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

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***Critical Care* 2023; 27:80**

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Conflict-of-Interest - disclosures - spectrum of activities

- Consulting companies
  - ⇨ B. Braun
  - ⇨ CSL Behring
  - ⇨ CSL Vifor (International)
  - ⇨ Haemonetics
  - ⇨ Werfen
- ABC trauma faculty, managed by Thomson Physicians World GmbH with unrestricted educational grant from
  - ⇨ CSL Behring
  - ⇨ LFB Biomédicaments
  - ⇨ Alexion Pharma Germany GmbH
- Consulting Universities
  - ⇨ Danube University of Krems
- Consulting Professional Societies
  - ⇨ European Society of Anaesthesiology and Intensive Care
  - ⇨ Korean Society of Anesthesiologists

Honoraria / travel support for occasional consulting / lecturing

Companies		
Alexion	AstraZeneca	Baxter
Bayer	Celgene	Daiichi Sankyo
LFB Biomédicaments	Merck Sharp & Dohme	Novo Nordisk
Octapharma	Pharmacosmos	Pierre Fabre
Portola	Roche Diagnostics	Sarstedt
Shire	Takeda	Zuellig Pharma Holdings

Foundations		
Eur-Asia Heart Foundation	Heart Team Education Association	Network for the Advancement of PBM, Haemostasis and Thrombosis (NATA)
ESAIC	Swiss Foundation for Anesthesia Research	International Foundation for Patient Blood Management
Society for the Advancement of Blood Management (SABM)		

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

- **The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition** provides evidence-based recommendations developed by a multi-disciplinary task force that aim to support best practice in the management of severely injured trauma patients. If incorporated into local practice, improvement in outcomes will be achieved by optimising and standardising trauma care in line with the available evidence across Europe and beyond

Rossaint et al. Crit Care 2023; 27:80.

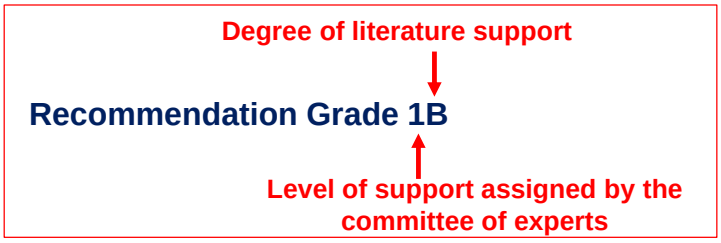
Literature used for the guideline update

- This sixth edition of the European guideline on the management of major bleeding and coagulopathy following traumatic injury[1] represents an update of the editions published by the same core author group in 2007, 2010, 2013, 2016 and most recently in 2019[2]
  - It cites only the highest-quality studies and most relevant literature rather than attempting to provide a comprehensive literature review to accompany each recommendation (references ⬇ from 870 ➡ 386)
  - Rationale was limited to approx. 500 words per recommendation (pages ⬇ from 74 ➡ 45)
  - Additional older literature citations and an extended discussion around some of the recommendations included here can be found in previous editions of this guideline
- **Citations V1-V6 (2023-04-20): 3'223**
- **Downloads V1-V6 (2023-03-20): 877'000 (V6: 35'000)**

1. Rossaint et al. Crit Care 2023; 27:80. 2. Spahn DR, et al. Crit Care 2019, 23(1):98.

Consensus approach to formulate recommendations

- Recommendations were formulated using a **structured, evidence-based consensus approach** by the author group, including representatives of the professional societies involved[1]
- The **GRADE** (Grading of Recommendations Assessment, Development and Evaluation)[2] hierarchy of evidence was employed



1. Rossaint et al. Crit Care 2023; 27:80. 2. Guyatt G, et al. Chest 2006; 129:174-81.

New to this edition

- New to this edition of the guideline is a recommendation and discussion around the **use of cell salvage** (R17) under appropriate circumstances
- This edition also discusses the potential **pre-hospital use of blood products** (R4) but does not include a recommendation or suggestion for or against this practice
- POC platelet function analysis (R12) is not recommended any more
- Formal inclusion of anedxanet alfa (R34) to antagonize Xa-inhibitors

Rossaint et al. Crit Care 2023; 27:80.

Limitations to this edition

- Only a limited number of the recommendations are based on high-quality evidence. However, all recommendations are based on the best available evidence.
- 75% of recommendations were Grade 1 recommendations
- Specific recommendations for paediatric patients have not been included
- Implementation is likely to be feasible within most European healthcare systems, but possibly not in other regions of the world

Rossaint et al. Crit Care 2023; 27:80.

Endorsement

The guideline has been endorsed by the

- European Society of Anaesthesiology and Intensive Care (ESAIC)
- European Society of Intensive Care Medicine (ESICM)
- European Shock Society (ESS)
- European Society for Trauma and Emergency Surgery (ESTES)
- European Society for Emergency Medicine (EuSEM)
- Network for Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA)

Rossaint et al. Crit Care 2023; 27:80.

Acknowledgements and Disclosures

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- CSL Behring GmbH supported the development and production of this slide deck
- The grantors had no authorship or editorial control over the content of the meetings or any subsequent publication

Rossaint et al. Crit Care 2023; 27:80.

Focus of my short presentation

- Highlight the key updates in the 6th version of The European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma
- Discuss the evidence supporting individualized goal-directed coagulation management and its impact on the outcome of severely injured trauma patients
- Assessment and treatment of trauma patients with known or suspected anticoagulation

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 4
Pre-hospital blood product use

New

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

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 12
Platelet function monitoring

In 2019 use of POC platelet function analysis was suggested (2C)

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

Grade 1C

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 12 – Rationale
POC platelet function devices

- Current **platelet function POC** devices vary in sensitivity, are not interchangeable in the assessment of platelet reactivity, and results may be less reliable for low platelet counts
- Results may vary when using different POC platelet function tests (PFTs) **to detect antiplatelet agents (APAs) and induced platelet inhibition** in trauma patients[1-4]
  - The use of POC-PFTs in the detection or exclusion of pre-injury APA treatment is limited, as several studies found that trauma patients, especially those with TBI, had therapeutic assay results below the reference interval, independent of APA intake history[5-8]
  - Diagnostic cut-offs for pathologic platelet dysfunction after traumatic injury have not been established
  - It is not easy to distinguish pharmacologic from trauma-induced platelet receptor hypofunction
  - In vivo platelet response to the individual agonists used in POC-PFTs to induce activation and aggregation may not be adequate for detecting traumatic platelet dysfunction

1. Choi PA, et al. Neurosurgery 2017, 80(1):98-104. 2. Lindblad C, et al. Front Neurol 2018, 9:15. 3. Barton CA, et al. J Trauma Acute Care Surg 2021, 91(5):803-808. 4. Eastman DK, et al. J Surg Res 2021, 263:186-192. 5. Sirajuddin S, et al. J Trauma Acute Care Surg 2016, 81(2):328-332. 6. Alvikas J, et al. J Trauma Acute Care Surg 2022, 92(1):167-176. 7. Guillotte AR, et al. Brain Inj 2018, 32(13-14):1849-1857. 8. Miles MVP, et al. J Trauma Acute Care Surg 2022, 92(4):701-707

Recommendation 17
Cell salvage

New

We suggest that cell salvage be considered in the presence of severe bleeding from an abdominal, pelvic or thoracic cavity

Grade 2B

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 23
Antifibrinolytic agents

Also TXA administration en route now is strongly recommended (1A instead of 1C)

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

Grade 1A

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 26
Goal-directed therapy

Unchanged

We recommend that resuscitation measures be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM

Grade 1B

Rossaint et al. Crit Care 2023; 27:80.

2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

Developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC)

Endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC)

Halvorsen S. et al. Eur Heart J. (2012); 43: 3826

Recommendation Table 17 — Recommendations for intra- and post-operative complications associated with blood loss

Recommendations	Class[a]	Level[b]
In patients undergoing surgery with expected blood loss of ≥500 mL, use of washed cell salvage is recommended.[377,378]	I	A
It is recommended to use point-of-care diagnostics for guidance of blood component therapy, when available.[370,379–383]	I	A

Halvorsen S. et al. Eur Heart J. (2012); 43: 3826

Recommendation 29
Fibrinogen supplementation

Unchanged

ABC Advanced Bleeding Care

We recommend treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤1.5 g/L)

Grade 1C*

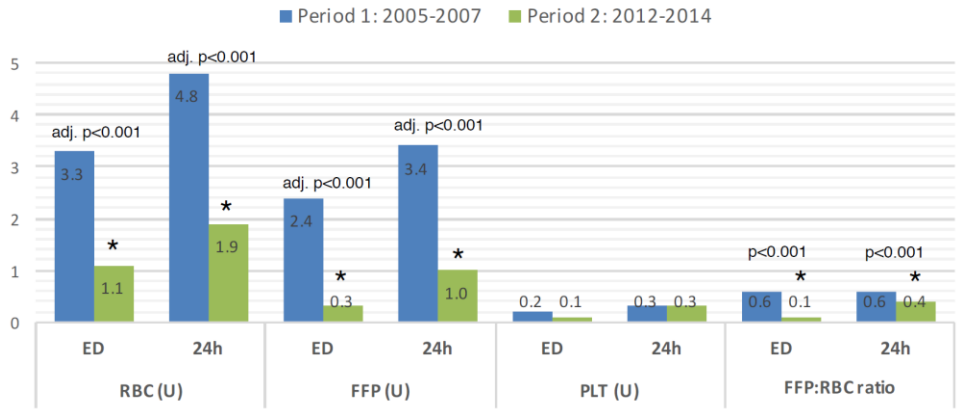
Rossaint et al. Crit Care 2023; 27:80.

*Based on the weak level of the evidence, the proposed grading of this recommendation was 2B. After voting, the group decided to revert the grading to 1C, as in the previous edition of the guideline, because several authors felt that downgrading to a suggestion might risk misinterpretation to the detriment of fibrinogen concentrate use as part of daily clinical practice

Detect low fibrinogen	
FIBTEM ≤ 7 mm	Fibrinogen 2–4 g i.v. (after 6 g of fibrinogen, administer factor XIII, 15 U/kg i.v.)
Detect fibrinolysis	
EXTEM/INTEM: Clot lysis after MCF and APTEM: normal = Hyperfibrinolysis	**Tranexamic acid** • Bolus: 15 mg/kg i.v. (consider empiric use) • Consider continuous infusion 1–2 mg/kg/h
Ongoing bleeding	
• Factor XIII < 60%	Factor XIII, 15 U/kg i.v.
Platelet count/function • EXTEM / INTEM MCF < 40 mm • Platelet count ≤ 50 000/µl (≤ 100 000/µl in cardiac surgery or traumatic brain injury) • Platelet function (Impedance aggregometry)	Platelet concentrate Consider desmopressin 0.3 µg/kg (max 16 µg) in case of aspirin (like) platelet dysfunction
• INR > 2.3 (Quick's value < 30%)	Four-factor prothrombin complex concentrate (slow continuous infusion of small repeated doses – e.g. 500 IU)
• Factor V < 20%	FFP (2–4 units)
Detect heparin	Antagonize heparin
INTEM (CT/CFT) or ACT prolonged and HEPTEM or heparinase-ACT normal	Protamine (1: 1) to antagonize heparin

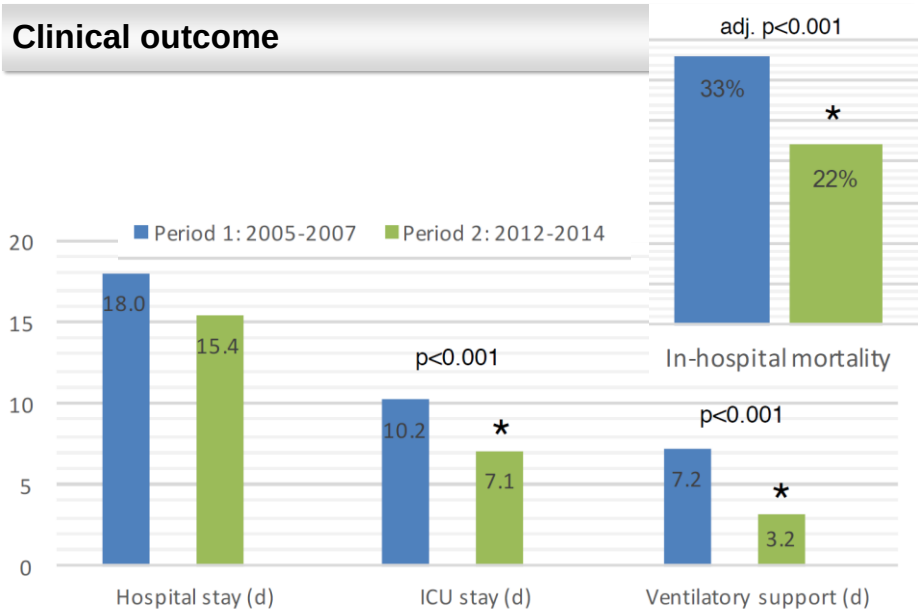
Stein P. et al., Semin Thromb Hemosth (2017) 43: 367

Allogeneic blood products and coagulation factors (U)



Stein P. et al., Anaesthesia (2017) 72: 1327

Clinical outcome



Stein P. et al., Anaesthesia (2017) 72: 1327

RANDOMIZED CONTROLLED TRIAL

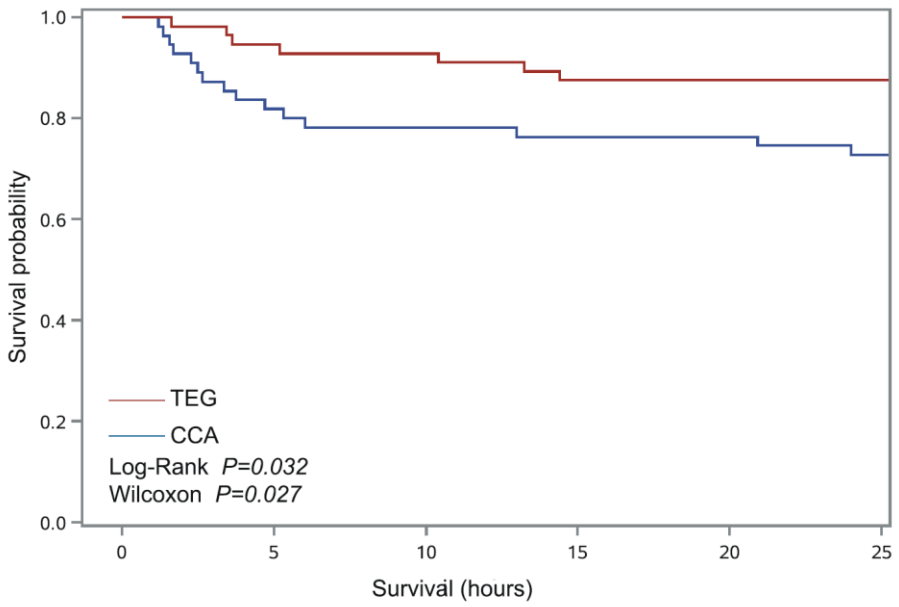
DENVER HEALTH
Level One Care For ALL

Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays

- Prospective, weekly-randomized trial in severely injured patients (n=111, ISS=32) with massive transfusion protocol activation at a level-1 trauma center
- Protocols
  - ⇨ Conventional coagulation assay (INR, fibrinogen level, platelet count)
  - ⇨ TEG
- Outcome
  - ⇨ Primary Outcome: 28-d survival
  - ⇨ Secondary Outcome
    - ⇨ Transfusion
    - ⇨ Mechanical ventilation
    - ⇨ ICU length of stay

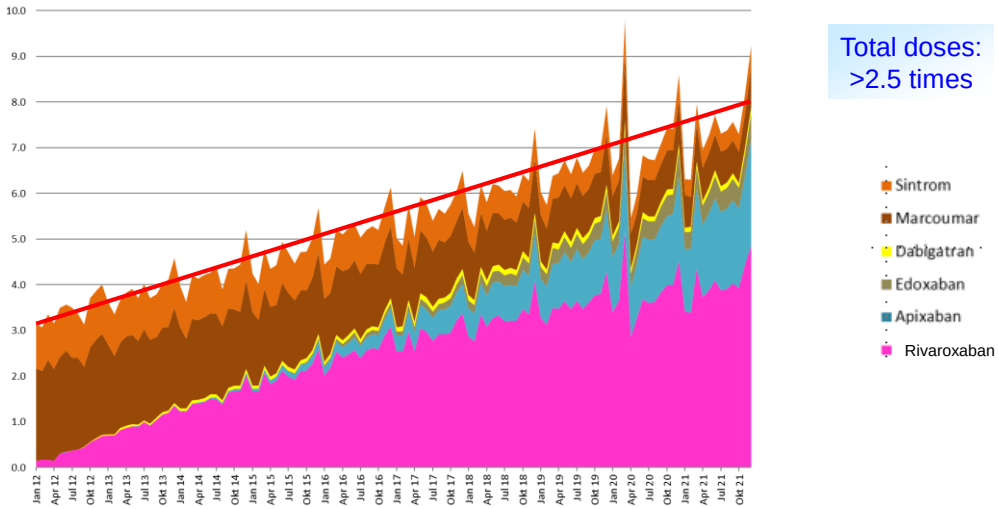
Gonzalez E. et al. Ann Surg (2016) 263: 1051



Gonzalez E. et al. Ann Surg (2016) 263: 1051

The number of anticoagulated patients in Switzerland continues to grow

Daily doses (mio) per month (2012 – 2021)



Source: National sales data in counting units / Channels: APO/SD/SPI (data on file)
DDD: Rivaroxaban 1x, Marcoumar 1x, Edoxaban 1x, Sintrom 2x, Apixaban 2x, Dabigatran 2x

Is the patient anticoagulated ?

Table 1. Pathognomonic Changes due to Different Classes of Anticoagulants

	Prothrombin Time/INR	Anti-Xa Activity	Thrombin Time
Vitamin K antagonist	↑	-	-
Xa inhibitor	-(↑)	↑	-
Thrombin antagonist	-(↑)	-	↑

INR, international normalized ratio.

Spahn D. R. et al. Anesthesiology (2021) 135: 570

Unchanged

Recommendation 33
Reversal of vitamin K-dependent oral anticoagulants

In the bleeding trauma patient, we recommend the emergency reversal of vitamin K-dependent oral anticoagulants with the early use of both PCC and 5–10 mg i.v. phytomenadione (vitamin K_1)

Grade 1A

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 34
Management of direct oral anticoagulants – factor Xa inhibitors

Unchanged

We suggest the measurement of plasma levels of oral direct anti-factor Xa agents such as apixaban, edoxaban or rivaroxaban in patients treated or suspected of being treated with one of these agents

Grade 2C

Rossaint et al. Crit Care 2023; 27:80.

Recommendation 34
Management of direct oral anticoagulants – factor Xa inhibitors

LMWH calibrated tests are new

We suggest that measurement of anti-Xa activity be calibrated for the specific agent. If not possible or available, we suggest low molecular weight heparin (LMWH)-calibrated anti-Xa assays as a reliable alternative

Grade 2C

Rossaint et al. Crit Care 2023; 27:80.

Prediction of plasma concentration of Xa inhibitor by anti-Xa test (LMWH)

- 867 patients treated with rivaroxaban, apixaban or edoxaban
- Parallel measurement of anti-Xa test (LMWH) and liquid chromatography / mass spectrometry in 7 labs

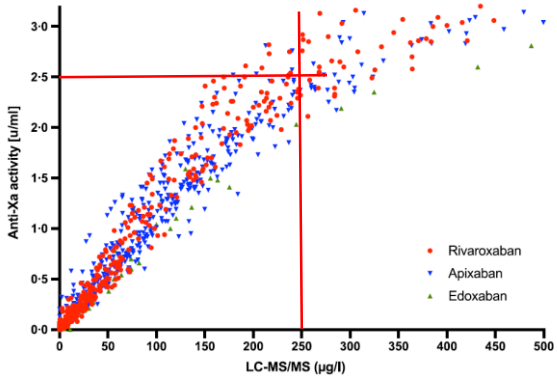


Table I. Application of the low-molecular-weight heparin (LMWH)-calibrated, universal assay.

Measure	Result
DOAC cut-off value 30 µg/l	0·35 U/ml
DOAC cut-off value 50 µg/l	0·58 U/ml
DOAC cut-off value 100 µg/l	1·14 U/ml
Regression equation rivaroxaban	120 × [U/ml]−19
Regression equation apixaban	115 × [U/ml]−22
Regression equation edoxaban	164 × [U/ml]−24

Rivaroxaban: x 100
Apixaban: x 100
Edoxaban: x 150

Willekens G. et al. Br J Haematol (2021) 193: 1203

Recommendation 34
Management of direct oral anticoagulants – factor Xa inhibitors

Andexanet alfa is new

ABC Advanced Bleeding Care

If bleeding is life-threatening in the presence of an apixaban or rivaroxaban effect, especially in patients with TBI, we suggest reversal with andexanet alfa

Grade 2C

Rossaint et al. Crit Care 2023; 27:80.

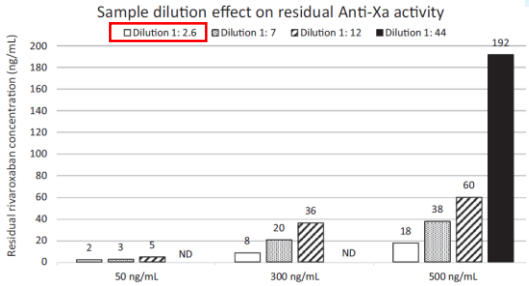
Coagulation monitoring following the administration of andexanet alfa

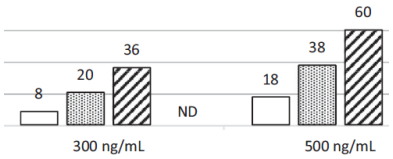
- Commercial anti Xa assays overestimate direct Xa antagonist concentration following the administration of andexanet alfa
- A modified automated test set-up with a reduced sample dilution was developed using standard reagents and analyzers

Overestimation

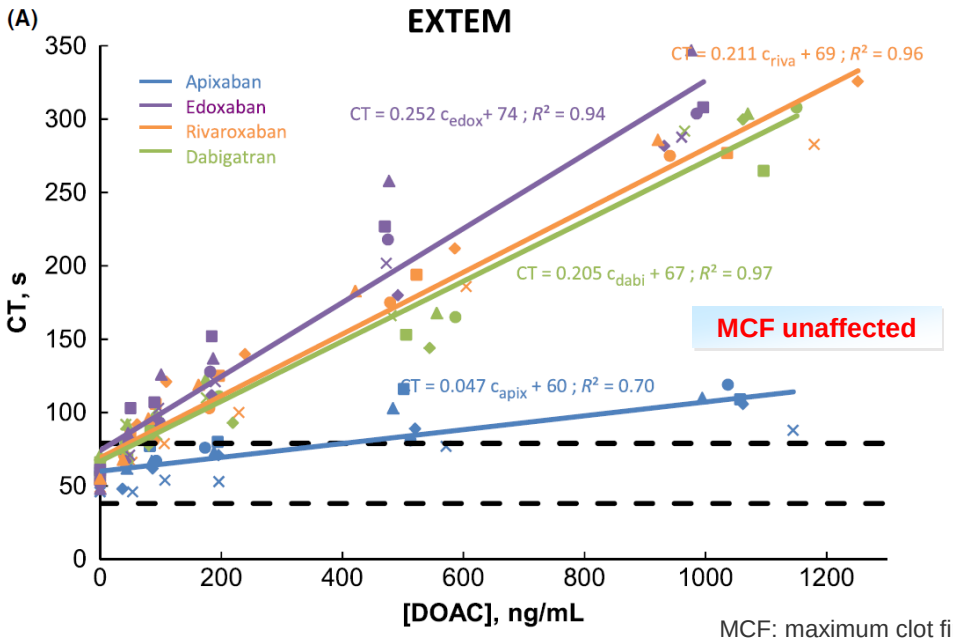
FIGURE 1 Sample dilution effect on residual anti-Xa activity based on ng/mL. The results are compared following different dilutions with rivaroxaban (50 to 500 ng/mL)-spiked plasma samples and AnXa concentration of 2.3 µmol/L. The residual concentrations are expressed in ng/mL for each bar which corresponds to a sample and its dilution

AnXa = Andexanet alfa





Bourdin M. et al. Int J Lab Hematol (2021) 43: 795



MCF: maximum clot firmness

Seyve L. et al., Int J Lab Hematol (2018) 40: 84

Conclusions

- European Trauma Treatment Guidelines are high quality recommendations for best practice treatment of major trauma patients
- They are short, concise and endorsed by 6 major European professional societies including ESAIC and ESICM
- Individualized goal-directed coagulation management based on visco-elastic methods with a positive effect on outcome has been confirmed
- Management of anticoagulated trauma patients has been clearly defined
- Now it is time to adapt / create local trauma treatment pathways, implement them and measure adherence and success in your hospital

Recommendation Table 16 — Recommendations for intra- and post-operative complications associated with anaemia

Recommendations	Class[a]	Level[b]
It is recommended to measure haemoglobin pre-operatively in patients scheduled for intermediate- to high-risk NCS.[350,354]	I	B
It is recommended to treat anaemia in advance of NCS, in order to reduce the need for RBC transfusion during NCS.[357,361]	I	A

Halvorsen S. et al. Eur Heart J. (2012); 43: 3826

https://apps.who.int/iris/bitstream/handle/10665/346655/9789240035744-eng.pdf
Online since October 19, 2021 – accessed March 20, 2023