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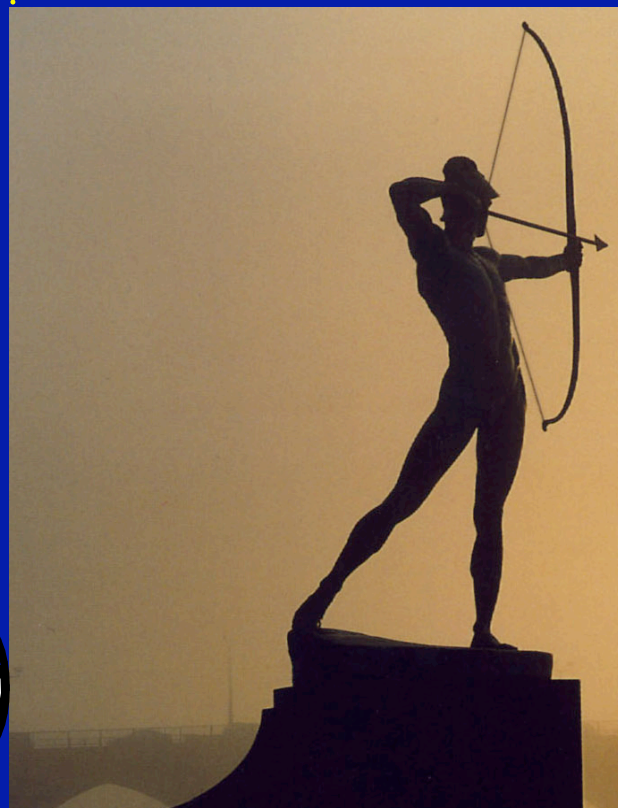
- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

Bleeding Management in Severe Trauma



Marc Maegele

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University of Witten/Herdecke

Campus Cologne-Merheim

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Trauma-induced coagulopathy

Guideline-Surgery

Guideline-Haemostasis

Conculusions

Disclosures

Marc Maegele has received support and honoraria for lecturing and travelling over the past from the following:

NovoNordisk, CSL Behring, Pfizer, TEM International, Pentapharm, Siemens and Astra Zeneca

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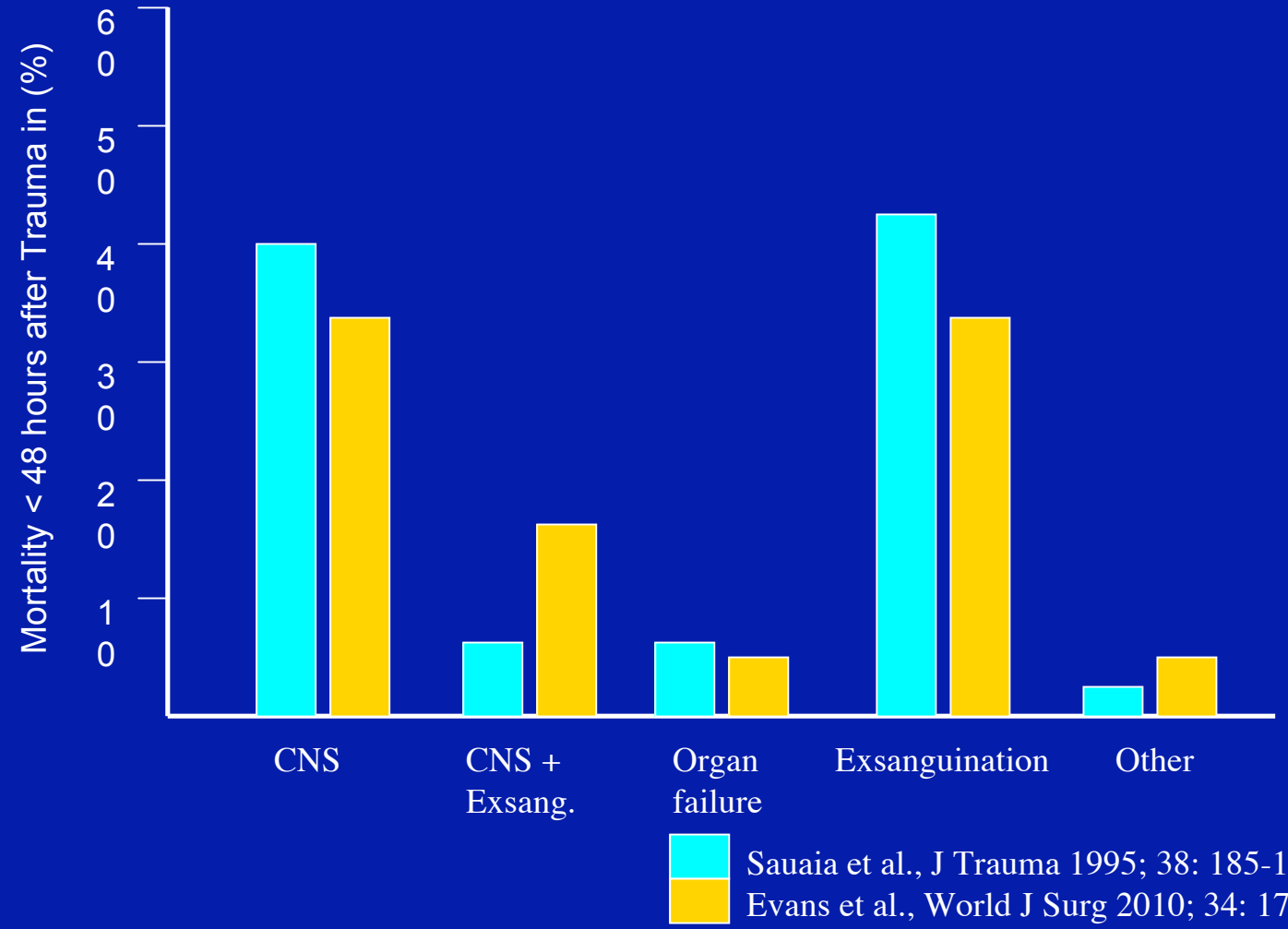
Uncontrolled Bleeding is a Major Cause of Death in Trauma

(Patients dying in-hospital within the first 48 hours after trauma)



Sauaia et al., J Trauma 1995; 38: 185-193

Evans et al., World J Surg 2010; 34: 1720-21

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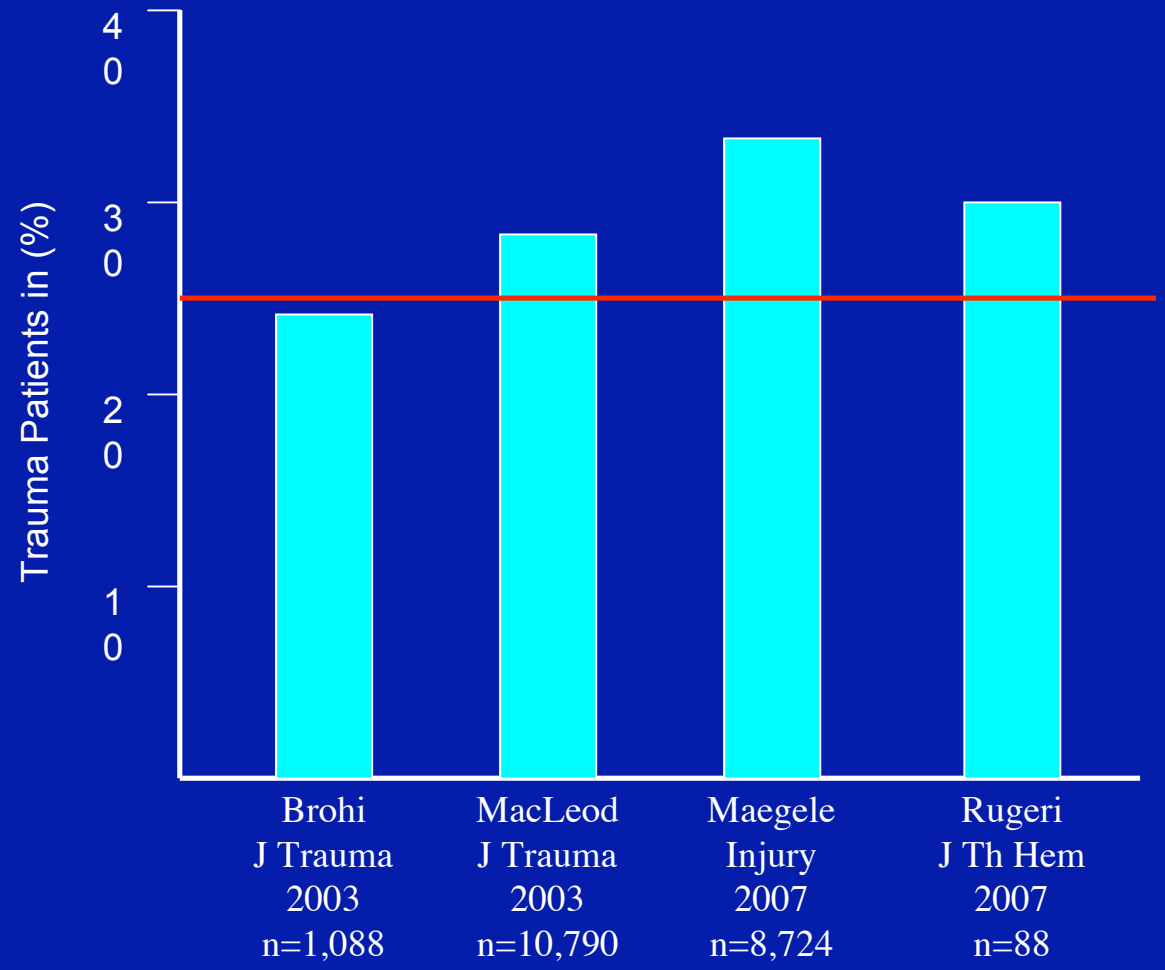
The Incidence of Acute Post-Traumatic Coagulopathy upon ER Admission

(25% of trauma patients are coagulopathic upon ER admission)



25% !

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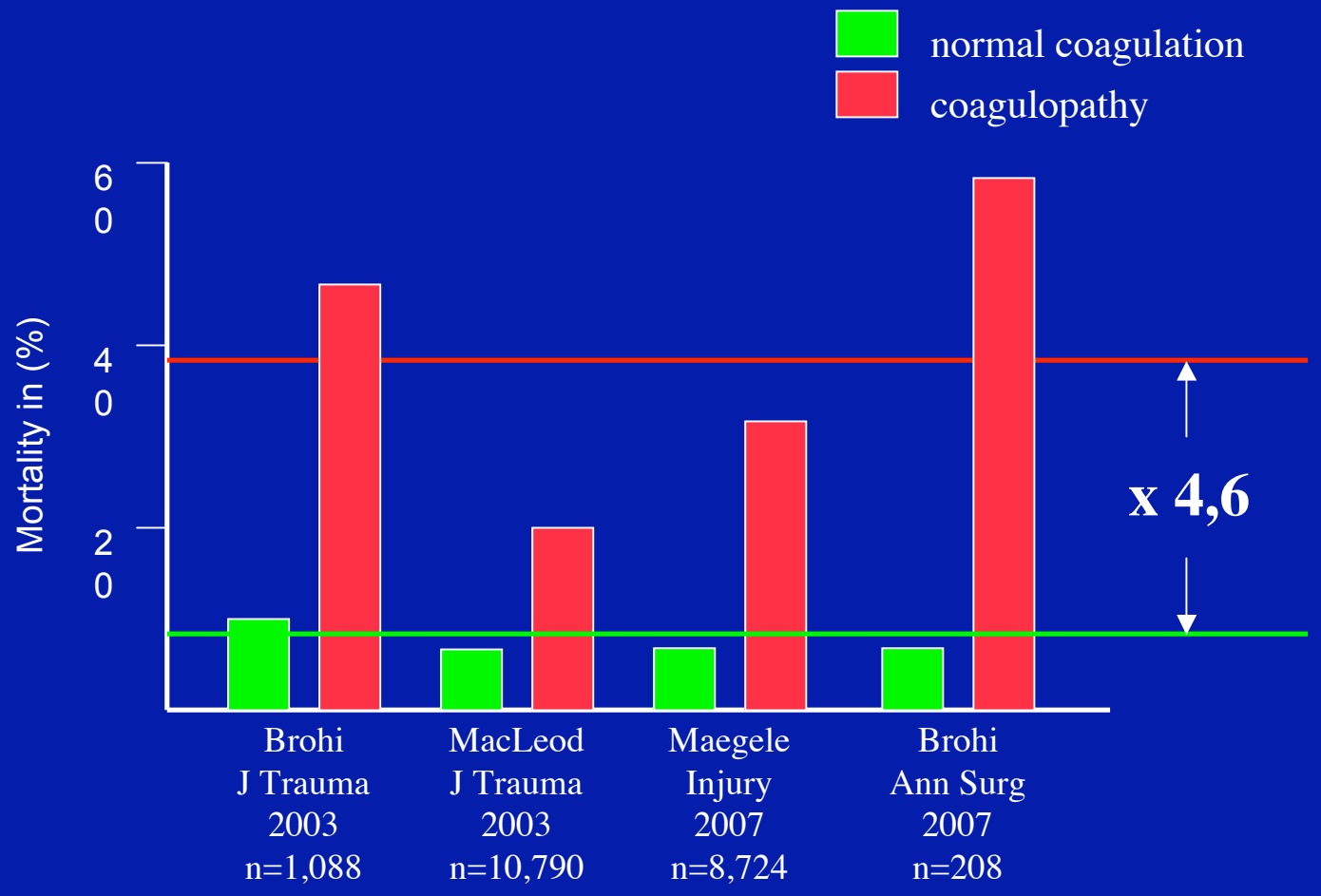
The Clinical Significance of Acute Post-Traumatic Coagulopathy : Mortality



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Uncontrolled bleeding is still the major cause of preventable/potentially preventable death after trauma

J Trauma. 2007 Dec;63(6):1338-46; discussion 1346-7. doi: 10.1097/TA.0b013e31815078ae.

Preventable or potentially preventable mortality at a mature trauma center.

Teixeira PG, Inaba K, Hadjizacharia P, Brown C, Salim A, Rhee P, Browder T, Noguchi TT, Demetriades D.

Division of Trauma Surgery and Surgical Critical Care, Department of Surgery, University of Southern California, Los Angeles, California, USA.

2,081 trauma death analyzed (1 Level 1 Trauma Center/ USA = 8 years)

51 deaths classified as „preventable or potentially preventable deaths“ (2,5%)

mean age 40 yrs; 66,7% male; mean ISS 27; 74,5% blunt

Caused of death:	bleeding (20; 39,2%)
	multi-organ failure / MOF (14; 27,5%)
	cardio-circulatory arrest (8; 15,6%)
Caused by:	delay in treatment (27; 52,9%)
	wrong or missing diagnostic assessment (17; 33,4%)
Time of death:	≤ 24 hrs (26; 51,1%)
	≥ 7 Tage (16; 31,4%)

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Key recommendations „Management of Acute Traumatic Haemorrhage“ S3-Guideline Polytrauma

Schlüsselempfehlungen für die Gerinnungstherapie	GoR der S3-Leitlinie
Die *trauma-induzierte Koagulopathie* ist ein eigenständiges Krankheitsbild mit deutlichen Einflüssen auf das Überleben. Aus diesem Grund soll die Gerinnungsdiagnostik und Therapie im Schockraum unmittelbar begonnen werden.	A „soll“
Ein spezifisches *Massivtransfusionsprotokoll* sollte eingeführt und fortgeführt werden.	B „sollte“
Die *Auskühl*	B „sollte“
Eine *Azidäm*	B „sollte“
Wird die Geri Verhältnis	B „sollte“
Eine Substitu	B „sollte“
Bei Patienten arterieller D bei Verletzungen des zentralen Nervensystems kontraindiziert.	0 „kann“
Die *Thrombelastographie bzw. -metrie* kann zur Steuerung der Gerinnungsdiagnostik und -substitution durchgeführt werden.	0 „kann“
Eine *Hypokalzämie* <0,9 mmol/l sollte vermieden und kann therapiert werden.	0 „kann“
Bei einem aktiv blutenden Patienten kann die Indikation zur Transfusion bei *Hämoglobinwerten* unter 10 g/dl bzw. 6,2 mmol/l gestellt und der *Hämatokritwert* bei 30% gehalten werden.	0 „kann“

Trauma-induced coagulopathy

=

„own clinical entity“

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- Trauma-induced coagulopathy
- Guideline-Surgery
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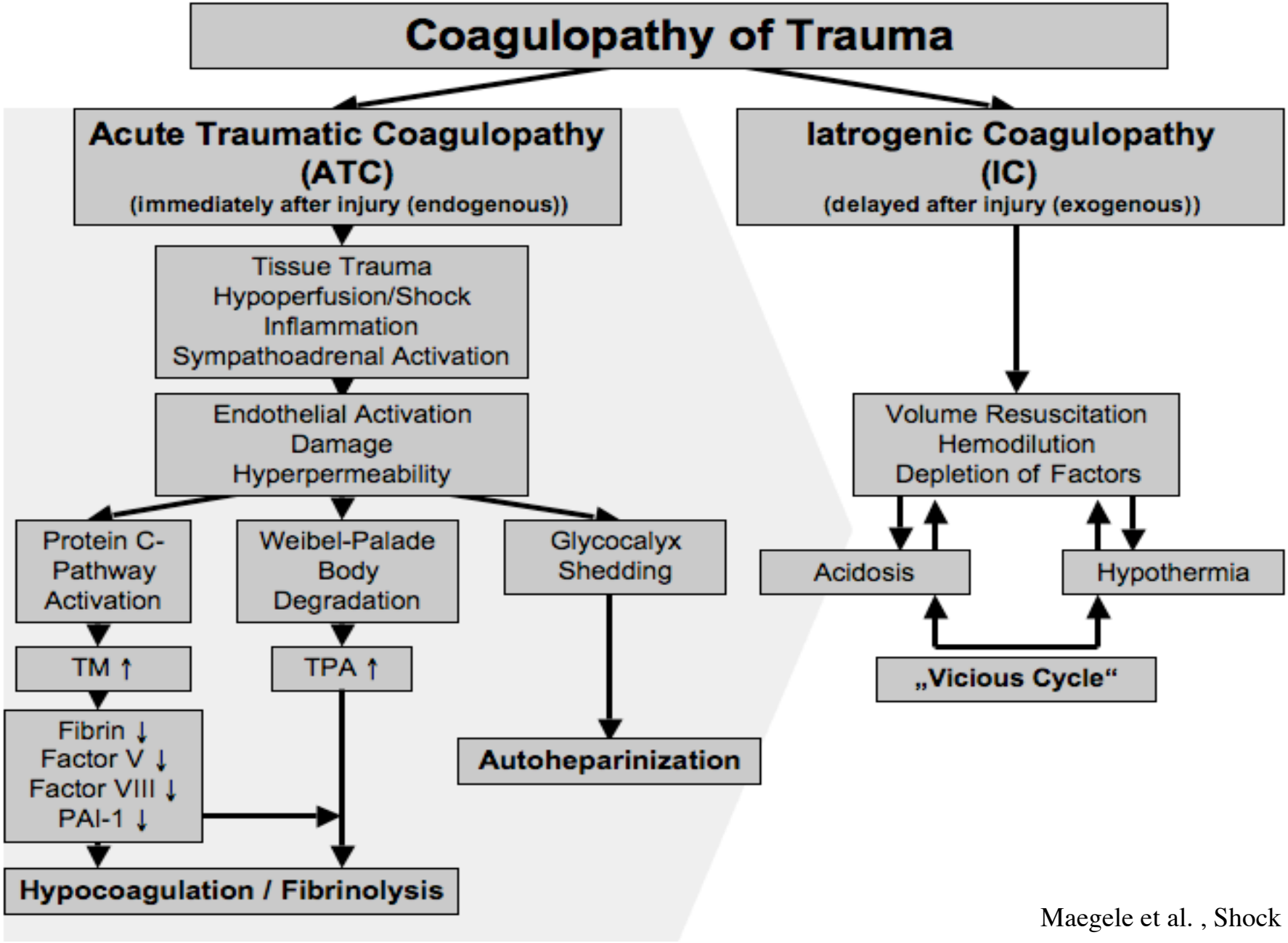
- Conculusions

What are the triggers for the acute coagulopathy of trauma ?

The current concept



Maegele et al. , Shock 2013

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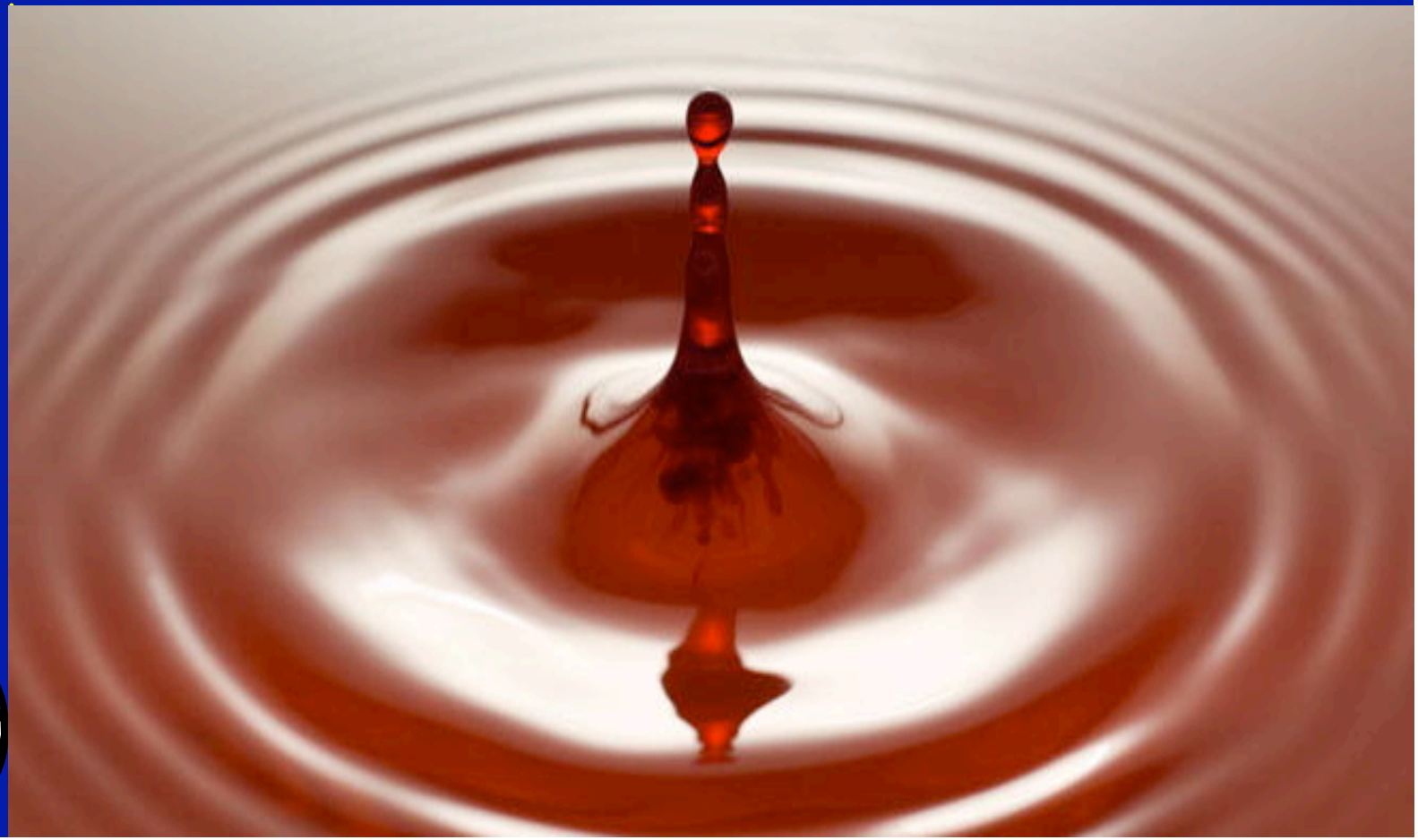
- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

What can we do?

Therapeutic Options



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- Conculusions

Critical Care 2007, 11:R17 (doi:10.1186/cc5686)
This article is online at: http://ccforum.com/content/11/1/R17

Research

Open Access

Management of bleeding following major trauma: a European guideline

Donat R Spahn[1], Vladimir Cerny[2], Timothy J Coats[3], Jacques Duranteau[4], Enrique Fernández-Mondéjar[5], Giovanni Gordini[6], Philip F Stahel[7], Beverley J Hunt[8], Radko Komadina[9], Edmund Neugebauer[10], Yves Ozier[11], Louis Riddez[12], Arthur Schultz[13], Jean-Louis Vincent[14] and

Rossaint et al. Critical Care 2010, 14:R52
http://ccforum.com/content/14/2/R52

CRITICAL CARE

RESEARCH Open Access

Management of bleeding following major trauma: an updated European guideline

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3], Timothy J Coats[4], Jacques Duranteau[5], Enrique Fernández-Mondéjar[6], Beverley J Hunt[7], Radko Komadina[8], Giuseppe Nardi[9], Edmund Neugebauer[10], Yves Ozier[11], Louis Riddez[12], Arthur Schultz[13], Philip F Stahel[14], Jean-Louis Vincent[15], Donat R Spahn[16*]

Spahn et al. Critical Care 2013, 17:R76
http://ccforum.com/content/17/2/R76

CRITICAL CARE

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Management of bleeding and coagulopathy following major trauma: an updated European guideline

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R1: Minimal elapsed time

R2: Tourniquet use

R3: Initial assessment

R5: Immediate intervention

R6: Further investigation

R7: Imaging

R8: Intervention

Σ = 37 Recommendations
13/37 „surgical“

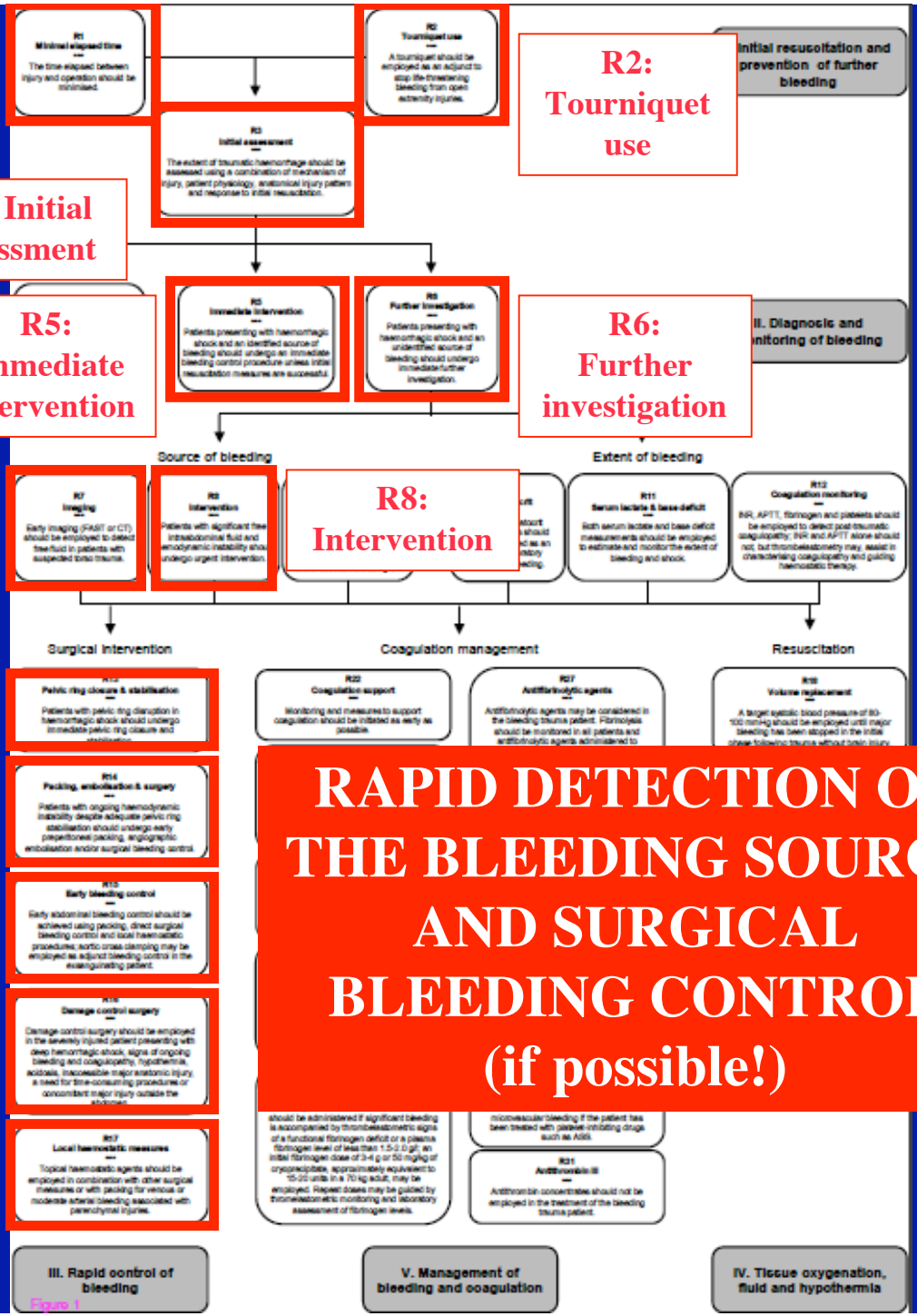
R13: Pelvic ring closure & stabilization

R14: Packing, embolisation & surgery

R15: Early bleeding control

R16: Damage control surgery

R17: Local haemostatic measures



RAPID DETECTION OF THE BLEEDING SOURCE AND SURGICAL BLEEDING CONTROL (if possible!)

Recommendation 4:

We recommend that the physician clinically assess the extent of traumatic hemorrhage using a combination of patient physiology, anatomical injury pattern, mechanism of injury and the patient´s response to initial resuscitation! > ATLS-Concept!

(R4: Initial assessment; 1C)

Table 2. American College of Surgeons Advanced Trauma Life Support (ATLS) classification of blood loss* based on initial patient's presentation. Table reprinted with permission from the American College of Surgeons [37]

4 classes of hypovolemic shock

	Class I	Class II	Class III	Class IV
Blood loss (ml)	Up to750	750-1500	1500-2000	>2000
Blood loss (% blood volume)	Up to 15%	15%-30%	30%-40%	>40%
Pulse rate	<100	100-120	120-140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14-20	20-30	30-40	>35
Urine output (ml/h)	>30	20-30	5-15	Negligible
CNS / mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

*for a 70 kg male

Recommendation 4:

We recommend that the physician clinically assess the extent of traumatic hemorrhage using a combination of patient physiology, anatomical injury pattern, mechanism of injury and the patient´s response to initial resuscitation! > ATLS-Concept!

(R4: Initial assessment; 1C)

Table 3. American College of Surgeons Advanced Trauma Life Support (ATLS) responses to initial fluid resuscitation. Table reprinted with permission from the American College of Surgeons [37]

	Rapid response	Transient response	Minimal or no response
Vital signs	Return to normal	Transient improvement, recurrence of decreased blood pressure and increased heart rate	Remain abnormal
Estimated blood loss	Minimal (10%-20%)	Moderate and ongoing (20%-40%)	Severe (>40%)
Need for more crystalloid	Low	High	High
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and crossmatch	Type-specific	Emergency blood release
Need for operative intervention	Possibly	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

* 2000 ml of isotonic solution in adults; 20 ml/kg bolus of Ringer's lactate in children

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Recommendation 2:

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

(R2: Tourniquet use; 1C > 1B !)

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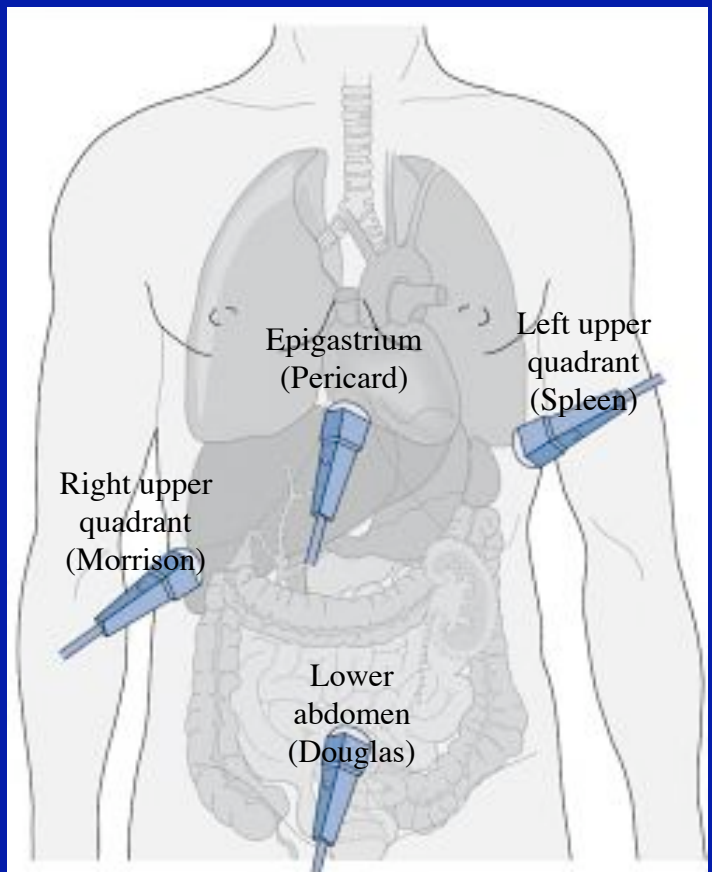
Recommendation 7:

We recommend early imaging (FAST ultrasound and/or CT) for the detection of free fluid in patients with suspected torso trauma!

(R7: Imaging; 1B)

FAST (Focused Assessment Sonography of Trauma): 4 Views !



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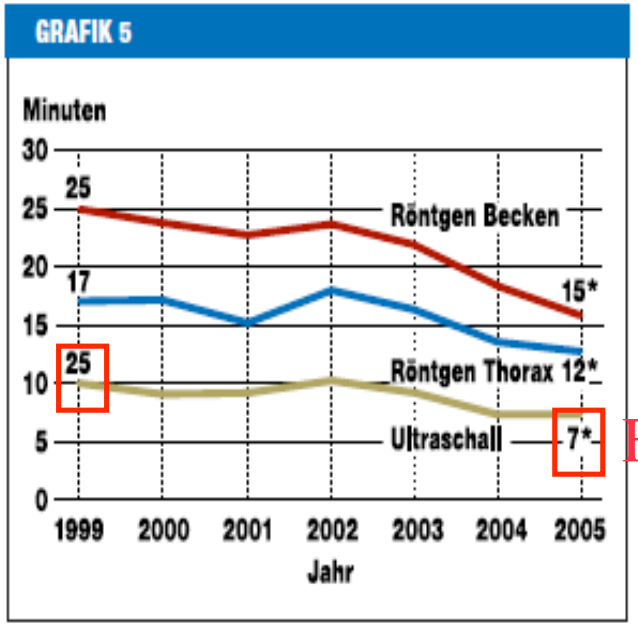
We recommend early imaging (FAST ultrasound and/or CT) for the detection of free fluid in patients with suspected torso trauma!

(R7: Imaging; 1B)



Dauer der sonografisch-radiologischen Basisdiagnostik in Minuten (* $p < 0,05$ für im Vergleich zu 1999)

FAST

Ruchholz et al., Dt Ärzteblatt 2008;105:225-231

Jahresbericht 2012

für den Zeitraum bis Ende 2011

Primärdiagnostik	TR-DGU 2011 (23.416) %	TR-DGU 2011 (23.416) n	TR-DGU gesamt (93.024) %	TR-DGU gesamt (93.024) n
Sonographie Abdomen	85,2%	16.741	87,9%	64.416
Röntgen Thorax	53,2%	9.265	68,7%	46.101
CCT (separat oder Ganzkörper)	86,5%	17.826	82,2%	64.681
Ganzkörper-CT *	71,8%	14.801	60,6%	42.710
Abbruch der SR-Diagnostik**	4,1%	417	4,2%	2.261

Zeit zwischen Klinikaufnahme und Durchführung der ersten **Abdomen-Sonographie** bei schwerem Trauma (ISS ≥ 16) [∅ min ± SD]	7 ± 11 n=7.544
Dauer bis zur Durchführung eines **Ganzkörper-CT** bei allen Patienten, falls durchgeführt [∅ min ± SD]	24 ± 19 n=13.487

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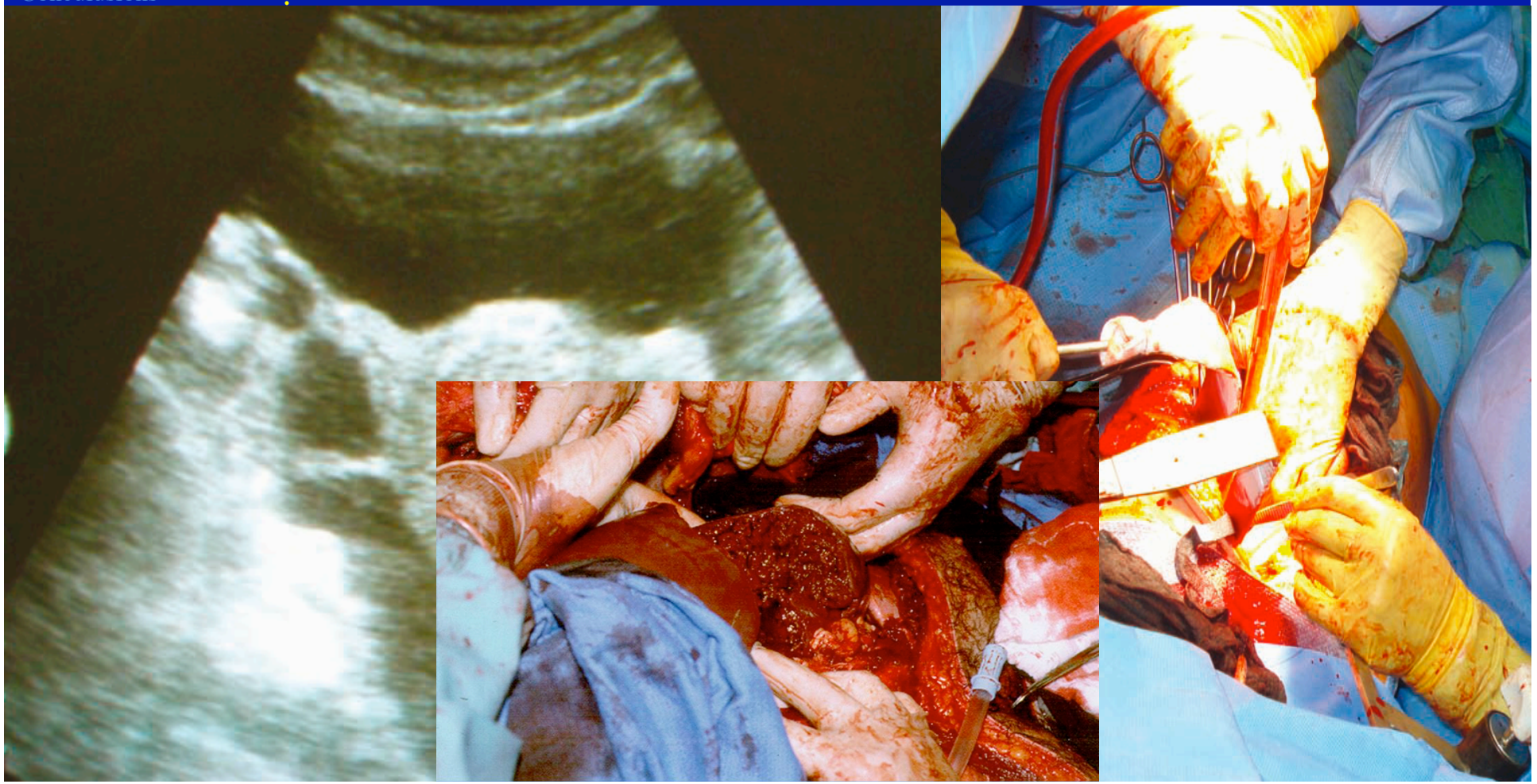
Recommendation 8:

Patients with significant free intra-abdominal fluid and hemodynamic instability undergo urgent intervention!

(R8: Intervention; 1A)



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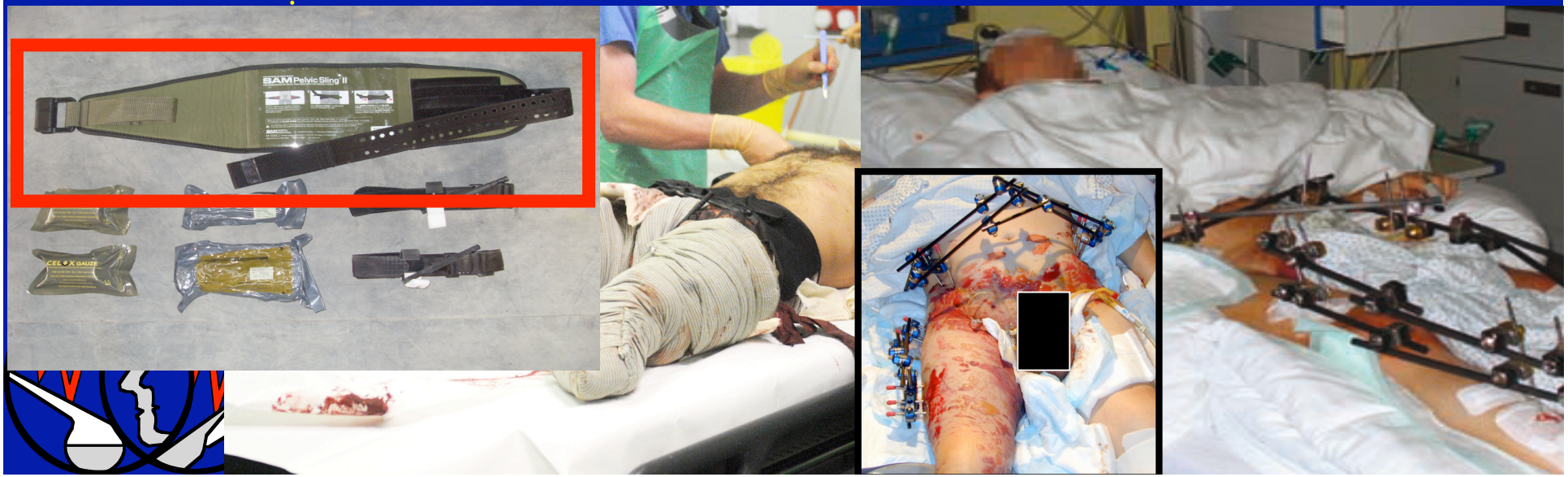
Recommendations 18, 19 and 20:

Early bleeding control of the abdomen be achieved using:

Packing, direct surgical bleeding control and the use of local hemostatic procedures (R18; 1C)

Pelvic ring closure and stabilisation in case of pelvic ring disruption and hemorrhagic shock (R19; 1B)

Angiographic embolisation (R20; 1B)



Recommendation 19:

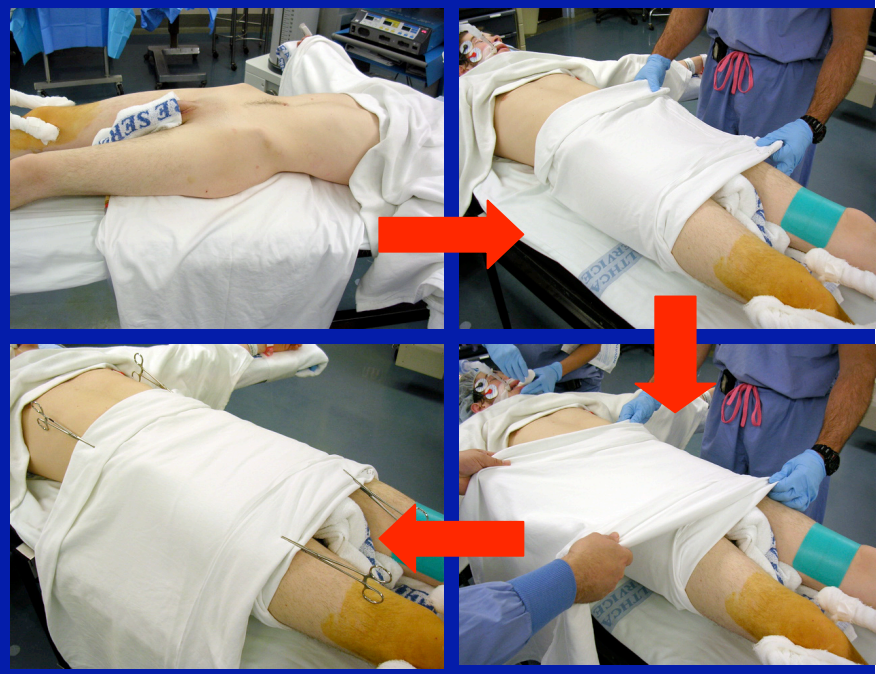
Patients with pelvic ring disruoption in hemorrhagic shock undergo immediate pelvic ring closure and stabilisation

(R19: Pelvic ring closure and stabilisation; 1B)

Closed reduction in the Emergency Room

Circumferential Sheeting

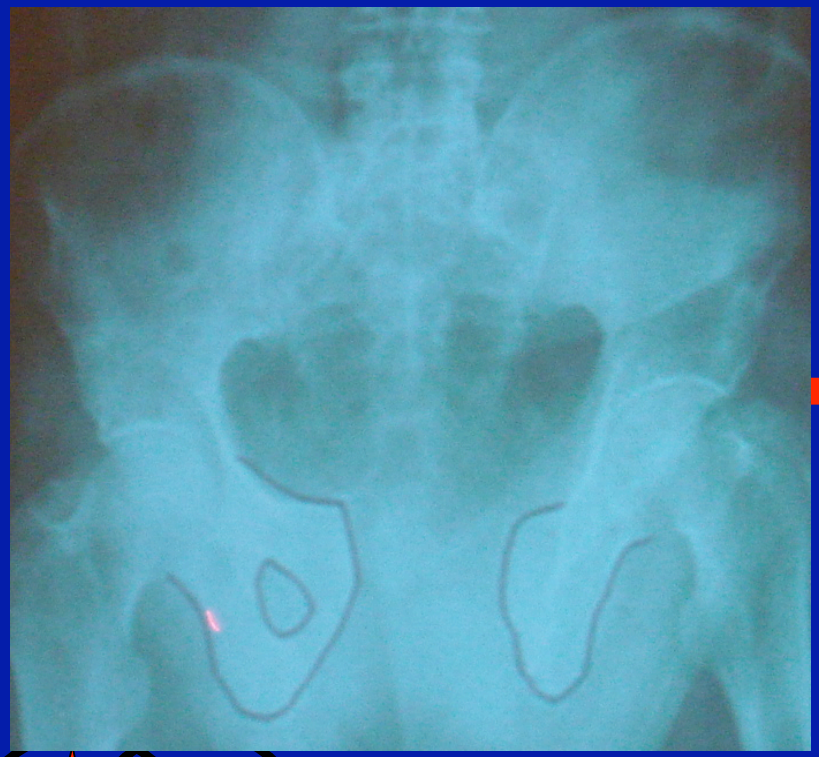
- Supine with limbs in inner rotation, adduction and knees slightly flexed adduction
- 2 “Wrappers” over trochanterics and knees
- Placement
- Apply
- “Clamper”
- 30 Seconds



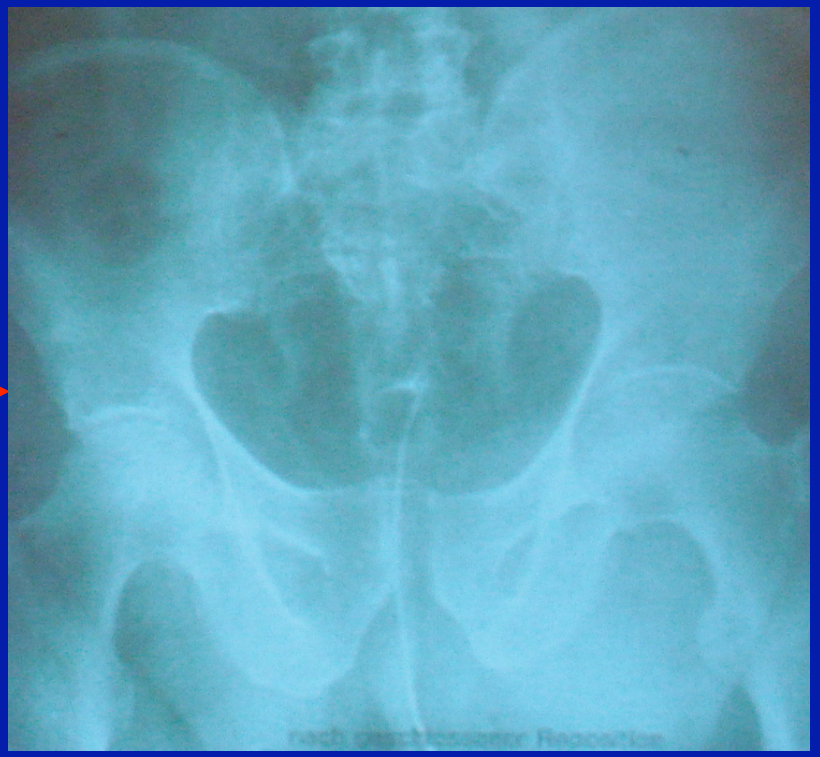
Closed reduction in the Emergency Room

Circumferential Sheeting

- Before



- After



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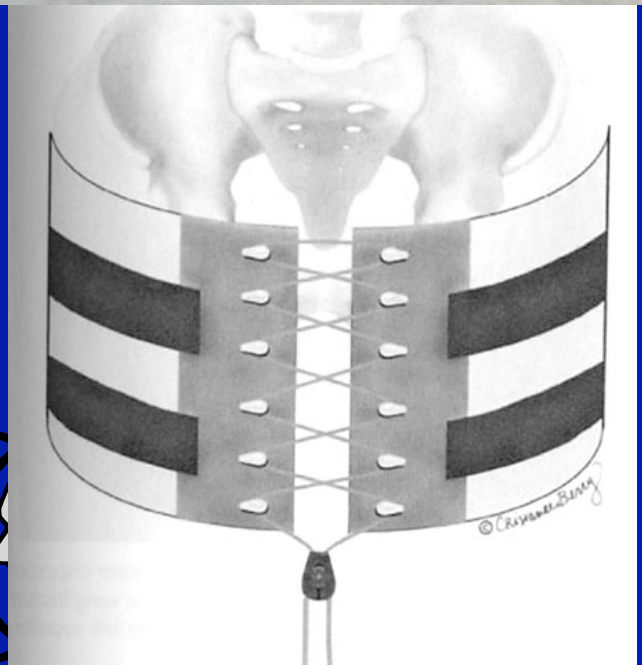
Pelvic Binders



Pelvic Binders

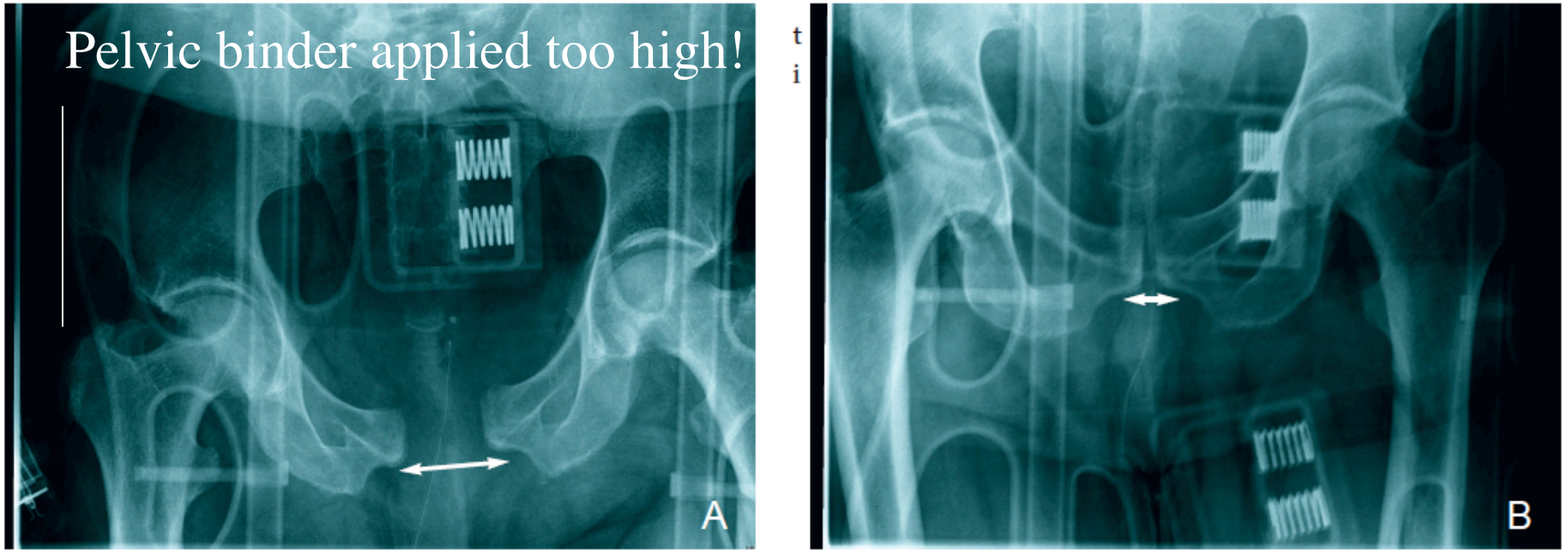


Abbildung 7 Inkompletter Beckenringverschluß bei Symphysensprengung durch zu hohe und dadurch fehlerhafte Anlage eines SAM- Sling-Beckengurts im Rahmen der präklinischen Versorgung (**A**) und nach Korrektur im Schockraum (**B**). Durch Positionierung des Beckengurts auf Höhe der Trochantären wird die maximale Kompression gewährleistet und der Beckenring vorne verschlossen! Abb. 7: M. Maegele

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Recommendation 21:

„Damage control“-surgery be employed in the severely injured patient presenting with deep hemorrhagic shock, signs of ongoing bleeding and coagulopathy!

(R21: Damage control surgery; 1C > 1B !)

Restore physiology first,

restore anatomy later!

Indications for „Damage Control“-Strategies

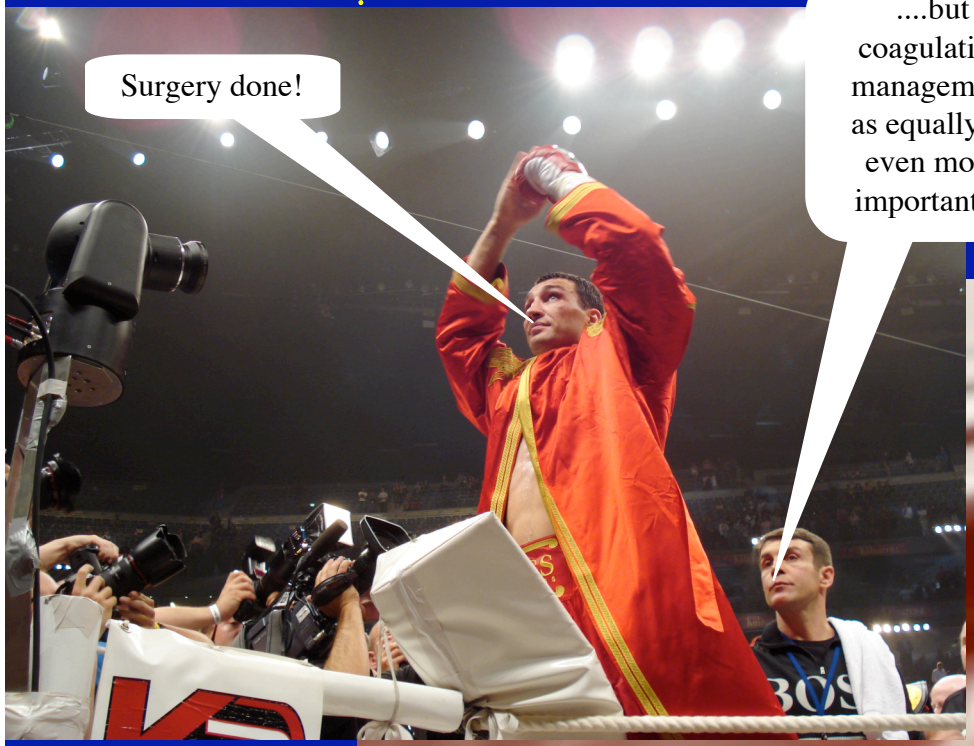
Table 1. Indications for Damage Control Surgery

Physiological Factors	Characterization of injury severity
1. Hypotension<90mmHg systolic pressure	1. Inability to establish hemostasis
2. Hypothermia (temperature < 35° C)	2. High energy blunt abdominal/chest trauma
3. Acidosis (pH < 7.2 or base deficit > 8)	3. Multiple penetrating abdominal/chest injuries
4. Coagulopathy (increase in PT and/or PTT, thrombocytopenia, hypofibrinoginemia)	4. Combined visceral injury with major vascular trauma
5. Prohibitive operative time needed for definitive repair (> 90 minutes)	5. Major intra-abdominal vascular injury
6. Massive blood requires > 10 units pRBC or body volume replacement	6. Pelvic fracture with associated abdominal/vascular life-threatening injury
	7. Massive abdominal contamination
	8. Life-threatening extra-abdominal injuries
	9. Abdominal wall reconstruction failure (IAH, ACS)

PT-prothrombin; PTT- partial thromboplastin time; pRBC-packed red blood cells; IAH- intraabdominal hypertension; ACS- abdominal compartment syndrome

Karamarkovic and Doklestic , BH Surgery 2012

Focus on coagulation support



Spahn et al. Critical Care 2013, 17:R76
http://ccforum.com/content/17/2/R76

CRITICAL CARE

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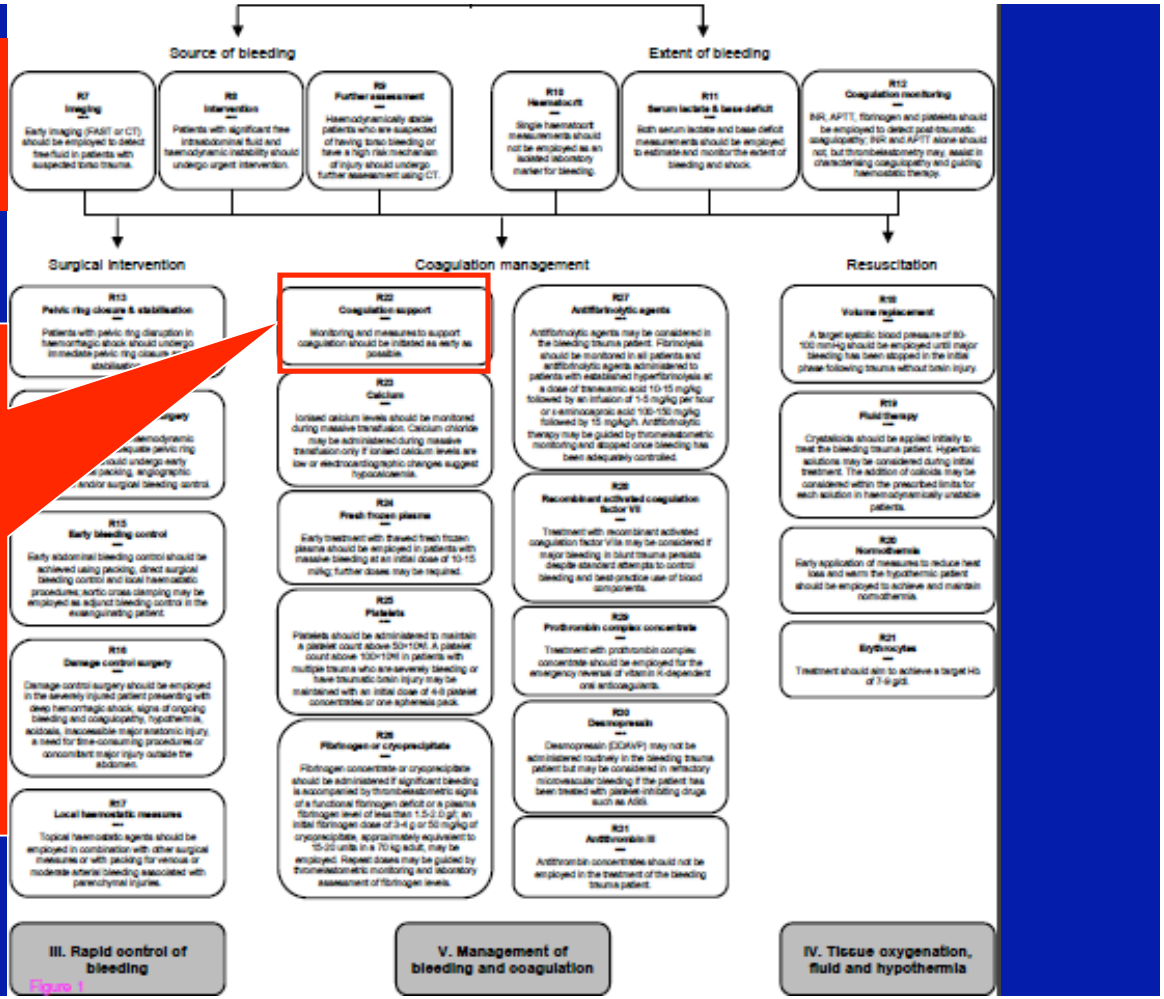
- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conclusions

Σ = 37 Recommendations
24/37 „non surgical“

Recommendation 23:
We recommend that monitoring and measures to support coagulation be initiated as early as possible (Grade 1C).



Key recommendations „Management of Acute Traumatic Haemorrhage“ S3-Guideline Polytrauma

Schlüsselempfehlungen für die Gerinnungstherapie	GoR der S3-Leitlinie
Die *trauma-induzierte* … issen auf das Überleben. Aus diese… nittelbar begonnen werden.	A „soll“
Ein spezifisches *Massiv* …	B „sollte“
Die *Auskühlung* des Pa… rden.	B „sollte“
Eine *Azidämie* sollte vermiede… en.	B „sollte“
Wird die Gerinnungstherapie b… hrt, sollte ein Verhältnis von *FFP:EK* im E…	B „sollte“
Eine Substitution von *Fibrinog*… erden.	B „sollte“
Bei Patienten, die aktiv bluten … arterieller Druck ~65 mmHg … bei Verletzungen des zentralen Nervensystems kontraindiziert.	„kann“
Die *Thrombelastographie bzw. -metrie* kann zur Steuerung der Gerinnungsdiagnostik und -substitution durchgeführt werden.	0 „kann“
Eine *Hypokalzämie* <0,9 mmol/l sollte vermieden und kann therapiert werden.	0 „kann“
Bei einem aktiv blutenden Patienten kann die Indikation zur Transfusion bei *Hämoglobinwerten* unter 10 g/dl bzw. 6,2 mmol/l gestellt und der *Hämatokritwert* bei 30% gehalten werden.	0 „kann“

Spahn *et al. Critical Care* 2013, **17**:R76
http://ccforum.com/content/17/2/R76

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Coagulation monitoring

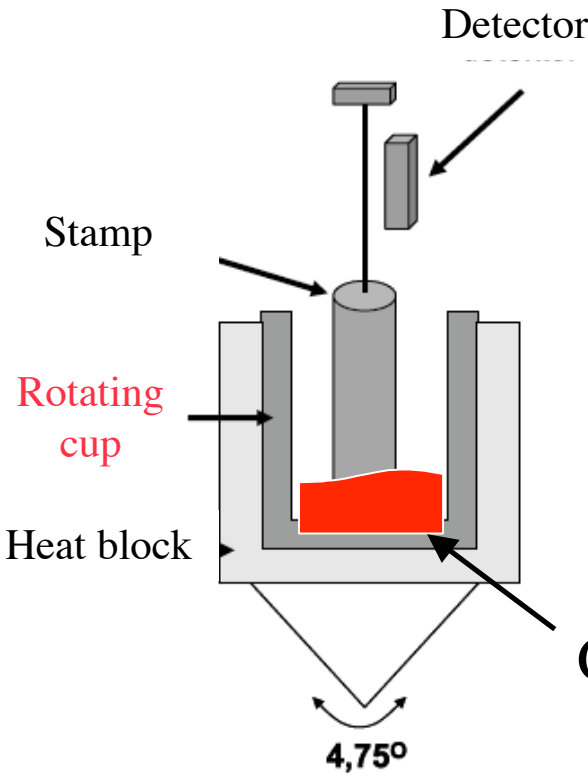
Recommendation 12 **We recommend that routine practice to detect post-traumatic coagulopathy include the early, repeated and combined measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and platelets. (Grade 1C)**

We recommend that viscoelastic methods also be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy. (Grade 1C)

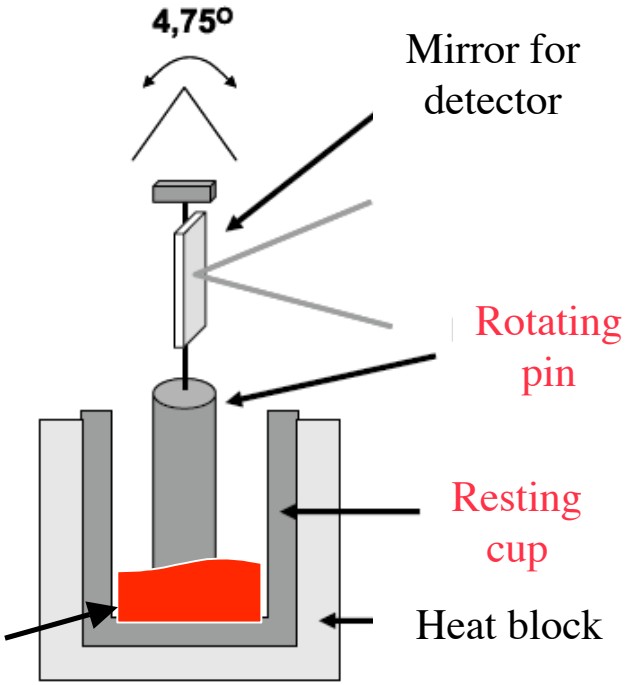
Previously 2C > now 1C !

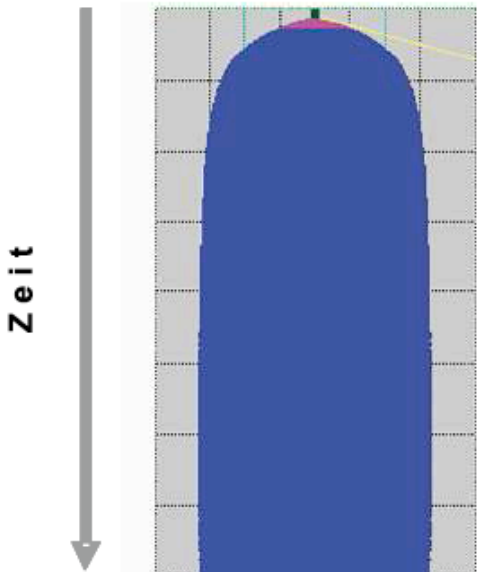
Viscoelastic assays: Principle

Thrombelastography (TEG)



Thrombelastometry (ROTEM)





Citrated blood probe with coagulation activator

- Ex vivo initiation of clotting in cup by adding a coagulation activator
- Clotting in the cup increases resistance against the rotating cup (TEG)/ pin (ROTEM)
- Degree of resistance is translated into the curve signal

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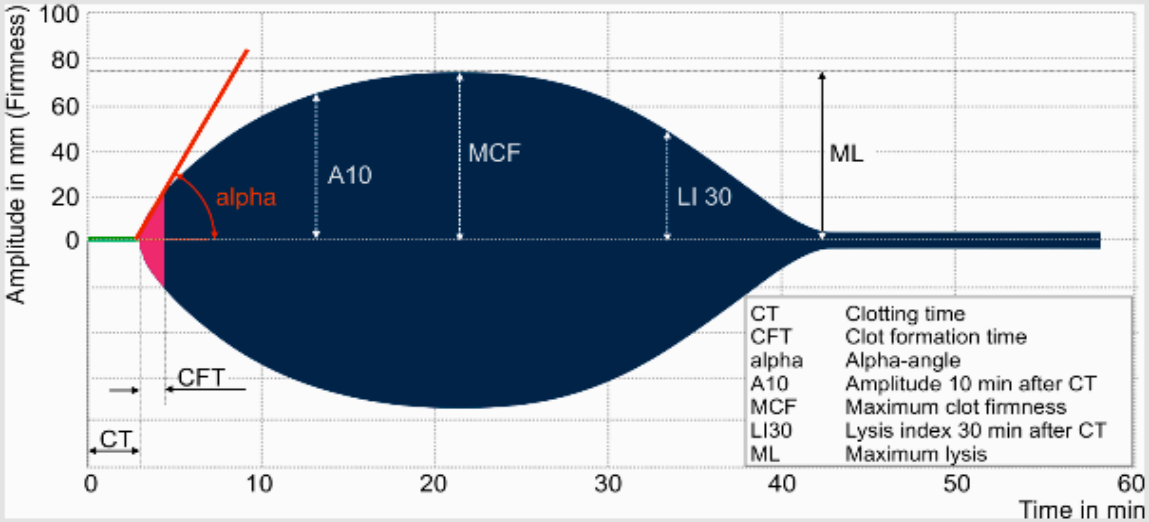
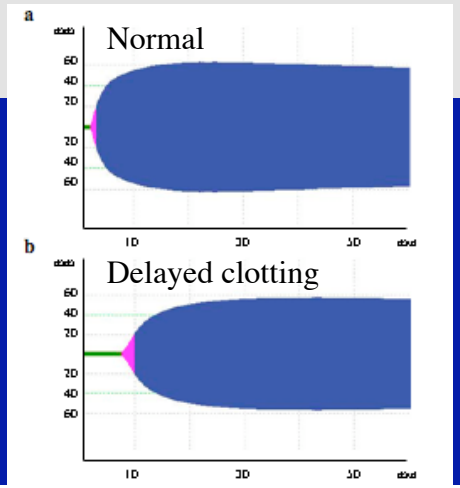
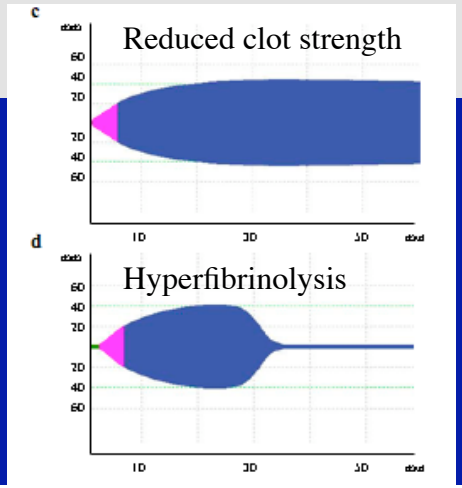
Viscoelastic assays: ROTEM®







ROTEM® Analysis

While standard clotting assays just detect the starting time of clotting, thromboelastometry (TEM®) provides information on the whole kinetics of haemostasis: clotting time, clot formation, clot stability and lysis.

The different parameters in thromboelastometry (TEM®) are dependent on:

- the activity of the plasmatic coagulation system
- platelet function
- fibrinolysis
- many factors which influence these interactions
- including several drugs

This gives a complete view of the secondary haemostasis.

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- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

Fast results > „point-of-care“

Information about

Initiation of clot formation („clotting time“)

Dynamics of clot formation

Quality of formation
(stability / sustainability)

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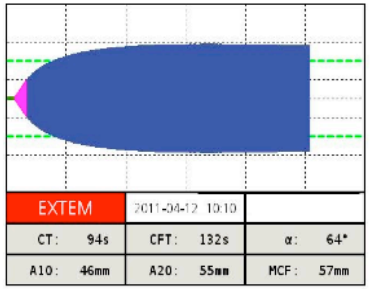
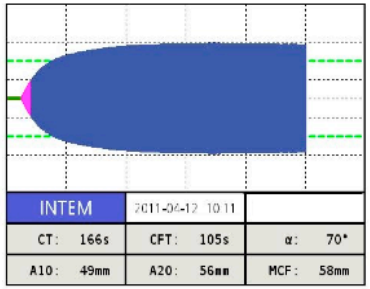
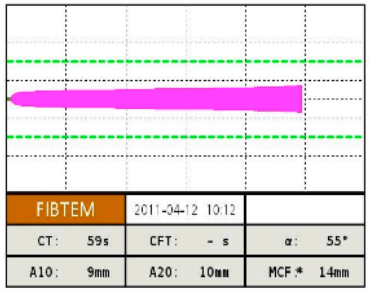
Viscoelastic assays

Reference ROTEM®







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KÖLN

21.09.2012 - 17:24 Uhr

EMPFEHLEN | DRUCKEN | KONTAKT

VOR DEN AUGEN DER SCHÜLER

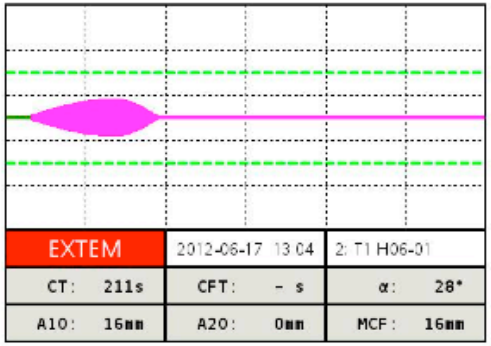
Mathelehrer von KVB-Bahn erfasst – Lebensgefahr!

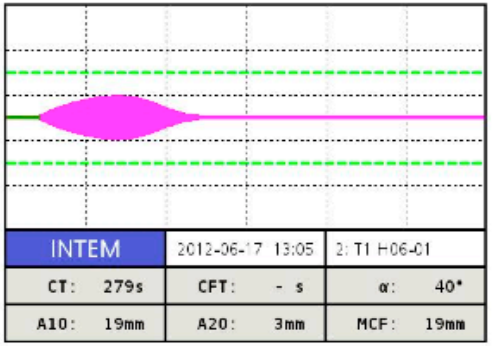
Bergischer Ring, Mülheim. Die Linie 4 erfasste einen Radler (45).
Foto: Jasmin

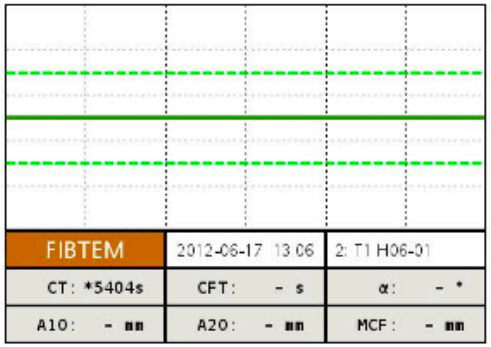
KÖLN – Ein Mathelehrer wollte mit seinem Fahrrad nach Hause fahren. Gegen 12.45 Uhr überquerte er in Höhe der Rhodiusstraße den Bergischen Ring in Mülheim.

Dabei wurde er von der KVB-Linie 4 erfasst, die Richtung Wiener Platz unterwegs war. Einige seiner Schüler wurden Zeugen des Unfalls, bei dem der Mann (45) lebensgefährlich verletzt wurde.

Auch der Bahnfahrer erlitt einen Schock, kam in die Klinik. Der komplette Verkehr Richtung Mülheim war bis 13.40 Uhr gesperrt.







Key injury:

Combined liver/spleen rupture with massive intraabdominal bleeding

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Standard coagulation assays

- long turn-around times!
- No information about the quality and dynamics of the clooting process (initiation ONLY!)

platelet measurements. It is often assumed that the conventional coagulation screens (international normalised ratio (INR) and APTT) monitor coagulation; however, these tests monitor only the initiation phase of blood coagulation, and represent only the first 4% of thrombin production [133]. It is, therefore, possible that the conventional coagulation screen appears normal, while the overall state of blood coagulation is abnormal [134-139].

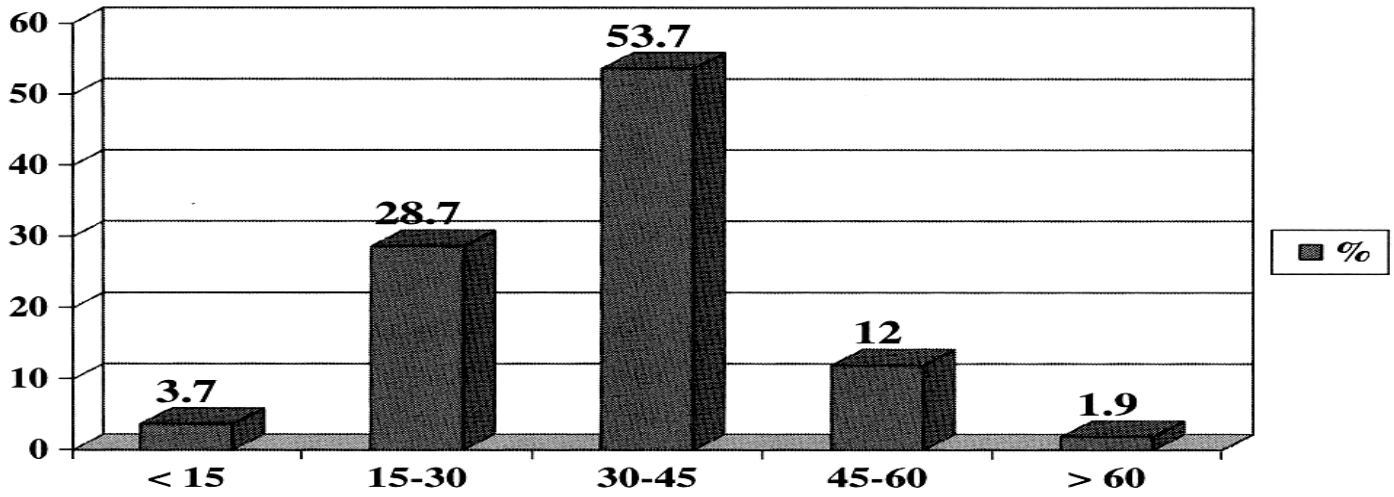

Figure 1. **Results of a TED survey "How long do you have to wait for results of conventional coagulation parameters from the central laboratory?" at the German Anesthesiology Congress 2007.**

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Standard coagulation assays

- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

➢ long turn-around times!

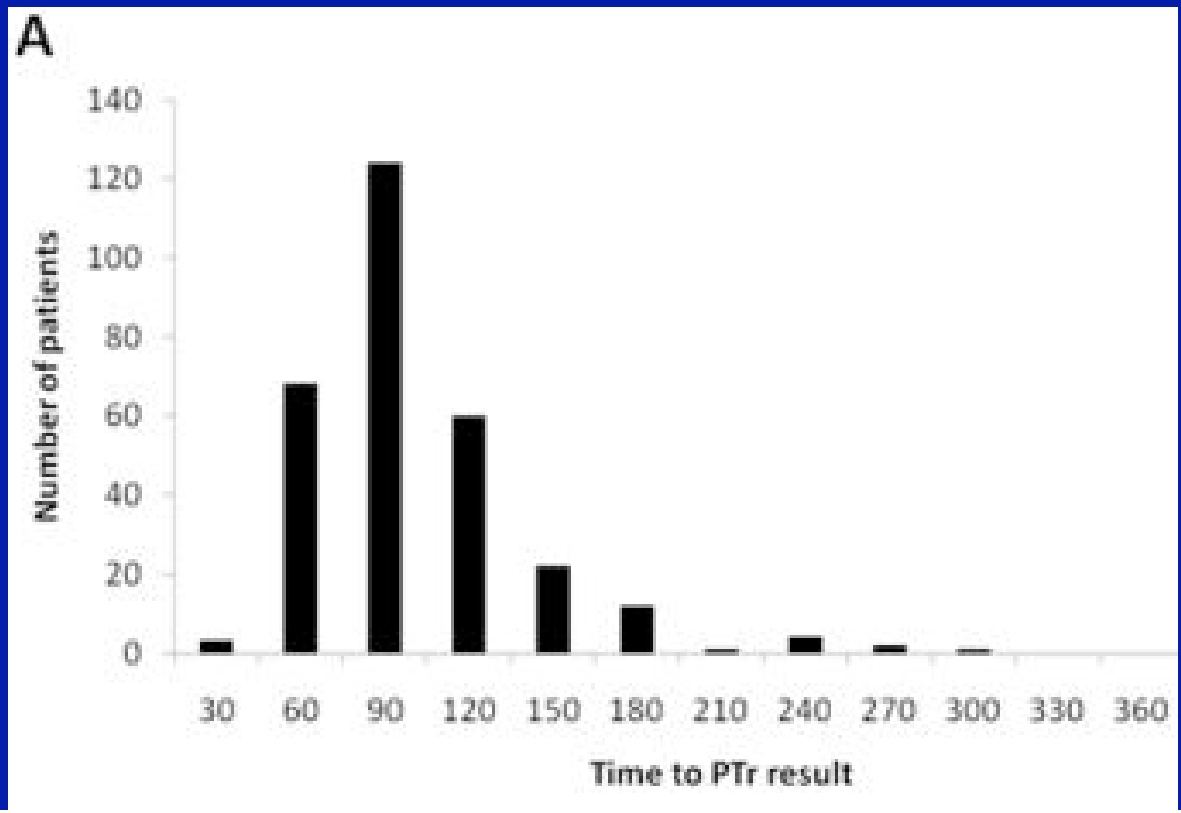
Crit Care Med. 2011 Dec;39(12):2652-8. doi: 10.1097/CCM.0b013e3182281af5.

Functional definition and characterization of acute traumatic coagulopathy.

Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, Stanworth S, Brohi K.

Trauma Sciences, Blizard Institute of Cell and Molecular Science, Bart's and the London School of Medicine and Dentistry, Queen Mary University of London, UK.

MAIN RESULTS: Three hundred patients were included in the study. Laboratory prothrombin time results were available at a median of 78 (62-103) mins. Point-of-care prothrombin time ratio had reduced agreement with laboratory prothrombin time ratio in patients with acute traumatic



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Spahn et al. Critical Care 2013, 17:R76
http://ccforum.com/content/17/2/R76

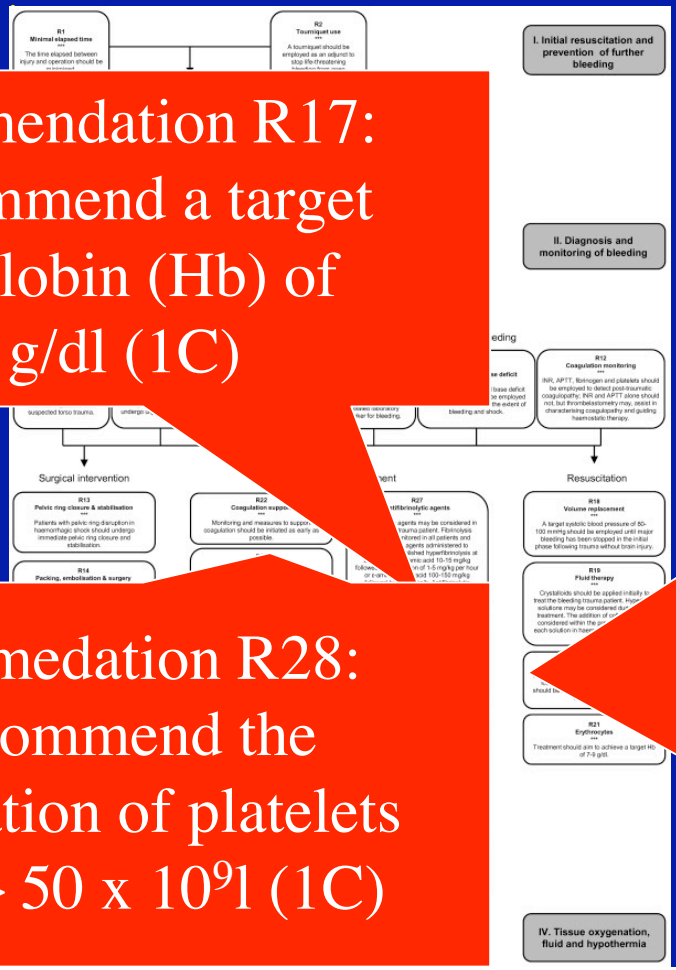
CRITICAL CARE

RESEARCH Open Access

Management of bleeding and coagulopathy following major trauma: an updated European guideline

Donat R Spahn[1], Bertil Bouillon[2], Vladimir Cerny[3,4], Timothy J Coats[5], Jacques Duranteau[6], Enrique Fernández-Mondéjar[7], Daniela Filipescu[8], Beverley J Hunt[9], Radko Komadina[10], Giuseppe Nardi[11], Edmund Neugebauer[12], Yves Ozier[13], Louis Riddez[14],

BLOOD PRODUCTS



Recommendation R17:
We recommend a target Hemoglobin (Hb) of 7-9 g/dl (1C)

Recommedation R28:
We recommend the administration of platelets to keep > 50 x 10^9l (1C)

Recommendation R26:
We recommend in massively bleeding patients the initial administration of plasma (1B) or Fibrinogen (1C). Optimum ratio FFP:pRBC of at least 1:2 (2C)
NO administration in patients that do not need !! (1B)

Recommeded initial dose 10-15 mls/kg
Additional dose according to coagulations status and neded of other blood products (Grad 1C).

Special Commentary

The Journal of TRAUMA® Injury, Infection, and Critical Care

Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma

John B. Holcomb, MD, FACS, Don Jenkins, MD, FACS, Peter Rhee, MD, FACS, Jay Johannigman, MD, FS, FACS, Peter Mahoney, FRCA, RAMC, Sumeru Mehta, MD, E. Darrin Cox, MD, FACS, Michael J. Gehrke, MD, Greg J. Beilman, MD, FACS, Martin Schreiber, MD, FACS, Stephen F. Flaherty, MD, FACS, Kurt W. Grathwohl, MD, Phillip C. Spinella, MD, Jeremy G. Perkins, MD, Alec C. Beekley, MD, FACS, Neil R. McMullin, MD, Myung S. Park, MD, FACS, Ernest A. Gonzalez, MD, FACS, Charles E. Wade, PhD, Michael A. Dubick, PhD, C. William Schwab, MD, FACS, Fred A. Moore, MD, FACS, Howard R. Champion, FRCS, David B. Hoyt, MD, FACS, and John R. Hess, MD, MPH, FACP

J Trauma. 2007;62:307–310.

In the severely injured casualty, damage control resuscitation consists of two parts and is initiated within minutes of arrival in the ED. First, resuscitation is limited to keep blood pressure at approximately 90 mm Hg, preventing renewed bleeding from recently clotted vessels.[15,17,39,57–62] Second, intravascular volume restoration is accomplished by using thawed plasma as a primary resuscitation fluid in at least a 1:1 or 1:2 ratio with PRBCs.[8,10,48–50] Our initial clinical experience shows these ratios decrease mortality in similarly injured casualties (Borgman MA, et al. unpublished data).

pRBC : FFP ratio: Does it matter?

Evidence from the Military

(Borgman M et al., J Trauma 2007; 63: 805)

- **US-Combat Support Hospital Irak 2003-2005**
- **Patients with massive transfusion (> 10 pRBCs/24h)**
- **246 patients (94% with penetrating injuries)**
- **Grouped according to pRBC:FFP ratios transfused during acute care**

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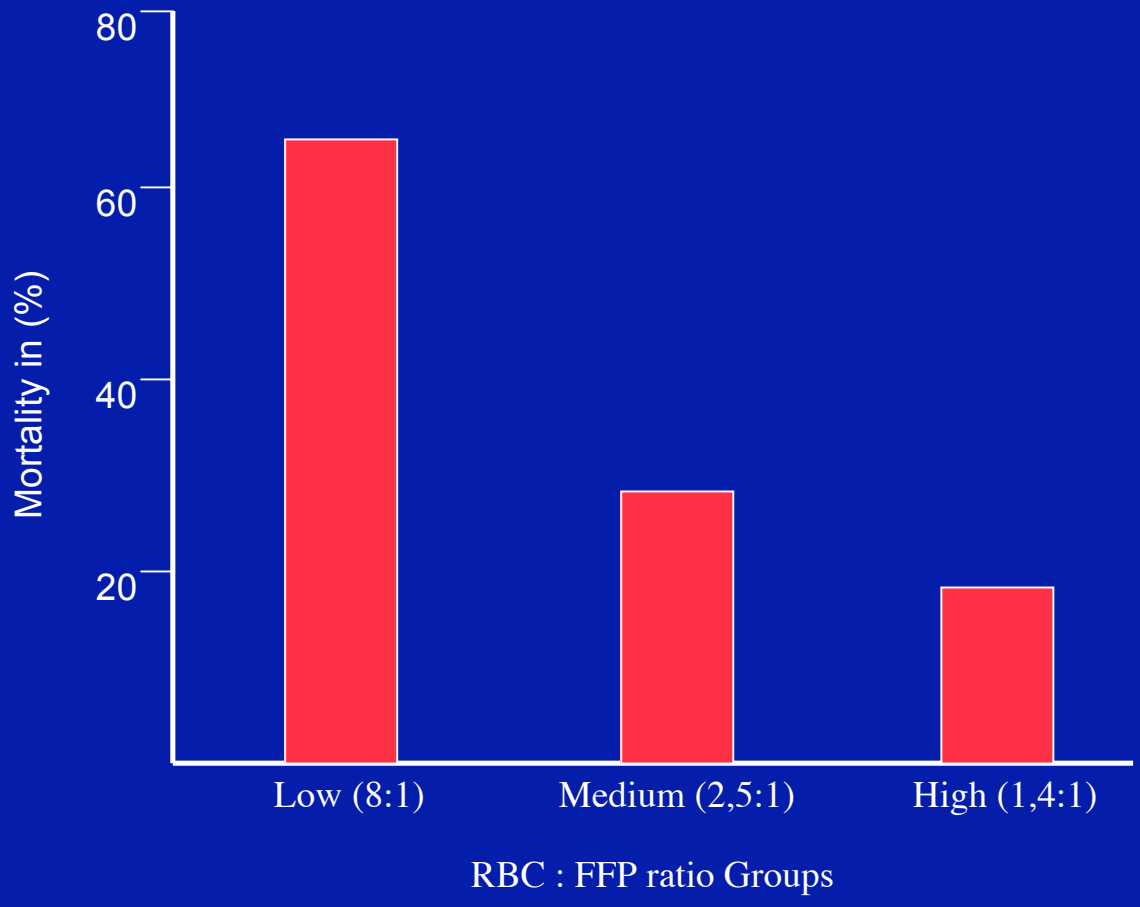
pRBC : FFP Ratio Groups



Borgman et al., J Trauma 2007; 63: 805

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The Ratio-Concept: Studies

- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

Table 1 Summary of selected, recently published studies (2007/2008) in the peer-reviewed literature, analyzing the optimal dosage (ratio) of fresh frozen plasma transfusions for coagulopathic trauma patients

Citation	Patient cohort	Study center, study period	Investigated FFP concentration/ FFP:RBC ratio	Recommended FFP concentration/ FFP:RBC ratio	Pitfalls and limitations
Kashuk *et al.* [21]	$n=133$ trauma patients, >10 RBCs/6 h	Level 1 trauma center, 2001–2006	1:1, 1:2, 1:3, 1:4, <1:5	1:2	Retrospective study; no mechanisms
Sperry *et al.* [43]	$n=415$ trauma patients, ≥8 RBCs/12 h	Multicenter study ($n=7$), 2003–2005	1:1, 1:2, 1:3, 1:4, <1:5	≥1:1.5	Retrospective study; no mechanisms
Duchesne *et al.* [44]	$n=135$ trauma patients, >10 RBCs/24 h; $n=250$ trauma patients, ≤10 RBCs/24 h	Level 1 trauma center, 2002–2006	1:1, 1:4	1:1	Retrospective study; no mechanisms
Maegele *et al.* [45]	$n=713$ trauma patients, >10 RBCs between ED and ICU admission	German Trauma Registry (DGU), 2002–2006	>1:1, 1:1, <1:1	1:1 (?)	Retrospective analysis of a prospective database; no mechanisms
Holcomb *et al.* [46]	$n=467$ trauma patients, ≥10 RBCs/24 h	Multicenter study ($n=16$), 2005–2006	≥1:2, <1:2	1:1	Retrospective study; no mechanisms
Gonzalez *et al.* [17]	$n=97$ trauma patients, ≥10 RBCs/24 h	Level 1 trauma center, 1998–2003	1:1	1:1	Retrospective study; no mechanisms
Spahn *et al.* [12••]	Systematic review of the literature	European guidelines by the Multidisciplinary Task Force for Advanced Bleeding Care in Trauma	Systematic review of the literature	10–15 ml/kg (initial FFP dose) for PT or aPTT > 1.5 × control	Review of the literature; recommendations based on limited available science
Spinella *et al.* [47]	$n=708$ combat trauma patients, ≥1 RBCs overall	Combat support hospital, 2003–2004	0–4:2–7	Each FFP unit increased survival; each RBC unit decreased survival	Retrospective study; no mechanisms
			1:1.4, 1:2.5, 1:8	1:1.4	Retrospective study; no mechanisms
			0:1–1:2.9, 1:3–1:1.49, 1:1.5–0.9:1, ≥1:1	2:3	Retrospective study; no mechanisms
			1:1 versus any other ratios	1:1 does not improve outcome	Small group of patients ($n=51$) in 1:1 cohort

in time; DGU, Deutsche Gesellschaft fur Unfallchirurgie (German Trauma tensive care unit; PT, prothrombin time; RBC, red blood cell units.

TABLE II.—*MTP examples.*

Study	Package 1	Package 2	Package 3	Notes
Cotton *et al.*[31]	10 RBC, 4 AB- TP, 2 SDP	6 RBC, 4 TP, 2 SDP	Repeat Package 2	Cryo with physician request
Dente *et al.*[10]	6 RBC, 6 AB TP	6U RBC, 6 TP, 1 SDP	6 RBC, 6 TP, 10 Cryo	FVIIa at clinician discretion
O'Keeffe *et al.*[32]	5 RBC, 2 AB TP	5 RBC, 2 TP, 1 SDP	5 RBC, 2 TP, 10 Cryo, FVIIa	
Nunez *et al.*[46]	10 RBC, 6 AB TP, 2 SDP	Repeat Package 1	Repeat Package 1	
Riskin *et al.*[28]	6 RBC, 4 TP, 1 SDP	Repeat Package 1	Repeat package 1	Consider FVIIa after 2 rounds
Unpublished data from author (MC)	5 RBC, 4 TP, 1 SDP	5 RBC, 5 TP, 1 SDP	5 RBC, 5 TP, 1 SDP, 5 Cryo	5 mg FVIIa in package 4

TP: thawed plasma; SDP: single donor platelet; Cryo: cryoprecipitate; FVIIa: recombinant factor VIIa; AB: blood type AB.

Cushing und Shaz, Minerva Anesthesiologica 2011
Stahel et al., Curr Opin Anesthesiol 2009

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Reviews und Meta-analyses

Zehtabchi and Nishijima (Acad Emerg Med 2009;16:371-378) > 4 observational studies
Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1:1 ratio on survival of emergency department patients with severe trauma.

∑ = Inadequate evidence to support or refute the use of a high FFP:PRBC ratio in patients with severe trauma.

Phan and Wisner (Vox Sang 2010;93:395-402) > 11 retrospective studies
Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: what is the evidence?

∑ = There is some evidence to support the increase use of plasma and platelets in massive transfusion, but true efficacy has not yet been proven by prospective RTCs

Johansson and Stensballe (Transfusion 2010;50:701-710) > 14 retrospective studies
Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets-a review of the current literature.

∑ = High FFP- and PLT-to-RBC ratios seem to improve survival in massive bleeding. RCTs with TEG-guided transfusion therapy vs fixed ratios are highly warranted.

Murad et al. (Transfusion 2010;50:1370-1283)
> 37 observational studies
The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis.

∑ = Very-low-quality evidence suggests that plasma in the setting of massive transfusion may be associated with a reduction in the risk of death and multiorgan failure.

PROP:P:R

Prospective Randomized Optimum Platelet and Plasma Ratios

- Holcomb, Center Translational Injury Research, UT Houston
- DoD and NIH funded
- 12 centers
- Randomized RBC:FFP:PLT ratios
- 580 patients over 2 years
- 24 hour mortality

27

Which RBC:FFP:PLT-ratio is „best“?

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma

The PROPPR Randomized Clinical Trial

John B. Holcomb, MD[1]; Barbara C. Tilley, PhD[2]; Sarah Baraniuk, PhD[2]; Erin E. Fox, PhD[1]; Charles E. Wade, PhD[1]; Jeanette M. Podbielski, RN[1]; Deborah J. del Junco, PhD[1]; Karen J. Brasel, MD, MPH[3,22]; Eileen M. Bulger, MD[4]; Rachael A. Callcut, MD, MSPH[5]; Mitchell Jay Cohen, MD[5]; Bryan A. Cotton, MD, MPH[1]; Timothy C. Fabian, MD[6]; Kenji Inaba, MD[7]; Jeffrey D. Kerby, MD, PhD[8]; Peter Muskat, MD[9,23]; Terence O'Keeffe, MBChB, MSPH[10]; Sandro Rizoli, MD, PhD[11]; Bryce R. H. Robinson, MD[9]; Thomas M. Scalea, MD[12]; Martin A. Schreiber, MS[13]; Deborah M. Stein, MD[12]; Jordan A. Weinberg, MD[6]; Jeannie L. Callum, MD[14]; John R. Hess, MD, MPH[15]; Nena Matijevic, PhD[1]; Christopher N. Miller, MD[16]; Jean-Francois Pittet, MD[17]; David B. Hoyt, MD[18]; Gail D. Pearson, MD, ScD[19]; Brian Leroux, PhD[20]; Gerald van Belle, PhD[20,21] ; for the PROPPR Study Group

[+] Author Affiliations

JAMA. 2015;313(5):471-482. doi:10.1001/jama.2015.12.

Text Size: A A A

Objective To determine the effectiveness and safety of transfusing patients with severe trauma and major bleeding using plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio.

Design, Setting, and Participants Pragmatic, phase 3, multisite, randomized clinical trial of 680 severely injured patients who arrived at 1 of 12 level I trauma centers in North America directly from the scene and were predicted to require massive transfusion between August 2012 and December 2013.

Results No significant differences were detected in mortality at 24 hours (12.7% in 1:1:1 group vs 17.0% in 1:1:2 group; difference, −4.2% [95% CI, −9.6% to 1.1%]; $P = .12$) or at 30 days (22.4% vs 26.1%, respectively; difference, −3.7% [95% CI, −10.2% to 2.7%]; $P = .26$). Exsanguination, which was the predominant cause of death within the first 24 hours, was significantly decreased in the 1:1:1 group (9.2% vs 14.6% in 1:1:2 group; difference, −5.4% [95% CI, −10.4% to −0.5%]; $P = .03$). More patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group (86% vs 78%, respectively; $P = .006$). Despite the 1:1:1 group receiving more plasma (median of 7 U vs 5 U, $P < .001$) and platelets (12 U vs 6 U, $P < .001$) and similar amounts of red blood cells (9 U) over the first 24 hours, no differences between the 2 groups were found for the 23 prespecified complications, including acute respiratory distress syndrome, multiple organ failure, venous thromboembolism, sepsis, and transfusion-related complications.

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Problems associated 1:1 FFP:RBC administration in acute hemorrhage

> it may take time !

1:1 took 14.8 hours to achieve an INR < 1.5

Gonzales et al., J Trauma 2007

> it may support dilution !

Armand and Hess, Transfusion Med Rev 2003

> is associated with immunological disturbances

volume loading

TRALI

Immunological consequences of increased plasma transfusion > infection!

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Mortality higher in 1:1 („Fixed ratio“) !

More waste of blood products !

Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results–guided transfusion in patients with severe trauma: a randomized feasibility trial

Bartolomeu Nascimento MD MSc, Jeannie Callum MD, Homer Tien MD MSc, Gordon Rubenfeld MD MSc, Ruxandra Pinto PhD, Yulia Lin MD, Sandro Rizoli MD PhD

Table 4: Mortality outcomes

Variable	Group; *n*/*N* (%)		Relative risk (95% CI)	Difference (95% CI)
	Fixed-ratio group *n* = 37	Control group *n* = 32		
All-cause 28-day mortality in ITT analysis*	13/40 (32.5)	5/35 (14.3)	2.27 (0.98 to 9.63)	18.2 (–0.4 to 36.8)
All-cause 28-day mortality per protocol	11/37 (29.7)	3/32 (9.4)	3.17 (1.15 to 18.24)‡	20.3 (2.5 to 38.2)
Death from exsanguination†				12.2 (–4.4 to 28.9)
Neurologic death (traumatic brai injury/withdrawal of care)				5.4 (–1.8 to 12.7)
Death from multiple organ failu				2.7 (–2.5 to 7.9)

Note: CI = confidence interval, IQR = inte
*For the ITT analysis, data were includec
†Median time of occurrence after arrival
‡95% CI generated by bootstrap technic
of the simulations.

1).
4) in the control group.
esent in the control group in any

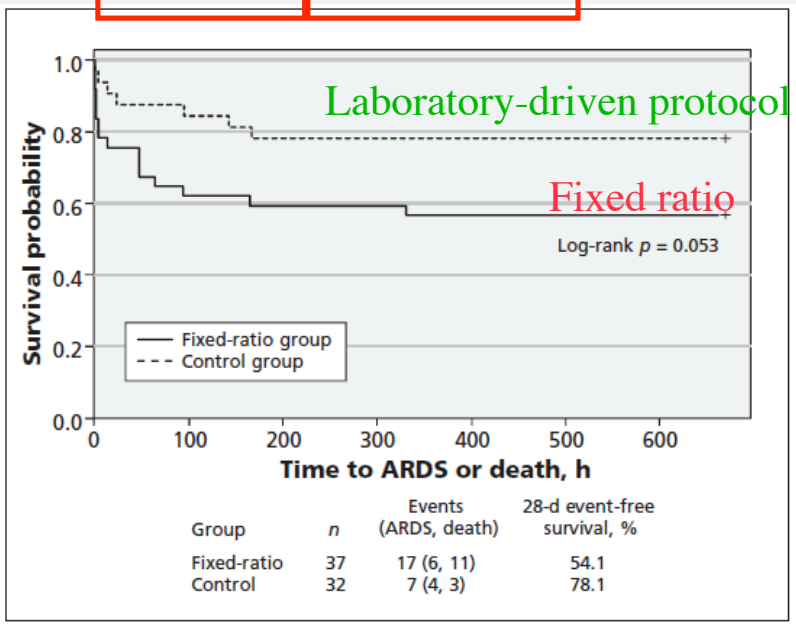

Figure 2: Kaplan–Meier curves for event-free survival (free of acute respiratory distress syndrome [ARDS] or death) within 28 days after enrolment.

CMAJ 2013. DOI:10.1503 /cmaj.121986

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Damage Control Resuscitation does not always correct trauma induced coagulopathy

Intensive Care Med. 2015 Feb;41(2):239-47. doi: 10.1007/s00134-014-3584-1. Epub 2014 Dec 2.

Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage.

Khan S[1], Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, Curry N, Stanworth S, Gaarder C, Brohi K.

RESULTS: One hundred six patients who received at least four PRBC units were included. Thirty-four patients (32 %) required a massive transfusion. On admission 40 % of patients were coagulopathic (ROTEM CA5 ≤ 35 mm). This increased to 58 % after four PRBCs and 81 % after eight PRBCs. On average all functional coagulation parameters and procoagulant factor concentrations deteriorated during hemorrhage. There was no clear benefit to high-dose FFP therapy in any parameter. Only combined high-dose FFP, cryoprecipitate and platelet therapy with a high total fibrinogen load appeared to produce a consistent improvement in coagulation.

CONCLUSIONS: Damage control resuscitation with standard doses of blood components did not consistently correct trauma-induced coagulopathy during hemorrhage. There is an important opportunity to improve TIC management during damage control resuscitation.

J Trauma Acute Care Surg. 2014 Mar;76(3):561-7; discussion 567-8. doi: 10.1097/TA.0000000000000146.

Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage.

Khan S[1], Brohi K, Chana M, Raza I, Stanworth S, Gaarder C, Davenport R; International Trauma Research Network (INTRN).

RESULTS: Of the 106 study patients receiving at least 4 U of PRBC, 27 received 8 U to 11 U of PRBC and 31 received more than 12 U of PRBC. Average admission lactate was 6.2 mEq/L. Patients with high lactate (≥5 mEq/L) on admission did not clear lactate until hemorrhage control was achieved, and no further PRBC units were required. On admission, 43% of the patients were coagulopathic (clot amplitude at 5 minutes ≤ 35 mm). This increased to 49% by PRBC 4; 62% by PRBC 8 and 68% at PRBC 12. The average fresh frozen plasma/PRBC ratio between intervals was 0.5 for 0 U to 4 U of PRBC, 0.9 for 5 U to 8 U of PRBC, 0.7 for 9 U to 12 U of PRBC. There was no improvement in any ROTEM parameter during ongoing bleeding.

CONCLUSION: While hemostatic resuscitation offers several advantages over historical strategies, it still does not achieve correction of hypoperfusion or coagulopathy during the acute phase of trauma hemorrhage. Significant opportunities still exist to improve management and improve outcomes for bleeding trauma patients.

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Alternative approach:

ROTEM® -guided concentration factor based therapy

- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conclusions

Schöchl *et al. Critical Care* 2011, **15**:R83
http://ccforum.com/content/15/2/R83

CRITICAL CARE

RESEARCH Open Access

Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy

Herbert Schöchl[1,2], Ulrike Nienaber[3], Marc Maegele[4], Gerald Hochleitner[5], Florian Primavesi[2], Beatrice Steitz[6],

Schöchl *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2012, **20**:15
http://www.sjtrem.com/content/20/1/15

SCANDINAVIAN JOURNAL OF trauma, resuscitation & emergency medicine

Schöchl *et al. Critical Care* 2010, **14**:R55
http://ccforum.com/content/14/2/R55

CRITICAL CARE

RESEARCH Open Access

Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM®)-guided administration of fibrinogen concentrate and prothrombin complex concentrate

Herbert Schöchl[1,2], Ulrike Nienaber[3], Georg Hofer[1], Wolfgang Voelckel[1], Csilla Jambor[4], Gisela Scharbert[5], Sibylle Kozek-Langenecker[5] and Cristina Solomon*[6]

Grassetto *et al. Critical Care* 20
http://ccforum.com/content/1o/3/R28

CRITICAL CARE

REVIEW Open Access

Early and individualized goal-directed therapy for trauma-induced coagulopathy

Herbert Schöchl[1,2*], Marc Maegele[3], Cristina Solomon[1], Klaus Görlinger[4] and Wolfgang Voelckel[2]

LETTER

ROTEM®-guided coagulation factor concentrate therapy in trauma: 2-year experience in Venice, Italy

Alberto Grassetto*, Marco De Nardin, Bernadetta Ganzerla, Monica Geremia, Debora Saggioro, Elena Serafini, Silvia Zampieri, Manuela Toffoli, Daniele Penzo, Antonio Bossi and Carlo Maggiolo

da Luz *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2013, **21**:29
http://www.sjtrem.com/content/21/1/29

SCANDINAVIAN JOURNAL OF trauma, resuscitation & emergency medicine

REVIEW Open Access

Thrombelastography (TEG®): practical considerations on its clinical use in trauma resuscitation

Luis Teodoro da Luz[1], Bartolomeu Nascimento[2] and Sandro Rizoli[3*]

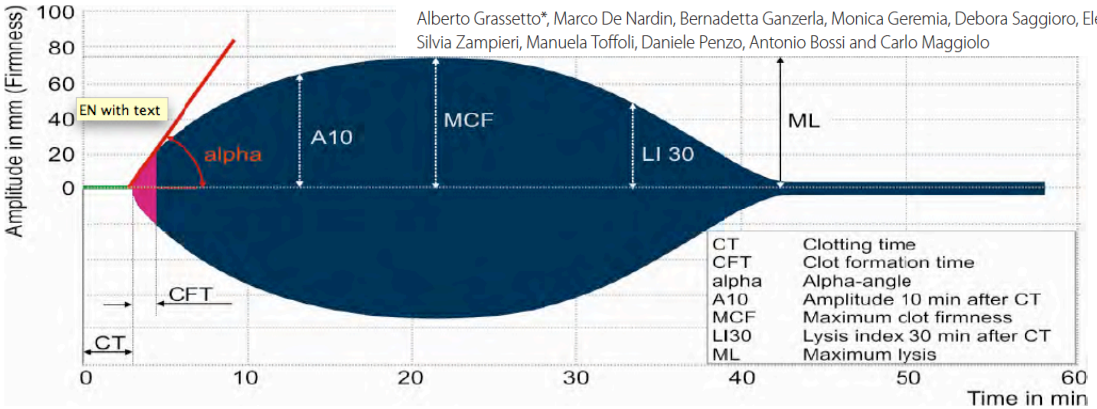

Figure 2 **Parameters and scaling of ROTEM[1]**

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Key recommendations „Management of Acute Traumatic Haemorrhage“ S3-Guideline Polytrauma

Schlüsselempfehlungen für die Gerinnungstherapie	GoR der S3-Leitlinie
Die *trauma-induzierte Koagulopathie* ist ein eigenständiges Krankheitsbild mit deutlichen Einflüssen auf das Überleben. Aus diesen … ittelbar begonnen werden.	A „soll“
Ein spezifisches *Massivt* …	B „sollte“
Die *Auskühlung* des Pat … den.	B „sollte“
Eine *Azidämie* sollte ver…	B „sollte“
Wird die Gerinnungsthera… te ein Verhältnis von *FFP:EK* …	B „sollte“
Eine Substitution von *Fib*…	B „sollte“
Bei Patienten, die akti… (mittlerer arterieller Druck ~65 mmHg, systolischer arterieller Druck ~90 mmHg) angestrebt werden. Dieses Konzept ist bei Verletzungen des zentralen Nervensystems kontraindiziert.	0 „kann“
Die *Thrombelastographie bzw. -metrie* kann zur Steuerung der Gerinnungsdiagnostik und -substitution durchgeführt werden.	0 „kann“
Eine *Hypokalzämie* <0,9 mmol/l sollte vermieden und kann therapiert werden.	0 „kann“
Bei einem aktiv blutenden Patienten kann die Indikation zur Transfusion bei *Hämoglobinwerten* unter 10 g/dl bzw. 6,2 mmol/l gestellt und der *Hämatokritwert* bei 30% gehalten werden.	0 „kann“

Spahn *et al. Critical Care* 2013, **17**:R76
http://ccforum.com/content/17/2/R76

CRITICAL CARE

RESEARCH Open Access

Management of bleeding and coagulopathy following major trauma: an updated European guideline

Donat R Spahn[1], Bertil Bouillon[2], Vladimir Cerny[3,4], Timothy J Coats[5], Jacques Duranteau[6], Enrique Fernández-Mondéjar[7], Daniela Filipescu[8], Beverley J Hunt[9], Radko Komadina[10], Giuseppe Nardi[11], Edmund Neugebauer[12], Yves Ozier[13], Louis Riddez[14], Arthur Schultz[15], Jean-Louis Vincent[16] and Rolf Rossaint[17*]

Coagulation monitoring

We recommend that viscoelastic methods also be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy. (Grade 1C)

2010 2C >>>> 2013 1C recommendation!

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- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

Alternative approach:

ROTEM®-guided concentration factor based therapy

Schöchl *et al. Critical Care* 2011, **15**:R83
http://ccforum.com/content/15/2/R83

CRITICAL CARE

RESEARCH Open Access

Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy

Herbert Schöchl[1,2], Ulrike Nienaber[3], Marc Maegele[4], Gerald Hochleitner[5], Florian Primavesi[2], Beatrice Steitz[6], Christian Arndt[7], Alexander Hanke[8], Wolfgang Voelckel[2] and Cristina Solomon[6*]

Retrospective comparison:

ROTEM-guided concentration factor therapy
(Salzburg-Trauma Register)

Fibrinogen concentrate (2-4g)+Prothrombin complex concentrate(1000-1500 IE))

F II (Prothrombin), F VII (Prokonvertin), F IX (antihaemophilic Factor B), F X (Stuart-Prower-Factor)
if Clottimg time (CT) > 1,5 x reference

versus

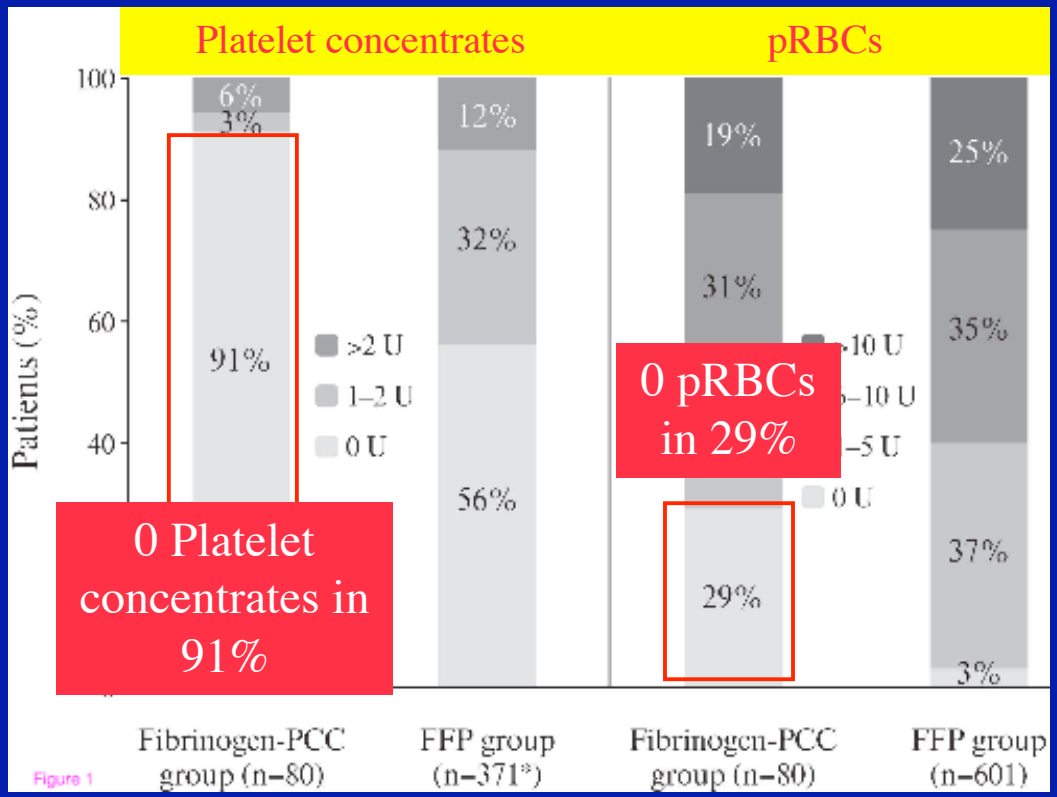
FFP-ratio based coagulation therapy (Traumaregister DGU)

Results

No difference in mortality

(7,5% Fibrinogen/PCC group versus 10% in FFP-ratio based group;p=0,69)

Significant difference in the use of allogenic blood products!



Schoechl et al. Crit Care 2011

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- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conculusions

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion

Ulrike Nienaber [a], Petra Innerhofer [b,*], Isabella Westermann [b], Herbert Schöchl [c], Rene Attal [d], Robert Breitkopf [b], Marc Maegele [a,e]

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[b] Department of Anaesthesiology and Critical Care Medicine, Innsbruck Medical University, Innsbruck, Austria
[c] Department of Anaesthesiology and Critical Care Medicine, Unfallkrankenhaus Salzburg, Salzburg, Austria
[d] Department of Trauma Surgery and Sportsmedicine, Innsbruck Medical University, Innsbruck, Austria
[e] Department of Trauma and Orthopedic Surgery, Cologne-Merheim Medical Center (CMMC), University of Witten/Herdecke, Cologne, Germany

Retrospective Matched-Pairs-Analysis (tight Match-Code):

ROTEM-guided concentration factor therapy (Innsbruck-Register)

(Fibrinogen concentrate + Prothrombin complex concentrate)

F II (Prothrombin), F VII (Prokonvertin), F IX (antihaemophilic Fakcor B), F X (Stuart-Prower-Factor)
if Clottimg time (CT) > 1,5 x reference

versus

FFP-ratio based coagulation therapy (Traumaregister DGU)

Nienaber et al. Injury 2011

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- Trauma-induced coagulopathy
- Guideline-Surgery
- Guideline-Haemostasis
- Conclusions

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion

Table 2
Blood components, coagulation factor concentrates and resuscitation volumes during the first 6 and 24 h after ER admission.

	TR-DGU (n=18)	Innsbruck TB (n=18)	p-Value
pRBC transfusions/units (n)+			
>0–6 h after admission	7.5 (4–12)	1.0 (0–3)	<0.005
>24 h after admission	12.5 (8–20)	3 (0–5)	<0.005
FFP transfusions/units (n)++			
>0–6 h after admission	6 (4–12)	0	N/A
>24 h after admission	10 (7–22)	0	N/A
Platelet concentrates (n)++			
>24 h after admission	2 (1–3)	0	<0.005
Coagulation factor concentrates			
0–6 h after admission			
>Fibrinogen concentrate (grs)	0	4 (2–4)	N/A
>Prothrombin complex concentrate (IU)*	0	1200 (1000–1200)	N/A
24 h after admission			
>Fibrinogen concentrate (grs)	0	4 (2–4)	N/A
>Prothrombin complex concentrate (IU)**	0	1200 (800–1200)	N/A
IV fluids 0–6 h after admission (ml)	4000 (3000–5500)	3850 (3000–5000)	0.650

pRBC:FFP1:1 ⟷ concentrates and Ø FFP

Data are presented as median (IQR_{25-75}).
*n=7; **n=8; +, 1 unit=230–260 ml); ++, 1 unit=220–280 ml).
ER=emergency room; FFP=fresh frozen plasma; IV=intravenous; N/A=not applicable; pRBC=packed red blood cell.

Table 3
Morbidity and mortality.

	All patients (n=36)	TR-DGU (n=18)	Innsbruck TB (n=18)	p-Value
Sepsis (n; %)	9 (25)	6 (33.3)	3 (16.7)	0.443
Multiple organ failure (n, %)	14 (38.9)	11 (61.1)	3 (16.7)	0.015
Ventilator days (days, range)	12 (6–20)	15 (6–22)	10 (5–20)	0.673
ICU LOS (days, range)	18 (10–29)	16 (13–25)	19 (9–33)	0.628
In-hospital LOS (days, range)	31 (19–49)	38 (21–48)	26 (19–50)	0.481
In-hospital mortality overall (n; %)	5 (13.9)	2 (11.1)	3 (16.7)	0.500

Data are presented as median (IQR_{25-75}).
ICU=intensive care unit; LOS=length of stay.

Nienaber et al. Injury 2011

Early and individualized goal-directed therapy for trauma-induced coagulopathy

Schöchl H, Maegele M, Solomon C, Görlinger K, Voelckel W.

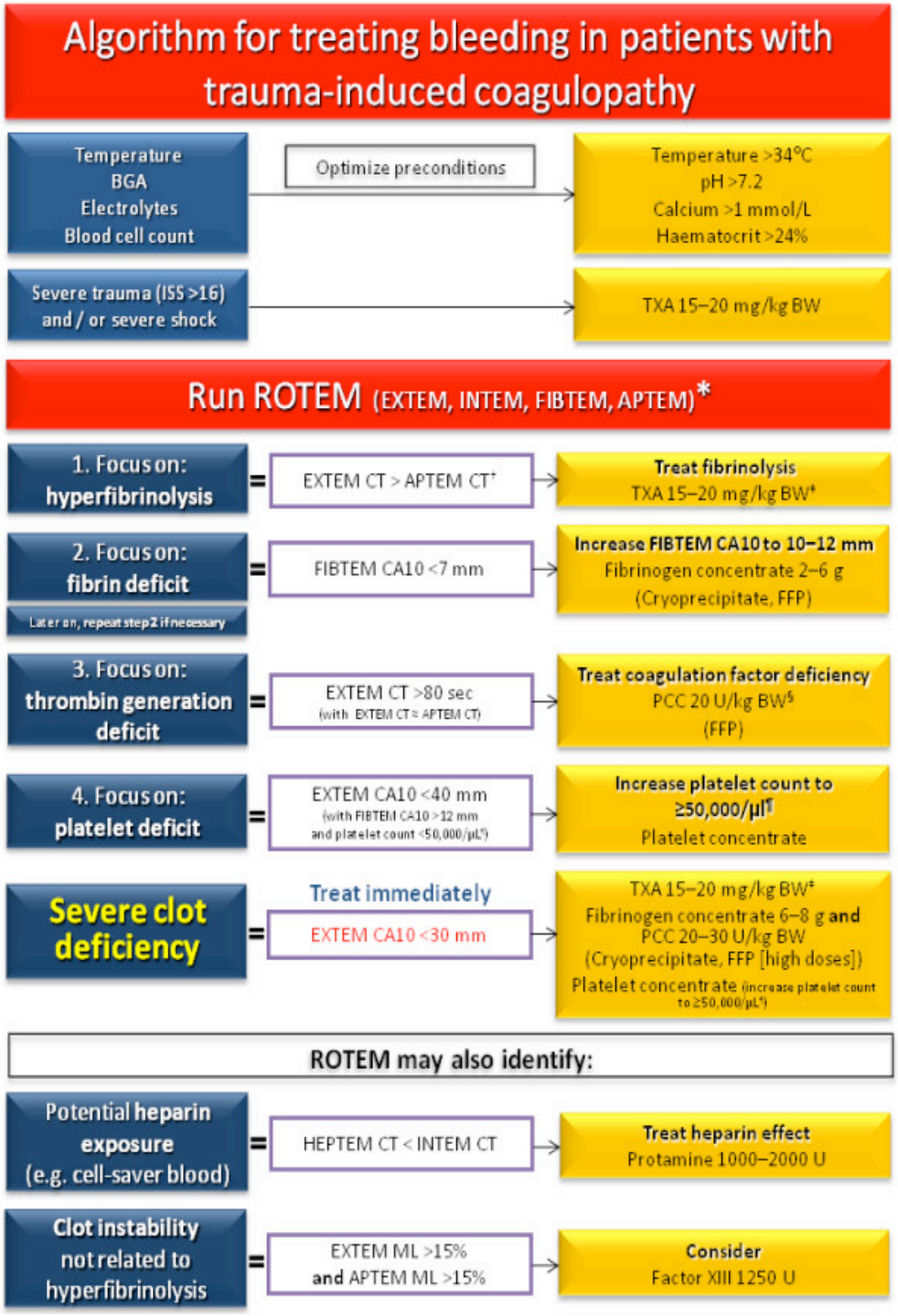
Ludwig Boltzmann Institute of Experimental and Clinical Traumatology, Vienna, Austria. Herbert.schoechl@auva.at

Abstract

Severe trauma-related bleeding is associated with high mortality. Standard coagulation tests provide limited information on the underlying coagulation disorder. Whole-blood viscoelastic tests such as rotational thromboelastometry or thrombelastography offer a more comprehensive insight into the coagulation process in trauma. The results are available within minutes and they provide information about the initiation of coagulation, the speed of clot formation, and the quality and stability of the clot. Viscoelastic tests have the potential to guide coagulation therapy according to the actual needs of each patient, reducing the risks of over- or under-transfusion. The concept of early, individualized and goal-directed therapy is explored in this review and the AUVA Trauma Hospital algorithm for managing trauma-induced coagulopathy is presented.

PMID: 22364525 [PubMed - indexed for MEDLINE] PMCID: PMC3306198

319765 (3) Aug12



Supporting Coagulation Function

R#	*Immediate Intervention (Hemostasis)*
R17	Target **hemoglobin** (Hb) of 7-9 g/dl *(1C)*
R26	Use **plasma** ((FFP) or pathogen-inactivated plasma) or **fibrinogen** in massive bleeding *(1B/1C)* If further plasma, use **plasma:red blood cell ratio** of at least 1:2 *(2C)* Avoid plasma in patients without substantial bleeding *(1B)* - !
R28	Administer **platelets** for platelet count > 50×10^9/l; > 100×10^9/l in ongoing bleeding and/or TBI *(1C/2C)* Use Initial dose of 4-8 single platelet units or one aphaeresis pack *(2C)*
R29	Use **platelets** if platelet dysfunction is documented with continued microvascular bleeding (2C)
R27	Use **fibrinogen concentrate** (dose 3-4g)/**cryoprecipitate** (50 mg/kg) if thromboelastometric signs of functional fibrinogen deficit or fibrinogen level < 1.5 to 2.0 g/l *(1C)* Guide repeated doses by viscoelastic monitoring and laboratory assessment of fibrinogen levels *(2C)*
R24	Use **TXA** as early as possible if bleeding/risk of bleeding at 1 g x 10 minutes, followed by 1g x 8 h *(1A)* Use TXA in the bleeding trauma patient within 3 h after injury *(1B)* Consider administration of the first dose of TXA en route to the hospital *(2C)*
R31	Use **PCC** if bleeding with thromboelastometric evidence of delayed coagulation initiation if a concentrate-based goal-directed strategy is applied (2C)
R33	Consider **rFVIIa** if bleeding/traumatic coagulopathy persist despite best-practice *(2C)* Not use rFVIIa with intracerebral hemorrhage caused by isolated head trauma *(2C)* - !
R25	Maintain ionised **calcium** levels within the reference range during massive transfusion (1C)

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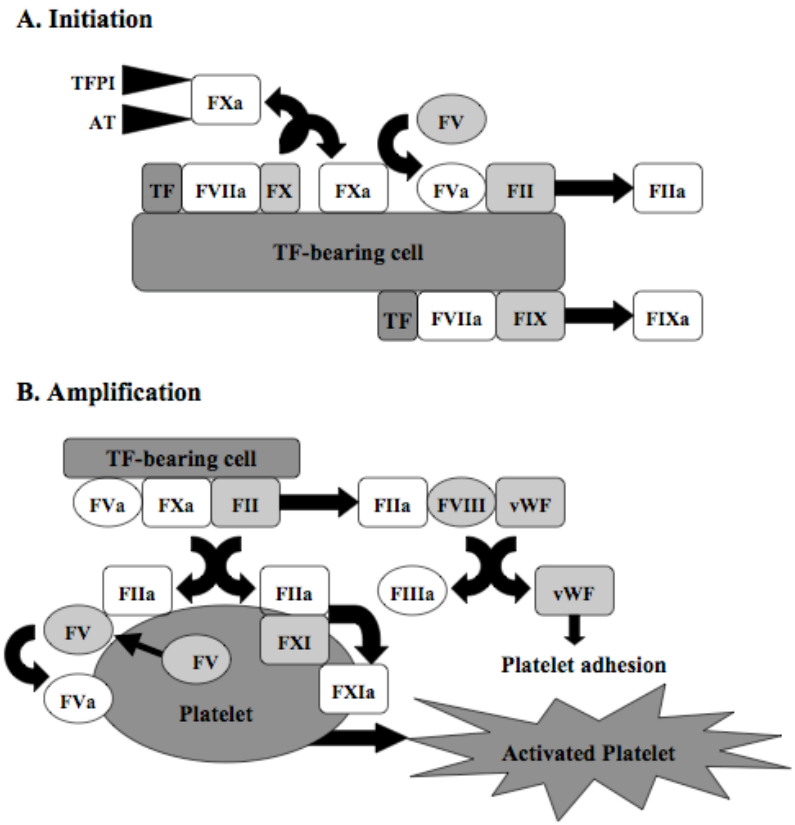
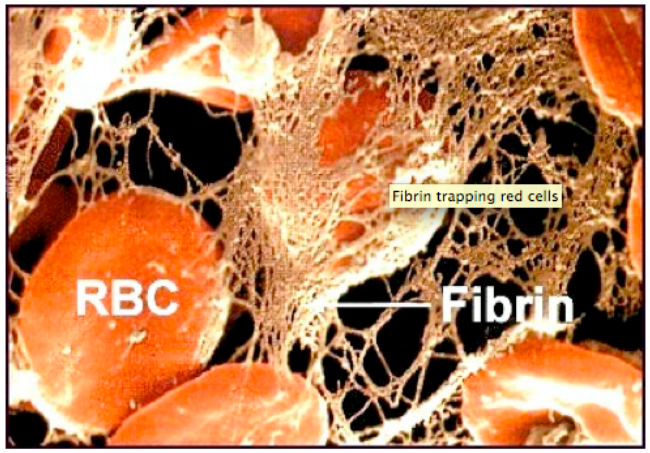
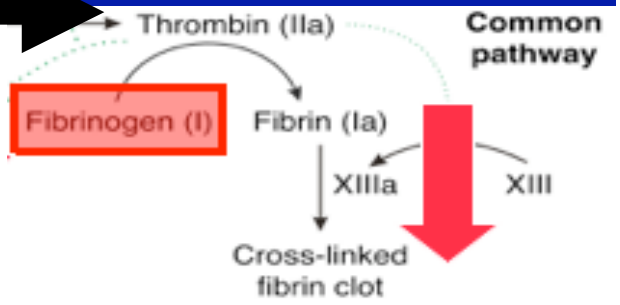
The role of Fibrinogen





Fibrin trapping red blood cells to make a clot.

Thrombin



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Fibrinogen is the first coagulation factor to reach critical levels

Anesth Analg. 1995 Aug;81(2):360-5.

Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates.

Hiippala ST[1], Myllylä GJ, Vahtera EM.

Critical factor concentrations and blood loss

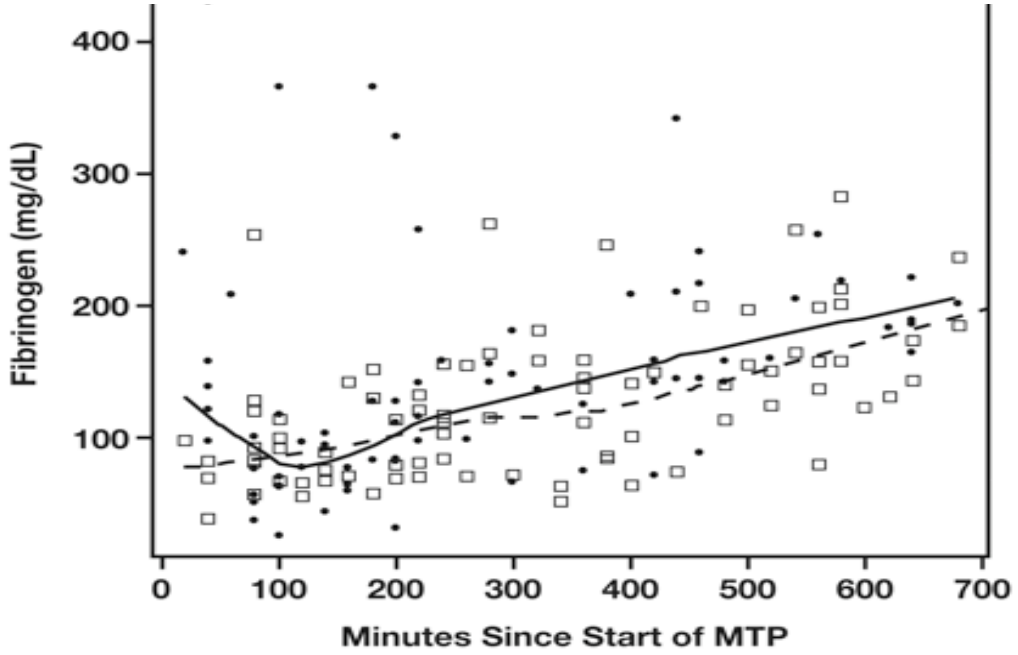
Factor	Critical value	Blood volume exchanged / Blood loss (%)
Platelets	50 x 10^3/mm^3	230% (CI 169-294%)
Fibrinogen	1.0 g/L	142% (CI 117-169%)
Prothrombin	20%	201% CI 160-244%)
Factor V	25%	229% (CI 167-300%)
Factor VII	20%	236% (CI 198-277%)

Fibrinogen is the first coagulation factor to reach critical levels

Am J Clin Pathol. 2011 Sep;136(3):364-70. doi: 10.1309/AJCPH16YXJEFSHEO.

Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol.

Chambers LA[1], Chow SJ, Shaffer LE.



View larger version:
» In a new window

Figure 2

Fibrinogen levels (mg/dL) over time for the 25 patients treated under the original protocol (dots and solid line) and 27 patients treated under the new protocol (boxes and dashed line) who survived at least 12 hours. To convert fibrinogen values to Système International units (μmol/L), multiply by 0.0294. MTP, massive transfusion protocol.

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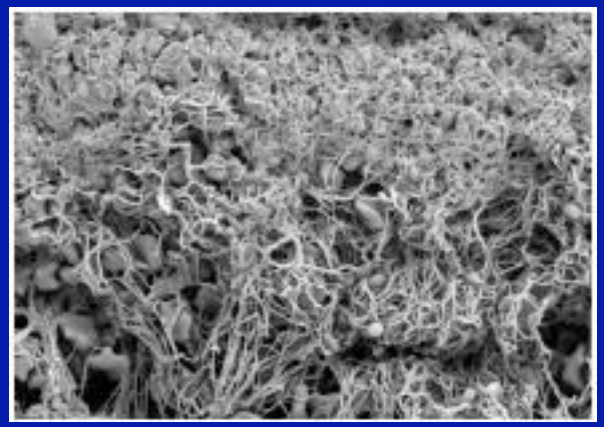
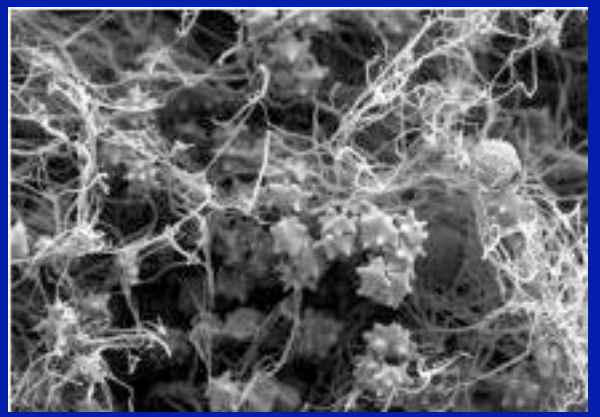
Fibrinogen in the treatment of acute post-traumatic coagulopathy

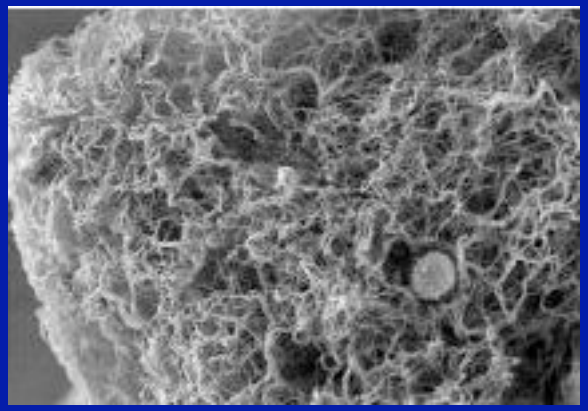
Elektronmicroscopy of clotting



Normal clotting



Dilution



„Diluted“ clot after administration of fibrinogen

Fries et al., Br J Anaesth 2005

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2 large-scale RCTs

CONTROL™

CLINICAL TRIAL ON THE EFFECT OF rFVIIa ON TRAUMATIC BLOOD LOSS

rFVIIa as ajunct to standard therapy in refractory trauma-associated bleeding

- **Futility Analysis revealed unexpected low mortality in control group (11% vs 28%)**
- **Study stopped after recruitment of 573/ 1502 patients**
- **NO survival benefit in verum group (rFVIIa-Gruppe)**

CRASH-2

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

Early tranexamic acid (antifibrinolytic) in trauma with severe bleeding

- **20.211 patients / 274 hospitals / 40 countries with severe trauma bleeing / risk of severe bleeding**
- **Early TXA (bolus 1g/10min, followed by 1g/8h) or placebo**
- **TXA reduced relative risk of death by 10 %, and of death by bleeding by 15%** **Number-needed-to-treat (NNT)** **Gesamtsterblichkeit 67** **Verbluten 125**
- **NO side-effects, safe, and cheap!**

If TXA > „give it early!“

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

*The CRASH-2 collaborators**

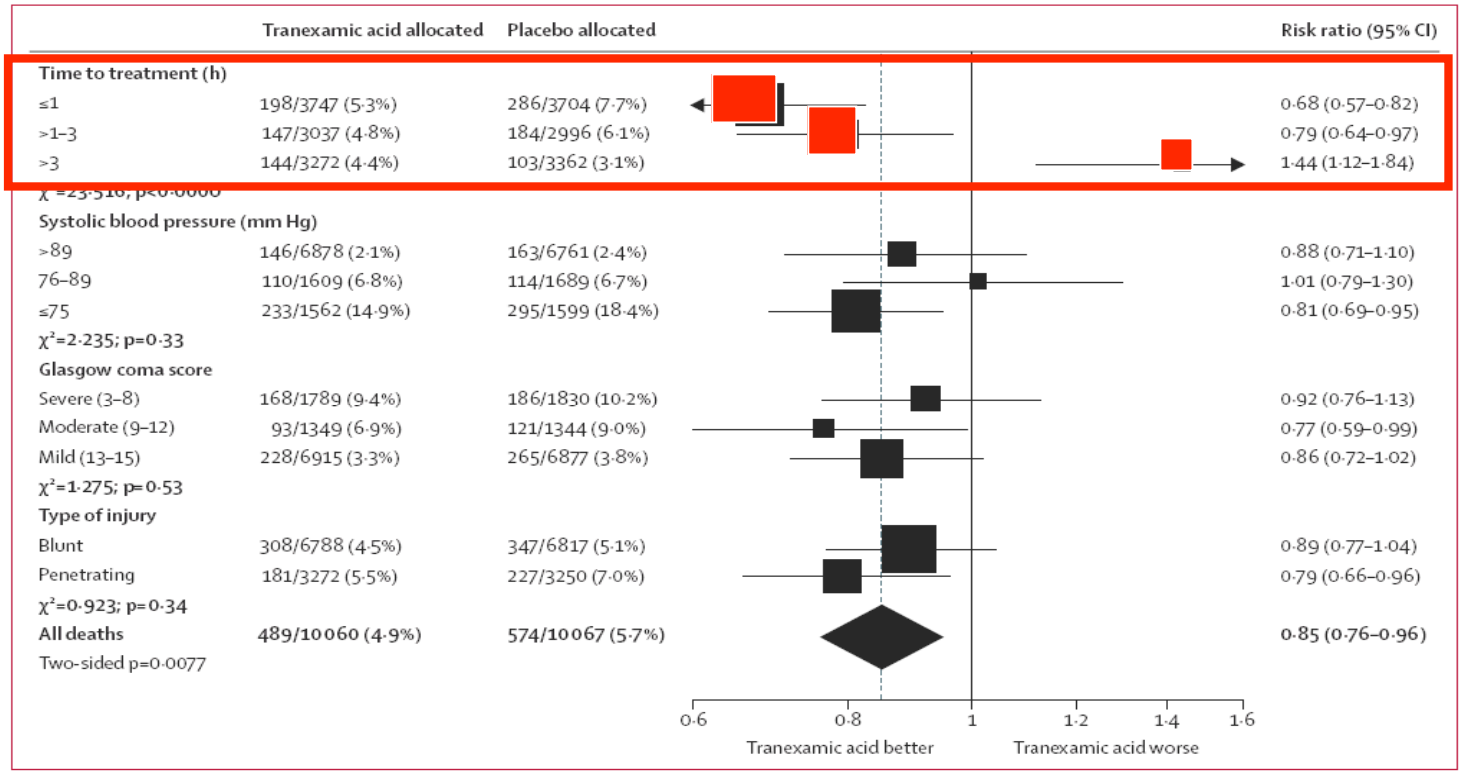

Figure 1: Mortality due to bleeding by subgroups

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Management of coagulopathic bleeding

1. Stabilisierung der Rahmenbedingungen (Prophylaxe und Therapie!)	Kerntemperatur ≥34°C pH-Wert ≥7,2 ionisierte Ca^{++}-Konzentration ≥0,9 mmol/l	GoR B GoR B GoR 0
2. Substitution von Sauerstoffträgern	EK Gabe (funktionelles Ziel: Hb 6[-8] g/dl, aber **hämostaseologisches Ziel bei massiver Blutung: Hkt ≥30% bzw. Hb ~10 g/dl** [6,2 mmol/l]) BÄK 2009	GoR 0
3. Hemmung einer potentiellen (Hyper-) Fibrinolyse (immer VOR Gabe von [illegible])	**Tranexamsäure *(Cyklokapron®)*** initial **2**(-4) **g** (15-30 mg/kgKG) [illegible] ancet 2010	(GoR B)
4. Substitution von Gerin[illegible] schwerer Blutungsneigu[illegible]	[illegible] atol 2004; AAGBI	(GoR 0)
Patienten, die Massivtransfu[illegible] blutungsbedingten, lebensb[illegible] einem hohen Verhältnis FFP:EK im Bereich von 1:2 bis 1:1 profitieren. **GoR B**	[illegible] 30-60 [illegible] → „…bei schwerer Blutung… trotz Gabe von FFP zusätzlich …" BÄK 2009	GoR B (GoR 0)
	ggf. 1-2x **FXIII *(Fibrogammin® P)* 1.250 IE** (15-20 IE/kgKG) BÄK 2009	(GoR 0)
und (bei V.a. Thrombozytopathie) verstärkte Thrombozyten-adhäsion an das Endothel + Freisetzung von „von Willebrand Faktor" und FVIII aus Lebersinusoiden	**DDAVP = Desmopressin *(Minirin®)*** 0,3 µg/kgKG über 30 Minuten („**1 Ampulle pro 10 kgKG über 30 Min.**") Zotz R et al. Hamostaseologie 2009, BÄK 2009	(GoR 0)
5. Substitution von Thrombozyten für die primäre Hämostase	**Thrombozytenkonzentrate** (Ziel **bei transfusionspflichtigen Blutungen: 100.000/µl**) BÄK 2009	(GoR 0)
6. ggf. Thrombinburst mit Thrombozyten- und Gerinnungs-aktivierung („Rahmenbedingungen" beachten!!)	im Einzelfall & bei Erfolglosigkeit aller anderen Therapieoptionen ggf. **rFVIIa *(NovoSeven®)*** initial **90 µg/kgKG** BÄK 2009	(GoR A) (GoR 0)
bei aktiver Blutung	kein Antithrombin (ATIII) Afshari A et al. BMJ 2007, fragliche Ausnahme laut BÄK 2009: DIC (keine ↓Letalität nachgewiesen; empfohlen bei nachgewiesener DIC und nachgewiesenem ATIII-Mangel [Evidenzgrad 1C+])	(GoR B)

Optimize conditions for coagulation !!!!

Modified according to AWMF S3-Leitlinie „Polytrauma" and Lier et al., Intensive Care Med 2011

How I treat patients with massive hemorrhage

Pär I. Johansson,[1,2] Jakob Stensballe,[1,3] Roberto Oliveri,[1] Charles E. Wade,[2] Sisse R. Ostrowski,[1] and John B. Holcomb[2]

[1]Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Department of Surgery, Division of Acute Care Surgery, Centre for Translational Injury Research, University of Texas Health Medical School, Houston, TX; and [3]The Trauma Centre, Department of Anesthesia, Centre of Head and Orthopedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

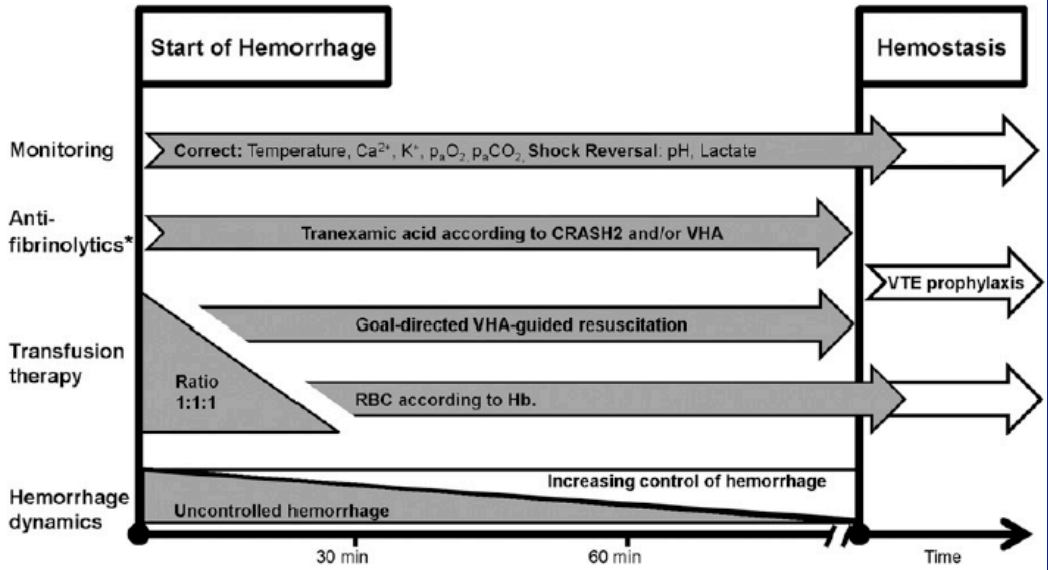
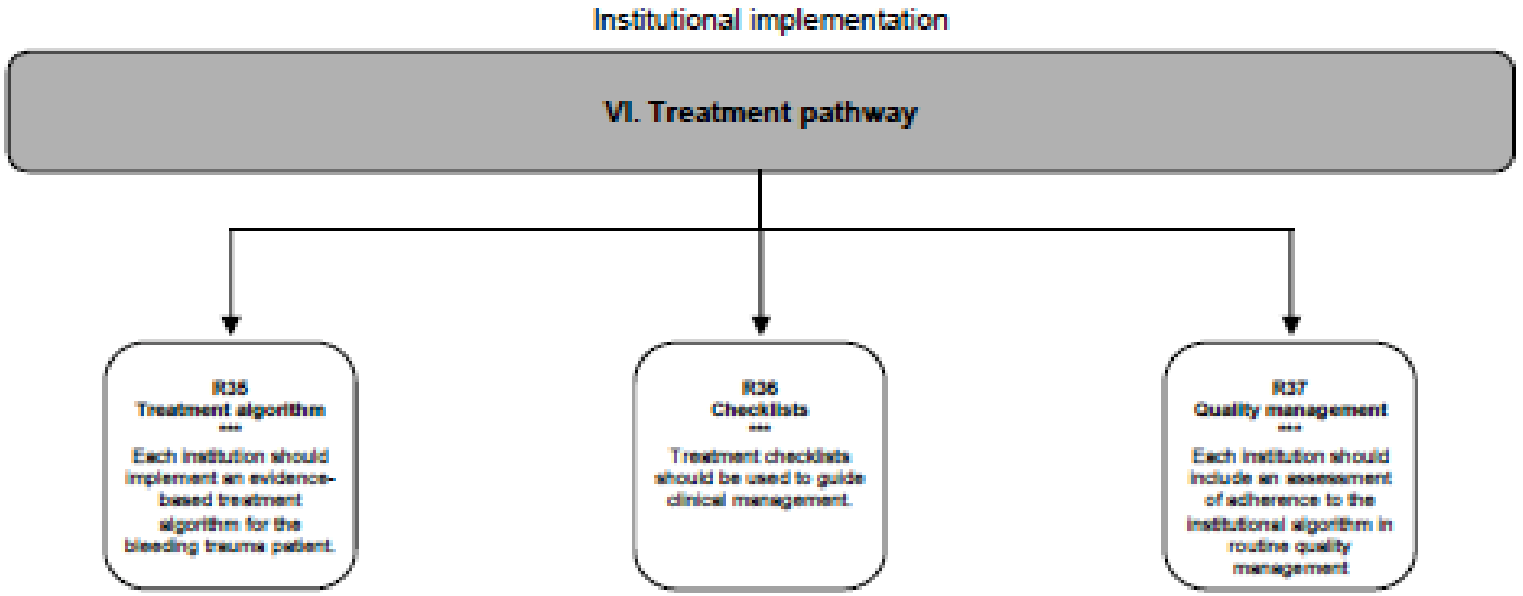


Table 1. TEG treatment algorithm from Copenhagen

TEG variables	Normal range	Patient value	Coagulopathy	Hemostatic therapy
R	3-9 minutes	10-14 minutes	Coagulation factors ↓	FFP 10-20 mL/kg
		>14 minutes	Coagulation factors ↓↓	FFP 30 mL/kg
Angle	55°-78°	<52°	Fibrinogen ↓	FFP 20-30 mL/kg
Functional fibrinogen MA	14-27 mm	<14 mm	Fibrinogen ↓	FFP 20-20 mL/kg or cryoprecipitate pool (3-5 mL/kg) or fibrinogen concentrate (adults 1-2 g)
KaolinTEG MA*	51-69 mm	45-49 mm	Platelets ↓	1 PC or 5 mL/kg
		<45 mm	Platelets ↓↓	2 PC or 10 mL/kg
KaolinTEG Ly30	0-4%	>4%	Primary hyperfibrinolysis	Tranexamic acid (adults 1-2 g)
		>4% + angle and/or MA ↑	Reactive hyperfibrinolysis	Tranexamic acids contraindicated
R in Kaolin/heparinaseTEG		>3-minute difference	Heparinization	Protamin sulfate (adults 50-100 mg) or FFP 10-20 mL/kg

Recommendations 35, 36 and 37:

Institutional Implementation !!!



R35:

Each institution should implement an evidence-based treatment algorithm for the bleeding trauma patient! (1C)

R36:

Treatment checklists should be used to guide clinical management! (1B)

R37:

Each institution should include an assessment of adherence to the institutional algorithm in routine quality management! (1C)

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Conclusions (I)

- **50% of all severely injured trauma patients to die from uncontrolled hemorrhage and TBI**
- **Post-traumatic coagulopathy is present in 1 out of 4 patients in the Emergency Room**
- **Viscoelastic testing may have advantages in early detecting trauma-associated coagulopathies**
- **Cornerstones in acute multi-disciplinary management are surgical bleeding control (incl. „Damage control“) and coagulation management according to the guidelines**

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Conclusions (II)

- Viscoelastic test-guided concentration factor therapy may be associated with less use and waste of allegenic blood products
- Maybe thereby reducing morbidity
- Each institution needs to develop, implement and adhere to an evidence-based management protocol that has be adapted to local circumstances and infrastructure

Thank you very much !