, CCT: 46%, OR 2.12, 95% CI 0.84–5.34

- time of study intervention 21 min earlier (VHA 61 min, IQR 48–85; CCT 80 min, IQR 60–106,) with more additional interventions (more fibrinogen supplementation, median dose VHA 4 g, CCT 0 g).

Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy

Probleme:

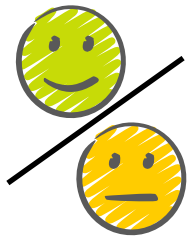
- Koagulopathie = prothrombin time ratio (PTr) >1,2, aber Patienten mit PTr > 1.2: VHA 25% vs. CCT 32%
- geplante Blutproduktgabe nur bei 67% vs. 36%
- in beiden Gruppen "initial transfusion pack" (EK 2[1-4] +FFP+TK) VOR Einschluss („hybrid strategy"), daher in beiden Gruppen wenig Transfusion: median EK 2(1-4), median FFP 0(0-2), TK 0(0-0); Massivtransfusion 26% vs. 28%
- keine Differenzierung ROTEM (A5!!!) vs. TEG
- Ausschluss bei Tod innerhalb 1h nach Einschluss („golden hour")

⇒ keine Berücksichtigung in der S3-LL

Is ROTEM Diagnostic in Trauma Care Associated with Lower Mortality Rates in Bleeding Patients?—A Retrospective Analysis of 7461 Patients Derived from the TraumaRegister DGU®.

Riehl K et al. J Clin Med 2022

retrospective analysis of the TraumaRegister DGU®; 2009-2016; 7461 patients from 371 hospitals; AIS ≥3 +coagulopathy (PTT ≥ 40, or INR ≥1.4 or Quick ≤60%) or the need for blood transfusion before ICU admission) + hospital with ≥10trauma per year; **non-ROTEM-using years** (279 hospital years = 5946 patients) **vs. ROTEM-using years** (ROTEM in >20% of pat.; 92 hospital years = 1515 patients);



- **patients receiving haemostatic therapy** (TXA, fibrinogen, PCC): ROTEM years 56.1% (850/1515) vs. Non-ROTEM years 45.7% (2717/5964); p <0.001
- **fibrinogen supplementation**: 54.4% vs. 29.1%, p <0.001
- **RBC transfusion rate**: ROTEM years with ROTEM use 14.0% (110/790) vs. ROTEM years without ROTEM use 6.1% (44/725); p ≤0.001
- **reduced mortality** in ROTEM years with ROTEM use: 30.6% vs. 35.6%; difference -5%; p =0.043

ROTEM ist zumindest sehr hilfreich!

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**

Wichtig!

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

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

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.

Frage:

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**)

Frage:

Ein Algorithmus?

eskalierende Therapieoptionen koagulopathischer Blutungen für die Nutzung ohne VET

1. Stabilisierung der Rahmenbedingungen (**Prophylaxe** und **Therapie!**)	Kerntemperatur ≥**34 C** (möglichst Normothermie) pH-Wert ≥ **7,2** ionisierte Ca^{++}-Konzentration **>0,9 mmol/l** (möglichst Normokalzämie)
2. frühestmögliche Hemmung einer potentiellen (Hyper-)Fibrinolyse (immer VOR Gabe von Fibrinogen!)	**Tranexamsäure** initial **1 g** (15 mg/kgKG), ggf. 1 g in 10 min + 1 g über 8 h
3. Substitution von Sauerstoffträgern	**EK**: hämostaseologisches Ziel bei massiver Blutung: Hb ~7-9 g/dl (4,3-5,5 mmol/l)
4. Substitution von Gerinnungsfaktoren (bei fortbestehender schwerer Blutungsneigung) Bei Patienten, die Massivtransfusionen benötigen (werden) oder einen blutungsbedingten, lebensbedrohlichen Schock haben und die Gerinnungstherapie bei Massivtransfusionen durch die Gabe von therapeut. Plasma durchgeführt wird, können von einem hohen Verhältnis Plasma:EK:TK im Bereich von 4(bis 5) zu 4(bis 5) zu 1 **oder** der kombinierten Gabe von therapeutischem Plasma und Faktorenkonzentraten sowie Thrombozytenkonzentraten profitieren. und (bei V. a. Thrombozytopathie) verstärkte Thrombozytenadhäsion an das Endothel + Freisetzung von „Von-Willebrand-Faktor“ und FVIII aus Lebersinusoiden (→ Agonist für Vasopressin Rezeptor Typ 2)	**Fibrinogen** 3-6 g (30–60 mg/kgKG; Ziel: 2-2,5 g/l) und ggf. **PPSB** initial 25 IE/kg KG ggf. **FXIII** 20 IE/kg KG; Ziel: FXIII-Aktivität >60% **DDAVP = Desmopressin** 0,3 µg/kgKG über 30 min („1 Ampulle pro 10 kgKG über 30 min“)
5. Zum Ersatz des Plasmavolumens	**therap.Plasma** ≥ 30 ml/kg KG
6. Substitution von Thrombozyten für die primäre Hämostase	**Thrombozytenkonzentrate**: Ziel bei transfusionspflichtigen Blutungen u./o. SHT > 100 000/µl
7. ggf. Thrombin-Burst mit Thrombozyten- und Gerinnungsaktivierung („Rahmenbedingungen“ beachten!! Off-Label-Use!)	im Einzelfall & bei Erfolglosigkeit aller anderen Therapieoptionen ggf. **rFVIIa** initial 90 µg/kgKG

CAVE:

- innerhalb von 24 Stunden nach Beendigung der zur Blutung führenden Pathologie ist eine **Thromboseprophylaxe** obligat!

VET-Algorithmen
Cave

- Standardisierung / Vergleichbarkeit der VETs bei verschiedenen Anwendern wurde durch die Nutzung von Kassetten, sog. "controlled cartridge systems" erreicht (ROTEM™sigma, TEG™6s) Amgalan A et al. J Thromb Haemost 2020.

- Die Ergebnisse unterschiedlicher VETs (ROTEM™ vs. TEG™ vs. ...) sind nicht untereinander austauschbar Rizoli S et al. Mil med 2016, unterschiedliche Generationen des gleichen Gerätes (d.h., ROTEM™delta vs. ROTEM™sigma bzw. TEG™5000 vs. TEG™6s [v.a. Lyse]) und selbst unterschiedliche Kassetten („single use" vs. „liquid reagent" vs. „controlled cartridge") können zu unterschiedlichen Ergebnissen führen Leal-Noval SR et al. Expert Rev Clin Pharmacol 2020; Baksaas-Aasen K et al. Ann Surg 2019; Gillissen A et al. Scand J Clin Lab Invest 2019.

- "... we recommend developing normal ranges locally as they need to be device- and manufacturer- specific." Amgalan A et al. JTH 2020

- Wichtig ist, dass VET ziemlich unsensible für gering / mäßig fibrinolytische Aktivität sind Curry NS et al. Br J Haematol 2019; Leal-Noval SR et al. Expert Rev Clin Pharmacol 2020.

- VET sollen die klinische Beurteilung unterstützen, nicht ersetzen Bugaev N et al. J Trauma Acute Care Surg 2020; behandelt wird der blutende Patient in der jeweiligen klinischen Situation, nicht ein Referenzwert.

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 **PPSB*** (initial 25 IE/kg bzw. ($Quick_{Ist}$ - $Quick_{Soll}$) x kg KG)	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 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

Vielen Dank !

Hemostasis = Love

Everybody talks about it,
nobody understands it.

JH Levy 2000

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