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Coagulopathy after Traumatic Brain Injury

Incidence, Mechanism, Time Course, and Therapeutic Options

Dr. med. Thomas Lustenberger



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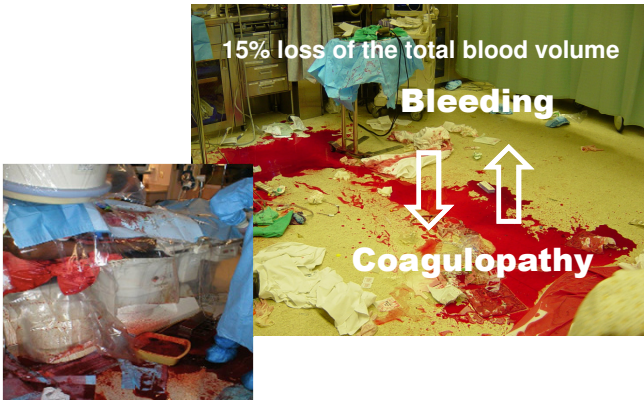
The next 15 minutes...

- **Coagulopathy of trauma:**
 - ✓ Incidence and mechanism
- **TBI associated coagulopathy:**
 - ✓ Incidence
 - ✓ Pathophysiology
 - ✓ Clinical outcome
 - ✓ Risk factors
 - ✓ Time course
 - ✓ Treatment options



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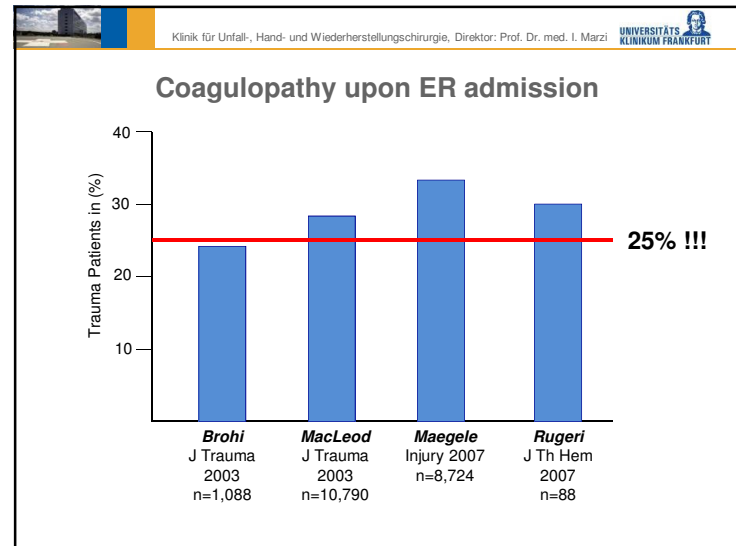
Coagulopathy of Trauma: The Clinical Relevance

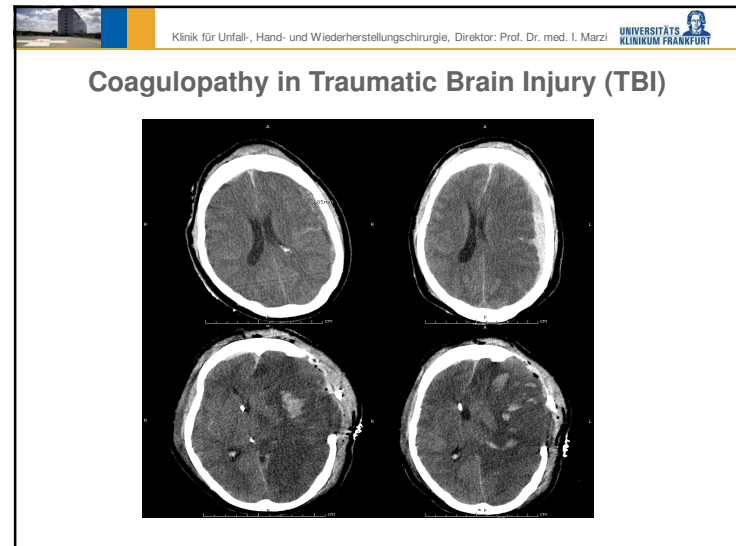
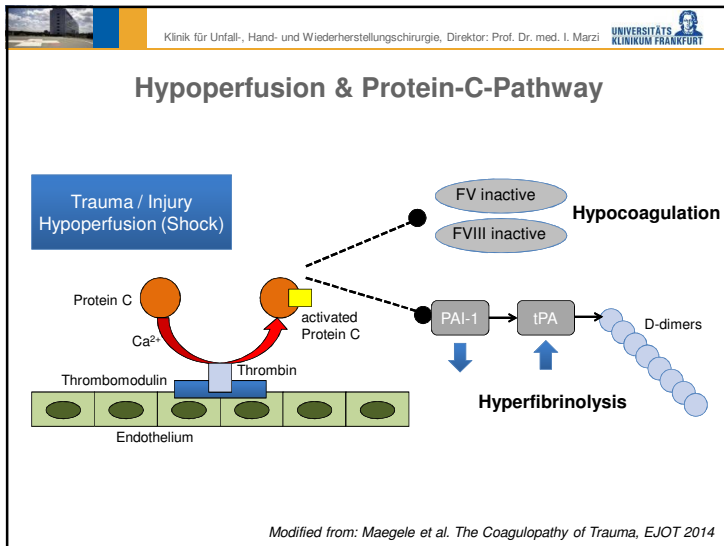
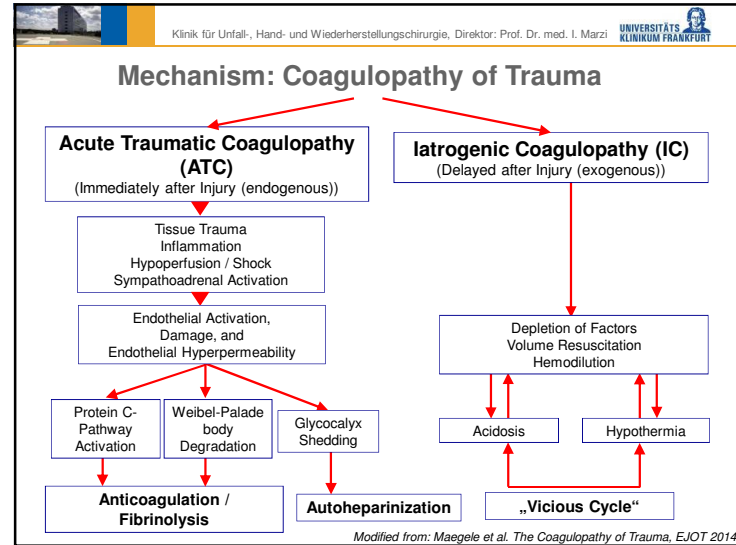
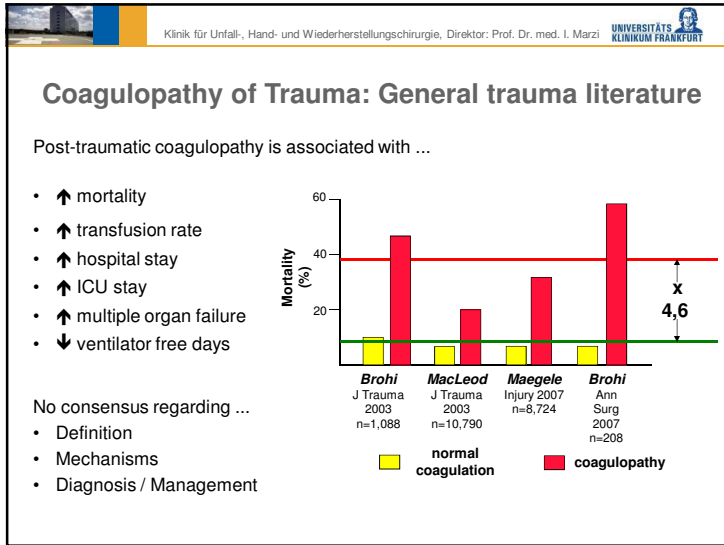


15% loss of the total blood volume

Bleeding

Coagulopathy





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Incidence of TBI-coagulopathy

Study	Definition of TBI	Definition of Cpthy	Proportion of Cpthy
Zehrabchi, 2008	AIS head ≥ 3 , brain hematoma on CT	INR >1.3 or PTT >34 sec	17%
Talving, 2009	Head AIS ≥ 3 , all other AIS <3	INR >1.1 or aPTT >36 sec or PLT <100	34%
Wafaisade, 2010	Head AIS ≥ 3 , all other AIS <3	INR >1.3 or PLT <100	22.7%
Lustenberger, 2010	Head AIS ≥ 3 , all other AIS <3	INR >1.2 or aPTT >36 sec or PLT <100	36.4%
Sun, 2011	Head AIS ≥ 2	DIC score ≥ 5 or PT >13.4 sec	36%
Greuters, 2011	CT confirmed isolated TBI, AIS extracranial <3	aPTT >40 sec or INR >1.2	54%
Franschmann, 2012	GCS ≤ 13 , CT confirmed brain injury, extracranial AIS <3	aPTT >40 sec or INR >1.2 or PLT count <120	34%


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Zehrabchi, 2008			17%
Talving, 2009			34%
Wafaisade, 2010			22.7%
Lustenberger, 2010	Severe head injury	Thrombocytopenia	36.4%
Sun, 2011	AIS head ≥ 3 Extracranial <3	Abnormal global coagulation tests (INR, aPTT)	36%
Greuters, 2011			54%
Franschmann, 2012			34%

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Incidence of TBI-coagulopathy



Review Article
Coagulation disorders after traumatic brain injury

B. S. Harhangi¹, E. J. O. Kompanje², F. W. G. Leebeek³, A. I. R. Maas⁴

- Meta-analysis of 34 articles
- Overall **32.7% of blunt TBI**
 - Not including hypercoagulability
- No standard definition between studies
- No standard diagnosis tests
- No standard treatment

Harhangi et al. Acta Neurochir, 2008

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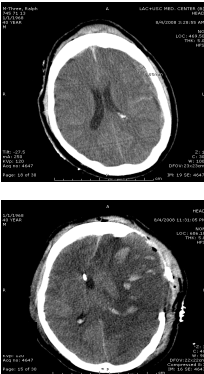
Pathophysiology of TBI coagulopathy

Multiple hypothesis associated with coagulation anomalies

- Combination of hypo- and hypercoagulability
 - Ischemic and hemorrhagic lesions
- Shock and hypoperfusion (Protein-C-pathway)
- Platelet dysfunction
- Tissue factor (TF) release
- Inflammation

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Tissue Factor Hypothesis



Traumatic brain injury
 ↓
 Tissue factor release
 ↓
 Extensive activation of coagulation & platelets
 ↓
 Deposition of microthrombi
 ↓
 Consumptive coagulopathy
 ↓
 Progressive bleeding & infarctions

Stein et al. Neurocritical Care, 2004

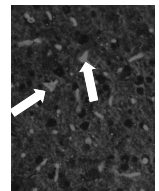
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Ischemic & Hemorrhagic Lesions

Ischemic lesions

- Microthrombi related to **hypercoagulability** state

Multiple microthrombi in arterioles and venules around injury and distant to injury site



Rat cerebral cortex 48h after fluid percussion brain injury

Coagulopathic patients: 85% ischemic lesions
 Non-coagulopathic patients: 31% ischemic lesions

Progression of hemorrhagic lesions

- **hypo**coagulability

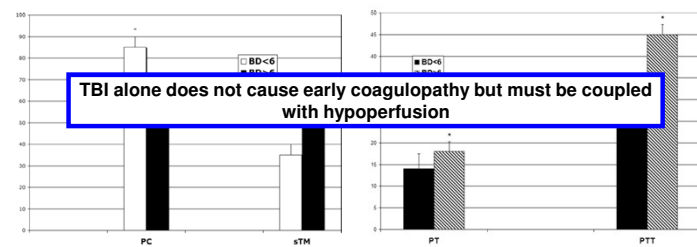
Stein et al. Neurocritical Care, 2004

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Hypoperfusion, Protein-C-Pathway, and TBI

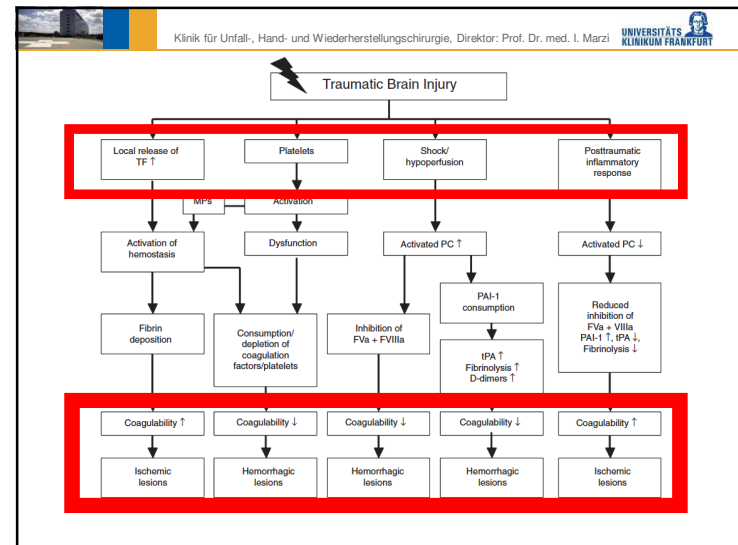
Early Coagulopathy After Traumatic Brain Injury: The Role of Hypoperfusion and the Protein C Pathway

Mitchell Jay Cohen, MD, Karim Brohi, FRCS, FRCA, Michael T. Ganter, MD, Geoffrey T. Manley, MD, PhD, Robert C. Mackersie, MD, and Jean-François Pittet, MD



TBI alone does not cause early coagulopathy but must be coupled with hypoperfusion

Cohen et al. J Trauma, 2007



What do we know?

Coagulopathy after TBI is associated with ...

- ↑ Mortality
- ↓ Outcome
- ↑ Ischemic lesions
- ↑ Hemorrhagic lesions

TBI-coagulopathy: Clinical Outcome

- Coagulopathy upon ED arrival = A powerful predictor related to outcome and prognosis!
- Risk of dying ≈ 10x higher compared to patients without coagulopathy

AIS head	No coagulopathy (%)	Coagulopathy (%)
AIS 3	~10	~20
AIS 4	~10	~25
AIS 5	~40	~70
AIS 6	~60	~85

Wafaisade et al, Acute Coagulopathy in isolated blunt TBI, Neurocrit Care, 2010

TBI-coagulopathy: Clinical Outcome

- Coagulopathy upon ED arrival = A powerful predictor related to outcome and prognosis!
- Risk of dying ≈ 10x higher compared to patients without coagulopathy

AIS head	No coagulopathy (%)	Coagulopathy (%)
AIS 3	~10	~20
AIS 4	~15	~30
AIS 5	~30	~40
AIS 6	~35	~55

AIS head	No coagulopathy (%)	Coagulopathy (%)
AIS 3	~90	~70
AIS 4	~80	~55
AIS 5	~35	~15
AIS 6	~5	~5

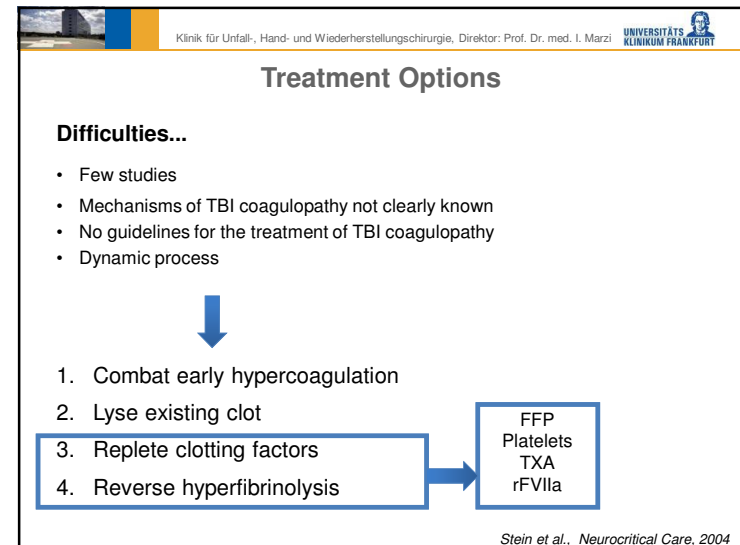
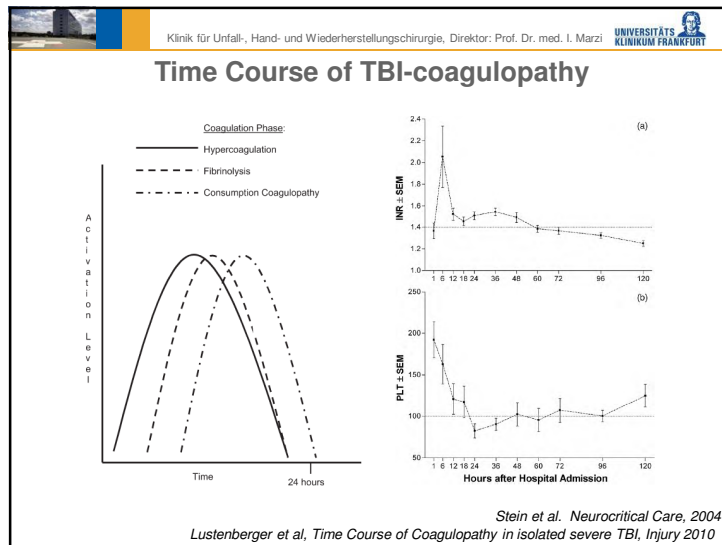
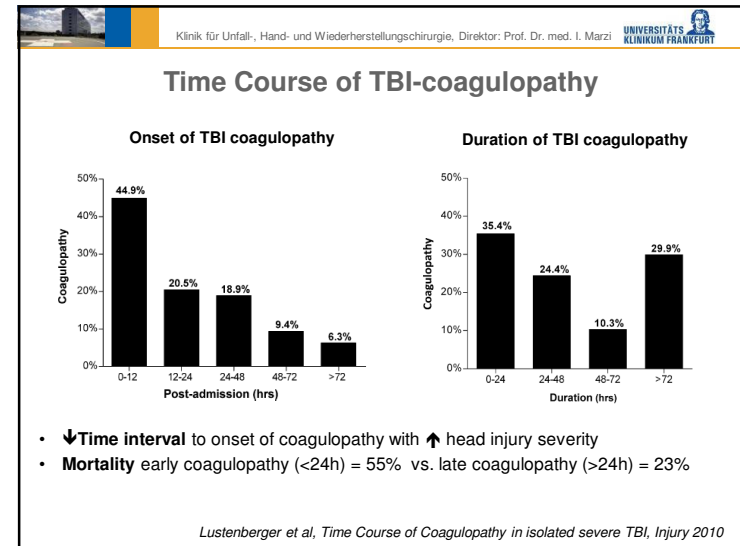
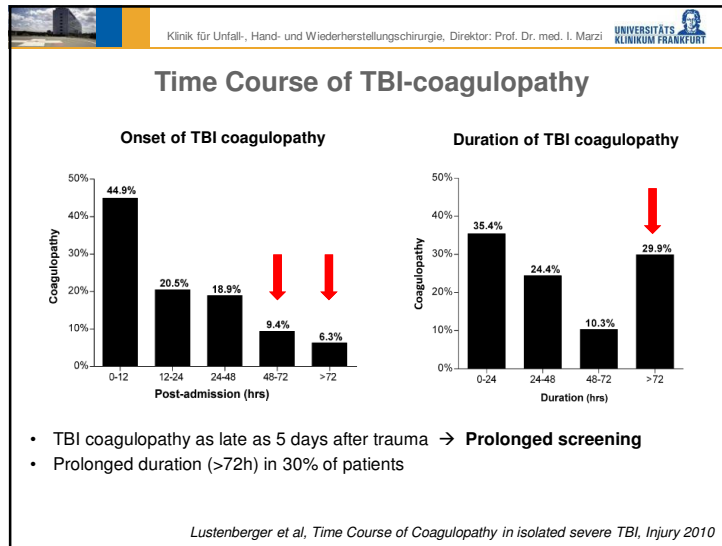
Wafaisade et al, Acute Coagulopathy in isolated blunt TBI, Neurocrit Care, 2010


TBI-coagulopathy: Risk Factors

Independent risk factors for the development of coagulopathy after blunt TBI

- Severity of head trauma (AIS_{head})
- GCS at scene ≤8 points
- Hypotension ≤90 mmHg at scene / ED arrival
- Prehospital iv fluid administration ≥2000 ml
- Age ≥75 years


Wafaisade et al, Acute Coagulopathy in isolated blunt TBI, Neurocrit Care, 2010




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Fresh Frozen Plasma (FFP)

- All coagulation factors in non-concentrated form
- Has to be thawed
- Volume!
 - Cave: Patients with cardiac, pulmonary or renal disease
- Human-derived product
 - Potential issues with crossmatching, ...
 - Transmission of infectious disease
 - TRALI



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Platelets


- Early administration of platelets in TBI still under discussion

The Impact of Platelets on the Progression of Traumatic Intracranial Hemorrhage

Beat Schnüriger, MD, Kenji Inaba, MD, FRCSC, FACS, Georg Abdelsayed, Thomas Lustenberger, MD, Barbara M. Eberle, MD, Galinos Barnmparas, MD, Peep Talving, MD, PhD, and Demetrios Demetriades, MD, PhD, FACS

- ✓ PLT count <100,000 → 9x risk of death
- ✓ PLT count <175,000 → predictor of progression.

- Increasingly utilized for reversal of aspirin therapy

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Tranexamic Acid (TXA)

BMJ **Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study)**

The first randomized, placebo controlled trial evaluating TXA in TBI patients


Trend toward ...

- ... ↓ mean total **hemorrhage growth** (nonsignificant)
- ... ↓ new focal cerebral **ischemic lesions** (nonsignificant)
- ... ↓ **deaths** (nonsignificant)

... in TXA cohort

Best effect when administered within first 3 hours (first hour) after injury

Crash-2-Collaborators, BMJ, 2011

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Recombinant Factor VIIa (rFVIIa)

Non-human derived, small volume boluses (1-8ml)

Quickly corrected INR into operable ranges


- ↓ Blood product transfusion
- More rapid neurosurgical intervention

Bartal et al., Coagulopathic patients with traumatic intracranial bleeding: the role of rFVIIa, J Trauma 2007
Stein et al., rFVIIa: Decreasing time to intervention in coagulopathic patients with TBI, J Trauma 2008

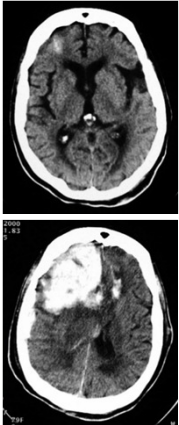
Prospective, randomized, placebo-controlled study

- Trend for dose-response to limit intracranial bleeding volume progression
- No difference in mortality
- Trend for more asymptomatic deep venous thrombosis

Narayan et al., rFVIIa in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial, Neurosurgery, 2008

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Pre-Injury Antiplatelet and Anticoagulant Use




Vitamin-K-Antagonist (Warfarin, Marcumar)

- Directly compete by giving Vit. K
- Replace coagulation factors (FFP, PCC)
- Bypass central part of coagulation cascade (rFVIIa)

Antiplatelet Agents (Clopidogrel)

- Desmopressin
- Transfusion of uninhibited platelets

Ivascu et al., Rapid Warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality, J Trauma, 2005

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The „new“ Anticoagulants



Direct thrombin (IIa) inhibitors


- Dabigatran (Pradaxa®)

Direct factor Xa inhibitors

- Rivaroxaban (Xarelto®)


Reversal 


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Summary

- Coagulopathy occurs **frequently** in TBI (≈1/3)
- Complex condition that is still **poorly defined**
 - ✓ Mechanism
 - ✓ Diagnosis
 - ✓ Treatment
- TBI coagulopathy is related to **poor prognosis** (mortality, complications, ...)
- Research needed to provide **evidence-based** treatment thresholds

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Thank you!



Thomas.Lustenberger@kgu.de