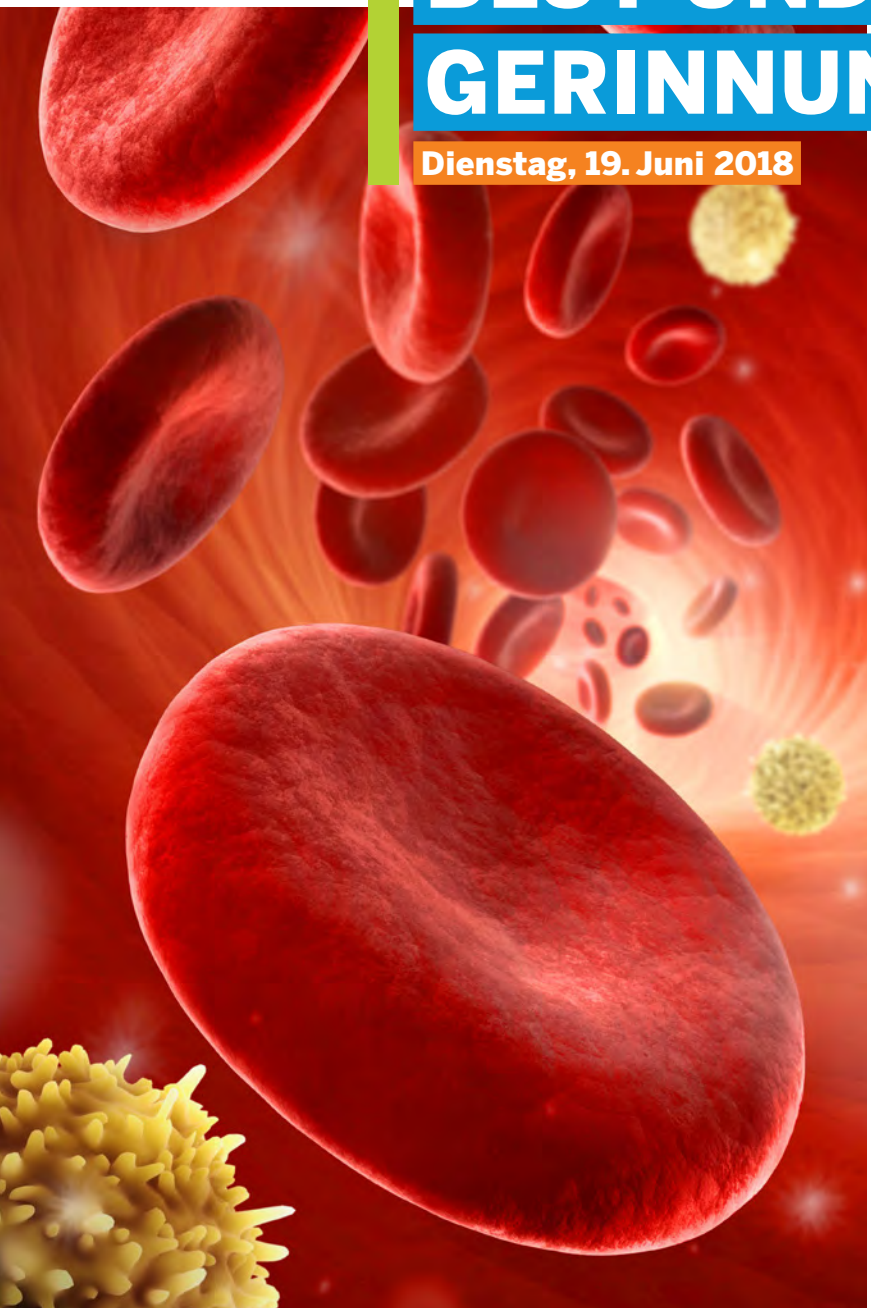
Institut für Anästhesiologie

SYMPOSIUM BLUT UND GERINNUNG

Dienstag, 19. Juni 2018



16.15–20.00 Uhr
KSW, Aula U1

KANTONSSPITAL WINTERTHUR

Liebe Kolleginnen
Liebe Kollegen

Blut ist ein besonderer Saft. Es sollte nicht zu dünn, nicht zu dick sein. Zu viel ist nicht gut, zu wenig ganz schlecht. Und schliesslich sollten auch die Zutaten stimmen.

Wahrlich eine Herkulesaufgabe für dieses Organ des menschlichen Körpers!

Durch seine physiologischen Eigenschaften fasziniert das Blut gerade uns Anästhesisten in besonderem Masse. Die Komplexität der biochemischen Prozesse macht ein Verstehen aber nicht immer ganz leicht.

Wir freuen uns, Sie zum Sommersymposium einladen zu dürfen, an dem das Blut im Zentrum steht. Unsere Referenten werden Ihnen zur gesamten perioperativen Phase spannende Inputs zum Thema Blut geben können: Mit Vorträgen über Patient Blood Management in der perioperativen Phase, über hämostaseologische Bedsidetests bis hin zum neuen Therapiealgorithmus bei Massenblutung der SGAR und schliesslich zur richtigen Gerinnungstherapie rund um die modernen kardiologischen Interventionen und Implantate haben wir für Sie praktische Themen gewählt, die durchaus auch als Entscheidungshilfen dienen.

Gerne erwarten wir Ihr Kommen, wiederum angeregte Diskussionen und grüssen Sie bis dahin herzlich!

Dr. med. Daniel Borer
Leitender Arzt
Institut für Anästhesiologie
Kantonsspital Winterthur

Prof. Dr. med. Michael Ganter
Direktor
Institut für Anästhesiologie
Kantonsspital Winterthur

Referenten

Prof. Dr. med. Michael Ganter
Direktor Institut für Anästhesiologie
Kantonsspital Winterthur

PD Dr. med. Lars Asmis
Hämatologe, Leiter Zentrum für perioperative Thrombose und Hämostase (ZPTH)
Zürich

PD Dr. med. Stefan Blöchlinger
Leitender Arzt
Kardiologie
Kantonsspital Winterthur

Dr. med. Martin Brüesch
Leitender Arzt
Institut für Anästhesiologie
Universitätsspital Zürich

Symposium
Blut und Gerinnung

Datum	**Dienstag, 19. Juni 2018**
Ort	**Kantonsspital Winterthur, Aula U1**
Zeit	**16.15–20.00 Uhr**

16.15 Uhr	**Eröffnung des Symposiums** Prof. Dr. med. Michael Ganter
16.20 Uhr	**Patient Blood Management** Prof. Dr. med. Michael Ganter
17.05 Uhr	**Was Sie schon immer über POCT wissen wollten und sich nie zu fragen getrauten** PD Dr. med. Lars Asmis
17.50 Uhr	**Pause mit Apéro**
18.20 Uhr	**Koronarstents – perioperative Herausforderungen** PD Dr. med. Stefan Blöchlinger
19.05 Uhr	**Gerinnungs- und Transfusionsalgorithmus der SGAR** Dr. med. Martin Brüesch
19.50 Uhr	**Diskussion**

Moderation	Dr. med. Daniel Borer

Die Veranstaltung wird von der SGAR mit 4 Credits anerkannt.

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SAVE THE DATE

Weiteres Symposium 2018
des Instituts für Anästhesiologie
«Big Data in der Anästhesie»
Dienstag, 2. Okt. 2018
16.15 bis 20.00 Uhr

Institut für Anästhesiologie

Organisation
Dr. med. Daniel Borer
Leitender Arzt

Prof. Dr. med. Michael Ganter
Direktor

Information und Anmeldung
Regina Broger
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Anmeldung bis spätestens 18. Juni 2018 an:
anaesthesiologie@ksw.ch

Die Veranstaltung wird unterstützt von:

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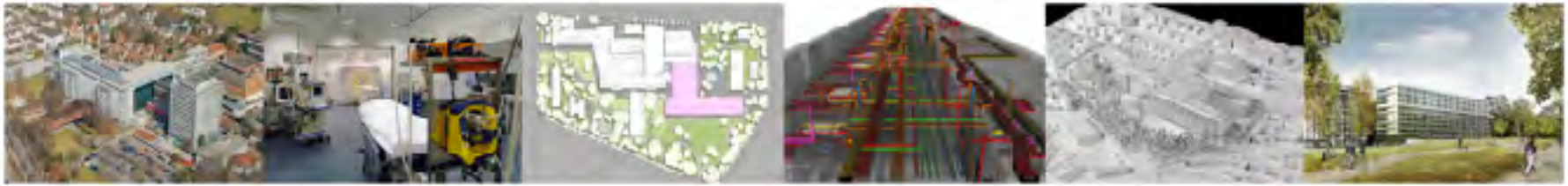
Symposium Institut für Anästhesiologie

Aula KSW, 19. Juni 2018

Patient Blood Management – PBM



Prof. Dr. med. Michael Ganter
michael.ganter@ksw.ch

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Conflict of interest statement

- Personal: None

- My institution gets financial support from industry for our tri-annual anesthesia symposia, current symposium:

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Agenda

- **Patient Blood Management**
  - The Program, Rationale
- **Pillar 1 – Optimise RBC Mass**
  - Anemia – Definition, Differential, Pre-operative Workup
  - Iron Deficiency
- **Pillar 2 – Blood Loss**
- **Pillar 3 – Manage Anemia**
- **Key Facts**

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PBM – THE PROGRAM

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PBM – Patient Blood Management

Multi-Disciplinary Quality Improvement Program

- 3 PILLARS
- 3 TIME POINTS
  - PRE-OP
  - INTRA-OP
  - POST-OP

https://www.nba.gov.au/patient-blood-management-pbm (05/2018)

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PBM – RATIONALE

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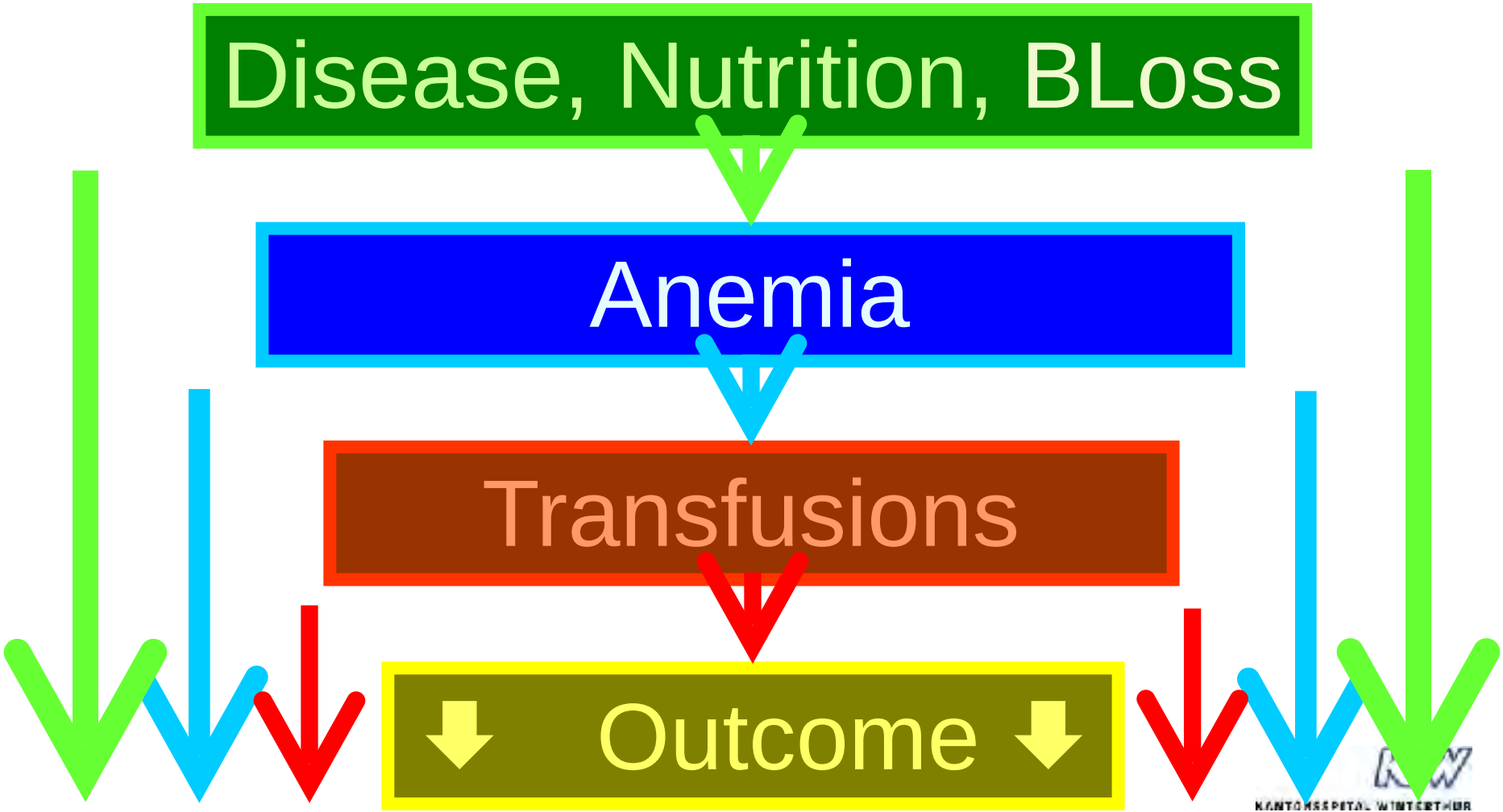
Disease, Nutrition, BLoss
Anemia
Transfusions
Outcome

Pre-op anemia – outcome

- Meta-analysis, 24 eligible studies, 949,445 pts, **39%** anemic
- Anemia was associated with
  - increased mortality (OR 2.90, 2.30 to 3.68)
  - acute kidney injury (OR 3.75, 2.95 to 4.76)
  - infection (OR 1.93, 1.17 to 3.18)
  - stroke (OR 1.28, 1.06 to 1.55)
  - increased RBC transfusions (OR 5.04, 4.12 to 6.17)
- ?? independent risk factor vs marker of underlying disease ??

Fowler AJ et al. *Br J Surg* 2015. 102:1314-24

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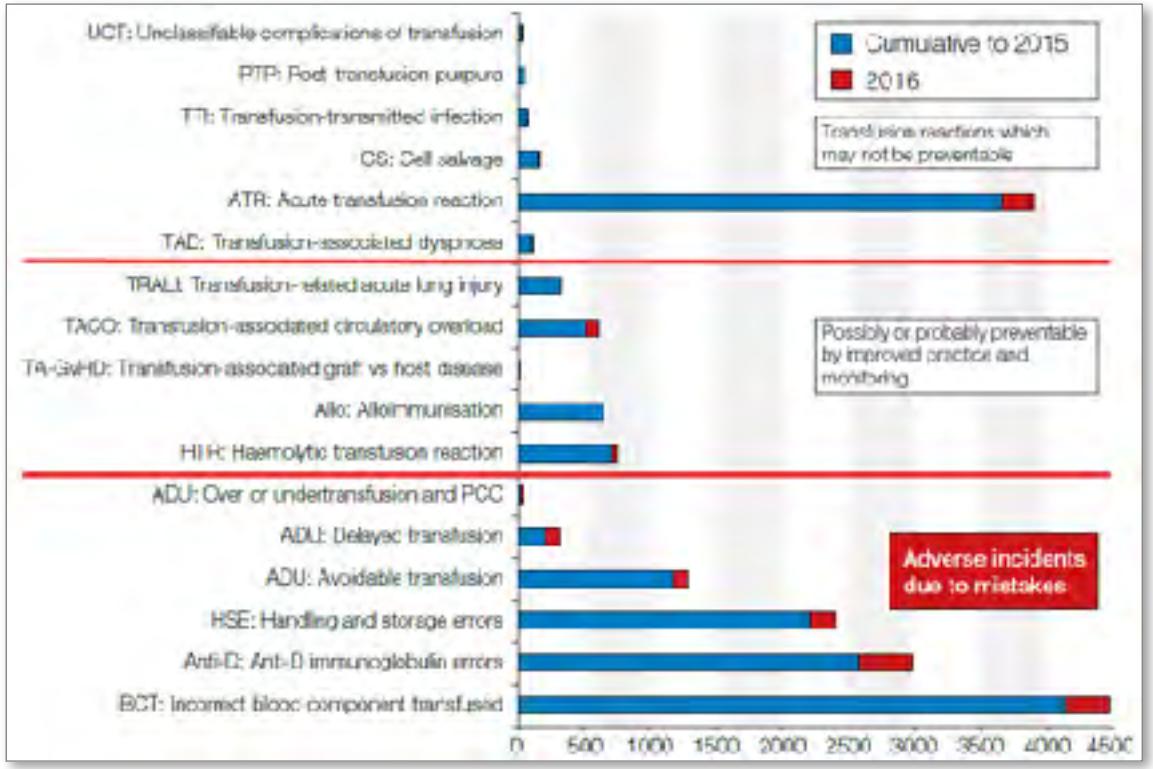
Transfusions – UK Hemovigilance



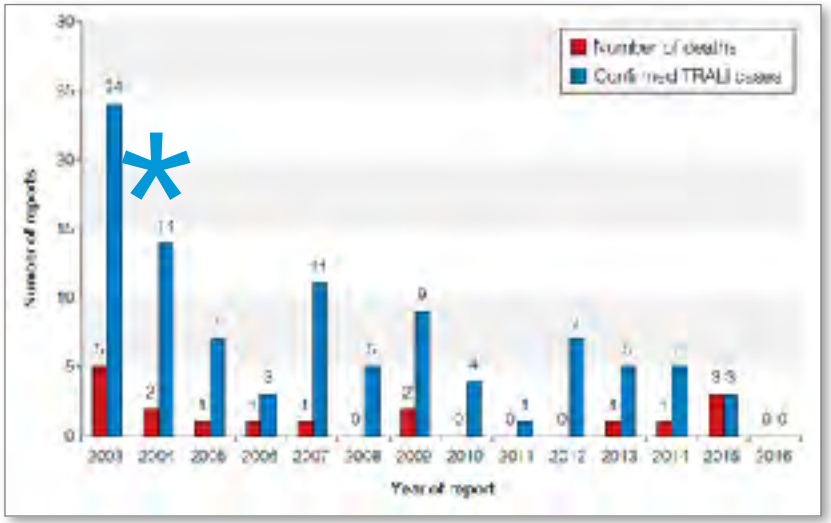
- **1996-2016** cumulative reports for SHOT categories
  n = 18,258 (50 Mio units)

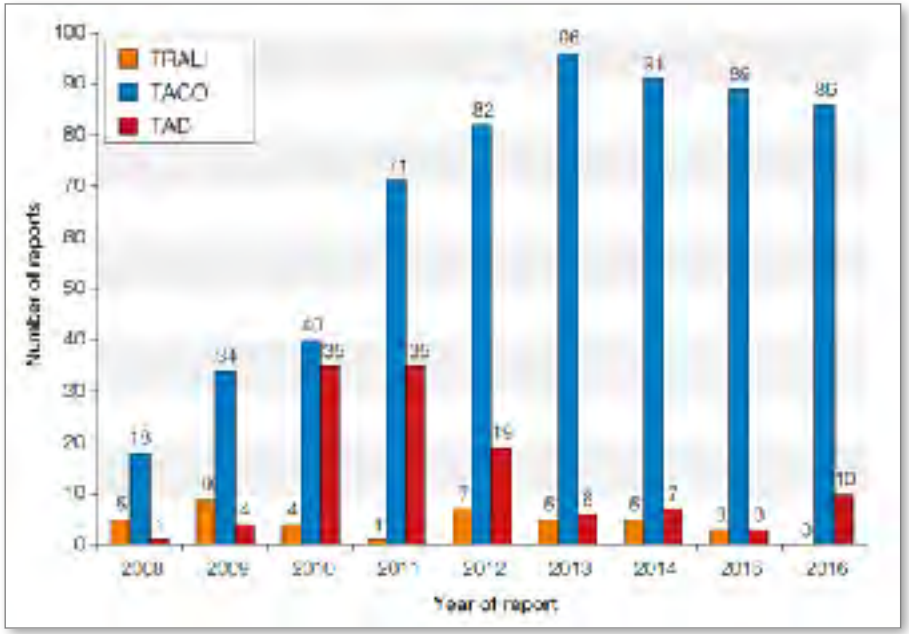
  last 7 yrs ~ 3,500 reports annually
  1 report per 5'000 units transfused

- **Majority** of incidents (90%) are caused by human error

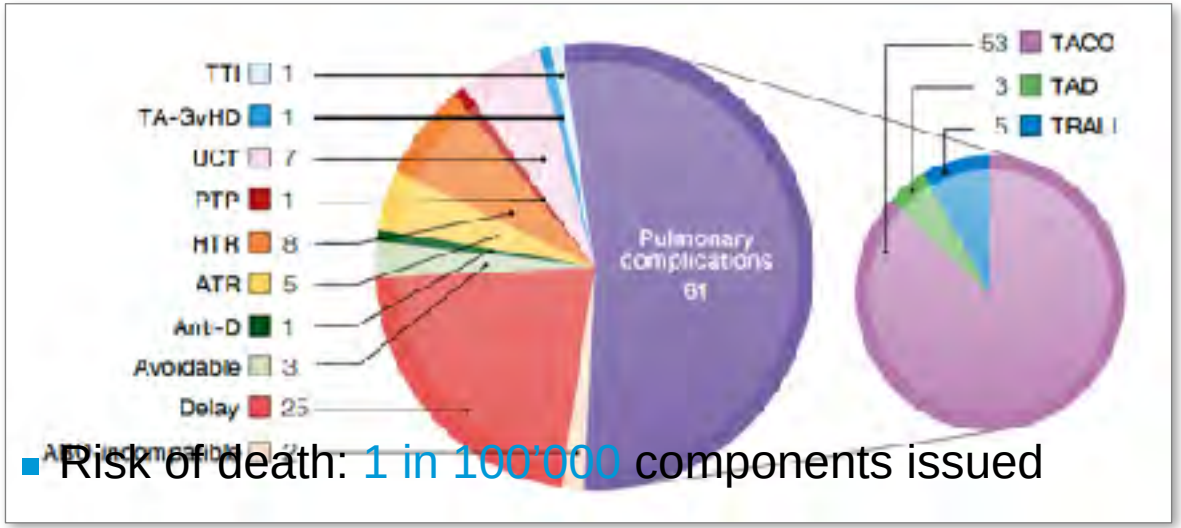
UK Hemovigilance – pulmonary

2004 male only plasma





UK Hemovigilance – deaths



- Risk of death: 1 in 100'000 components issued

- **2010-2016**
  transfusion-related deaths
  n = 115

last 7 yrs ~ 3,500 reports annually

Swiss Hemovigilance

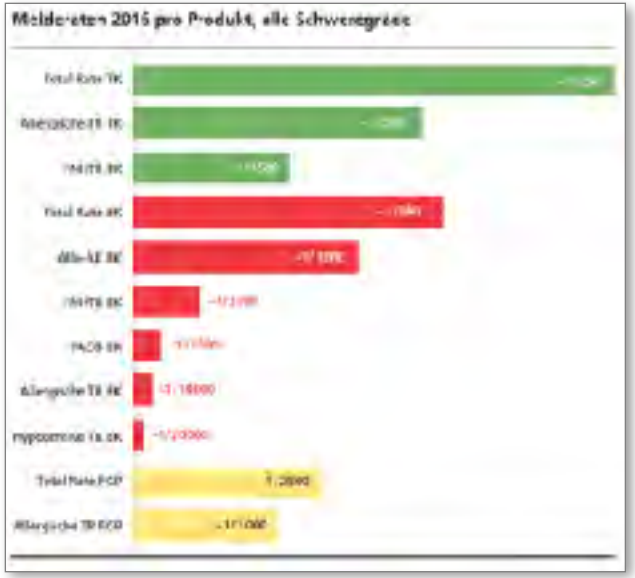
Transfusionszahlen Schweiz

Blutkomponenten	2008	2009	2010	2011	2012	2013	2014	2015	2016
Erythrozytenkonzentrate	313587	311521	308670	308627	297582	279510	262953	248647	239890
FCP (therap. Einheiten)	65800	70300	61500	50063	49832	44083	38183	33658	38374
TK (Produkte)	27600	29600	29900	33068	34265	34750	35328	36439	33310
Total Blutkomponenten	406987	411421	400070	391758	381679	358343	336464	318744	311574

-25%

Meldungen unerwünschter Vorkommnisse 2016

Typ	Anzahl
Transfusionsreaktionen	1777
Fehltransfusionen / inkorrektes Blut Produkt transfundiert (IBPT)	36
Near-Miss Ereignisse (NM)	1168
Spende-Nebenwirkungen	24
Qualitätsmängel und Schutzmassnahmen	122
Ausgewertete Meldungen total	3127



→ 1 Meldung pro 100 Transfusionen (sehr hoch !)

Swissmedic Haemovigilance 2016; www.swissmedic.ch

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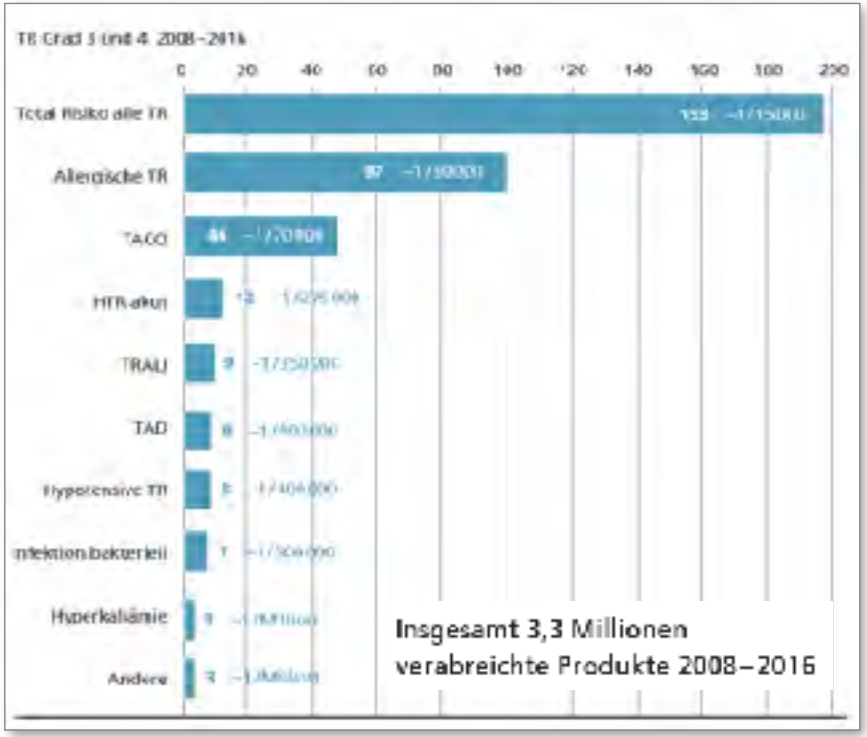
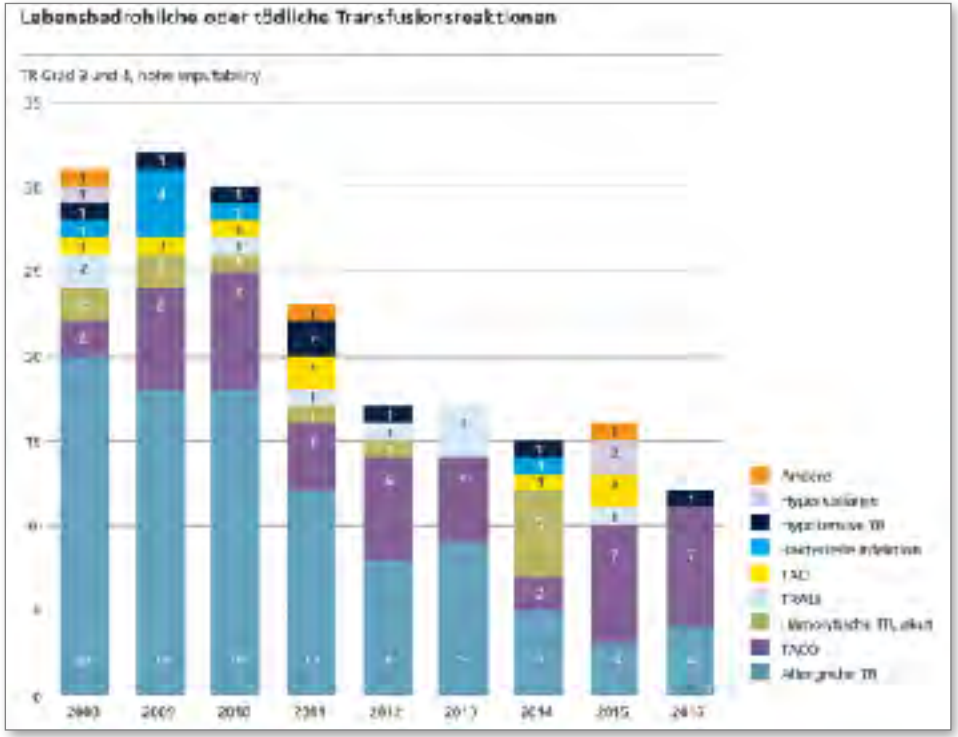
Swiss Hemovigilance – serious TR





Swissmedic Haemovigilance 2016; www.swissmedic.ch

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Transfusion risks

Why bother about allogeneic RBC, FFP and platelets ?

- RBC, FFP and platelet transfusions are associated with major adverse outcome
  - → Mortality ↑
  - → Major morbidity (ischemia) ↑
  - → Infection ↑
  - → TACO, TRALI ↑
  - → Transfusion reaction
  - → Tumor growth promotion ↑
  - → Costs ↑

PubMed 05/2018
«blood transfusion risk»
→ 25,360 search results

by courtesy of Spahn DR, USZ

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Pillar 1

ANEMIA

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WHO definition of anemia

Women (adult, non-pregnant): hemoglobin **< 120 g/L**

Men (adult): hemoglobin **< 130 g/L**

- *25% of the world's population affected !*
- *Iron deficiency is the leading cause (80%) of anemia !*

WHO Global Database on Anemia, 1993-2005, published 2008

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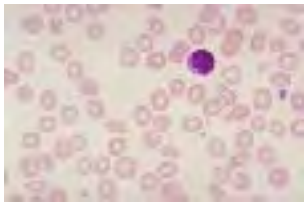
Anemia – etiologies



Microcytic (low mean corpuscular volume, MCV <80 fL)

- **Iron** deficiency, **Thalassemia**
- Other: Sideroblastic (congenital, lead, alcohol, drugs), copper deficiency, zinc poisoning

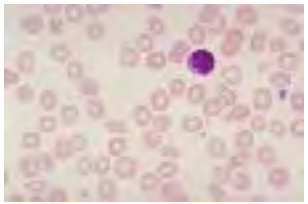
Normocytic (normal mean corpuscular volume, MCV 80-100 fL)

- **Bleeding** (acute), **Hemolysis**
- **Renal** insufficiency, **Aplastic**
- **Infection, chronic** disease

Macrocytic (increased mean corpuscular volume, MCV >100 fL)

- **Ethanol** excessive use
- **Vitamin B12**- and/or **Folic** acid deficiency
- **Myelodysplastic** syndromes
- **Reticulocytosis** (response to hemolysis, blood loss, hematinic therapy)
- Other: Hypothyroidism (normo- or macrocytic), liver disease, drug-induced (Zidovudin, Azathioprin – Imurek®, Chemotherapeuticals)

Anemia – pathogenesis



Bleeding (acute vs. chronic – reticulocytes high)

Hemolysis – increased RBC destruction (reticulocytes high)

- **Corpuscular:** Defect in **Membranes**, **Enzymes**, **Hemoglobins**
- **Extracorpuscular:** **Antibodies**, **Drugs/Poisoning**, **Infections**, **Microangiopathic**

Maturation disturbed – decreased effective RBC production (reticulocytes =)

- Lack of **nutrients**
- **Myelodysplastic** syndromes
- Thalassemia, Sideroblastic (congenital, lead, alcohol, drugs)

Proliferation disturbed – decreased overall RBC production (reticulocytes low)

- Severe lack of nutrients
- **Renal** insufficiency, **Aplastic**
- **Infection, chronic** disease

IRON DEFICIENCY

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Pre-op Hb levels and iron status

3’342 consecutive pts, major cardiac and non-cardiac surgery, over 7 yrs – Spain

Hb levels

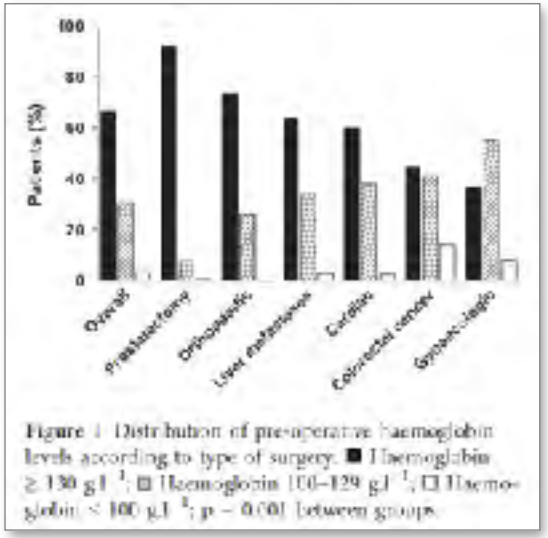
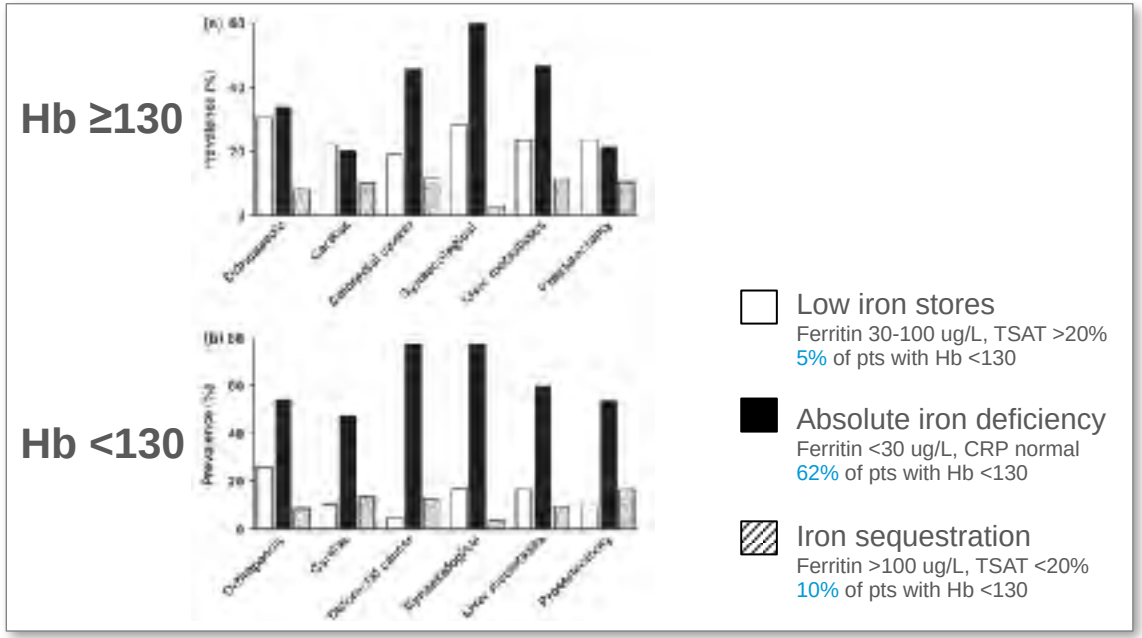


Figure 1 Distribution of pre-operative haemoglobin levels according to type of surgery. ■ Haemoglobin ≥ 130 g l^{-1}; ▨ Haemoglobin 100–129 g l^{-1}; □ Haemoglobin < 100 g l^{-1}; $p = 0.001$ between groups.

Prevalence of anemia 36%

Iron status



Muñoz M et al. Anaesthesia 2017, 72, 826–34

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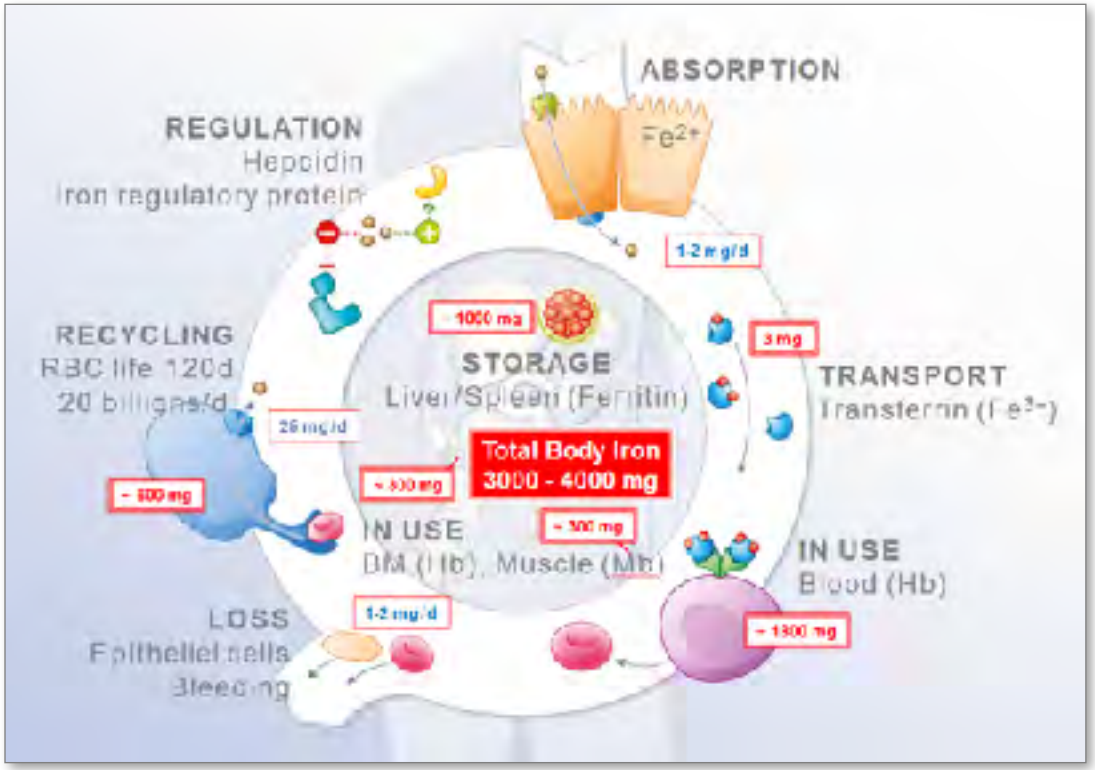
Iron metabolism



- **1 g Hb = 3.4 mg iron**
  Hb 140 g/L → 1L blood = 476 mg iron
- **Rule of thumb**

  2 mL blood ~ 1 mg iron

  monthly loss of 60 mL
  ~ 30 mg iron loss

  blood loss of 1 L
  ~ 500 mg iron loss

www.ironatlas.com

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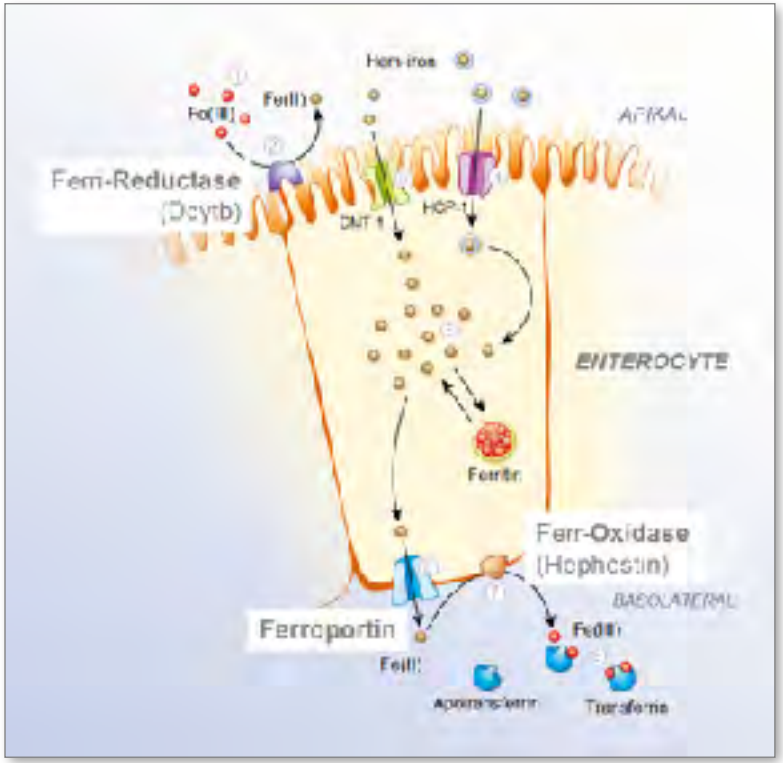
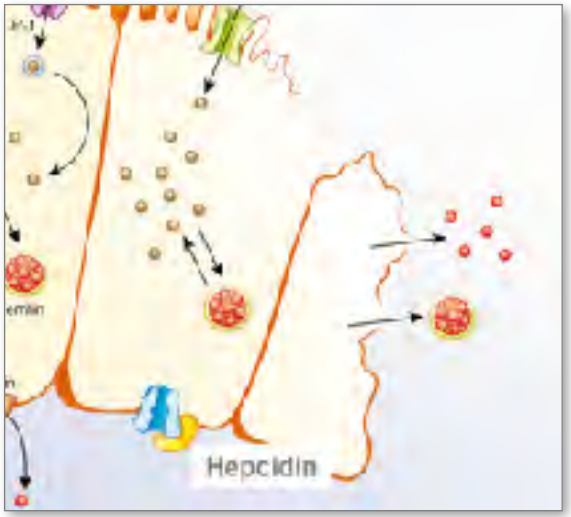
Iron metabolism – resorption



- regulation mainly through blockade of enteral resorption



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Lab tests in iron deficiency

	Normal	Iron deficiency, no anemia	Iron deficiency, intermediate	Iron deficiency, severe
Hemoglobin g/L	Normal	Normal	90 to 120	60 to 70
Ferritin µg/L	40 to 200	<40	<20	<10
Serum iron (Fe) µmol/L	10.7 to 26.7	10.7 to 26.7	<10.7	<7.1
Transferrin (~TIBC) µg/dL	300 to 360	300 to 390	350 to 400	>410
TF saturation (TSAT) %	20 to 50	30	<15	<10

- **Ferritin:** Infection, chronic disease → Ferritin ↑
- **Transferrin:** Iron deficiency → TF ↑ → TFsat may be falsely low
  Infection, chronic disease → TF ↓ → TFsat may be falsely high
- **TSAT** calculation: Fe / 2xTF (µM) or Fe / TF (µg/dL) x 70.9

UpToDate 2018

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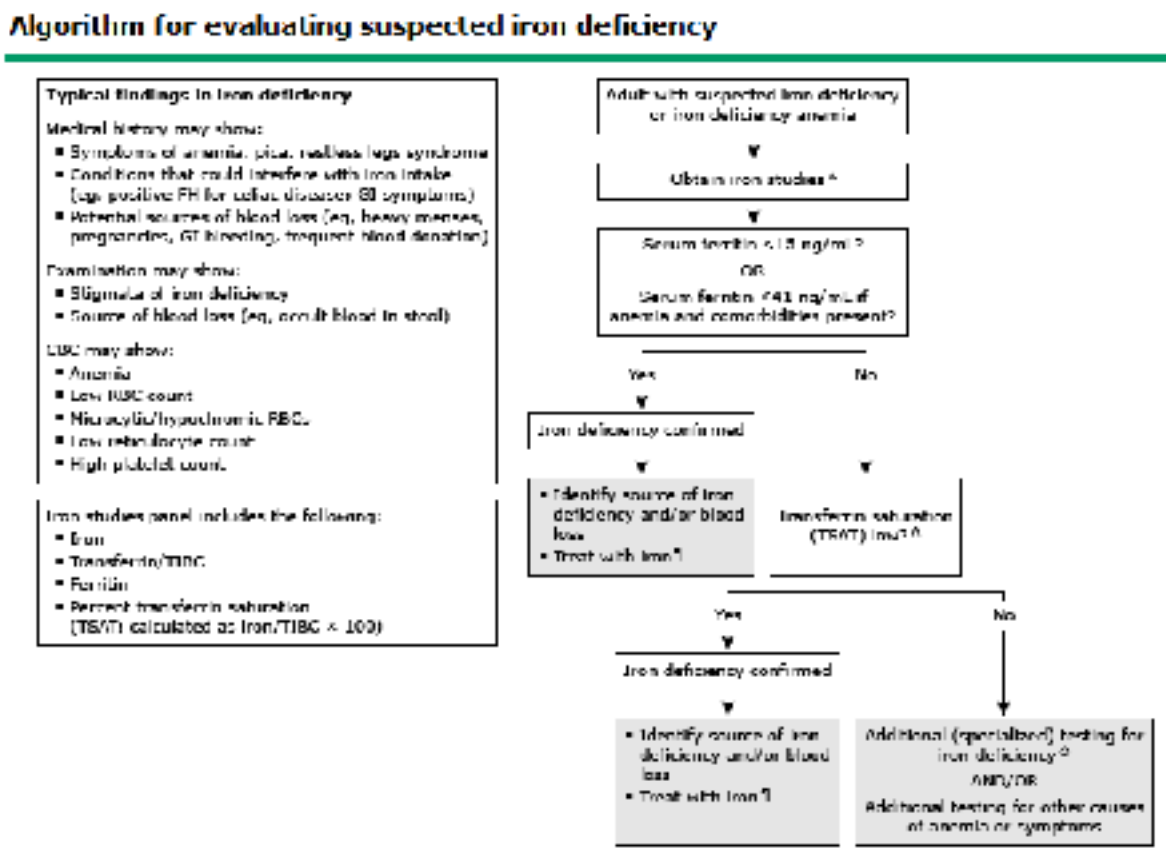
Iron deficiency anemia



Simplified cut-off values in most PBM programs:

- Hb <130 g/L
- Ferritin <100 µg/L
- TSAT <20 %

2018 UpToDate

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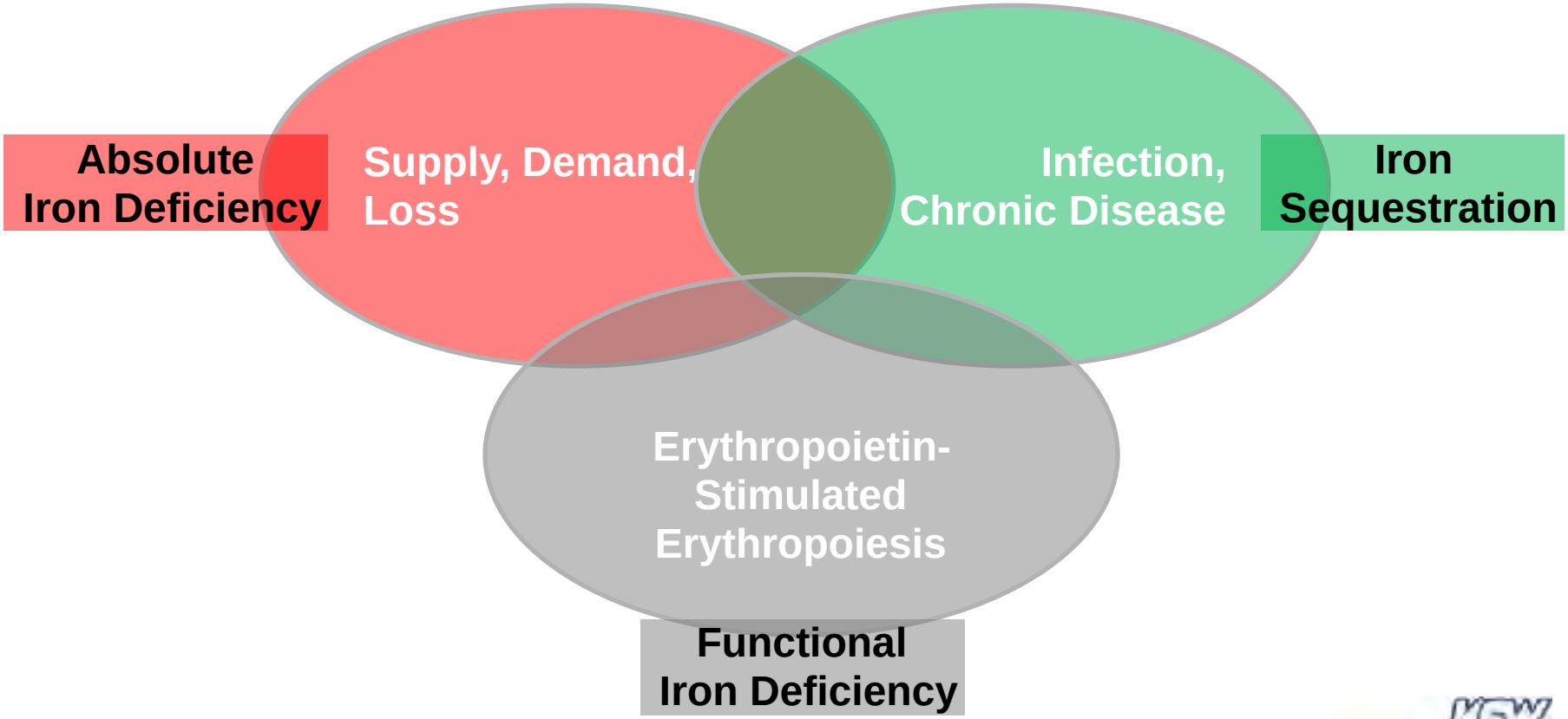
Iron deficiency syndromes



Goodnough LT et al. *Anesth Analg* 2013; 116:15-34

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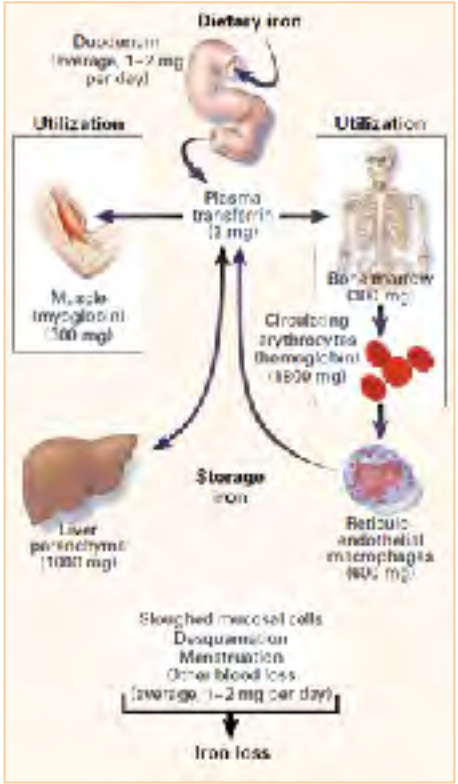
Absolute iron deficiency

Prevalence (developed countries) 36% of geriatric population

Conditions
Iron supply ↓
• Inadequate diet
Iron absorption ↓
• Celiac disease, HP infection, auto-immune atrophic gastritis
Iron demand ↑
• Growth / development, pregnancy, breast-feeding
Blood (iron) loss ↑
• GI loss (NSAID's, ulcers, diverticulosis, neoplasm, IBD, parasites) • GYN / URO loss (menstrual, post-menopausal, neoplasm) • Severe bleeding, Blood donation



Andrews NC. *N Engl J Med* 1999; 341:1986-95

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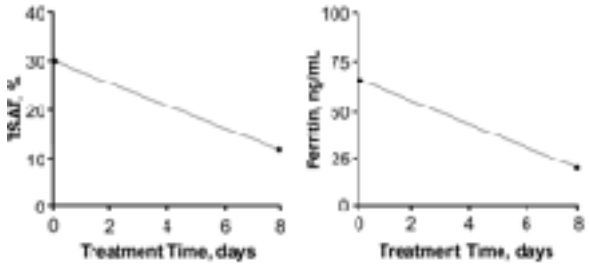
Functional (relative) iron deficiency

- **Endogenous EPO response →** moderate erythropoiesis
  - Serum iron, TFsat adequately maintained by storage iron
  - Little / no benefit of oral *or* iv iron supplementation
- **EPO response after ESA therapy →** massive erythropoiesis
  - Serum iron, TFsat decline despite ‘adequate’ storage iron (development of functional iron deficiency)
  - Oral *or* **iv** iron mandatory !



Goodnough LT et al. *Anesth Analg* 2013; 116:15-34

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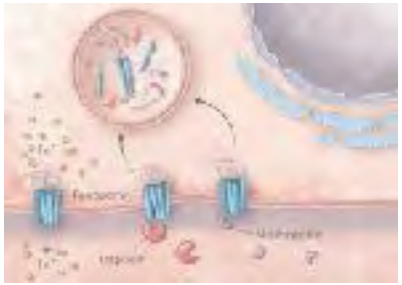
Iron sequestration – Hepcidin



- Hormone, secreted by the hepatocyte
- Central regulator of iron absorption / distribution
  - **Iron** ↑ (plasma & storage) → Hepcidin ↑
  - **State of inflammation** → IL6/STAT3 pathway → Hepcidin ↑

→ iron trapping in enterocytes and RES cells (Ferroportin internalized) → ↓ absorption and ↓ release from internal storage

→ hypoferremia → iron-restricted erythropoiesis
→ decreased responsiveness to ESA therapy

Andrews NC. *N Engl J Med* 2012; 366:376-77

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Hepcidin, Anemia of chronic disease

In contrast to ferritin levels, **changes in hepcidin concentrations are the cause** of, rather than the result of, iron disorders

Disorder	Hepcidin	Clinical Effect
IRIDA	Increased	Iron-deficiency anemia
Anemia of chronic disease	Increased	Decreased iron for erythropoiesis
Hemochromatosis	Decreased	Iron overload
Thalassemia	Decreased	Iron overload

??? Hepcidin antagonists may be an effective treatment for pts with iron-refractory iron-deficient anemia (IR-IDA) or anemia of chronic disease in the future ???

Etiology of **anemia of chronic disease** – hypoferremia (hepcidin) *PLUS* direct suppression of BM through inflammatory cytokines

Andrews NC. *N Engl J Med* 2012; 366:376-77

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Pre-operative workup

OPTIMISE RBC MASS

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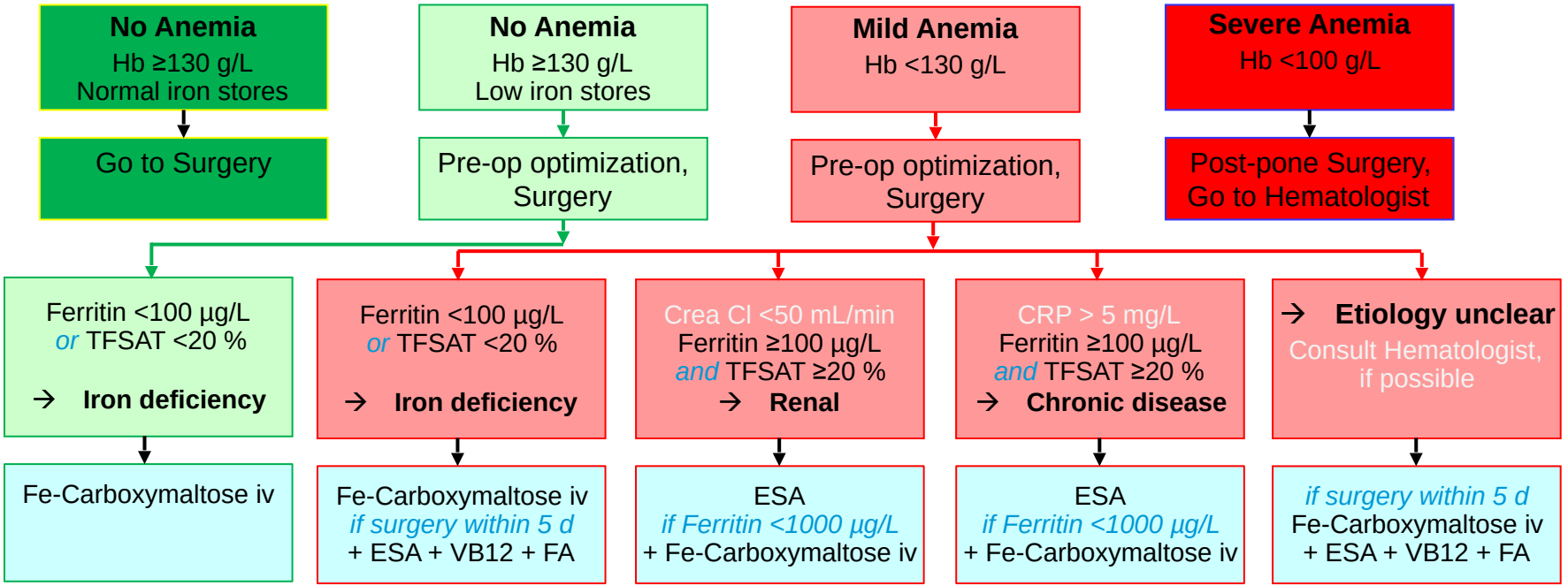
Pre-op flow chart – USZ approach

Elective cases at risk for bleeding complications (FOCUS: estimated BL >0.5 L or Trisk >10 %)
→ Pre-op Hemoglobin (Hb), Ferritin, Transferrin saturation (TFSAT)



- **Ferric-Carboxymaltose** (e.g. Ferinject®) 20 mg/kg, max. 1'000 mg i.v.: **70 kg** → **1'000 mg** in 250 mL NaCl 0.9% over 30 min
- **ESA** (Erythropoiesis Stimulating Agent): **Erythropoietin alpha** (e.g. Eprex®) 600 U/kg s.c. → **70 kg** → **40'000 U s.c.**
- **VB12** (Vitamin B12, e.g. Vitarubin®-superconc.) **1 mg** s.c. 1x (weekly up to every 2nd day) and **FA** (Folic Acid, e.g. Acidum folicum) **5 mg** p.o. daily

modified after **Spahn DR et al. *Schweiz Med Forum* 2017; 17: 1145-47**

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IV iron preparations

	Iron gluconate**	Iron sucrose††	Low molecular weight iron dextran (LMWID)‡‡	Ferric carboxymaltose§§	Iron isomaltoside 1000¶¶	Ferumoxytol***
Brand name	Ferrlecit®	Venofer®	Cosmofer® INFeD®	Ferinject® Injectafer®	Monofer® Monoferro®	FeraHeme® Rienso®
Carbohydrate shell	Gluconate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide	Isomaltoside (linear oligosaccharide)	Polyglucose sorbitol carboxymethylether
Complex type*	Type II	Type II	Type I	Type I	Type I	Type I
Molecular weight; kD	289–440	30–60	165	150	150	750
Initial distribution volume; l	6	3.4	3.5	3.5	3.4	3.16
Plasma half-life; h	1	6	20	16	20	15
Labile iron (% injected dose)†	3.3	3.5	2.0	0.6	1.0	0.8
Iron content; mg.ml^{-1}	12.5	20	50	50	100	30
Maximal single dose; mg	125	200	20 mg.kg^{-1}	20 mg.kg^{-1} (max 1000 mg)	20 mg.kg^{-1}	510
Infusion time for 1000 mg; min‡	720	300	90–150§	> 15	> 15	> 15
Product cost per 1000 mg; €¶	–	128	100	227	212	162

B03AC	Eisen dreiwertig, parenterale Zubereitungen				
Ferinject Vifor SA	Eisen (III)	100 mg/2 ml	Injektionslösung Vial 5 x 2 ml	35.15	A
Vifor SA	Eisen (III)	500 mg/10 ml	Injektionslösung Vial 5 x 10 ml	164.13	A

Eprex®

Janssen-Cilag AG

Zusammensetzung

Wirkstoff: Epoetinum alfa ADNr.

Galenische Form und Wirkstoffmenge pro Einheit

30'000 IE/0,75 ml, (252,0 µg/0,75 ml).

40'000 IE/1,0 ml, (336,0 µg/1,0 ml)	LPRLX 40000 IE/ml (Protecs)	Fertigspritze 1 ml	481.80

Indikationen/Anwendungsmöglichkeiten

Präoperativ zur Vermeidung von Fremdbluttransfusionen

Stimulierung der Erythropoese vor einem grossen orthopädischen Eingriff zur Reduktion von allogenen Bluttransfusionen und zur Korrektur einer postoperativen Anämie bei Erwachsenen ohne Eisenmangel. Die Behandlung mit Eprex sollte nur bei Patienten mit mittelschwerer Anämie (Hb 10–13 g/dl) und einem erwarteten Blutverlust von 900–1800 ml durchgeführt werden.

Dosierung/Anwendung

3. Präoperativ zur Vermeidung von Fremdbluttransfusionen

Eprex sollte subkutan appliziert werden.

Die empfohlene Dosierung beträgt 600 IE/kg Körpergewicht Eprex einmal wöchentlich in total 4 Gaben: beginnend 3 Wochen vor dem operativen Eingriff (Tag –21, –14 und –7) und am Operationstag (Tag 0).

Wenn der Hämoglobinwert ≥15 g/dl ist, sollten keine weiteren Eprex-Gaben mehr erfolgen.

http://www.swissmedicinfo.ch (accessed 05/2018)

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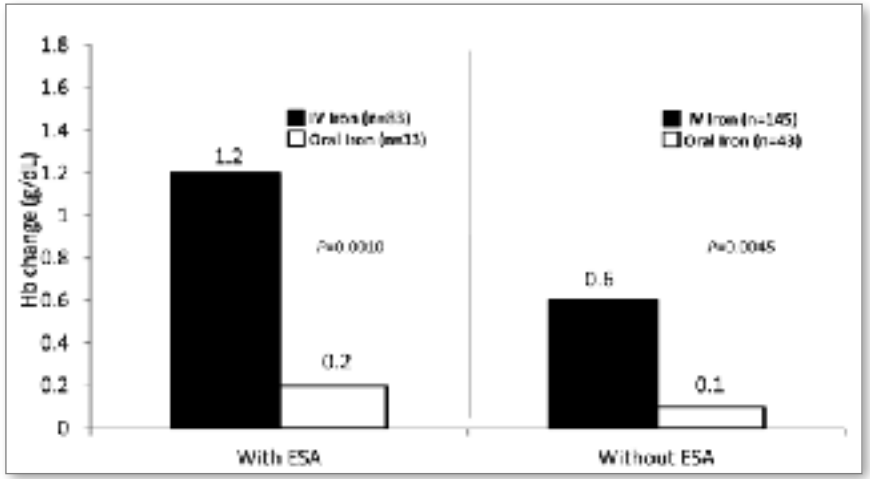
Iron supplementation in CKD
IV versus PO ± ESA

- Pts. with chronic kidney disease and iron deficiency
- Fe-oxytol IV (2x510 mg) *vs* Fe PO (200 mg/d) for 21d; ±EPO (500U/kg/wk)
- Hb measured after 4 and 5 weeks



Spinowitz BS et al. *J Am Soc Nephrol* 2008; 19:1599-605

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Select your patients !

Iron therapy as treatment of anemia: A potentially detrimental and hazardous strategy in colorectal cancer patients

ABSTRACT

In colorectal cancer patients, iron therapy, and especially intravenous iron therapy, is increasingly used to treat anemia and reduce the use of blood transfusions. However, iron has also been shown to be an essential nutrient for rapidly proliferating tissues and cells. In this respect, anemia of inflammation, characterized by limited duodenal iron uptake and sequestration of iron into the reticuloendothelial system, might be regarded as a potentially effective defense strategy of the human body against tumor growth. We therefore hypothesize that iron therapy, by supporting colorectal tumor growth and increasing the metastatic potential, may worsen tumor prognosis in colorectal cancer patients. This hypothesis is particularly supported for colorectal cancer by laboratory, epidemiological and animal studies, demonstrating the role of iron in all aspects of tumor development growth. Compared to non-malignant colon cells, tumor cells differ in the levels and activity of many iron import and export proteins, resulting in an increase in intracellular iron level and enhanced proliferation. In addition, it is demonstrated that iron is able to amplify Wnt signaling in tumors with Apc mutation, a critical mutation in the development of colorectal cancer. If our hypothesis is to be confirmed, current practice of iron administration, as treatment for anemia and as replacement of blood transfusions, can be hazardous and should be completely reconsidered.

Wilson MJ et al. *Medical Hypotheses* 2018. 110: 110-13

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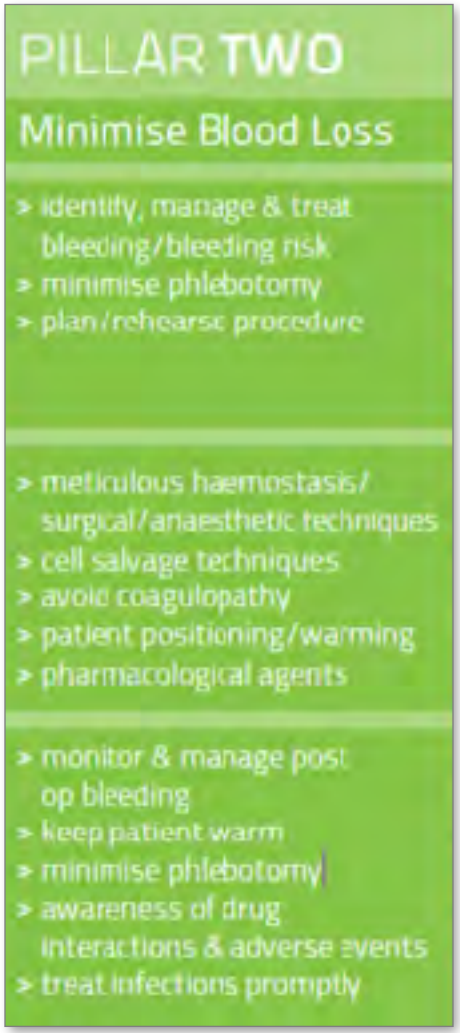

Pillar 2

BLOOD LOSS

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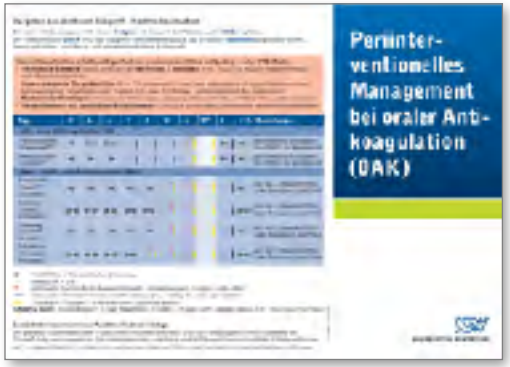
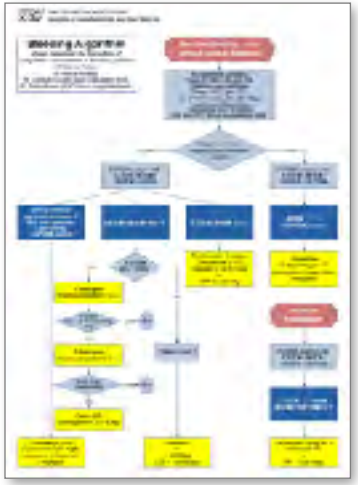
Blood loss – focus on

- Optimal peri-op anti-coagulation
- Surgical / coagulopathic bleeding
- Neglected sources of blood loss





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Anemia and Blood Transfusion in CC

Blood Sampling Sub-Study

- Prospective observational study, 146 ICU's in EU, 3,534 pts
- 2 aims – blood sampling *and* anemia / blood transfusion on ICU
- Mean (SD) **daily** blood volume for blood draws = **41.1 (39.7) mL**
  - 46% of pts had ≥5 blood samples drawn daily
  - Significant correlation: organ dysfunction and number of blood draws (*P*<.001) and total volume drawn (*P*<.001)

Vincent JL et al. *JAMA* 2002. 288: 1499-507

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Pillar 3

MANAGE ANEMIA

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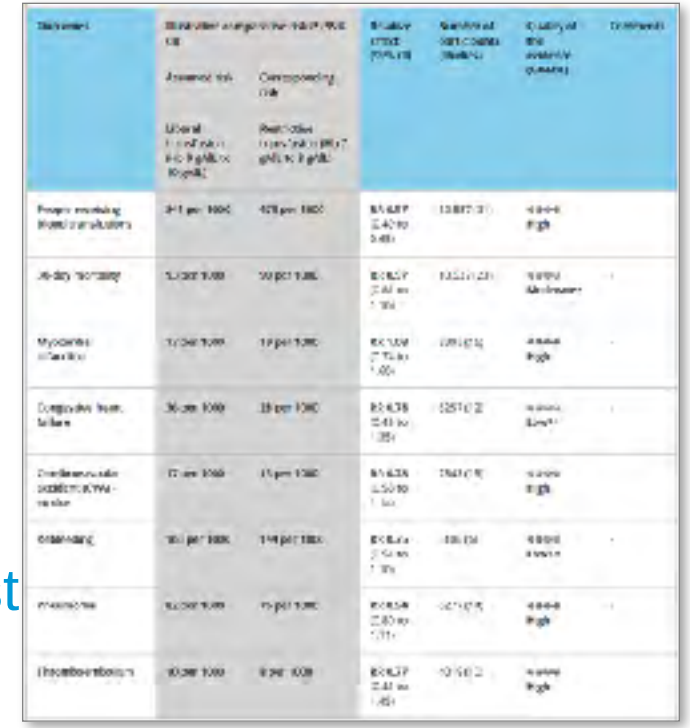
Restrictive Hb threshold

- 31 trials, involving 12,587 pts
- Restrictive **Hb 7-8 g/dL** transfusion threshold decreased the proportion of pts (broad clinical range) exposed to RBC transfusion by 43%
- Good evidence that transfusions with allogeneic RBCs can be avoided in most pts with Hb levels **>7 g/dL**



Carson JL et al. *Cochrane Database Syst Rev* 2016 Oct 12;10: CD002042
confirmed by Mazer CD et al. *N Engl J Med* 2017 377: 2133-44 (TRICCS III)

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Anemia in critical illness

- **Iron** IV – to be discussed, weak evidence so far
  Hb increased, transfusion rate not reduced (IRONMAN studies), infections ?
- **ESA** – resistance to EPO, no outcome benefit, thrombotic ?
- **Transfusion threshold**
  - **7 g/dL** in general
  - TBD for TBI, sepsis, co-existing cardiovascular disease

Docherty AB et al. *Transfus Med* 2018 Jan 25. [Epub ahead of print]

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Swiss medical boards

smartermedicine
Choosing Wisely Switzerland

- SGI (Schweiz. Gesellschaft für Intensivmedizin)
- SGAR (Schweiz. Gesellschaft für Anästhesiologie, Reanimation)

2 Beschränken Sie die Transfusion von Erythrozyten bei stabilen Patienten ohne Blutungen (Schwelle für Transfusion: Hämoglobinwert von 70 g/l).

Erwartete positive Wirkungen

- Einsparung von Blutprodukten und Kosten
- Verringerung transfusionsbedingter Komplikationen (Transfusionszwischenfälle, transfusionsassoziierte Kreislaufüberlastung ‹TACO›, transfusionsassoziierte Lungeninsuffizienz ‹TRALI›).

4 Vermeide eine Bluttransfusion, falls das Hämoglobin ≥ 70 g/L ist
dies gilt für Patienten ohne relevante Systemerkrankung, bei denen die Blutung kontrolliert ist

Verbesserung des Patientenoutcomes
Einsparen von Ressourcen (Blutprodukten)
Reduktion von Kosten

http://www.smartermedicine.ch/

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KSW 2017, SUMMARY

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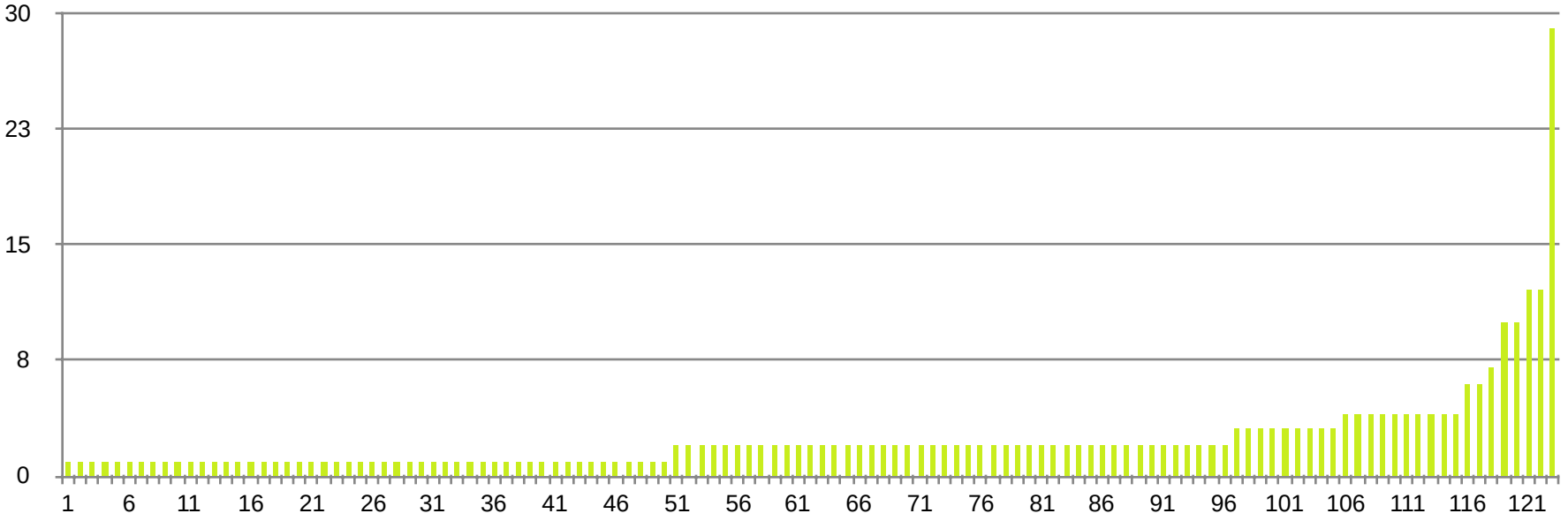
EC Transfusion bei 7 / 1’000 Patienten

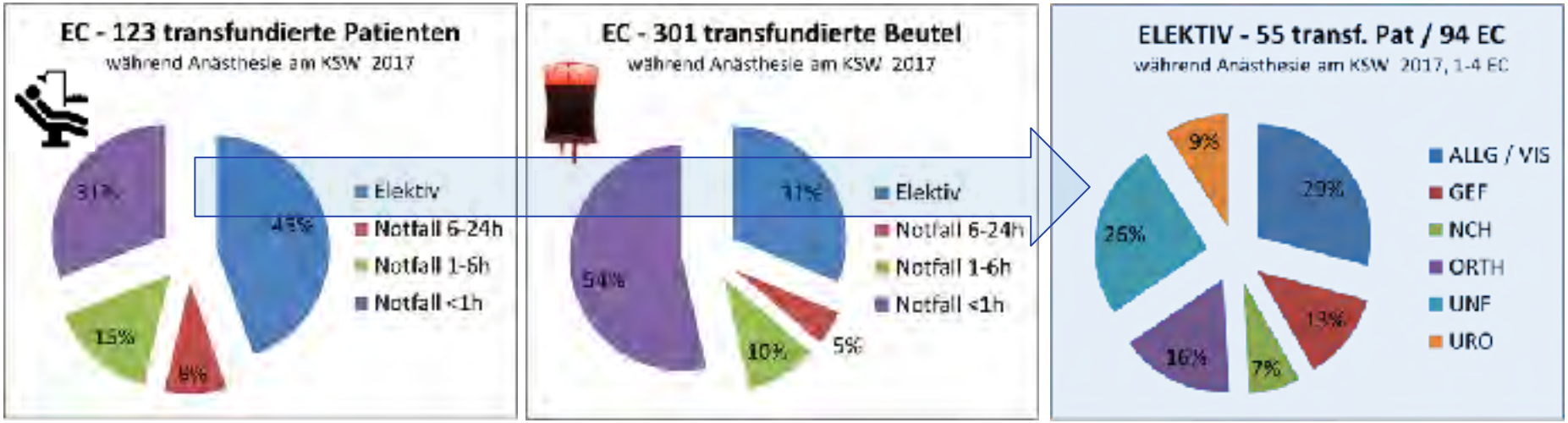
KSW 2017: 17’199 Anästhesien / 123 transfundierte Patienten / 301 EC

2017 Bluttransfusion (Fremdblut) notwendig:
Erythrozyten, Anzahl Beutel während Anästhesie am KSW



EC Transfusion – Patientenkollektiv

KSW 2017: EC Transfusion «elektiv» bei 3 / 1’000 Patienten



PBM – ↑ patient outcome and ↓costs

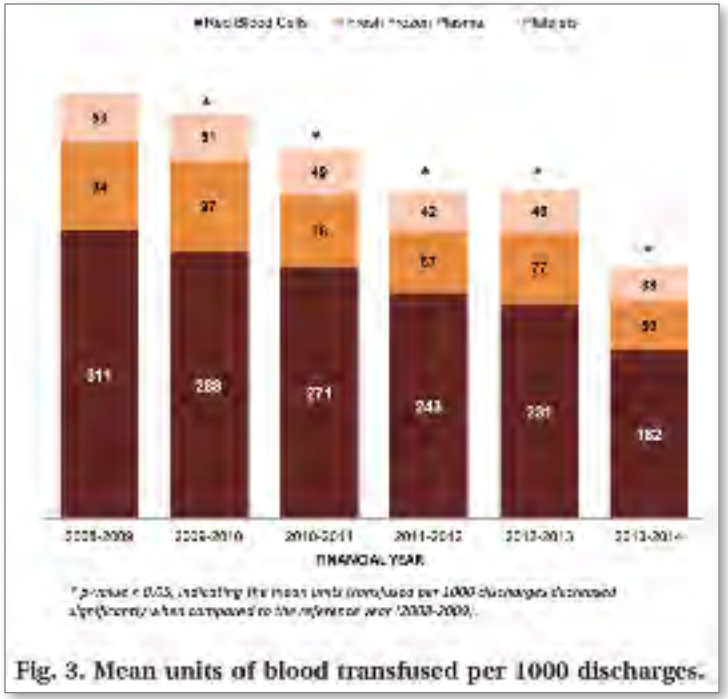


Fig. 3. Mean units of blood transfused per 1000 discharges.

- West Australia, 4 sites, 605,064 pts
- Achievements over 6 yrs:
  - Pre-op anemia 20.8 → 14.4%
  - Transfusion allog products **-41%**
  - Hosp-acquired Infections -21%
  - LOS -15%
  - Mortality -28%
- Savings $ 6.8-29 Mio yearly

Leahy MF et al. *Transfusion* 2017. 57: 1347-58

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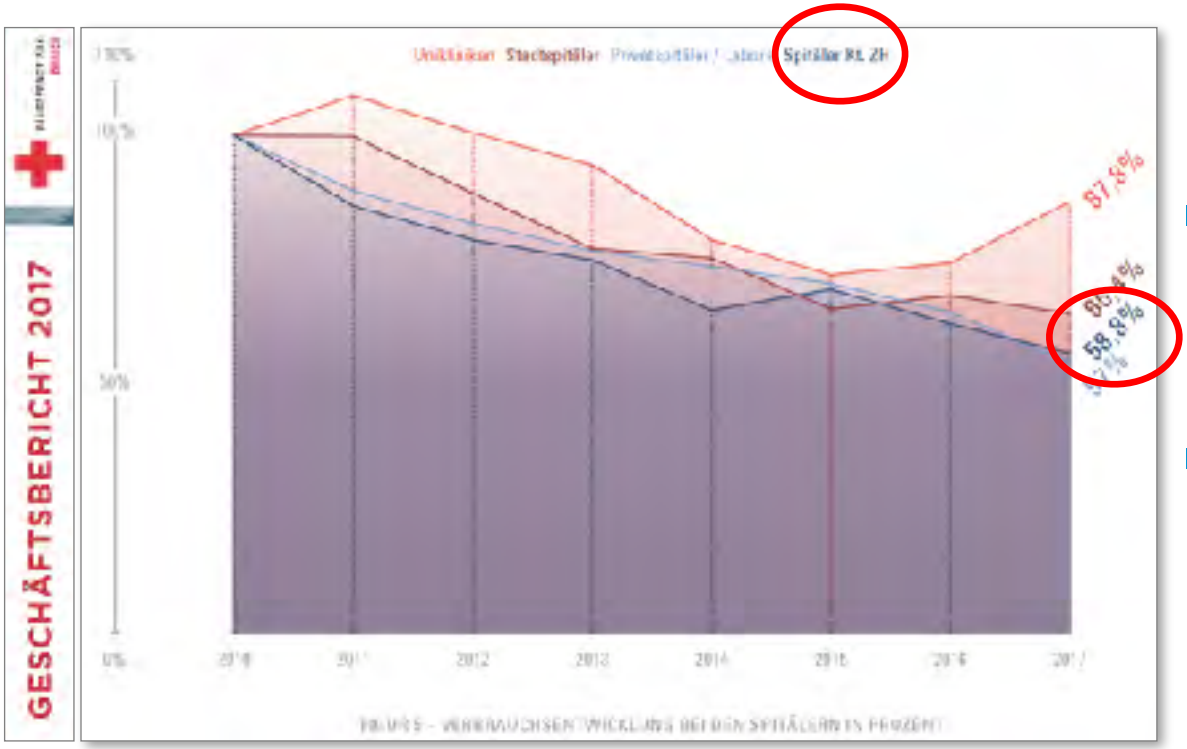
Blutverbrauch Zürcher Spitäler



- Keine aktuellen KSW Daten nach Klinik (Navision)
- Spitäler Kt. ZH **minus 41%** (Zeitraum 7 Jahre)

http://www.zhbsd.ch (Accessed 05/2018)

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PBM – Key Facts

1. **Anemia** – diagnose and treat, start pre-operatively
2. **Blood loss** – minimize peri-operatively
3. **Anemia tolerance** – accept low hb levels
4. **Blood products** – think twice, act rationally
   only use restrictive, individualized and targeted (algorithms)

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Slides available @

https://www.ksw.ch/klinik/anaesthesiologie/

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ORPHAN

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Pre-op anemia in non-cardiac surgery

- National Surgical Quality Improvement Program (U.S.), 2008
- 227,425 pts, major non-cardiac surgery
  - 30.4% have pre-op anemia
- Aim – effect of pre-op anemia on 30-day post-op composite morbidity (cardiac, respiratory, CNS, urinary tract, wound, sepsis, venous thrombo-embolism) and mortality
- Classification of anemia into 2 classes: moderate-to-severe (≤29%), mild (>29–<39% [m] –<36% [w])

Musallam KM et al. *Lancet* 2011; 378:1396-407

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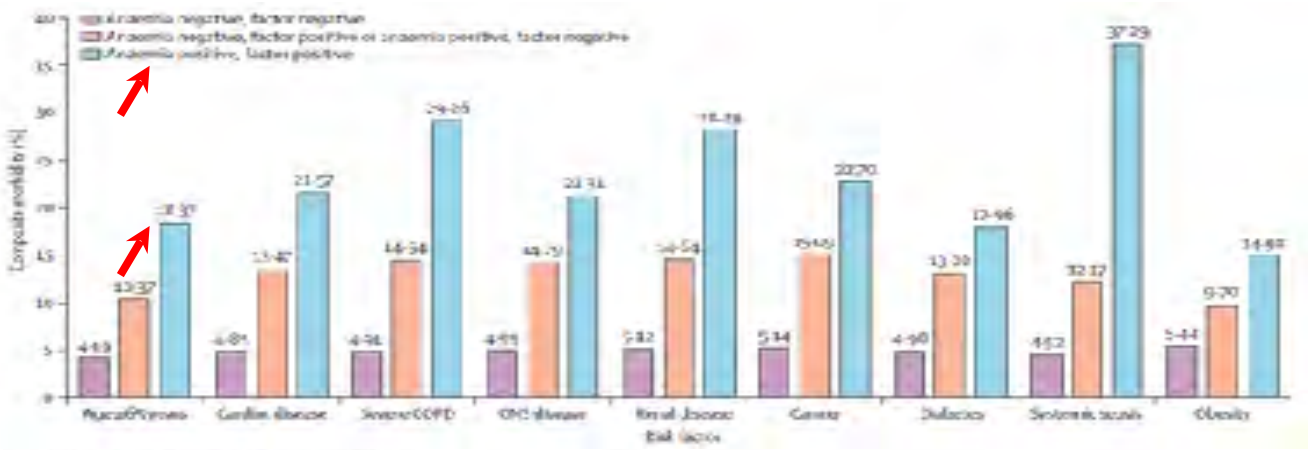

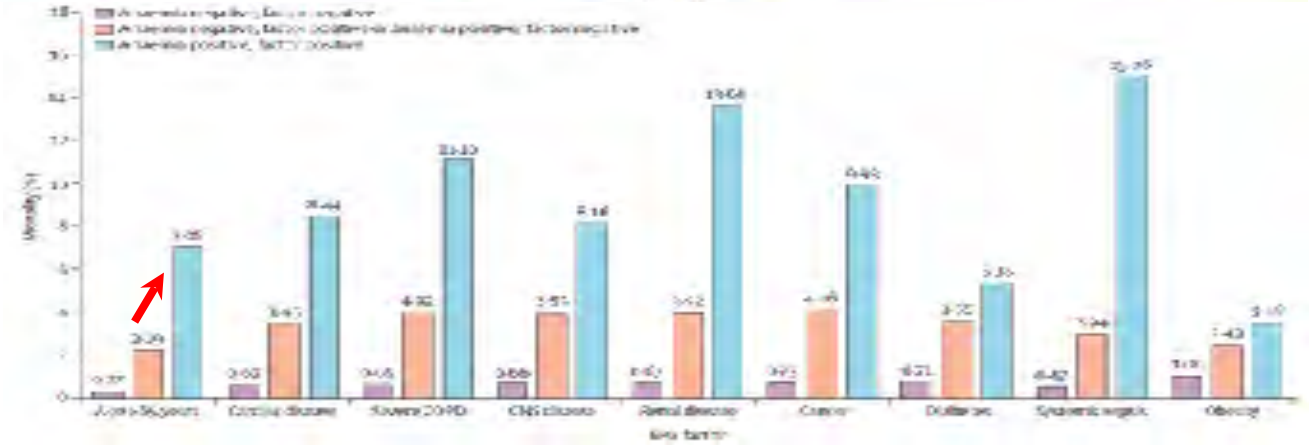

↑ **morbidity** in pts with pre-op anemia (mild **and** moderate-severe)

adjusted OR 1.35 (1.30–1.40)

↑ **mortality** in pts with pre-op anemia (mild **and** moderate-severe)

adjusted OR 1.42 (1.31–1.54)

Musallam KM et al. *Lancet* 2011; 378:1396-407

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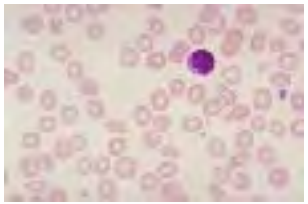
Anemia – etiologies



Microcytic (low mean corpuscular volume, MCV <80 fL)

- **Iron** deficiency, **Thalassemia**
- Other: Sideroblastic (congenital, lead, alcohol, drugs), copper deficiency, zinc poisoning

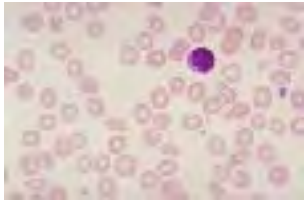
Normocytic (normal mean corpuscular volume, MCV 80-100 fL)

- **Bleeding** (acute), **Hemolysis**
- **Renal** insufficiency (chronic), **Aplastic** (bone marrow suppression, invasion)
- **Infection, chronic** disease (inflammation, malignancy)

Macrocytic (increased mean corpuscular volume, MCV >100 fL)

- **Ethanol** excessive use
- **Vitamin B12**- and/or **Folic** acid deficiency
- **Myelodysplastic** syndromes
- **Reticulocytosis** (response to hemolysis, blood loss, hematinic therapy)
- Other: Hypothyroidism (normo- or macrocytic), liver disease, drug-induced (Zidovudin, Azathioprin – Imurek®, Chemotherapeuticals)

Anemia – pathogenesis



Bleeding (acute vs. chronic – reticulocytes high)

Hemolysis – increased RBC destruction (reticulocytes high)

- **Corpuscular:** Defect in **Membranes** (Spherocytosis, Elliptocytosis, PNH), **Enzymes** (G6PDH or Pyruvate kinase deficiencies), **Hemoglobins** (Sickle cell disease, Thalassemia)
- **Extracorpuscular: Antibodies** (iso, auto), **Drugs/Poisoning** (dapsone, nitrites, hypotonic solutions; lead, copper, snake bites), **Infections** (malaria, clostridium), **Microangiopathic** (valve, TTP/HUS)

Maturation disturbed – decreased effective RBC production (reticulocytes =)

- Lack of **nutrients** (iron, vitamin B12, folic acid)
- **Myelodysplastic** syndromes
- Thalassemia, Sideroblastic (congenital, lead, alcohol, drugs),

Proliferation disturbed – decreased overall RBC production (reticulocytes low)

- Severe lack of nutrients (iron, vitamin B12, folic acid)
- **Renal** insufficiency (chronic), **Aplastic** (bone marrow suppression, invasion)
- **Infection, chronic** disease (inflammation, malignancy)
-

Siegenthaler, Differential Diagnosis in Internal Medicine

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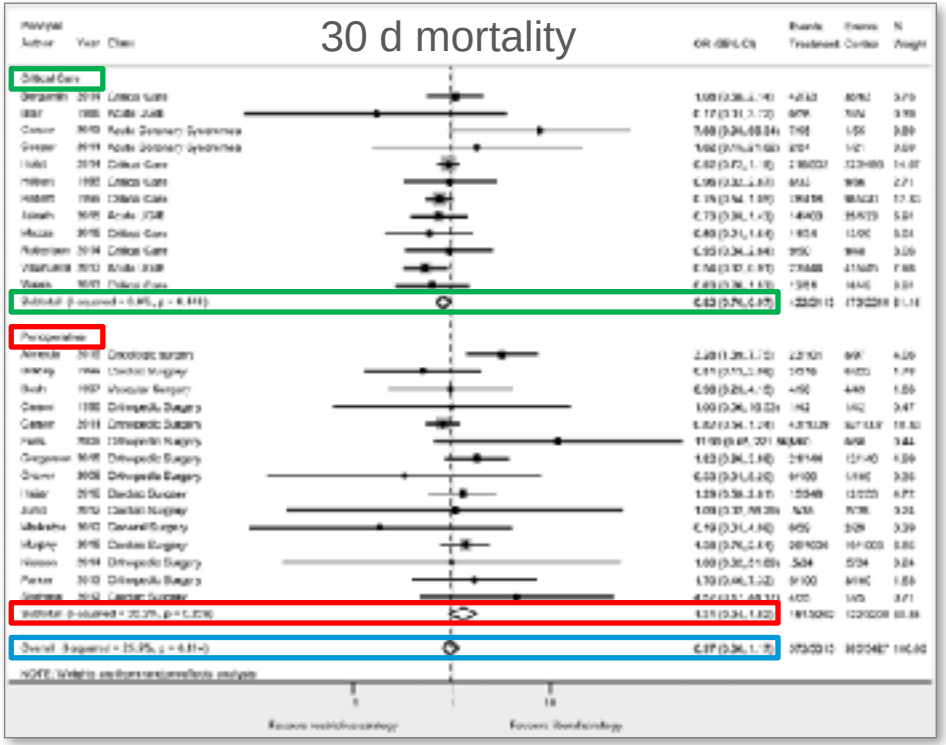
Transfusion threshold – ICU vs OR

- Meta-analyses, 27 RCT, 10,797 pts, sub-grouped ICU – OR (Perioperative)
- 1° 30d mortality (I)
- 2° myocardial infarction, stroke (I), renal failure, allogeneic blood exposure (I/O), and length of stay (I)



Chong MA et al. *Crit Care Med* 2018 46: 252-63

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PBM – key facts

Pre-op anemia, blood loss and allogeneic blood transfusions are independently associated with worse clinical outcome

- **Focus group** = anticipated BL >0.5 L, transfusion risk >10%

  look for (Hb, TF, TSAT), work up and correct anemia pre-op

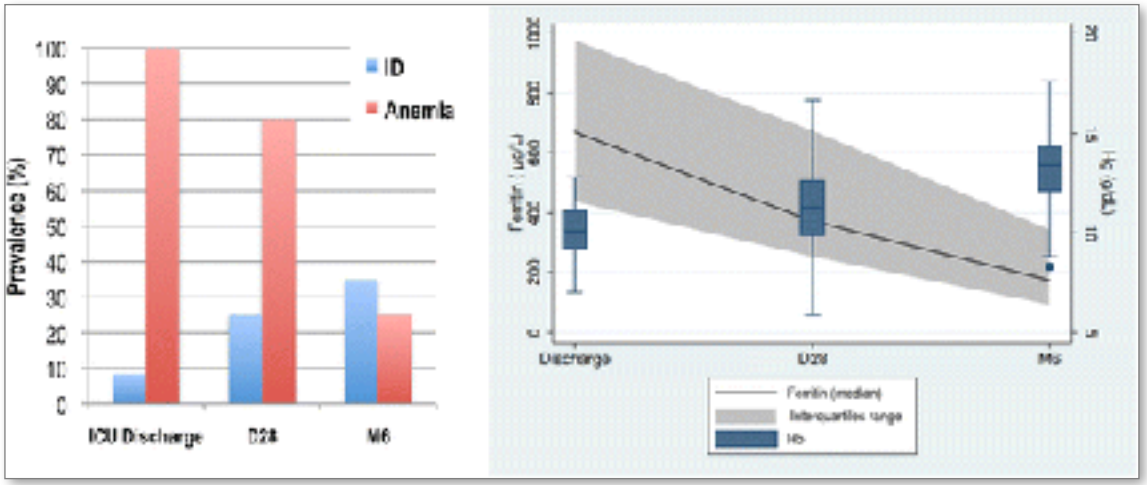
- **Peri-operative blood loss, minimize**

  surgical technique, minimize risk for bleeding (low CVP, avoid hypertension), cell salvage and re-transfusion, normothermia, goal-directed coagulation management with advanced coagulation testing and algorithms, avoid coagulopathy/hypercoagulability, avoid unnecessary blood draws

- **Anemia tolerance, rationale transfusion management**

Iron deficiency after ICU stay

- Prospective, multicenter, observational study in France
- Anemic pts at discharge from ICU – follow up 1M and 6M



→ *Watch for ID (increased fatigue) after ICU stay ! ID increases from 8% to 35% 6M after discharge from ICU*

Lasocky S et al. *Crit Care* 2014. 18: 542

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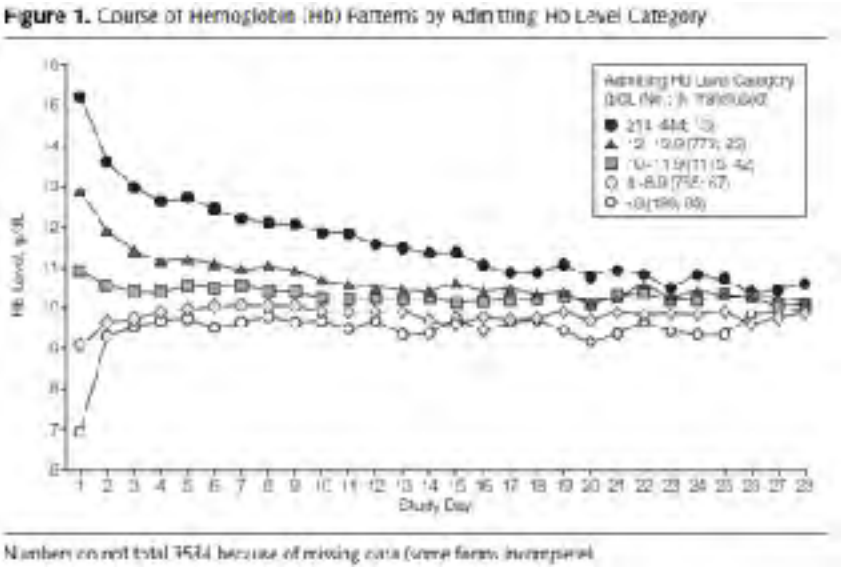
Anemia and Blood Transfusion in ICU

Anemia and Blood transfusion Sub-Study

- Hb mean at ICU admission 11.3 (2.3), 29% <10 g/dL
- Transfusion rate 37%



Vincent JL et al. JAMA. 2002 Sep 25;288(12):1499-507

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Anemia and Blood Transfusion in ICU

Anemia and Blood transfusion Sub-Study

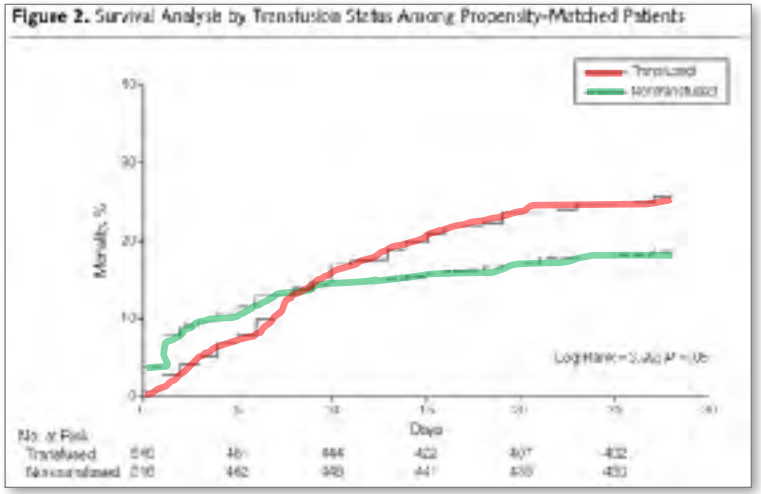
Table 3. Patient Characteristics by Transfusion Status*

Variable	Transfused	Not Transfused	*P* Value†

Table 8. Patient Characteristics by Transfusion Status for Propensity-Matched Patients*

Variable	Transfused	Not Transfused	*P* Value†
Age, mean (SD), y	64.0 (15.5)	64.1 (15.0)	.10
Men, No. (%)	193 (37.4)	203 (39.3)	.52
Admission characteristics			
Admitting Hb level, mean (SD), g/dL	10.8 (2.0)	10.9 (1.8)	.92
Admitting SOFA score, mean (SD)	5.5 (3.3)	5.5 (4.0)	.92
Admitting APACHE II score, mean (SD)	14.6 (7.0)	12.0 (7.5)	.54
Recent history of anemia, No. (%)	80 (15.5)	66 (12.8)	.21
Recent history of red blood loss No. (%)	162 (31.4)	170 (32.9)	.59
In shock at admission, No. (%)	117 (22.7)	106 (20.5)	.41
Admission type, No. (%)			
Elective surgery	271 (52.5)	261 (50.6)	.53
Emergency surgery	83 (16.1)	89 (17.2)	.62
Medical	128 (24.8)	130 (25.2)	.89
Trauma	29 (5.6)	31 (6.0)	.79
Other	5 (1.0)	5 (1.0)	>.99
Hospital length of stay, mean (SD), d	11.4 (6.8)	12.0 (7.5)	.21

Figure 2. Survival Analysis by Transfusion Status Among Propensity-Matched Patients



Vincent JL et al. JAMA. 2002 Sep 25;288(12):1499-507

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MASSIVE BLEEDING

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Bleeding Protocol @ KSW

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Institute of Anesthesiology and Pain Medicine

Bleeding Algorithm

always remember the four pillars of coagulation assessment in bleeding patients

I. Patients' history
II. Clinical findings
III. Laboratory (Lab) blood coagulation tests
IV. Point of care (POC) blood coagulation tests


pts history


clinical findings


lab testing


POC testing

Massive bleeding *and/or* diffuse clinical bleeding

Avoid further bleeding
Psys 60-100 in pts w/o TBI
Optimize preconditions
Temp >35°C, pH >7.2,
iCa 1.1-1.3 mmol/l, Hb >60-80 g/l
Treat (hyper)fibrinolysis
Tranexamic acid 15 mg/kg
Lab and POC blood coagulation tests

Heparin *unlikely* + ongoing hyperfibrinolysis *possible*

yes

no

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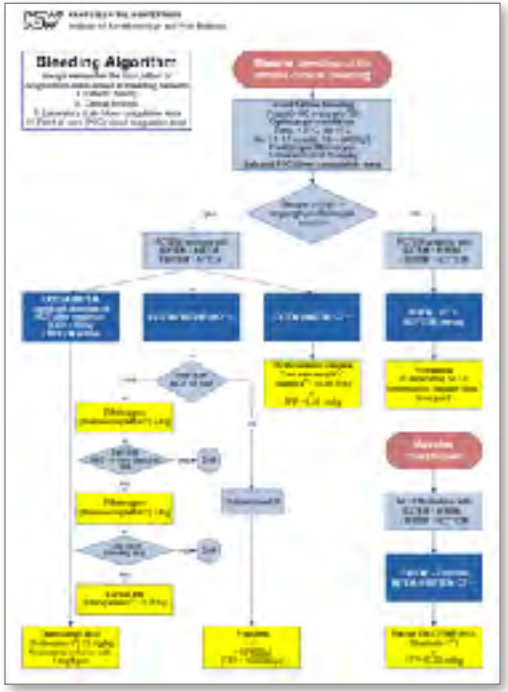
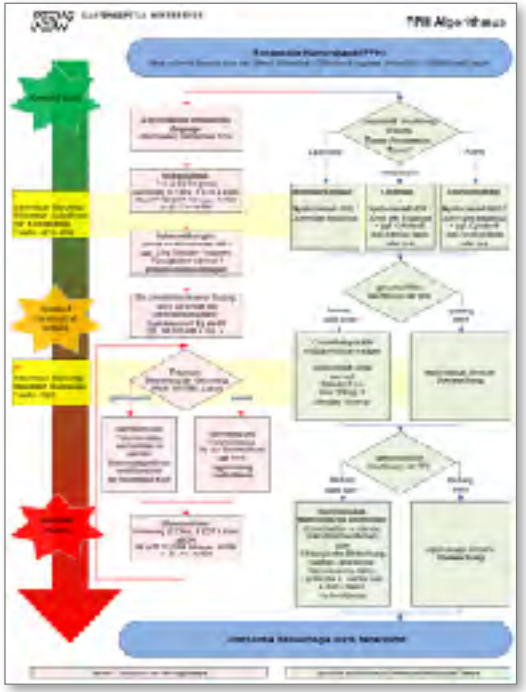
Bleeding Protocols / SOPs @ KSW





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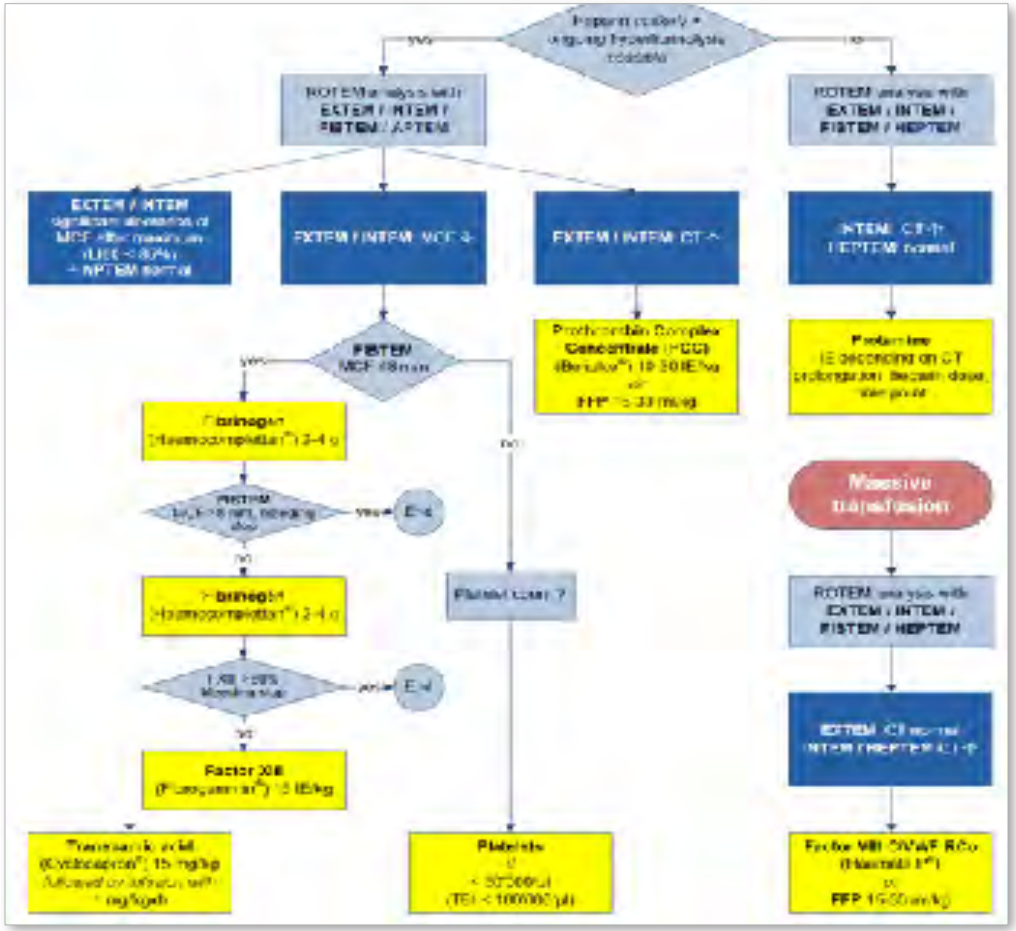


KANTONSSPITAL WINTERTHUR

Was sie schon immer über POCT wissen wollten und sich nie zu fragen getrauten

Symposium: Blut und Gerinnung

Kantonsspital Winterthur

19.06.2018

PD Dr Lars M. Asmis

Zentrum für perioperative Thrombose & Hämostase (ZPTH)

ZPTH

POCT

Conflict of Interest Statement

- In den letzten 5 Jahren habe ich von folgenden Firmen Honorare für advisory boards bzw Vorträge und/oder Forschungsunterstützung erhalten:
  Axon Lab, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Bering, Dade Behring/Siemens, Daiichi Sankyo, Glaxo Smith Kline, Pfizer, Roche und Sanofi Aventis
- Die Wahl des Inhalts dieses Vortrags war frei
- Diese Tätigkeit erfolgt gemäss den GL der SAMW
- Der Vortrag wird durch >= 2 Firmen gesponsert

ZFTH

POCT

Überblick

- Einführung
- Plättchenfunktion
- ACT
- Viskoelastische Tests
- Zusammenfassung und Schlussfolgerungen
- Diskussion

POCT

Definition

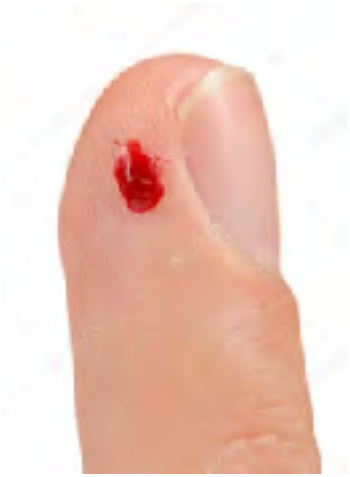
- Patienten-nahe Labordiagnostik
  - gemäss Wikipedia (aber es ist ja eben gerade nicht im Labor…)
- «Bed-side»
  - aber auch im Schockraum, OP, andere Orte
- «Ready to use»
  - keine Reagenzien, die man lange vorbereiten muss
- Möglichst wenige Pipettierschritte
  - durchführbar von «jedermann»
- Möglichst einfach gewinnbares Probenmaterial
  - bei Blut (Vollblut: mit oder ohne Antikoagulans)

ZFTH

POCT

Historische Beispiele

- Blutung per se als Lebenszeichen
- Blutsenkung
- Kupfersulfat Test (Hb > 125 g/l, ρ=1.053)
- Blutzucker und kapillärer Quick
- uvam…



ZFTH

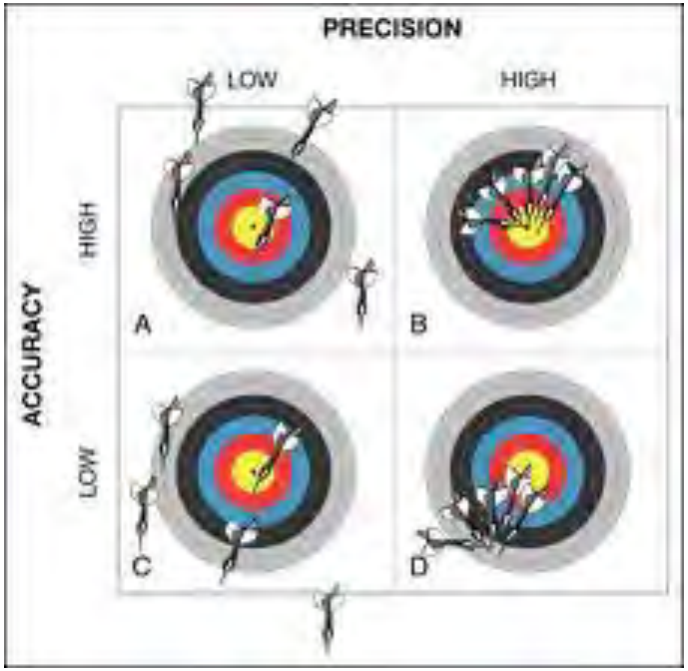
POCT

Vorteile

- Turn around Zeit
  wenige Minuten

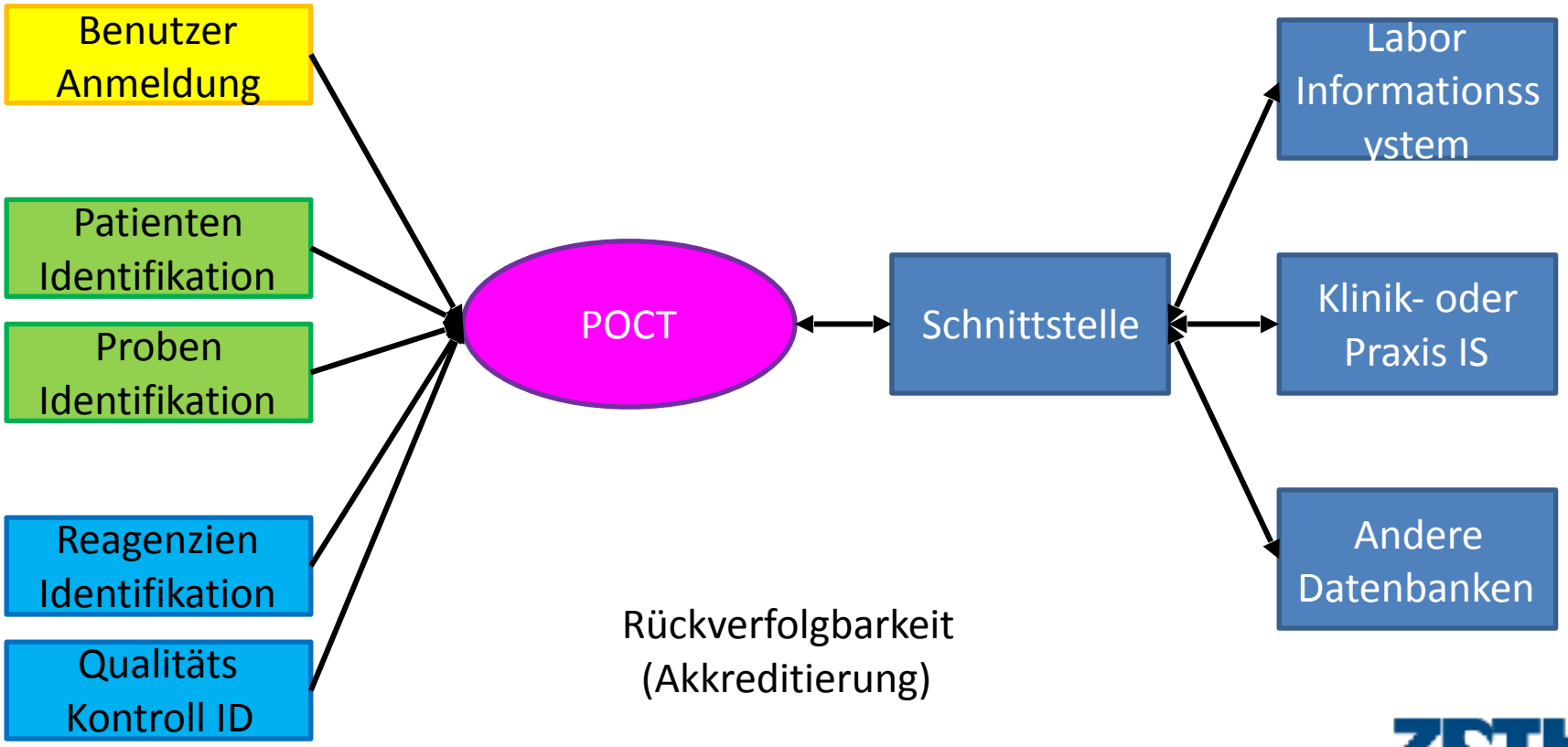
Nachteile

- Präzision & Genauigkeit



POCT

Organisation



POCT

Abrechenbarkeit

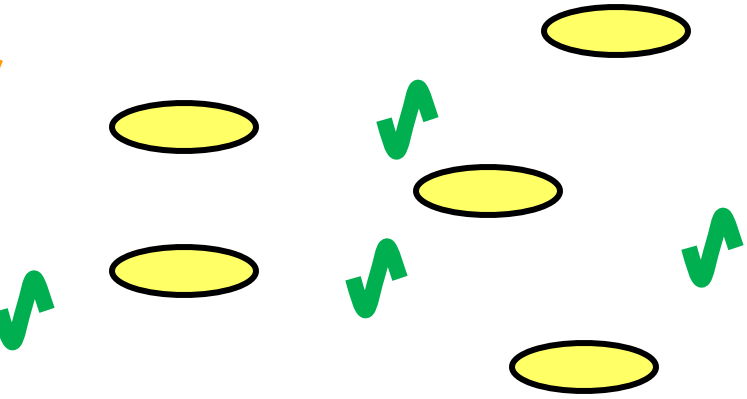
- Grundsätzlich ja, aber
  Fähigkeitsausweis Praxis Labor oder FAMH Titel
  Qualab ! (externe und interne Qualitätskontrollen)
- Ambulantes setting
  ja
- Hospitalisiertes setting
  «schwierig»
  bei allgemein Versicherten fällt das unter Tagespauschale bzw in Fallkosten inkludiert
  bei Halb-privat und Privaten Patienten kann man es separat abrechnen

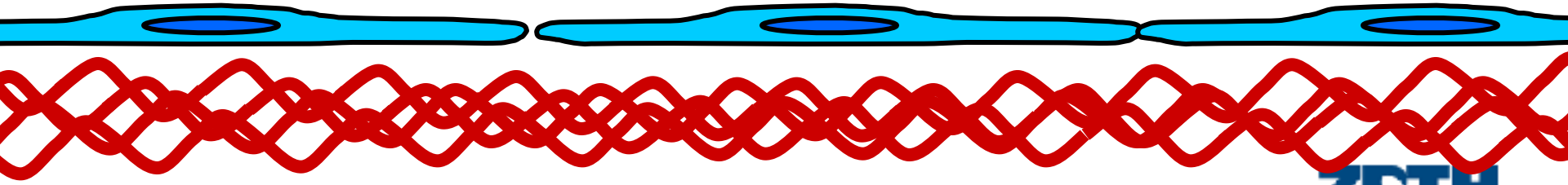
1. POCT: 1° Hämostase (Plättchenfunktion)

Initiation
- Adhäsion

Extension
- Sekretion (ADP, TxA2, VWF)

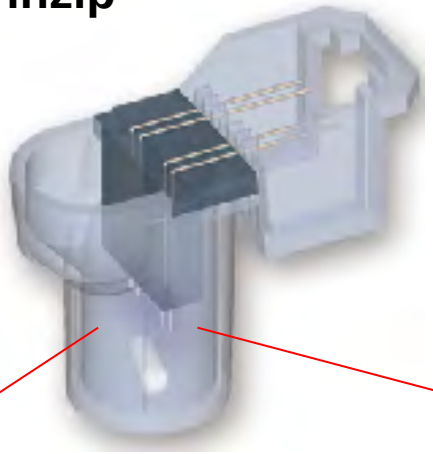
Stabilisation
- Aggregation
- Konsolidation

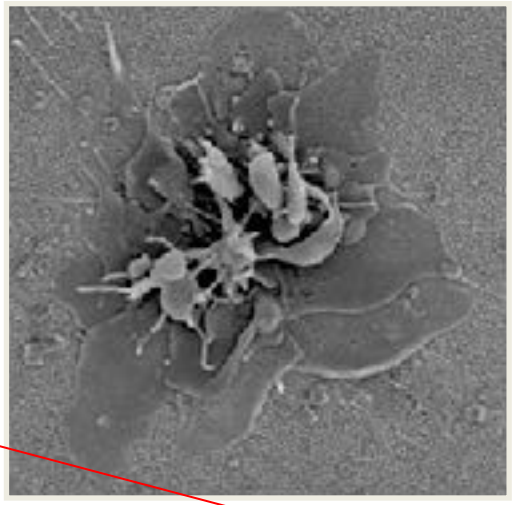


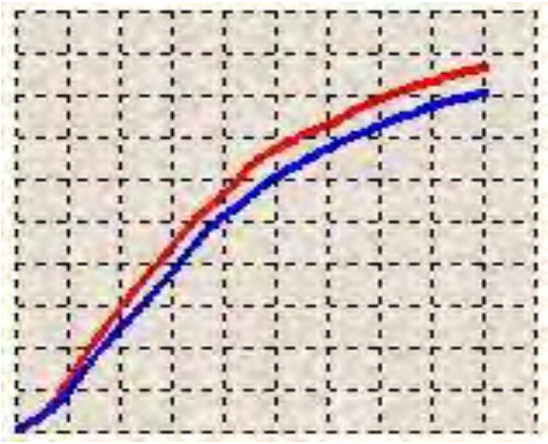


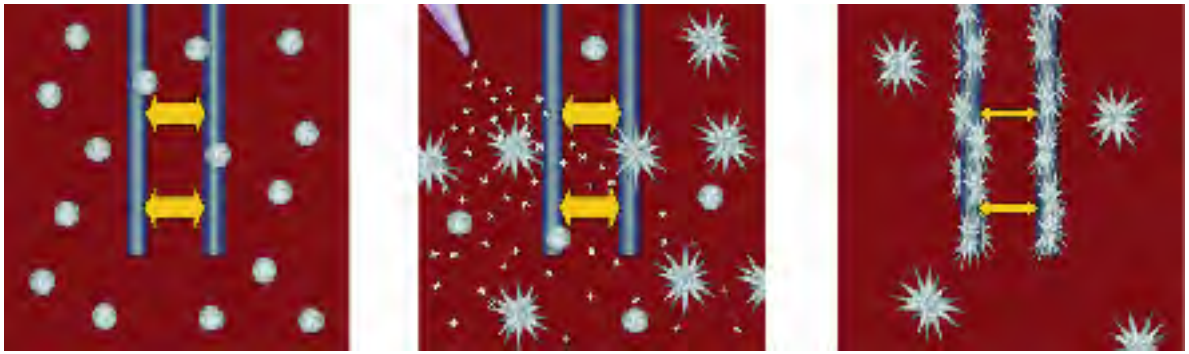
Multiplate (1° Hämostase)

Messprinzip









Parameter

Area under curve
(arbitrary units (AU))

Images by A Calatzis, personal communication.
D. Sibbing et al, Thromb Haemost. 2008 Jan;99(1):121-6.

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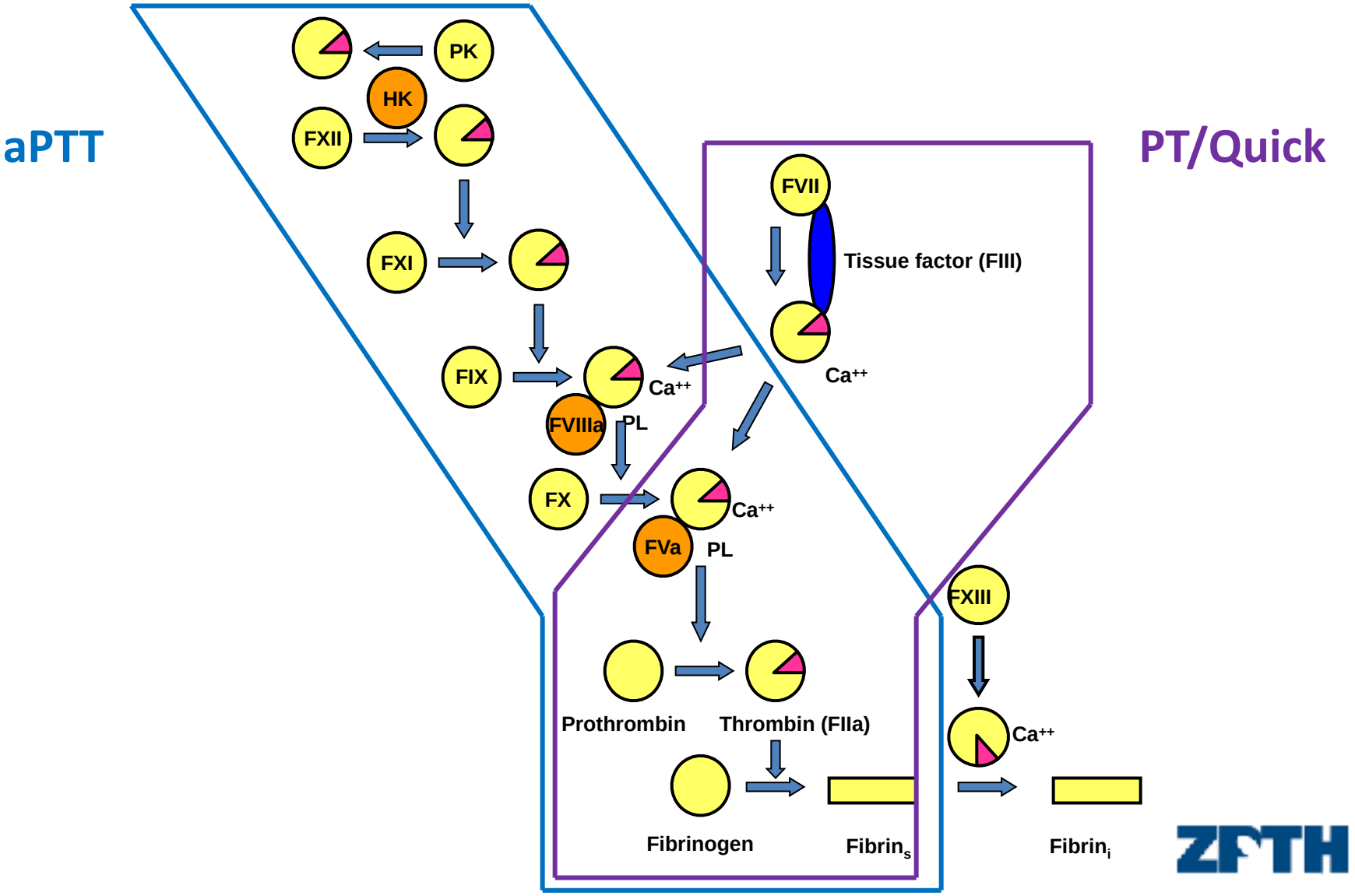
Multiplate (1° Hämostase)

Plättchen Adhäsion (als Teil der Tc-Funktion)

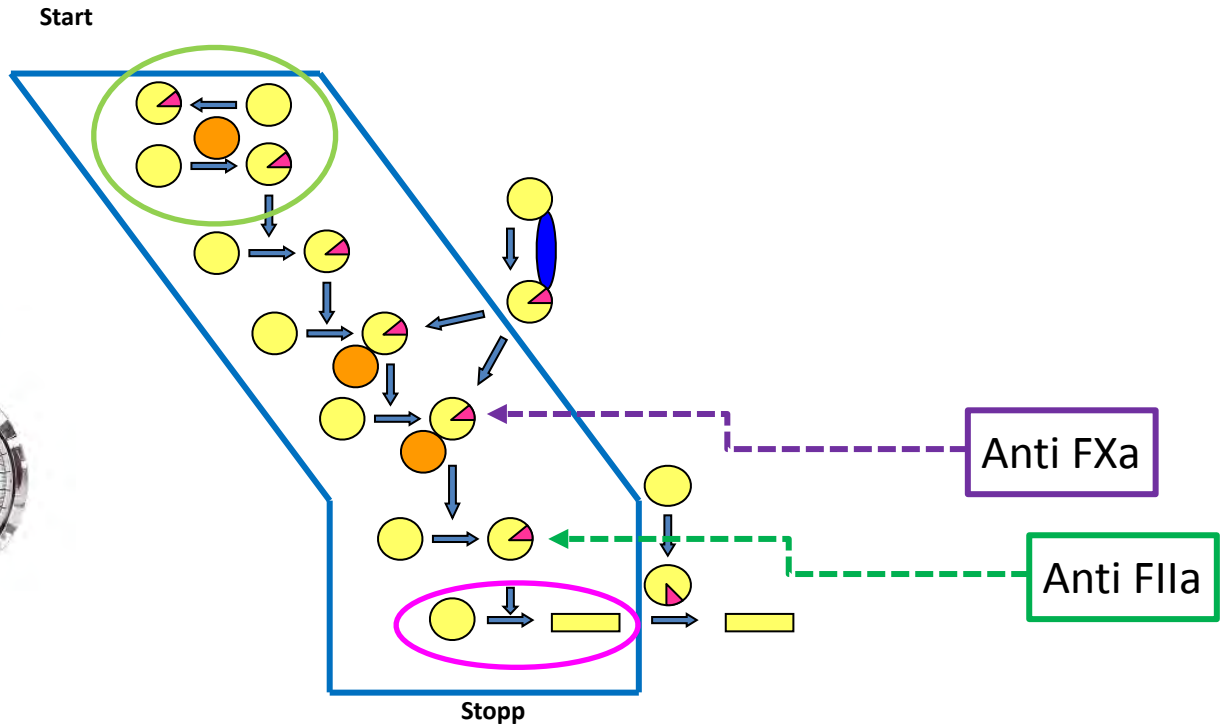
- Area under the curve (AUC)
  - Aspi Test: Cyclooxygenase abhängige Stimulation (AS)
  - ADP Test: P2Y12 abhängige Stimulation (ADP)
  - TRAP Test: “Thrombin” abhängige Stimulation (TRAP)
  - (vWF Test: gibt es leider nicht mehr)
- Messung sensitiv auf
  - verschiedene Aggregationshemmer
  - GPIIbIIIa Funktion
  - Thrombozytenzahl (falls <100 G/l)
  - Hämatorkit
- Messung nicht sensitiv auf
  - (Thrombozytenzahl solange > 100 G/l, vWF), FXIII

2. POCT: Gerinnungsmonitoring (vorw. plasmatisch)



Activated clotting time (ACT)

Vollblut PTT

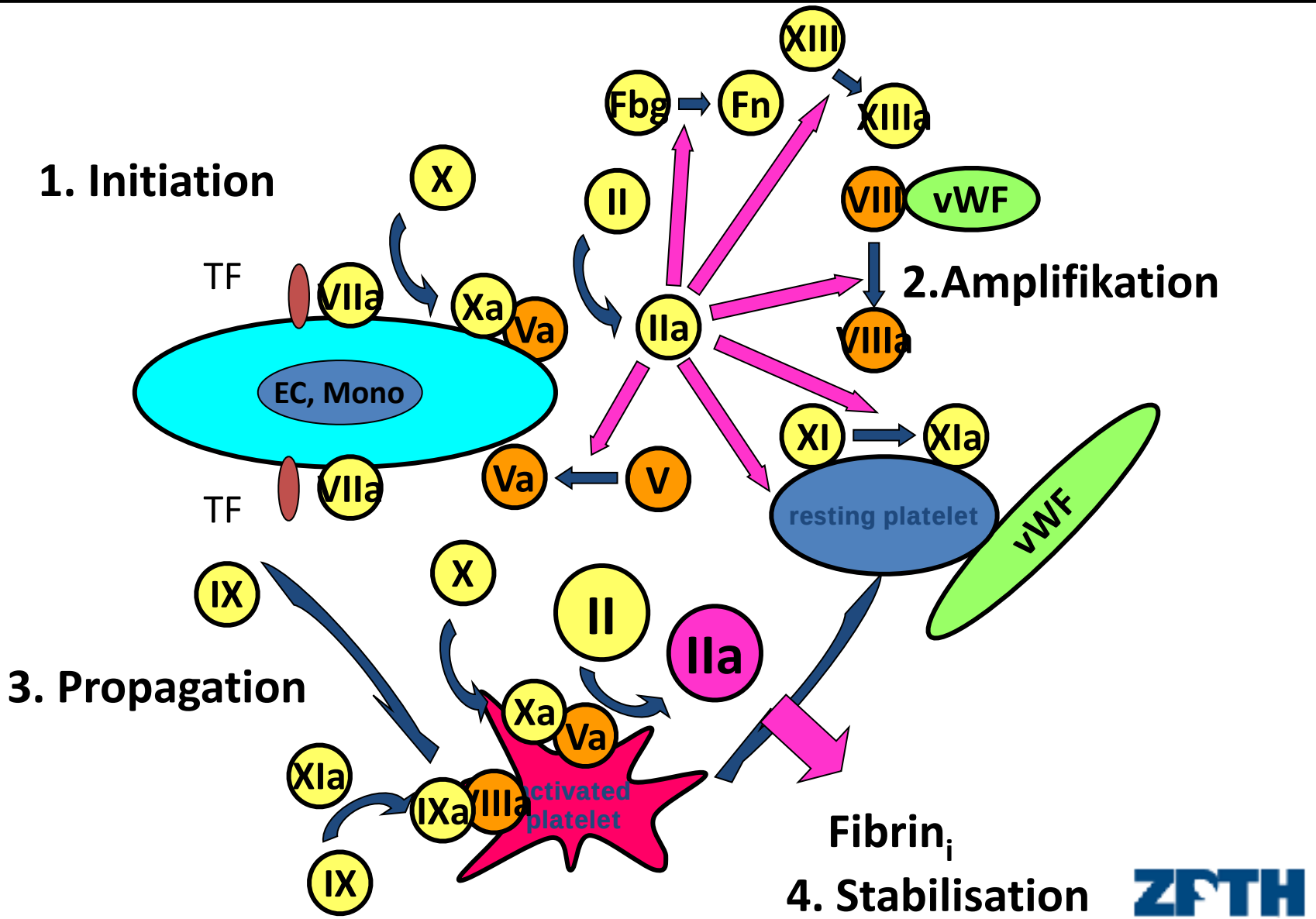


Activated clotting time (ACT)

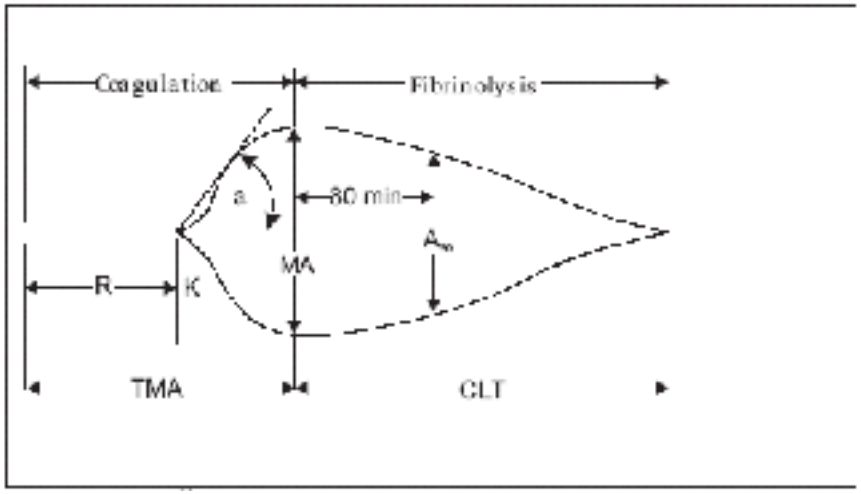
Vollblut PTT

- Gerinnungszeit
  - Start: Aktivator der Kontaktphase bzw FXII (Kaolin)
  - Stopp: Bewegungseinschränkung des Rührers
  - man misst die Zeit dazwischen in Sekunden
- Messung sensitiv auf
  - Hämatokrit (s. Vollblut)
  - anti FIIa: sowohl indirekte (~AT) auch direkte Antikoagulantien
  - anti FXa: s.o.
- Messung nicht sensitiv auf
  - Thrombozytenzahl und -funktion, vWF, FXIII
- Tipp
  - interne Kalibrierung “Eurer” aPTT, TZ, antiFXa vs ACT
  - verwendbar für Heparine aber auch zB DTI (HIT!)

VET Grundlage: das zelluläre Modell der Gerinnung



2. POCT: Viskoelastische Tests (vorw. plasmatische H.)



Korrelation zelluläres Modell – TEG/TEM

- R/CT	**Initiation**
- K/CFT	**Amplifikation**
- alpha angle:	**Thrombin burst**
- Ly30/CL30	**Fibrinolyse**

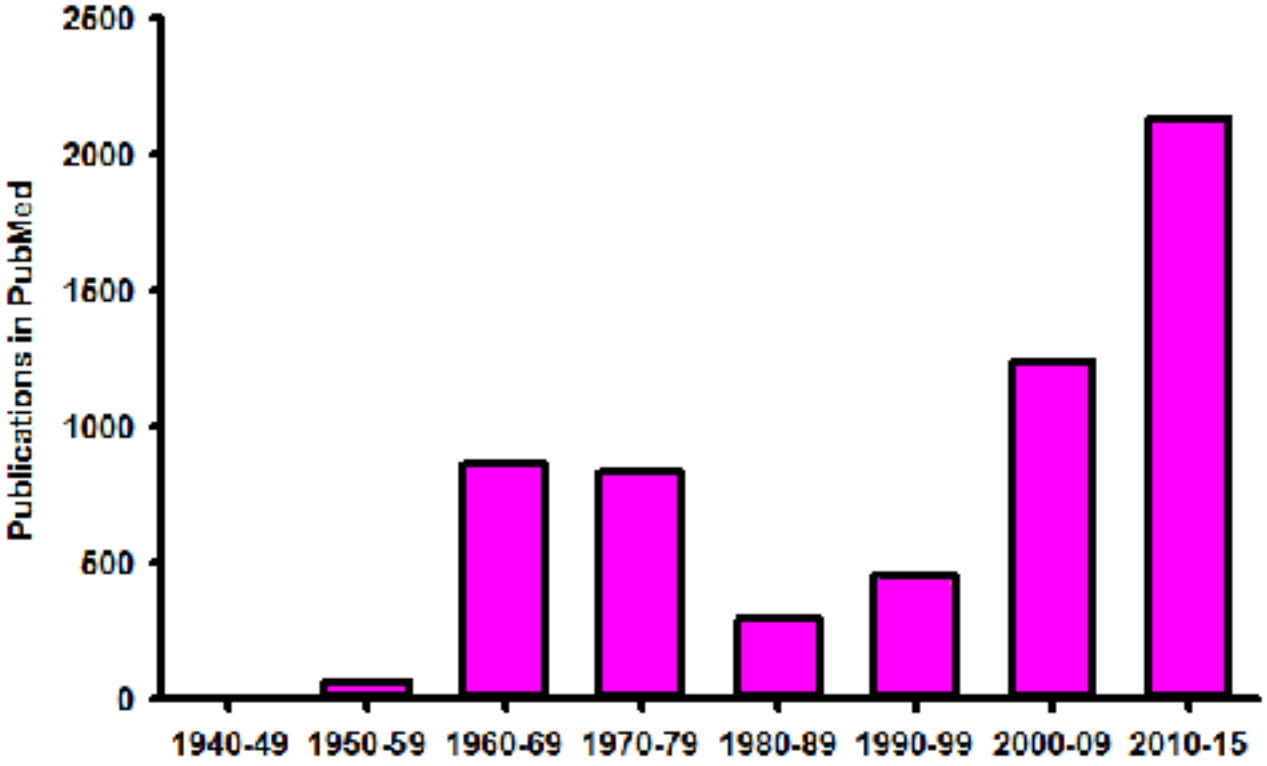
Johannson PI et al.: Thromboelastography and thromboelastometry in assessing coagulopathy in trauma Scand J Trauma Resusc Emerg Med 2009; 17:45 (guter Review, open access)

ZFTH

3. Viscoelastische Tests

Publikationen* seit Erstbeschreibung*: total ~ 8043

***Hartert H, 1948.**



***PubMed search (gestern): „Thromboelastography or thromboelastometry or thromboelastogram or TEG or ROTEM“**

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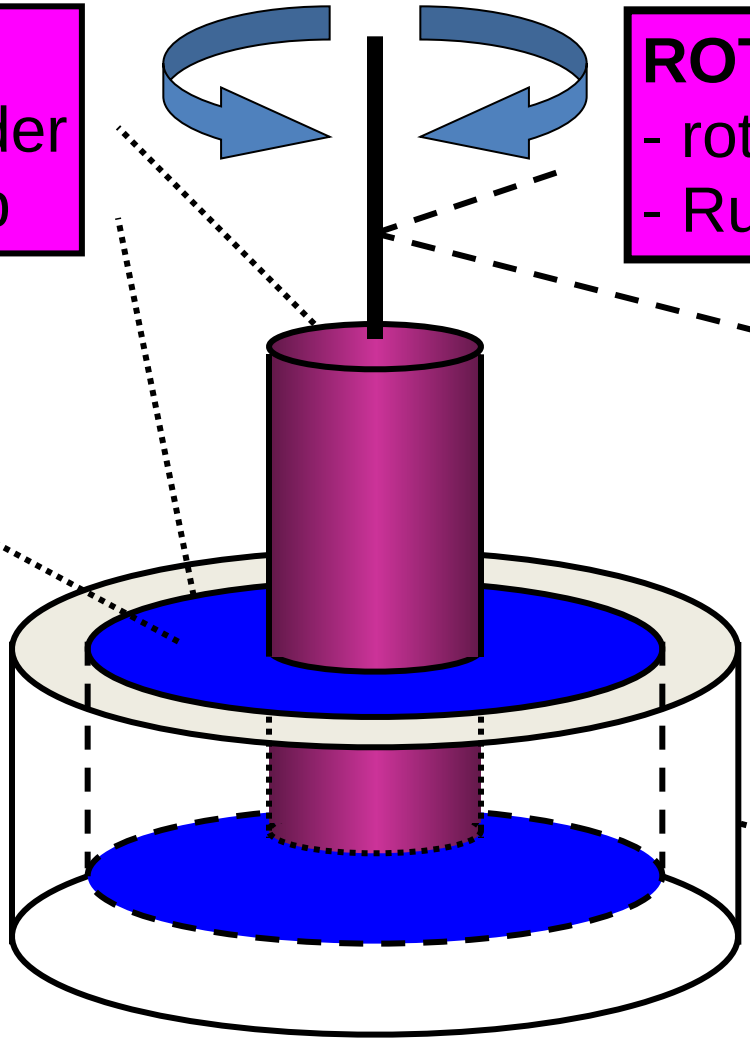
Viskolastische Tests: Basics

TEG
- ruhender Zylinder
- rotierender Cup

ROTEM
- rotierender Zylinder
- Ruhender cup

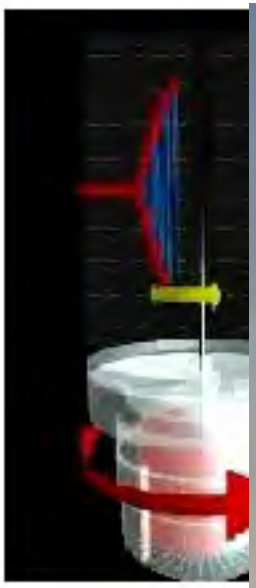


Voll Blut
+ Antikoaguans
+ Aktivator

Detektion

Heizelement (37°C)

Thromboelastography (TEG)



www.haemonetics.com

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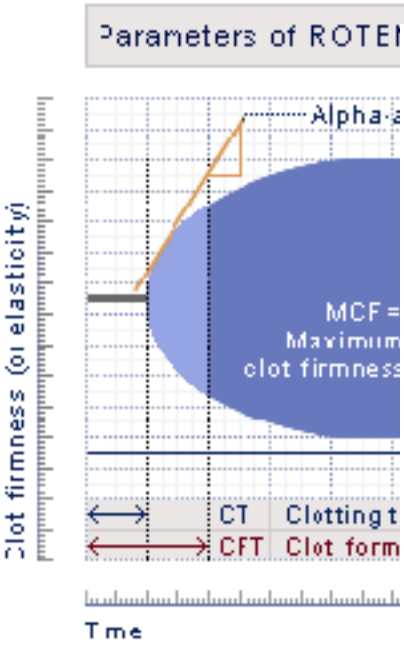
Rotational thromboelastometry (ROTEM)



Analysis

Definition
Time from start of measurement until the start of clot formation Time from the begin of clot formation until an amplitude of 20 mm is reached
Clot stability
Reduction of clot firmness during measurement

www.pentapharm.de

ZFTH

Viscoelastische Tests:

TEG	TEM
r-value: 0.3-0.8min time from adding activator to start of clot formation	**coagulation time** 100-240s
k-value: 0.1-0.3min time from start to amplitude of 20mm	**clot formation time** 30-110s
α angle 55-78° slope of curve	**α angle** 70-83°
Ma[illegible]	[illegible]72mm
Lysis index 30min compares amplitude or AUC after 30 or 60 minutes	**Lysis index** 60min

Die Tests sind ähnlich in der Konzeption, aber nicht direkt übertragbar!

Johannson PI et al.: Thromboelastography and thromboelastometry in assessing coagulopathy in trauma Scand J Trauma Resusc Emerg Med 2009; 17:45

ZFTH

Beispiele (ROTEM)

Tab. 1 Normalwerte in der ROTEM®-Analyse. (Lang u. von Depka [17])

Test	„Clotting time" [s]	„Clot formation time" [s]	Maximale Clot-festigkeit [mm]	Maximaler Lyse-Index [%/h]
EXTEM	38–70	34–160	50–72	<12
INTEM	100–240	30–110	50–72	<12
FIBTEM			8–24	
APTEM	Vergleich mit EXTEM			

EXTEM sensitive Gerinnungsaktivierung mit Gewebethromboplastin, INTEM intrinsische Gerinnungsaktivierung mit partiellen Thromboplastinen, FIBTEM durch Zugabe von Cytochalasin D inhibierte Thrombozytenfunktion, APTEM Zugabe von Aprotinin zum EXTEM.

Normal

ZFTH

Beispiele (ROTEM)

Tab. 1 Normalwerte in der ROTEM®-Analyse. (Lang u. von Depka [17])

Test	„Clotting time" [s]	„Clot formation time" [s]	Maximale Clot-festigkeit [mm]	Maximaler Lyse-Index [%/h]
EXTEM	38–70	34–160	50–72	<12
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FIBTEM			8–24	
APTEM	Vergleich mit EXTEM			

EXTEM sensitive Gerinnungsaktivierung mit Gewebethromboplastin, INTEM intrinsische Gerinnungsaktivierung mit partiellem Thromboplastin, FIBTEM durch Zugabe von Cytochalasin D blockierte Thrombozytenfunktion, APTEM Zugabe von Aprotinin zum EXTEM.

Fibrinogen Mangel

x Daumen Regel:

1g Fibrinogen Konzentrat
erhöht Fibtem MCF um 2mm
erhöht Fbg (Clauss) um 0.3 g/l
(in 70kg pt;)

Examples (TEM)

Tab. 1 Normalwerte in der ROTEM®-Analyse. (Lang u. von Depka [17])

Test	„Clotting time" [s]	„Clot formation time" [s]	Maximale Clot-festigkeit [mm]	Maximaler Lyse-Index [%/h]
EXTEM	38–79	34–160	50–72	<12
INTEM	100–240	30–110	50–72	<12
FIBTEM			8–24	
APTEM	Vergleich mit EXTEM			

EXTEM zeichnet eine Gerinnungsaktivierung mit Gewebethromboplastin, INTEM eine reine Gerinnungsaktivierung mit partiellen Thromboplastinen, FIBTEM durch Zugabe von Cytochalasin D eine Thrombozytenfunktionshemmung, APTEM Zugabe von Aprotinin zum EXTEM.

Thrombocytopenie

x Daumen Regel :

1 Tc Konzentrat

erhöht Intem MCF um 10mm

(bei Tc <50 G/l; 31→43 G/l)

Flisberg P. Anaesth Analg 2009; 108:1430)

ZFTH

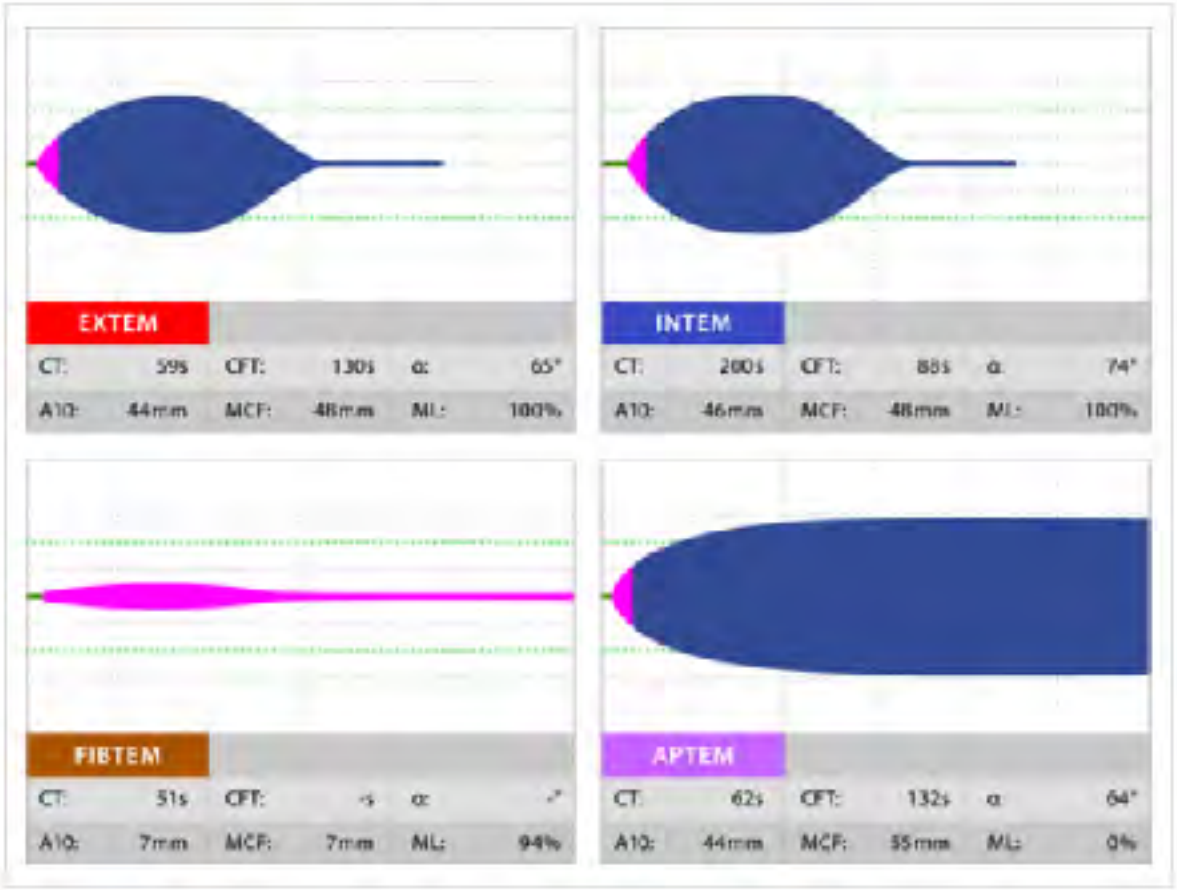
Examples (TEM)

Tab. 1 Normalwerte in der ROTEM®-Analyse. (Lang u. von Depka [17])

Test	„Clotting time" [s]	„Clot formation time" [s]	Maximale Clot-festigkeit [mm]	Maximaler Lyse-Index [%/h]
EXTEM	38–79	34–160	50–72	<12
INTEM	100–240	30–110	50–72	<12
FIBTEM			8–24	
APTEM	Vergleich mit EXTEM			

EXTEM sensitive zur Gerinnungsaktivierung mit Gewebethromboplastin, INTEM innerhalb Gerinnungsaktivierung mit partiellem Thromboplastin, FIBTEM durch Zugabe von Cytochalasin D blockierte Thrombozytenfunktion, APTEM Zugabe von Aprotinin zum EXTEM.

Hyperfibrinolyse



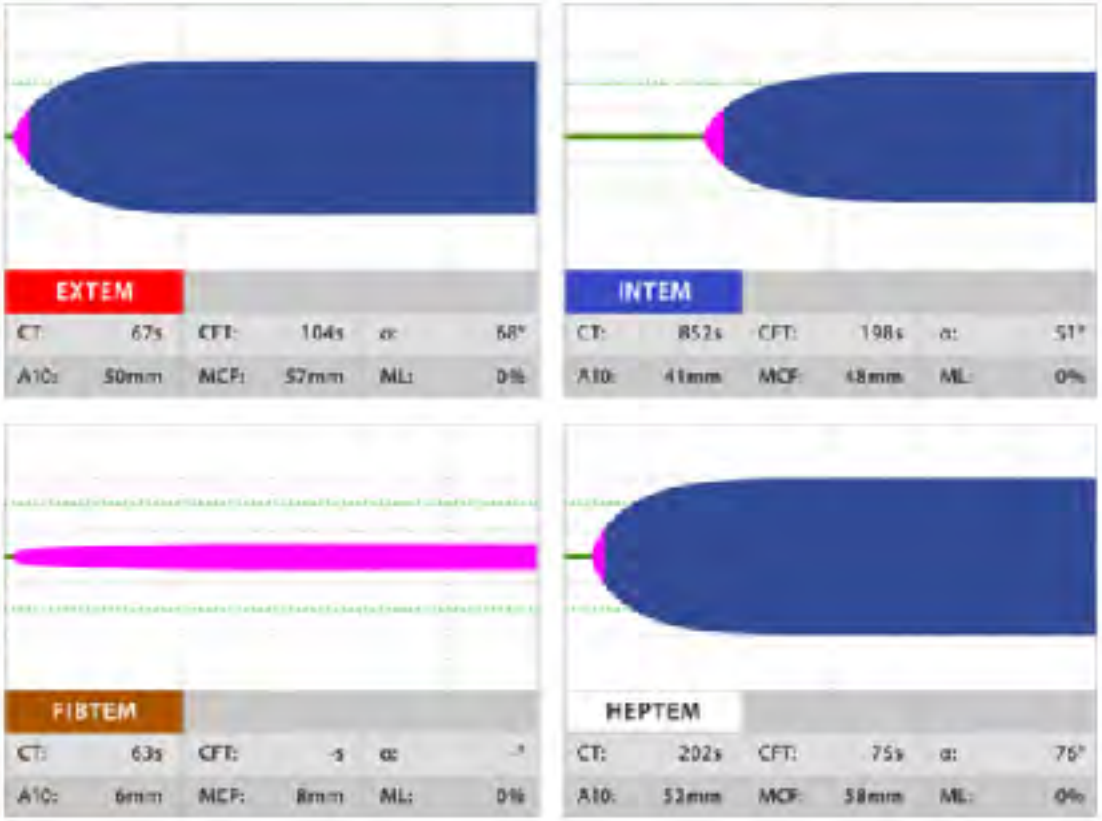
Examples (TEM)

Tab. 1 Normalwerte in der ROTEM®-Analyse. (Lang u. von Depka [17])

Test	„Clotting time" [s]	„Clot formation time" [s]	Maximale Clot-festigkeit [mm]	Maximaler Lyse-Index [%/h]
EXTEM	38–70	34–160	50–72	<12
INTEM	100–240	30–110	50–72	<12
FIBTEM			8–24	
APTEM	Vergleich mit EXTEM			

EXTEM reflektiert die Gerinnungsaktivierung mit Gewebethromboplastin, INTEM innerhalb Gerinnungsaktivierung mit partiellem Thromboplastin, FIBTEM durch Zugabe von Cytochalasin D blockierte Thrombozytenfunktion, APTEM Zugabe von Aprotinin zum EXTEM.

Heparin effect



Pathophysiologie
- Das Hiippala paper!

Hemostatic Factors and Replacement of Major Blood Loss with Plasma-Poor Red Cell Concentrates

Seppo T. Hiippala, MD, Gunnar J. Myllylä, MD, and Elina M. Vahtera, PhD

Department of Anesthesiology, Helsinki University Central Hospital, and Finnish Red Cross Blood Transfusion Service, Helsinki, Finland

The purpose of this study was to assess the change of platelet and fibrinogen concentrations and the change of activities of prothrombin and factors V and VII when major surgical blood loss was replaced with plasma-poor red cell concentrates (RCCs) and colloid plasma substitutes. Sixty patients were studied. The average blood loss was 65% ± 41% of the calculated blood volume (CBV). Blood loss was monitored carefully and replaced without delay to ensure stable blood volume.

Table 1. Critical Level of Hemostatic Factors and the Inversely Predicted Corresponding Blood Loss (95% Confidence Interval) as Percent of Calculated Blood Volume

Hemostatic factor	Critical level	Blood loss (%)
Platelets	$50 \times 10^3/mm^3$	230 (169–294)
Fibrinogen	1.0 g/L	142 (117–169)
Prothrombin	20	201 (160–244)
Factor V	25	229 (167–300)
Factor VII	20	236 (198–277)

For prothrombin, factor V, and factor VII, the critical level is expressed as percent of normal activity. (Edmunds LH, Salzman EW. Hemostatic problems, transfusion therapy, and cardiopulmonary bypass in surgical patients. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis: basic principles and clinical practice. Philadelphia: JB Lippincott; 1994:956–68).

Results

- Fbg intial 3.7 g/l
  1.0 after 142% (117-169)
- Plt initial 257 G/l
  50 after 230 (169-294)
- FII: 201% (160-244)
- FV: 229% (167-300)
- FVII: 236% (198-277)

Point of care testing (POCT)

Take home messages

- Form der Patien iagnostik
- Sinnvoll überall
  wo rasch therap arden müssen
- Risiko/Nutzen A
  pro: Z
  contra: C
- Bedingt ein orga
  Gewährle
  Fokus: Qu

Danke für Ihre Aufmerksamkeit

Koronarstents, DAPT, perioperatives Management

Symposium Blut und Gerinnung
19.06.2018

PD Dr. med. Dr. sc. nat. Stefan Blöchlinger
FMH Kardiologie, Intensivmedizin &
Allgemeine Innere Medizin

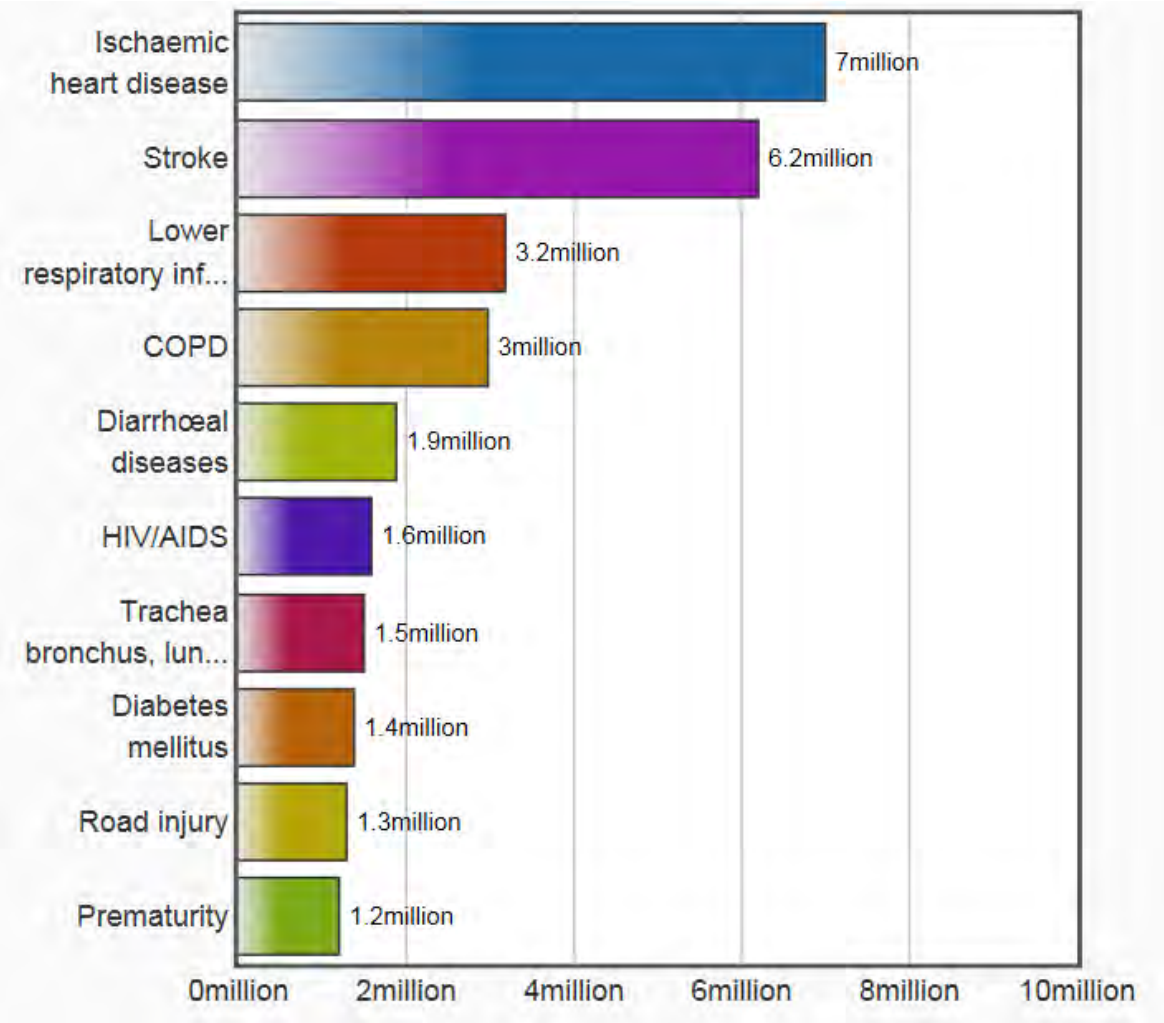
INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

KGW
KANTONSSPITAL WINTERTHUR

Inhalt

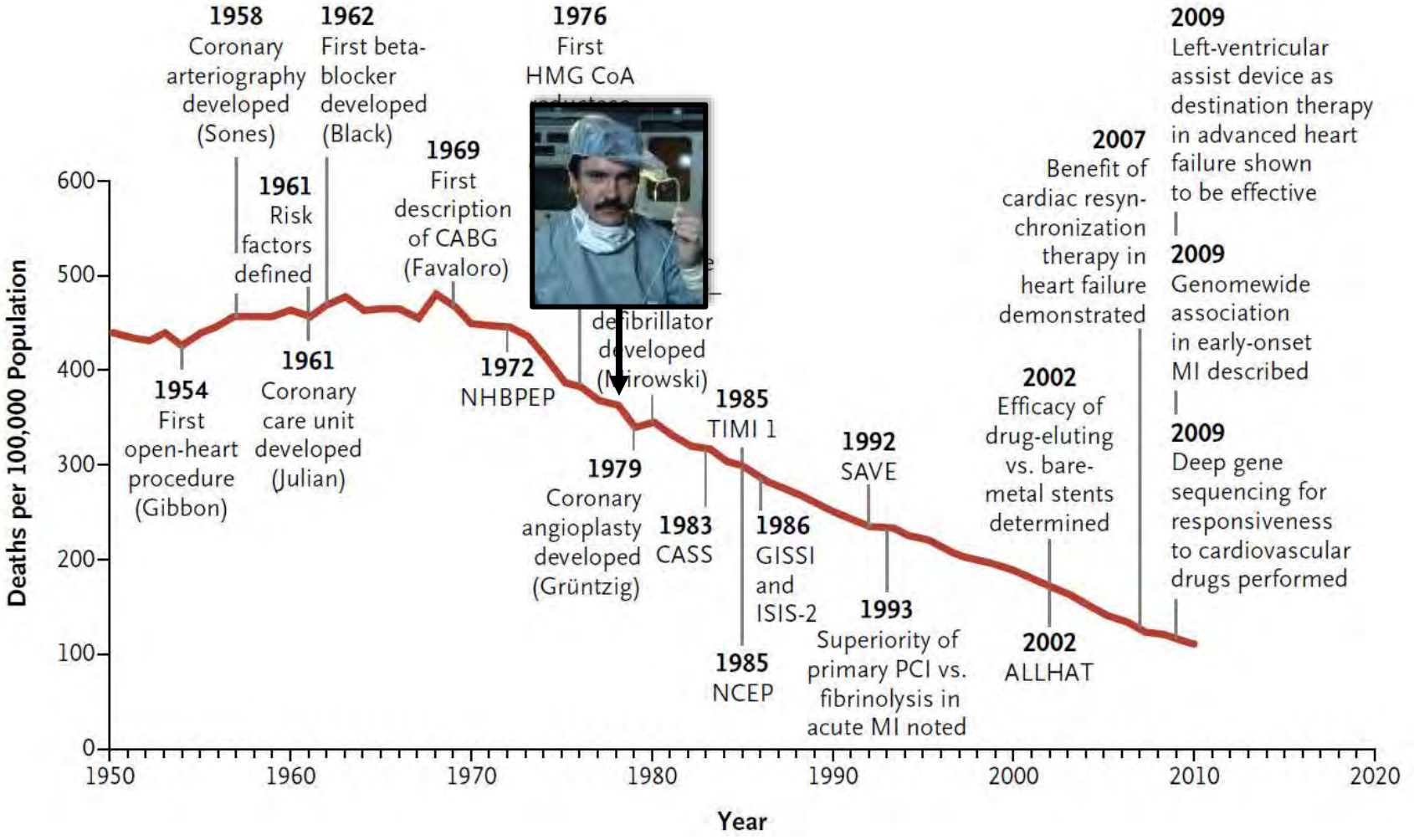
- Einführung
- Stenttypen – Sicherheit und Effektivität
- Doppelte Tc-Aggregationshemmung (DAPT)
- Richtlinien – perioperative Handhabung

Die 10 Haupttodesursachen weltweit
(WHO 2011)



Kardiovaskuläre Mortalität & medizinischer Fortschritt

Nabel, E.M. & Braunwald, E.; N Engl J Med 2012;366:54-63



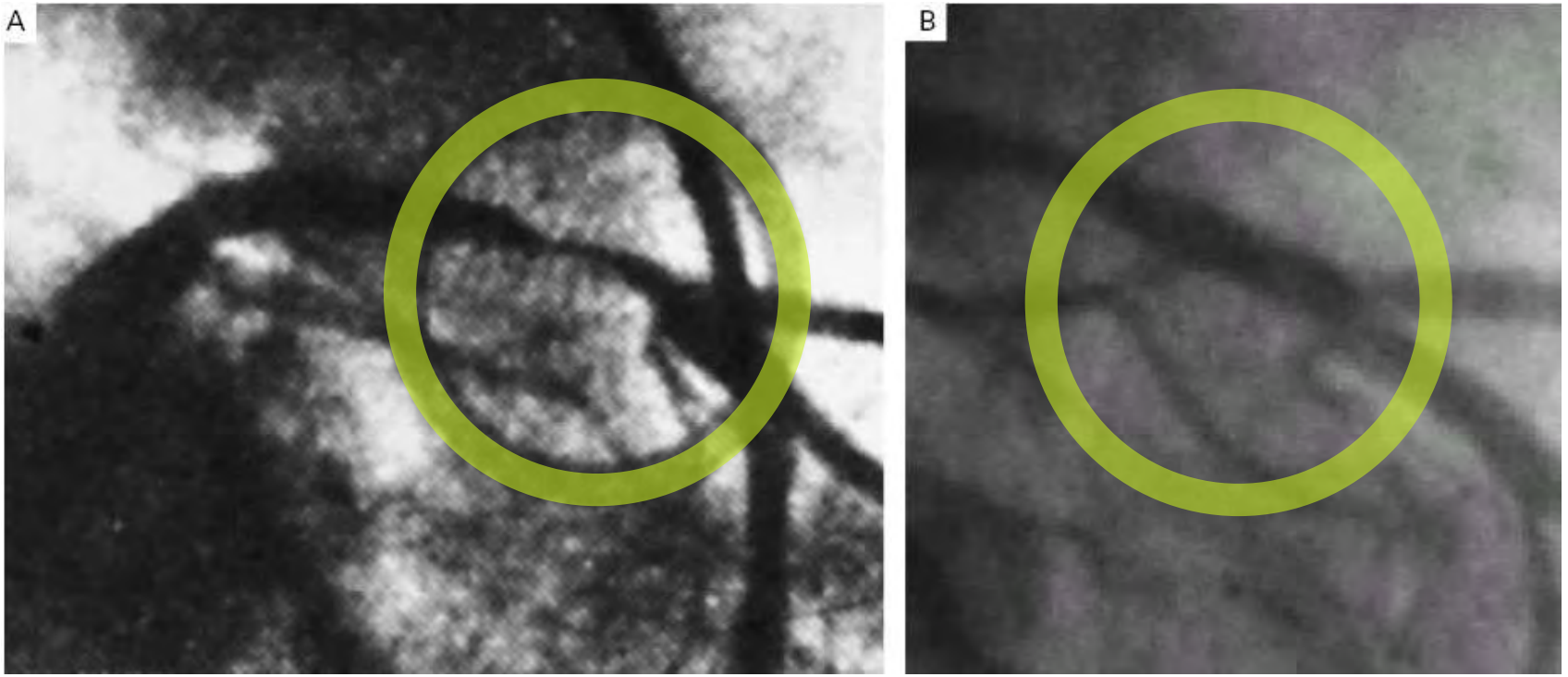
Nonoperative Dilatation of Coronary-Artery Stenosis – Percutaneous Transluminal Coronary Angioplasty

Andreas R. Grüntzig, M.D., Åke Senning, M.D., and Walter E. Siegenthaler, M.D.

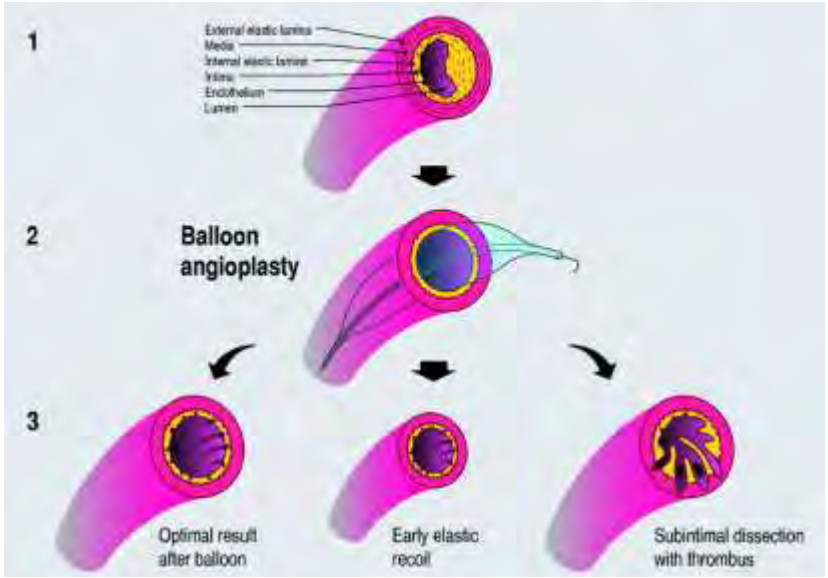
N Engl J Med 1979;301:61-68

16. September 1977, Zürich; 1. PTCA durch A. Grüntzig:
38-jähriger Patient mit isolierter proximaler RIVA-Stenose

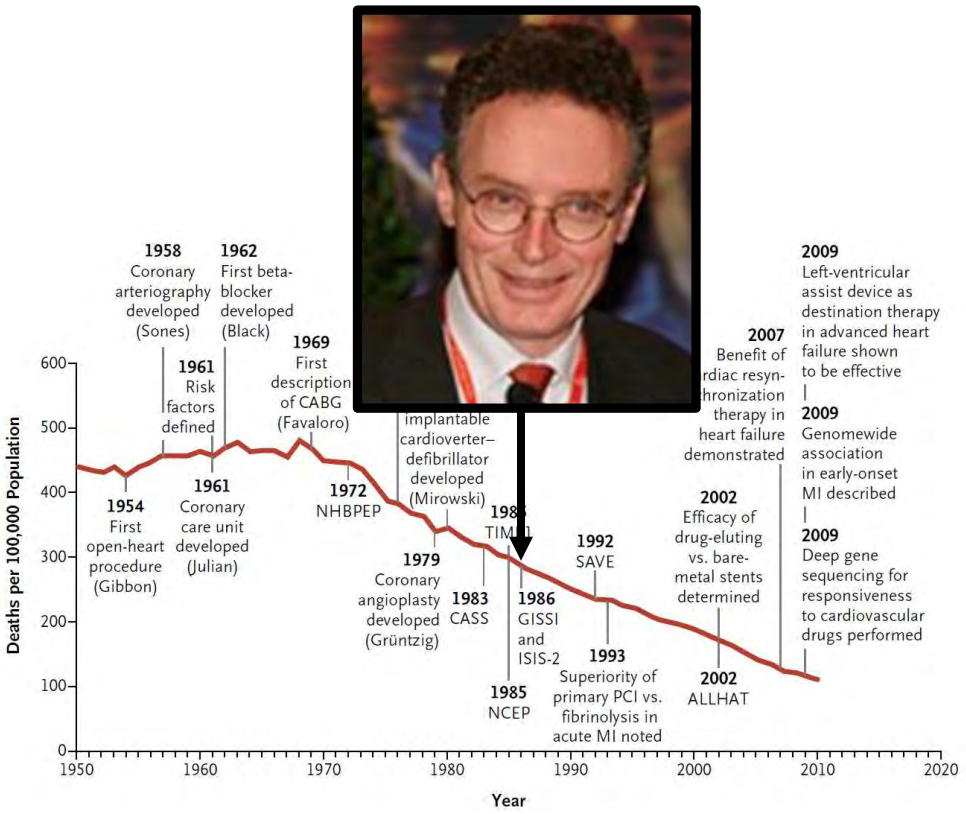
1977 **2000**



Percutaneous Coronary Intervention (PCI)

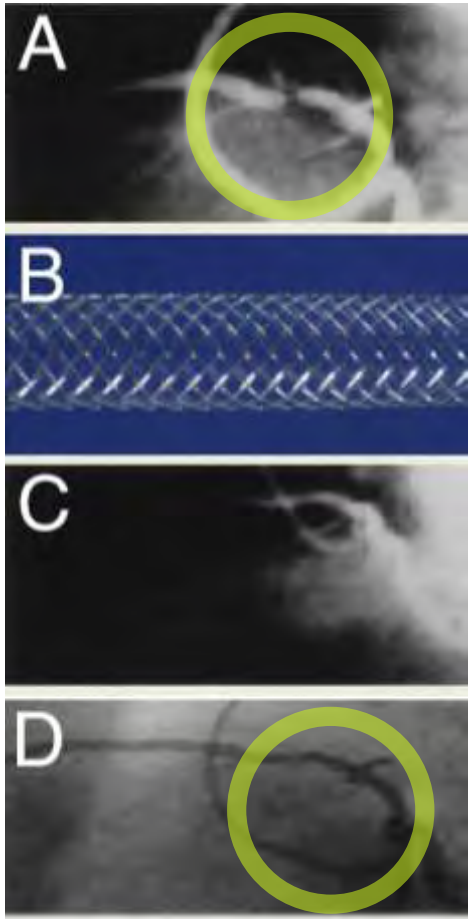


März 1986, Frankreich; erste koronare Stentimplantation durch Jacques Puel



Koronare Stentimplantation

Carrié, D. et al.; Am J Cardiol. 2000 Jan 1;85(1):95-8



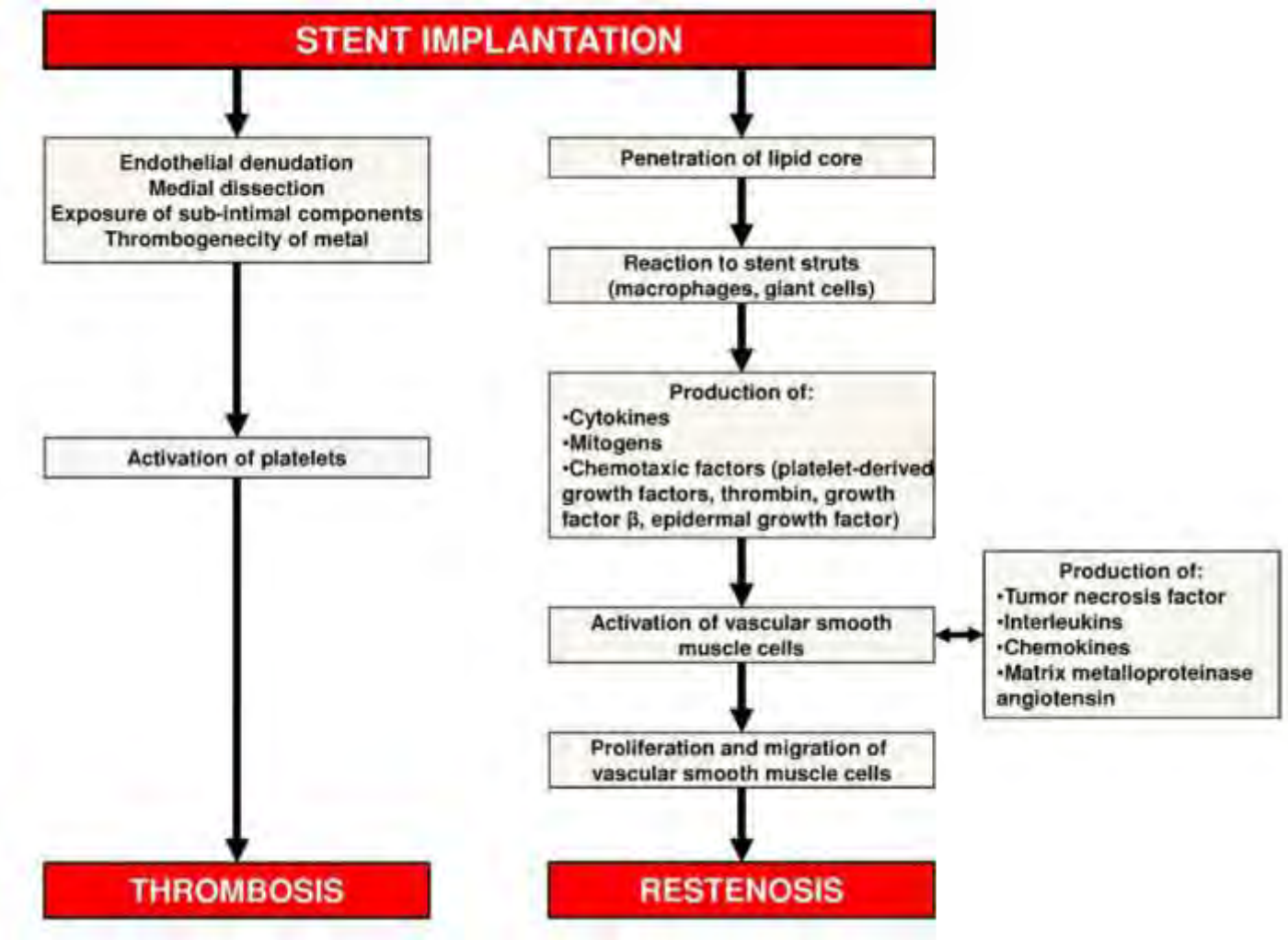
Restenose nach PTCA

Wallstent

Unmittelbar nach Implantation

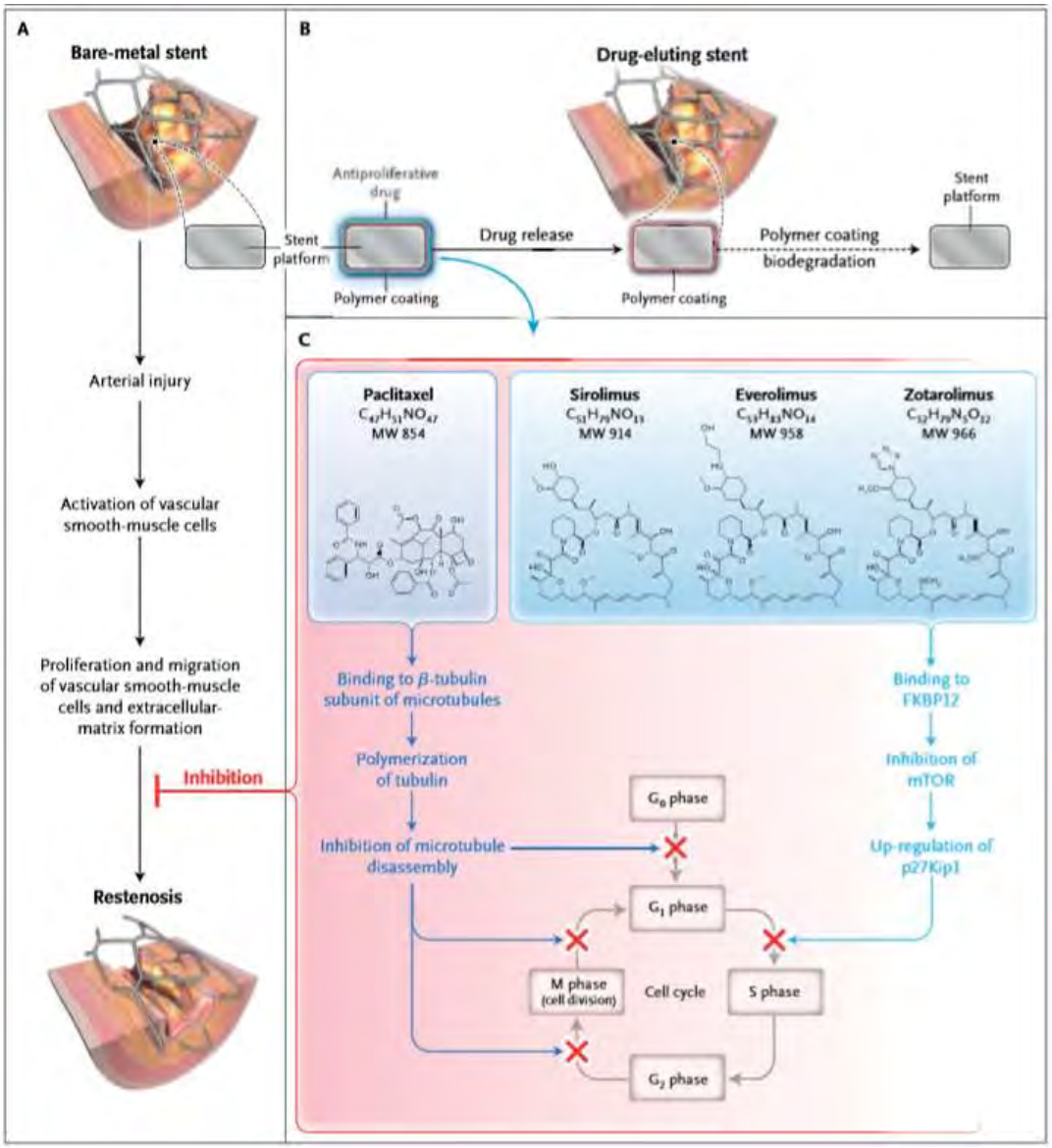
Nachkontrolle nach 11 Jahren

Koronare Stentimplantation



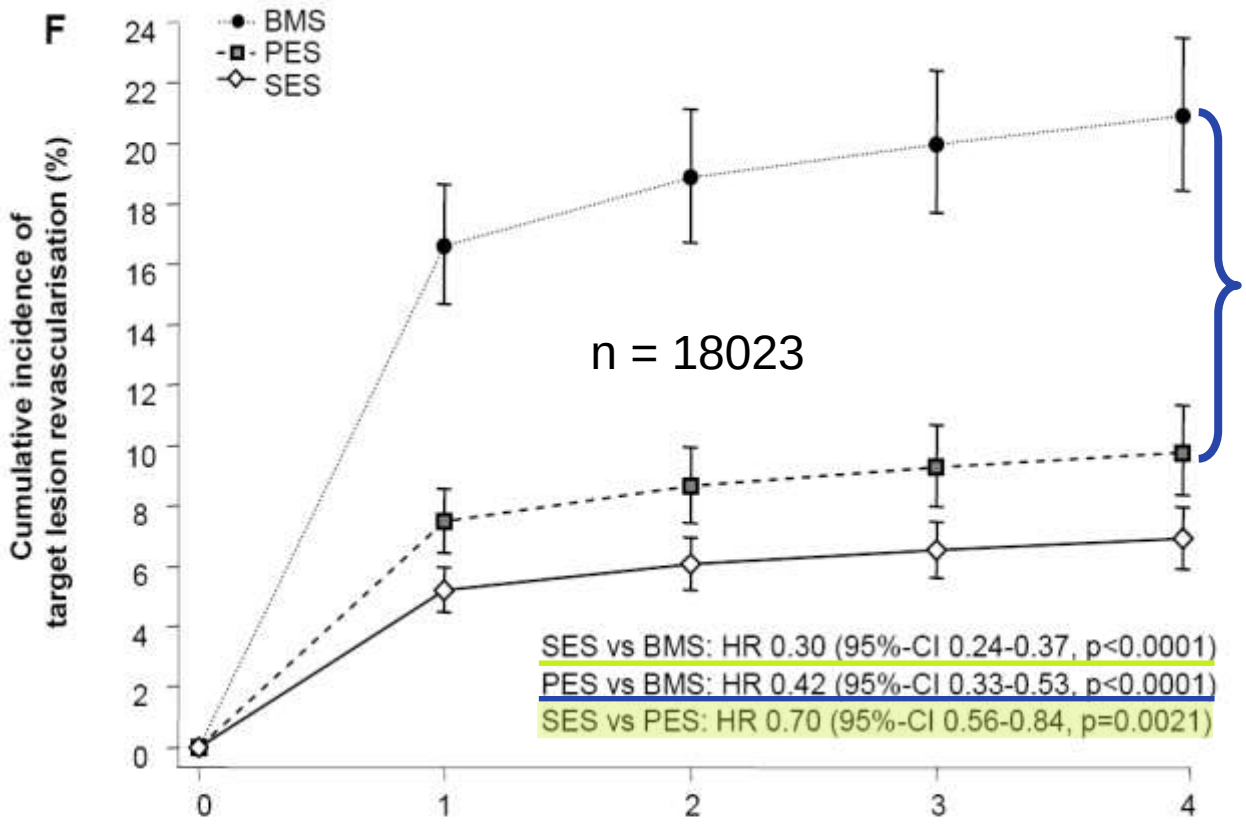
Koronarstents – Bare-metal (BMS) vs. Drug-eluting (DES)

Stefanini, G.G. and Holmes, D.R.; N Engl J Med 2013;368:254-65



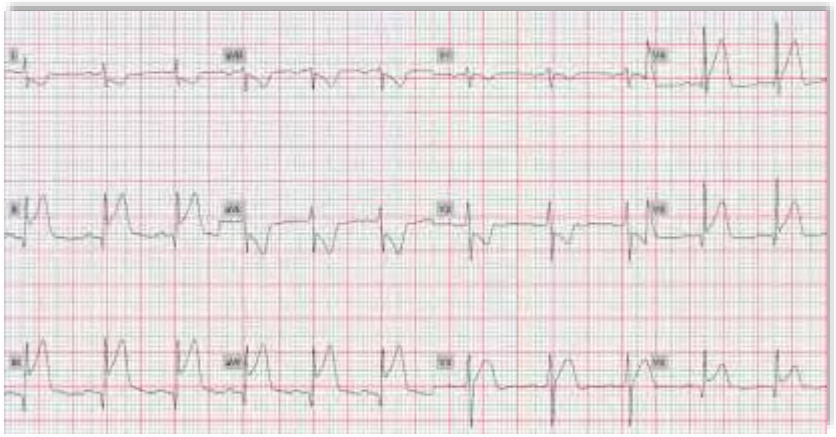
Koronarstents – Restenose

Stettler, D. et al.; Lancet 2007;370:937-48



N of events/patients					
BMS	4763	820/4746	53/2795	22/1871	10/1543
PES	6328	448/6280	98/3950	15/1999	6/832
SES	6621	356/6580	68/3801	16/2153	14/999

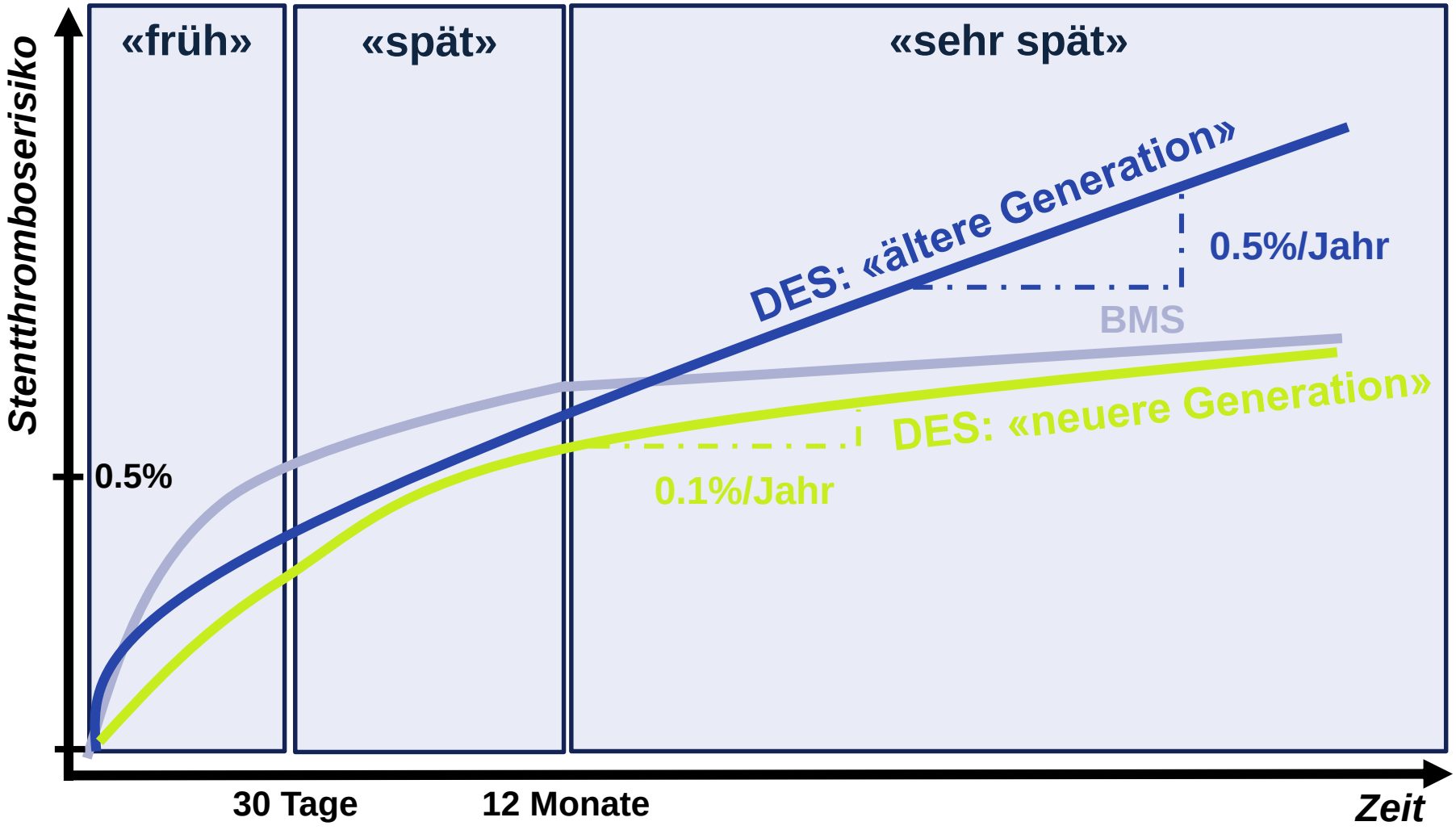
Koronarstents – Stentthrombose



30 Tage **12 Monate** ***Zeit***

Koronarstents – Stentthrombose

Stefanini, G.G. et al.; Lancet 2011;378:1940-8
Wenaweser, P. et al.; J Am Coll Cardiol 2008;52:1134-40

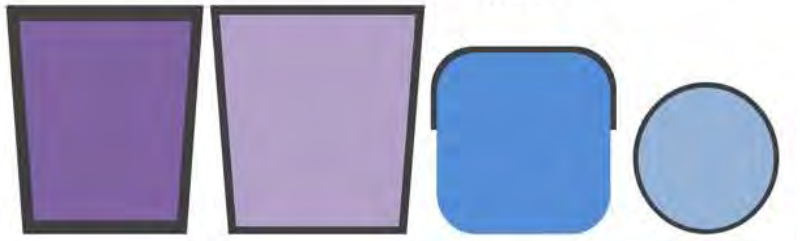


Drug-eluting Stents – Entwicklung

Stefanini, G.G. et al.; Heart 2014 Jul;100(13):1051-61

«ältere Generation DES»

«neuere Generation DES»



	Taxus	Cypher	BioMatrix Nobori	Endeavor	Xience Promus	Resolute	Synergy	Orsiro
Platform material	SS	SS	SS	CoCr	CoCr PtCr	CoCr	PtCr	CoCr
Strut thickness (µm)	132	140	120	91	81	91	74	60
Polymer type	Durable	Durable	Biodegradable	Durable	Durable	Durable	Biodegradable	Biodegradable
Polymer material	SIBS	PEVA/PBMA	PDLLA	MPC/LMA/HPMA/ 3-MPMA	PBMA/PVDF-HFP	PBMA/PHMA/ PVP/PVA	PLGA	PLLA
Coating distribution	Circumferential	Circumferential	Abluminal	Circumferential	Circumferential	Circumferential	Abluminal	Circumferential
Polymer thickness (µm)	22	13	10	6	8	6	4	7
Additional coating	-	-	-	-	-	-	-	Silicon carbide
Drug released	Paclitaxel	Sirolimus	Biolimus	Zotarolimus	Everolimus	Zotarolimus	Everolimus	Sirolimus

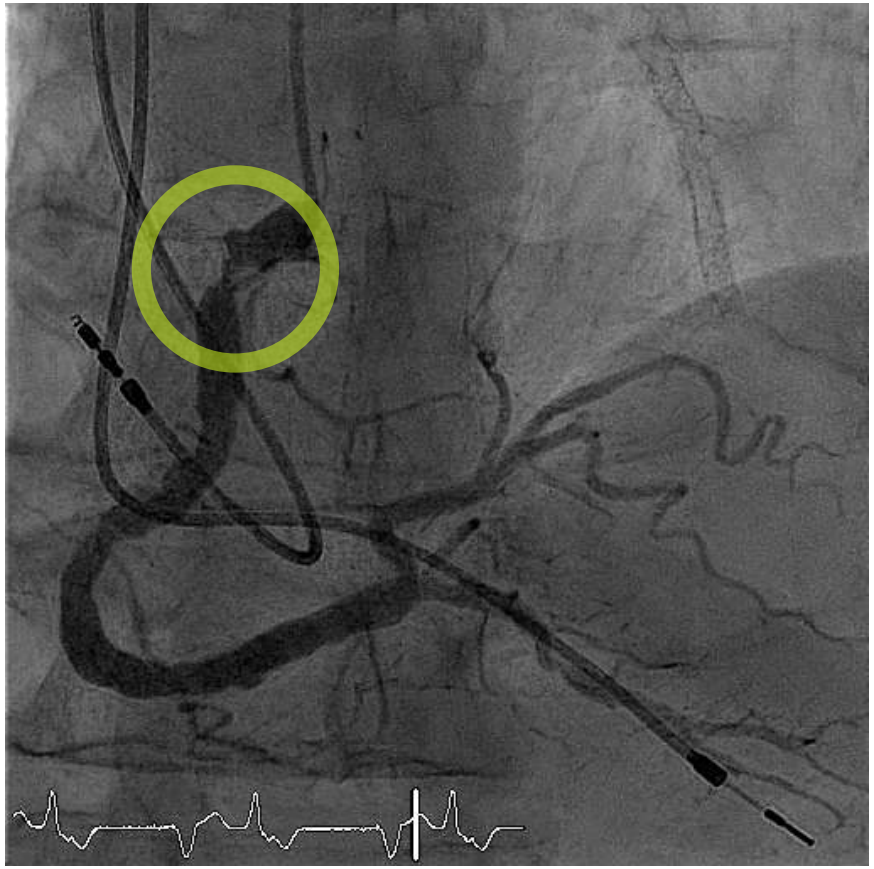
Myokardiale Revaskularisation: STEMI, NSTEMI, stabile KHK

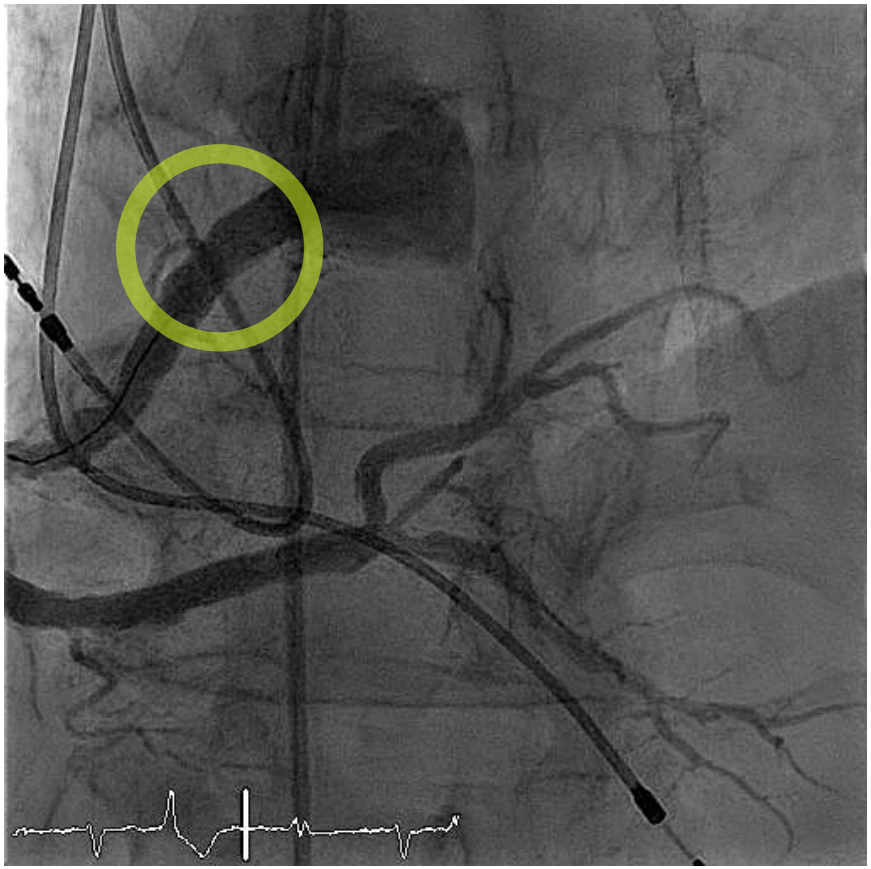
2014 ESC guidelines, European Heart Journal (2014) 35, 2541–2619

However, owing to a 20–30% rate of recurrence of angiographic stenosis within 6–9 months after implantation, restenosis with BMS has often been referred to as the 'Achilles' heel' of PCI.[645] There is no indication for BMS over new-generation DES, irrespective of patient and lesion subset. Similarly, there is no clear evidence of a difference between DES and BMS in the risk of stent thrombosis following unplanned disruption of DAPT.[648]

BMS – Verwendung

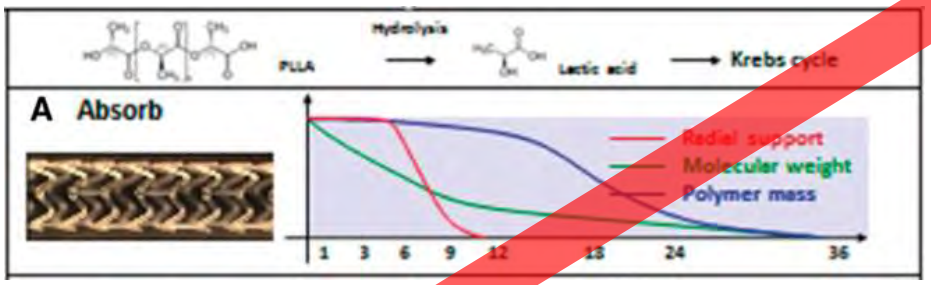
Beispiel

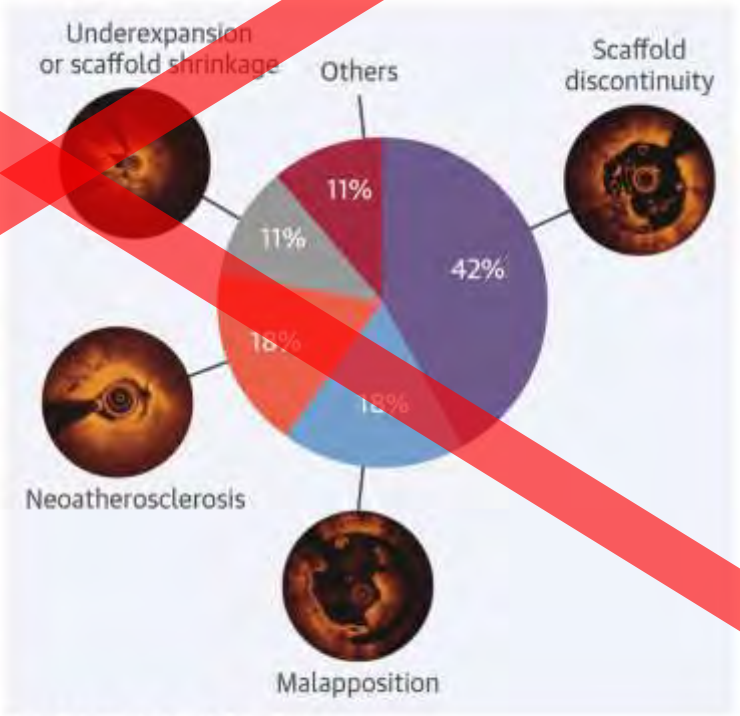




BRS (bioresorbable scaffold) stents – Absorb

Byrne, R.A. et al.; European Heart Journal (2017); epub ahead of print
Yamaji, K. et al.; J Am Coll Cardiol. 2017 Nov 7;70(19):2330-2344





Yamaji, K. et al. J Am Coll Cardiol. 2017;70(19):2330–44.

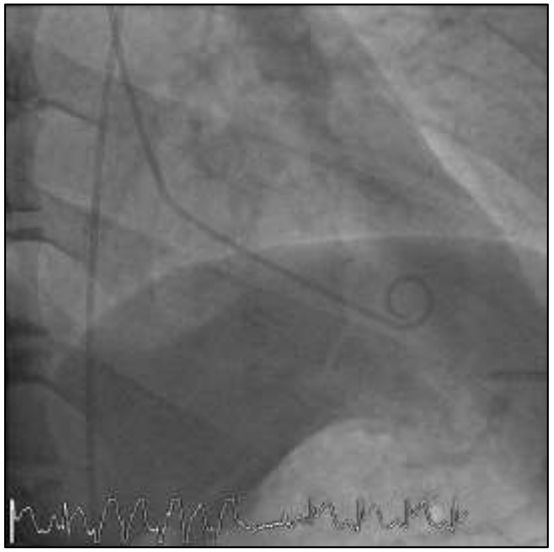
BRS (bioresorbable scaffold) stents – Absorb

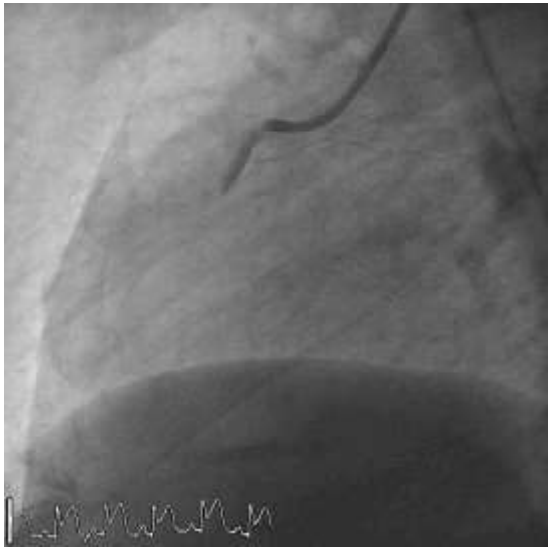
Byrne, R.A. et al.; European Heart Journal (2017); epub ahead of print

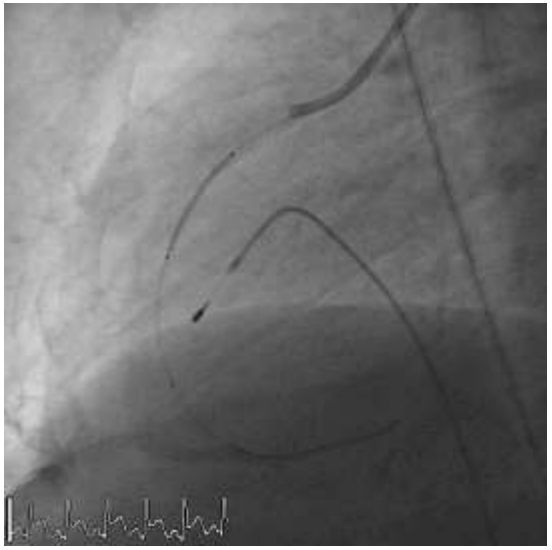
In patients who have already been treated with BRS, there are two scenarios to be considered:

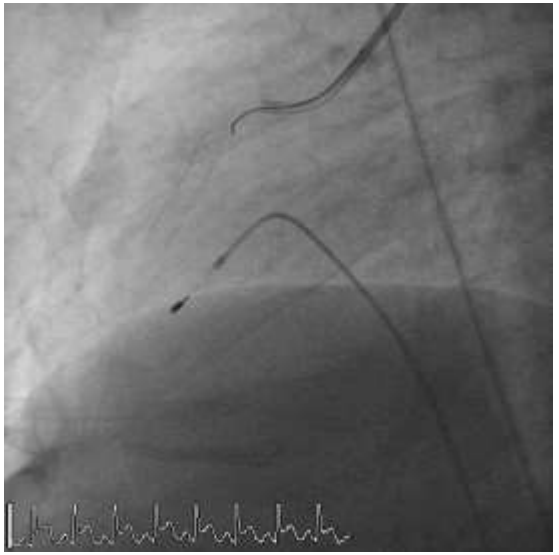
- In patients who remain on DAPT without clinical events, it is recommended to continue DAPT for the duration of bioresorption expected on the basis of existing non-clinical and clinical studies (e.g. at least 36 months in case of the Absorb pBRS).
- In patients who have discontinued DAPT prior to this time point, a decision to re-initiate DAPT should be made on a case-by-case basis after evaluation of the thrombotic and bleeding risks.

Patientenbeispiel

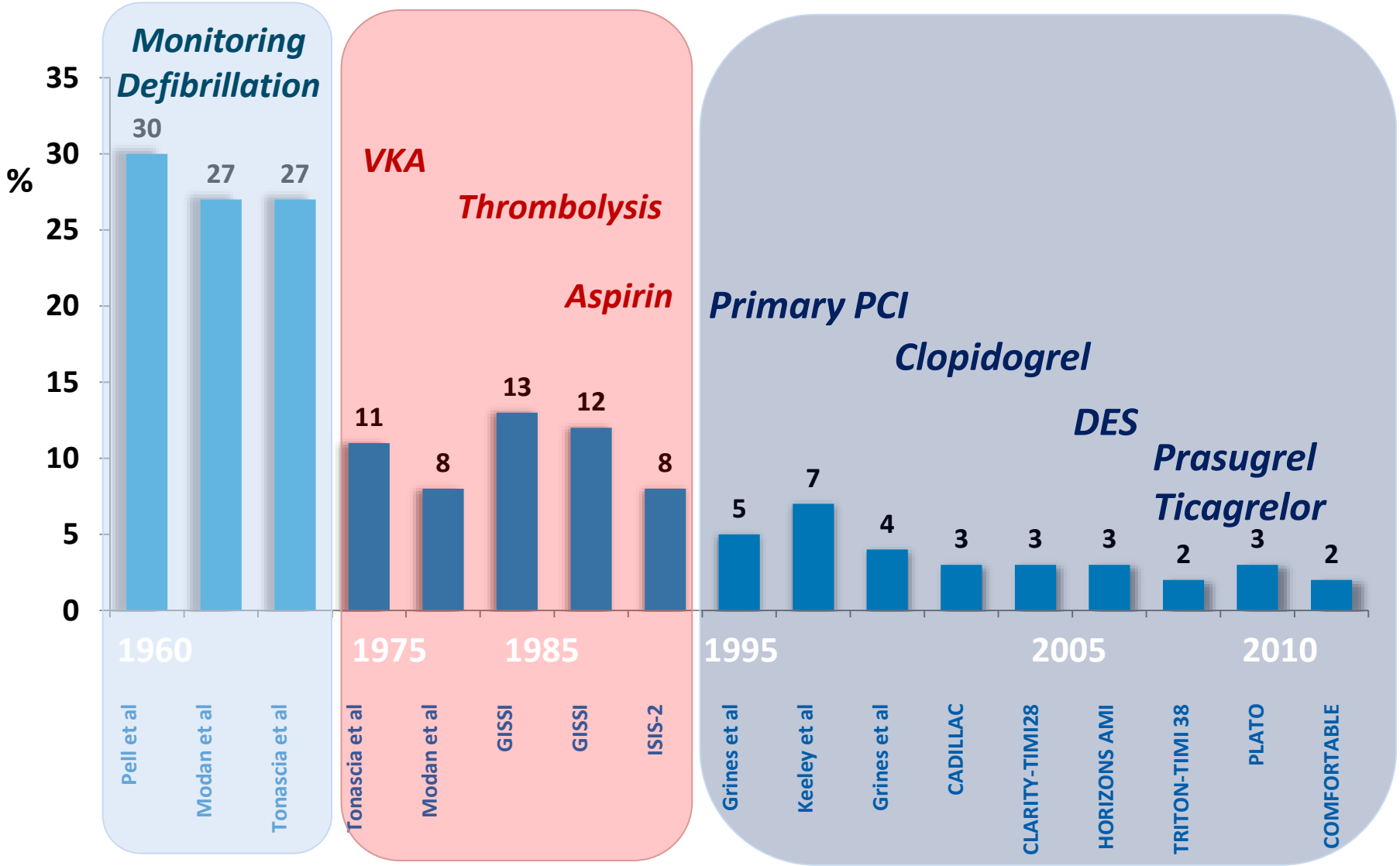




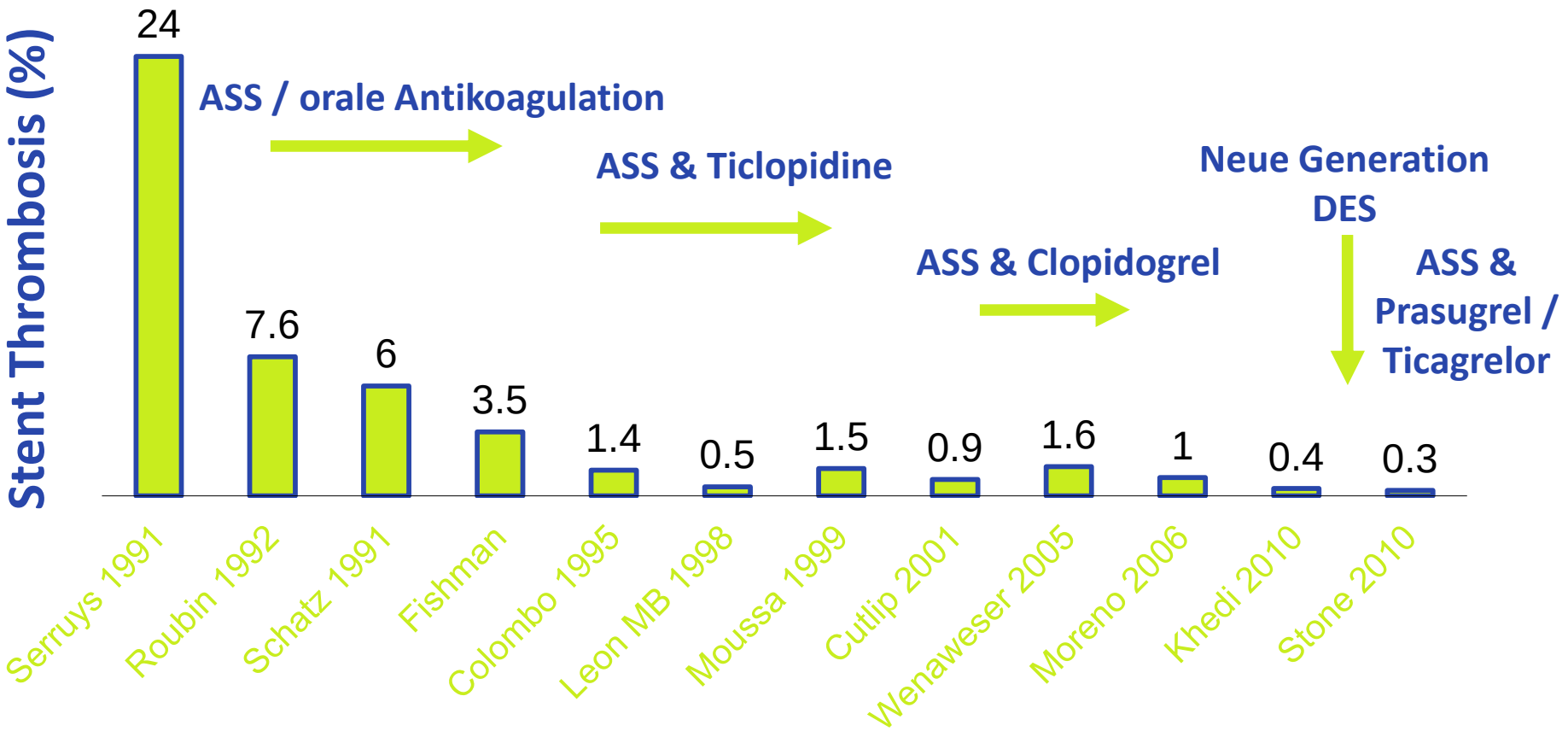




Mortalität bei Patienten mit Herzinfarkt

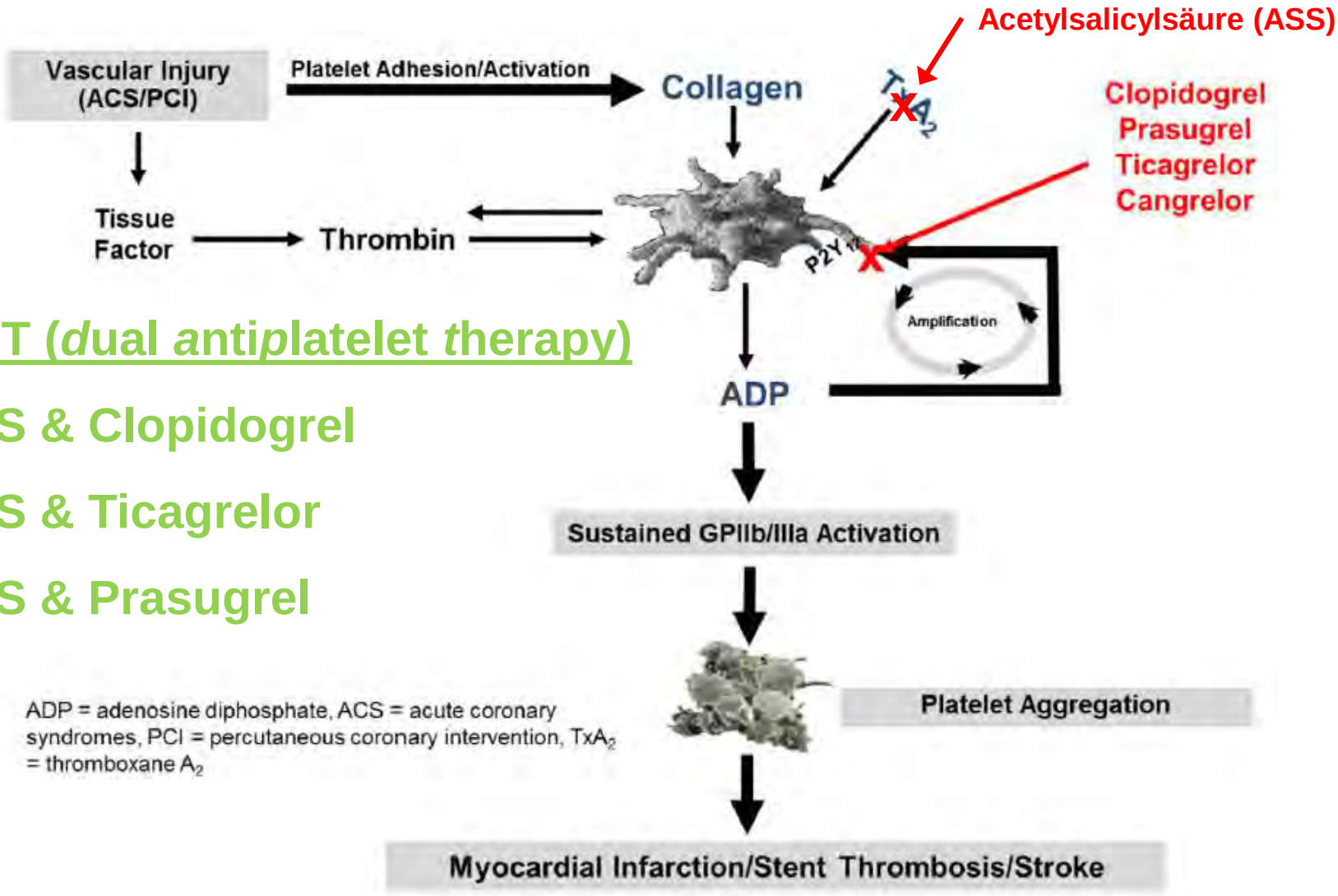


Historische Perspektive: Stents & Stentthrombose



Thrombozytenaggregationshemmer

Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470

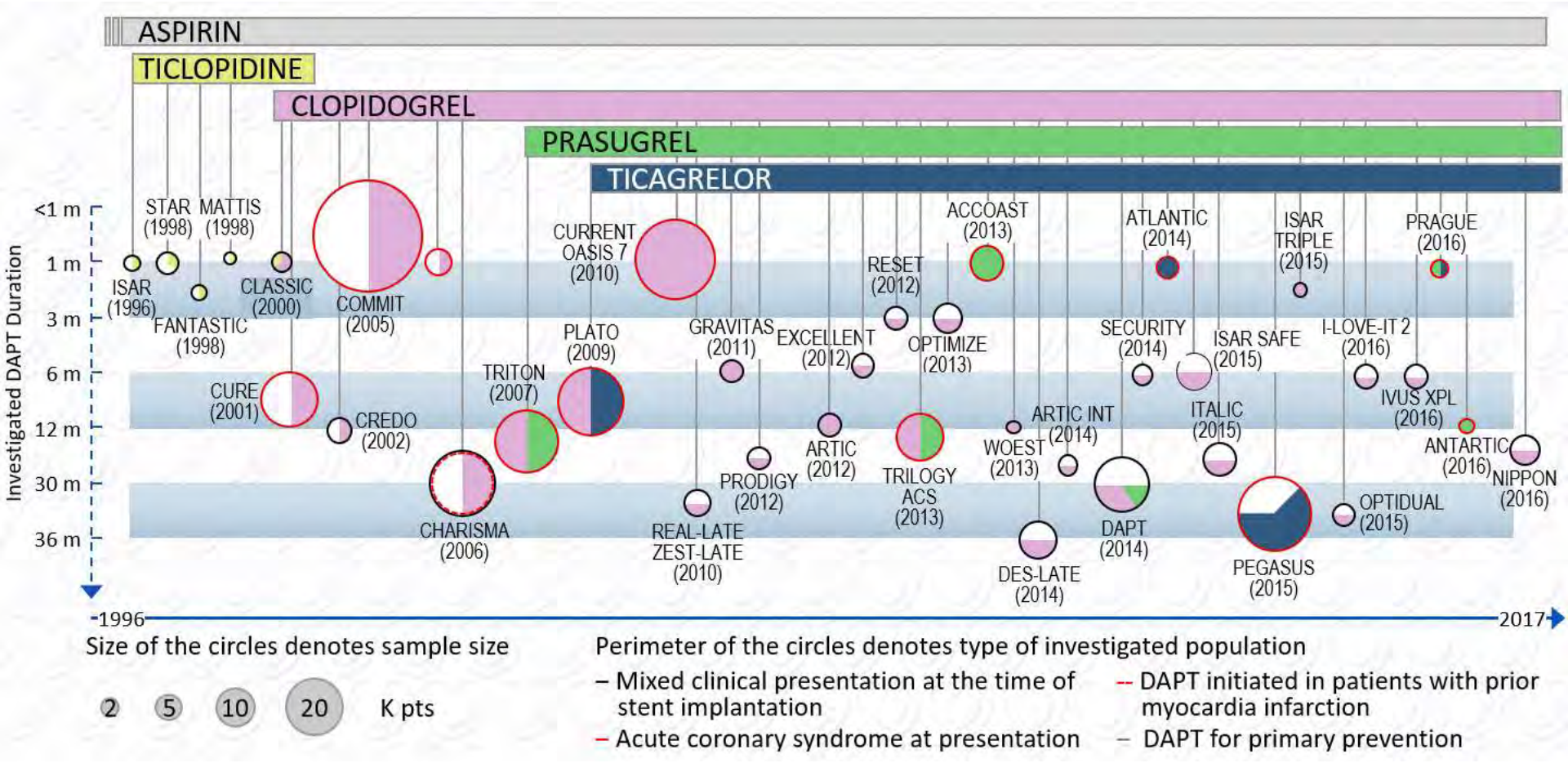


DAPT (*d*ual *anti*platelet *t*herapy)

- **ASS & Clopidogrel**
- **ASS & Ticagrelor**
- **ASS & Prasugrel**

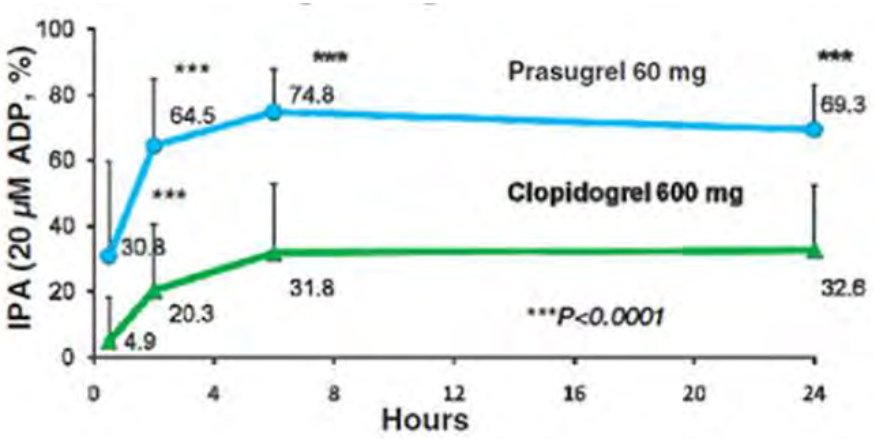
Duale Thrombozytenaggregationshemmung (DAPT)

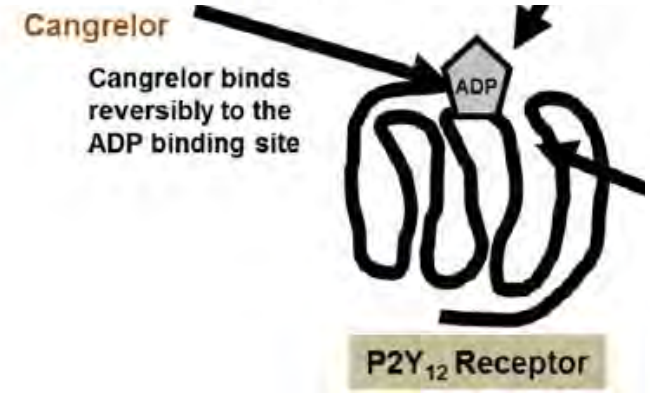
Eur Heart J. 2018 Jan 14;39(3):213-260.

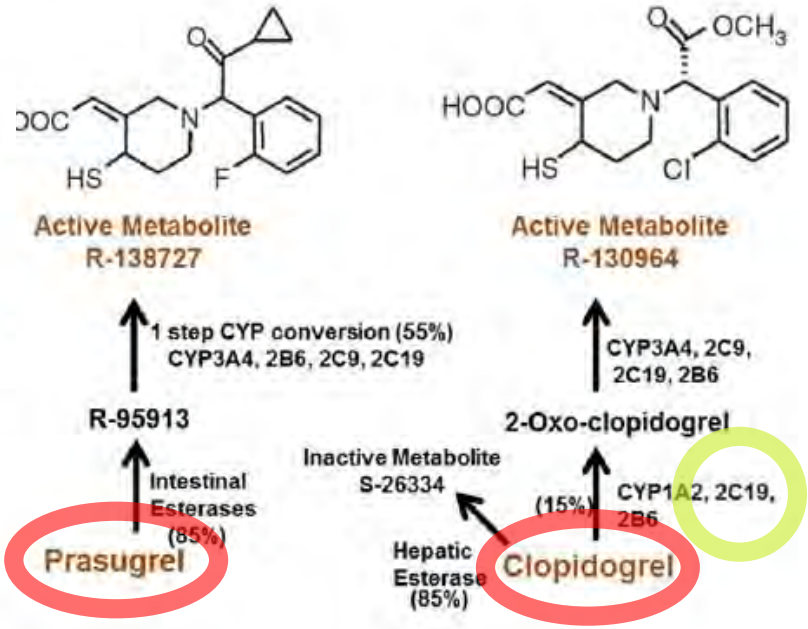


$P2Y_{12}$ Inhibitoren

Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470

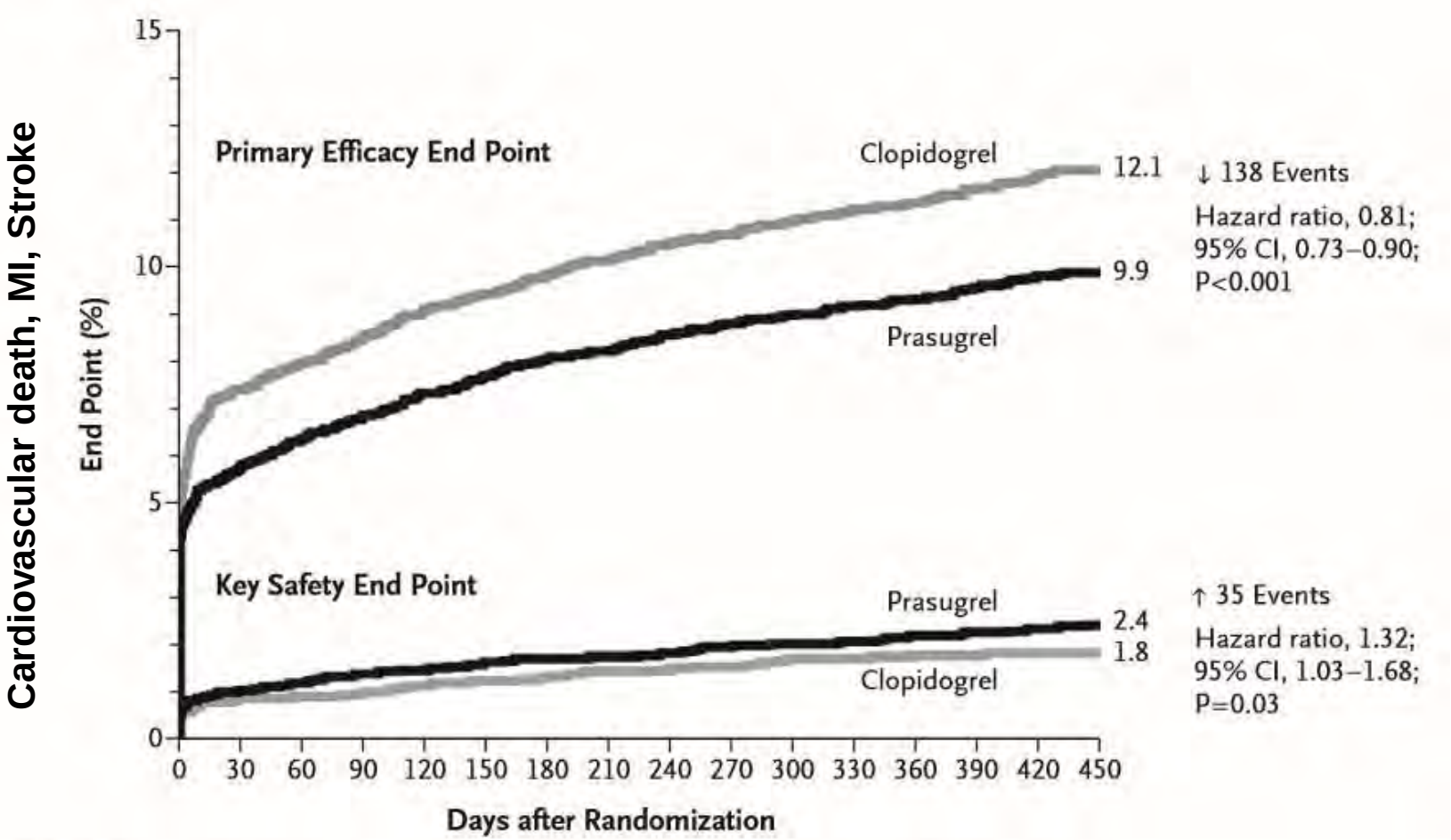






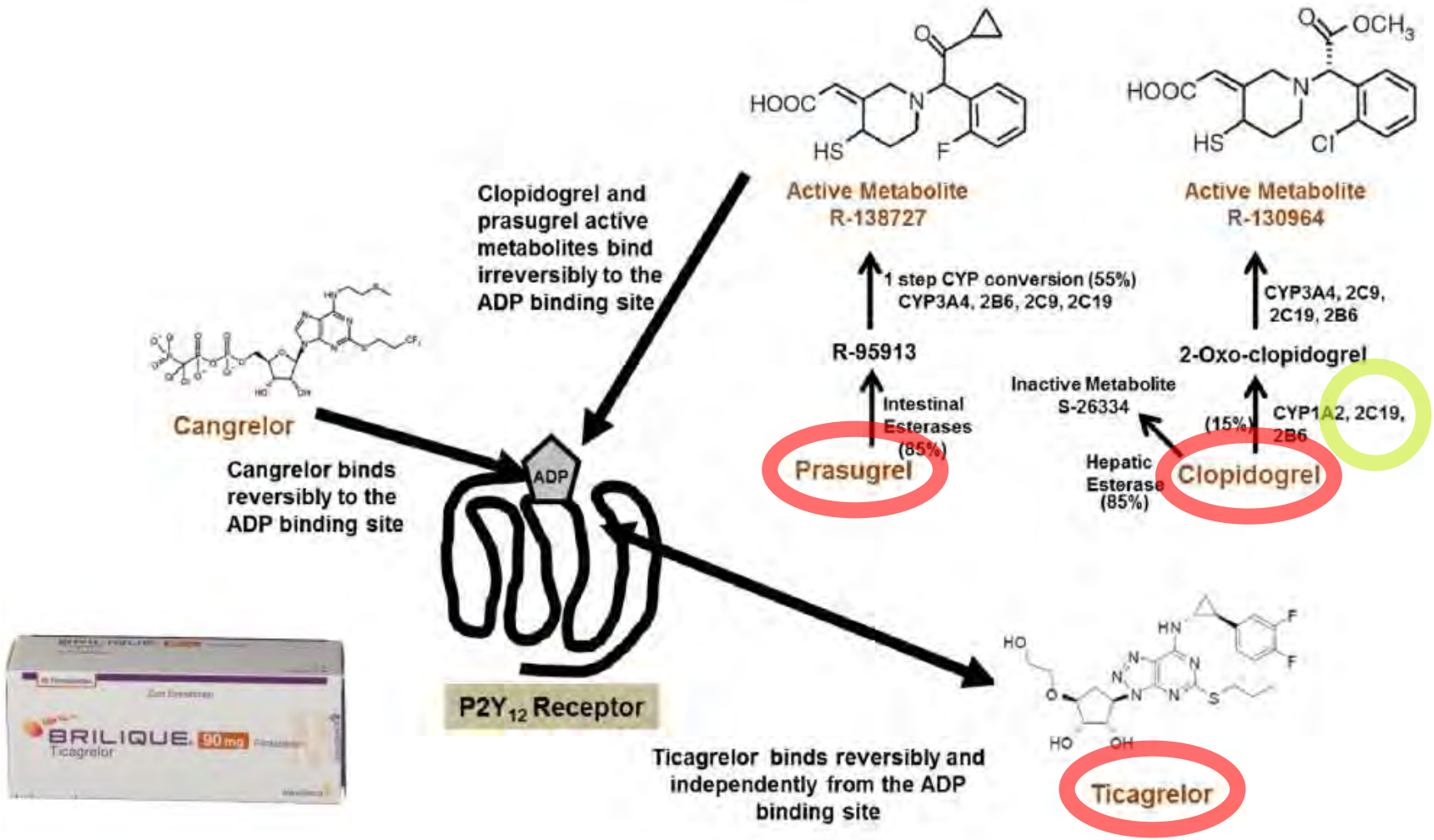
Prasugrel vs. Clopidogrel bei ACS (TRITON TIMI 38)

Wiviott, S.D. et al.; N Engl J Med (2007) 15;357(20):2001-15



$P2Y_{12}$ Inhibitoren

Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470



Ticagrelor vs. Clopidogrel

Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470

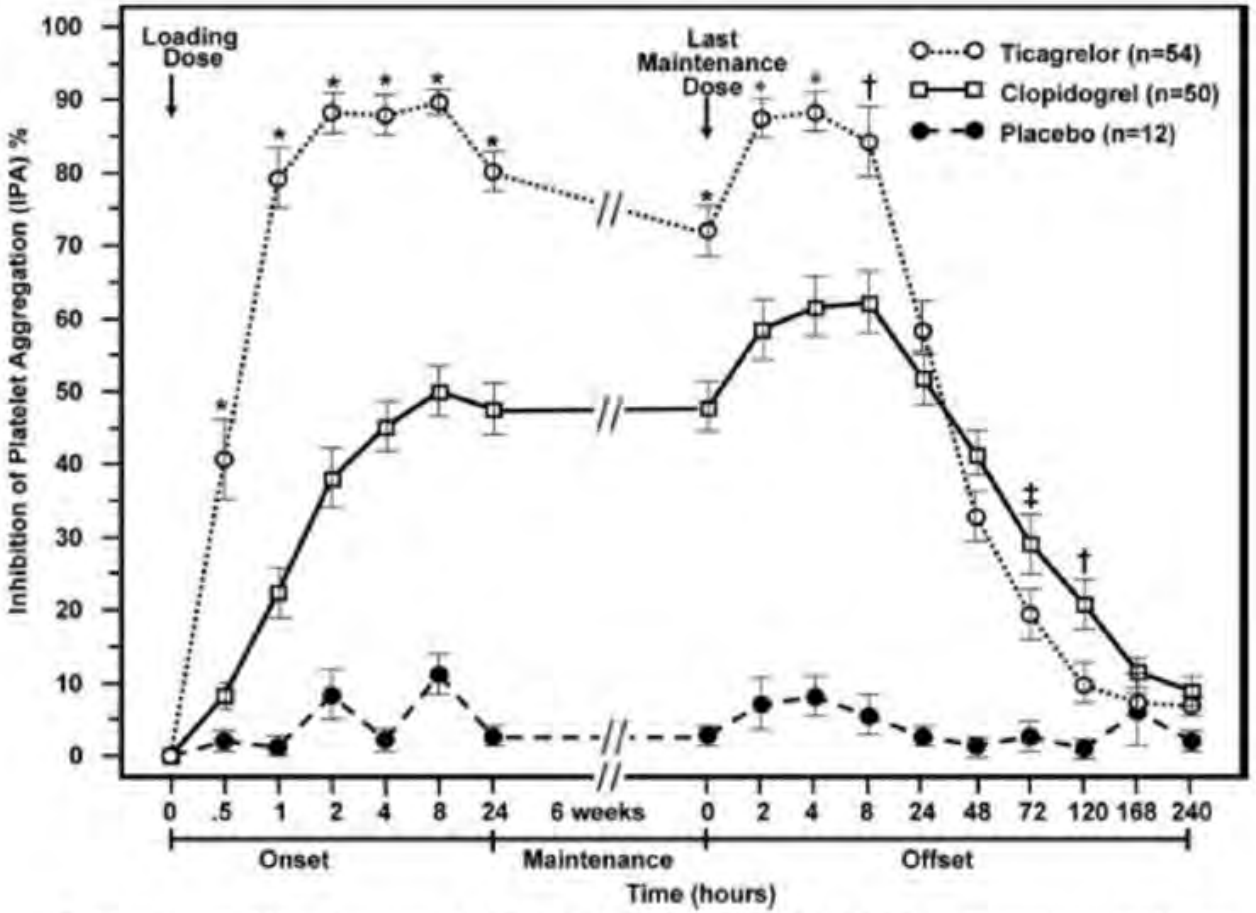
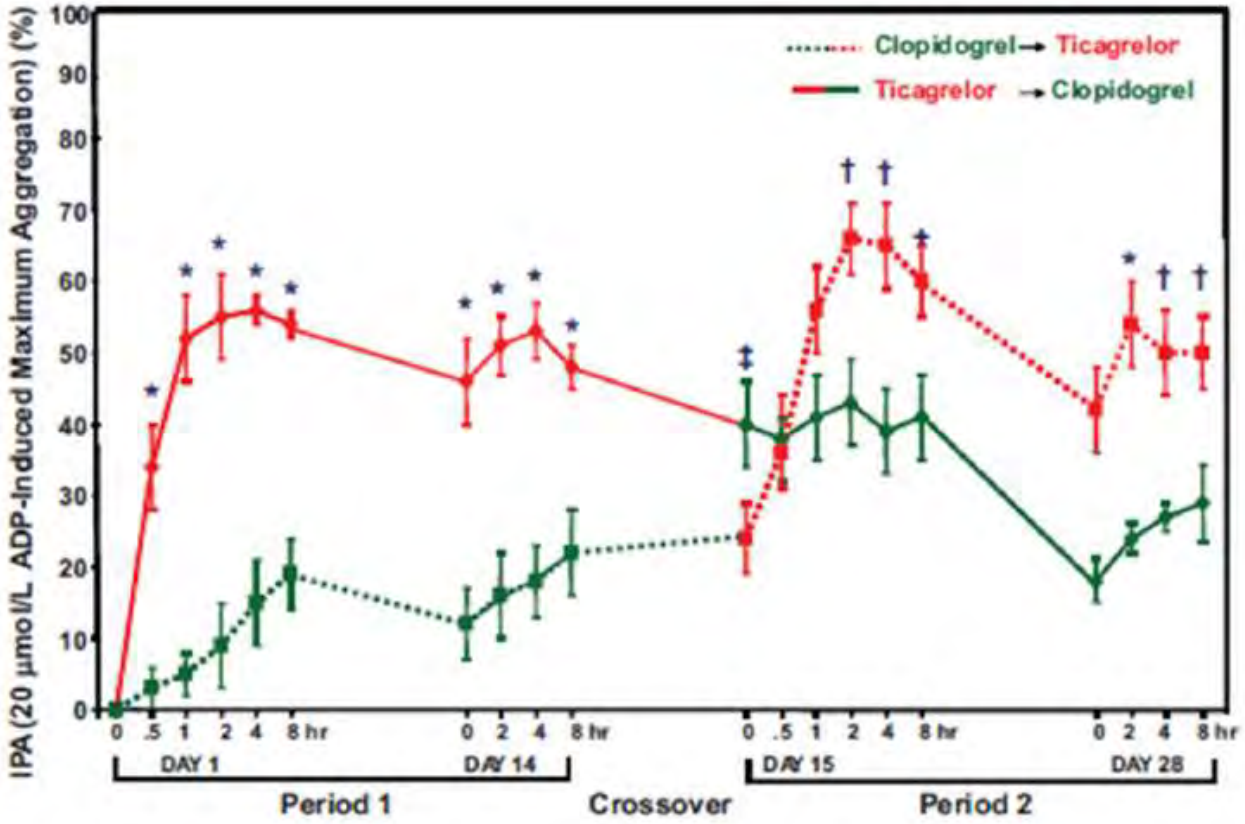


Fig 6. Inhibition of 20 μM adenosine diphosphate-induced platelet aggregation in stable coronary artery disease patients treated with clopidogrel and ticagrelor in.

Ticagrelor vs. Clopidogrel

Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470

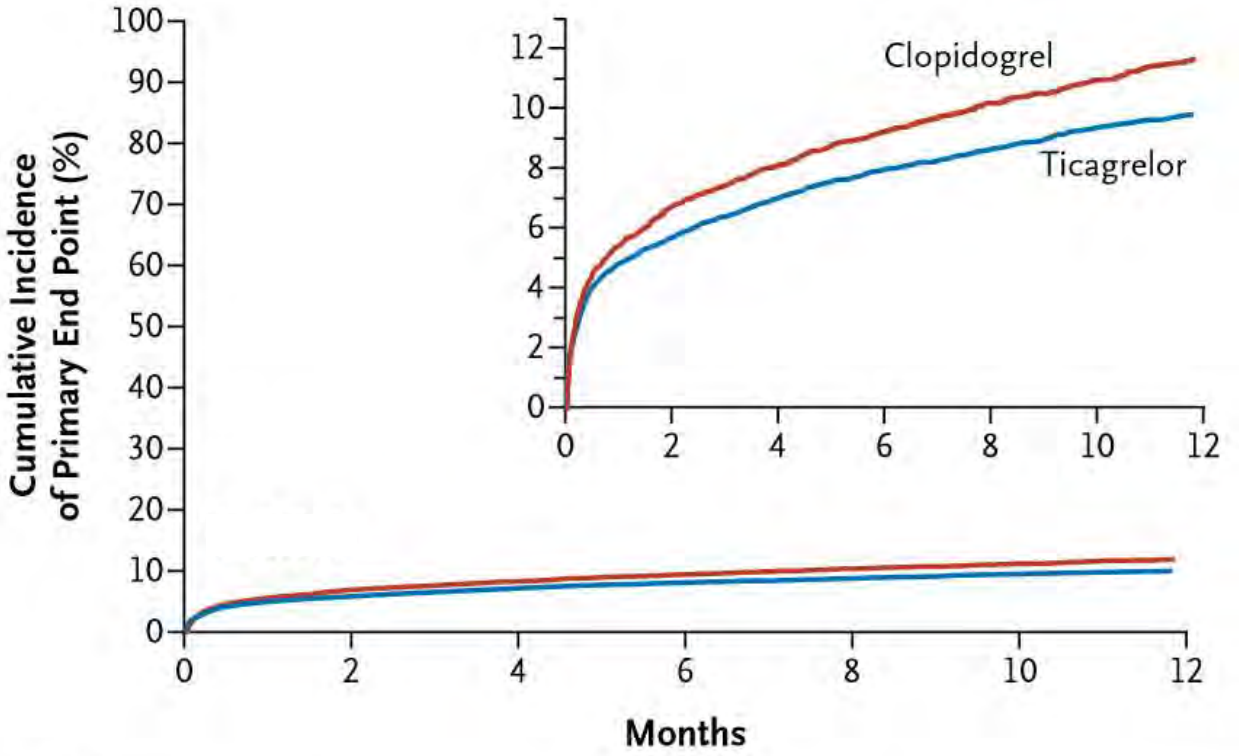


*P 0.0001, †P 0.001, ‡P 0.05.

Fig 7. Inhibition of platelet aggregation in response to ADP (20 µM, maximum extent) in clopidogrel nonresponsive patients with stable coronary artery disease.

Ticagrelor vs. Clopidogrel bei ACS (PLATO)

Wallentin L. et al., N Engl J Med (2009);361:1045-57



No. at Risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

11.7% vs. 9.8%

HR 0.84, 95%CI 0.77-0.92

p<0.001

Ticagrelor vs. Clopidogrel bei ACS (PLATO)

Wallentin L. et al., N Engl J Med (2009);361:1045-57

	Clopidogrel (%)	Ticagrelor (%)	HR (95% CI), p value
CV Death/nonfatal MI/nonfatal Stroke	11.7	9.8	0.84 (0.77 -0.92), p=0.001
Myocardial infraction	6.9	5.8	0.84 (0.75–0.9[illegible], p=0.005
All cause death	5.9	4.5	0.78 (0.69–0.8[illegible], p<0.001
Va			
St			
Is			
M			
M			
Li			
Any dyspnea	7.8	13.8 !	1.84 (1.68–2.02), p<0.001

BRILIQUE Filmtabl 60 mg Ticagrelor	Blister 56 Stk AstraZeneca AG	92.35
BRILIQUE Filmtabl 90 mg Ticagrelor	Blister 56 Stk AstraZeneca AG	104.30
BRILIQUE Schmelztabl 90 mg (iH 03/18) Ticagrelor	Blister 10 Stk AstraZeneca AG	

$P2Y_{12}$ Inhibitoren

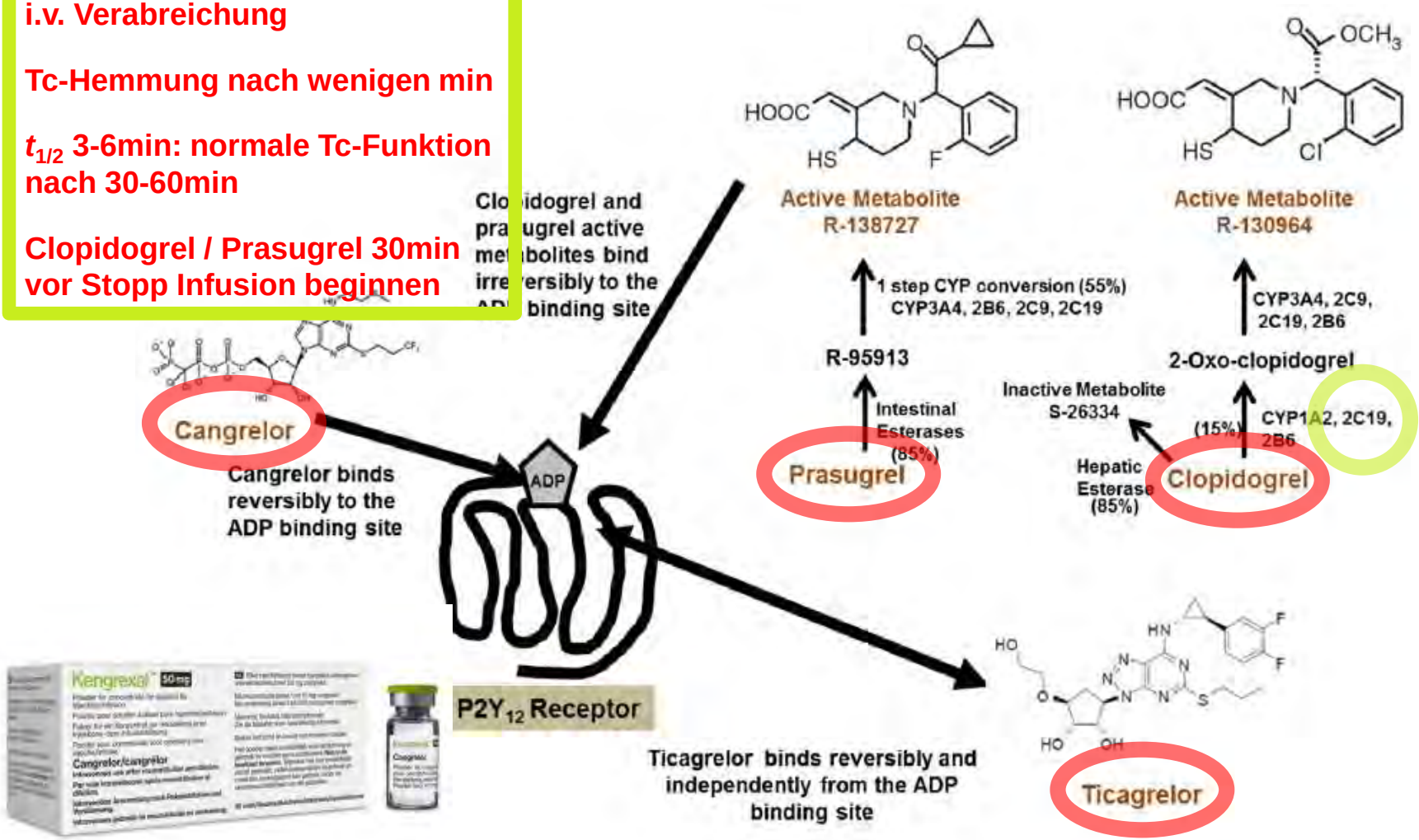
Tantry, U.S. et al., Progress in Cardiovascular Disease 60 (2018) 60, 460–470

i.v. Verabreichung

Tc-Hemmung nach wenigen min

$t_{1/2}$ 3-6min: normale Tc-Funktion nach 30-60min

Clopidogrel / Prasugrel 30min vor Stopp Infusion beginnen



2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with EACTS

Eur Heart J. 2018 Jan 14;39(3):213-260.

The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

ESC Chairperson: Marco Valgimigli (Bern, Switzerland).

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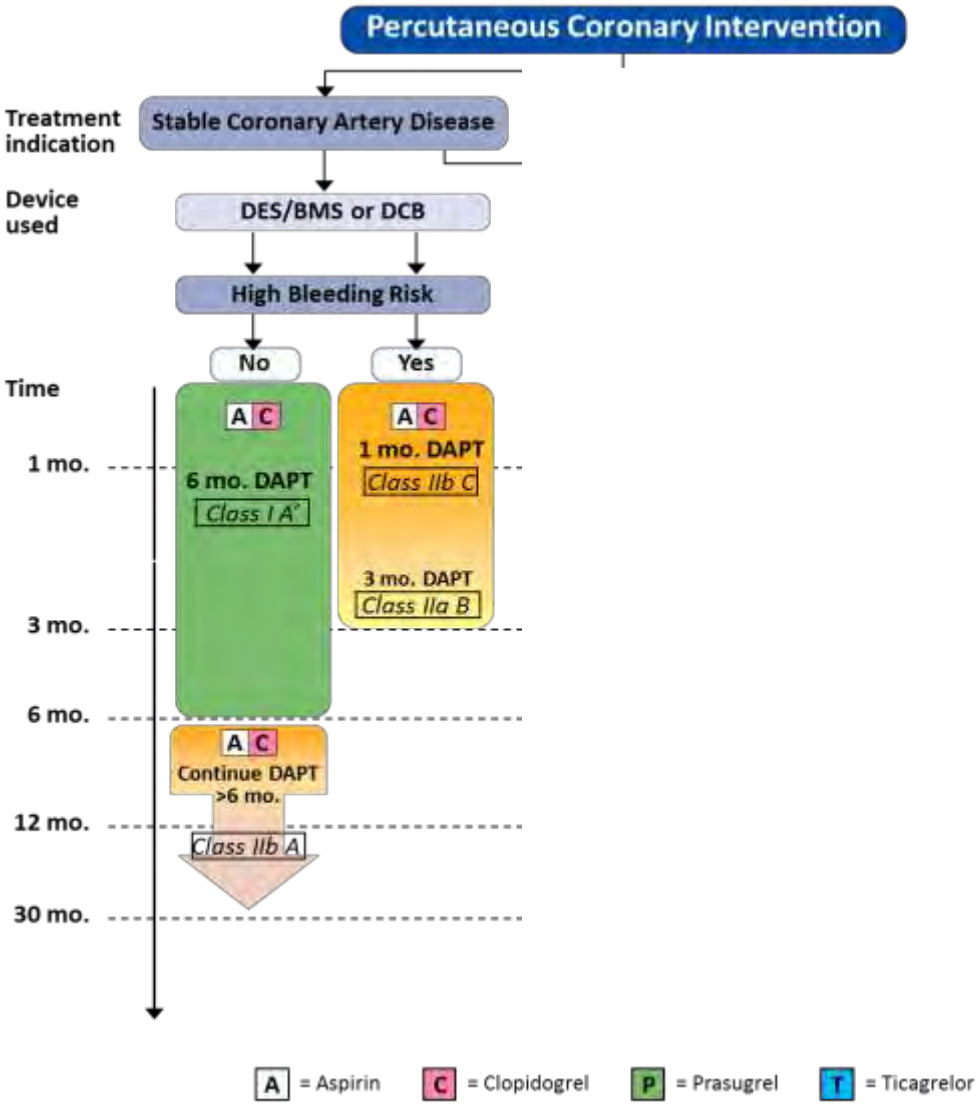
19.06.2018, S. Blöchlinger

KANTONSSPITAL WINTERTHUR

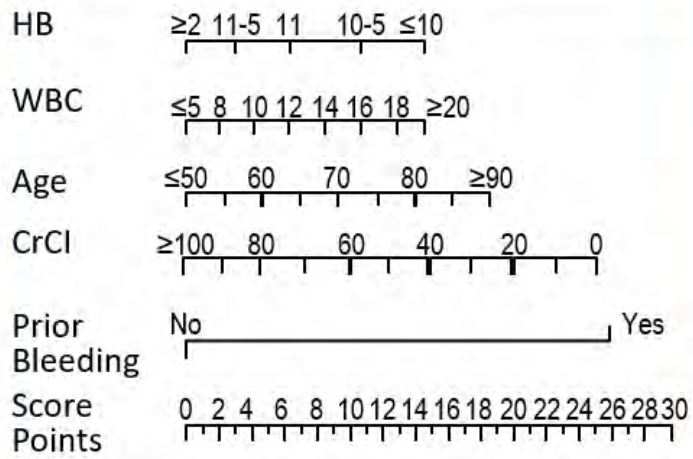
DAPT Algorithmus nach PCI

Eur Heart J. 2018 Jan 14;39(3):213-260.



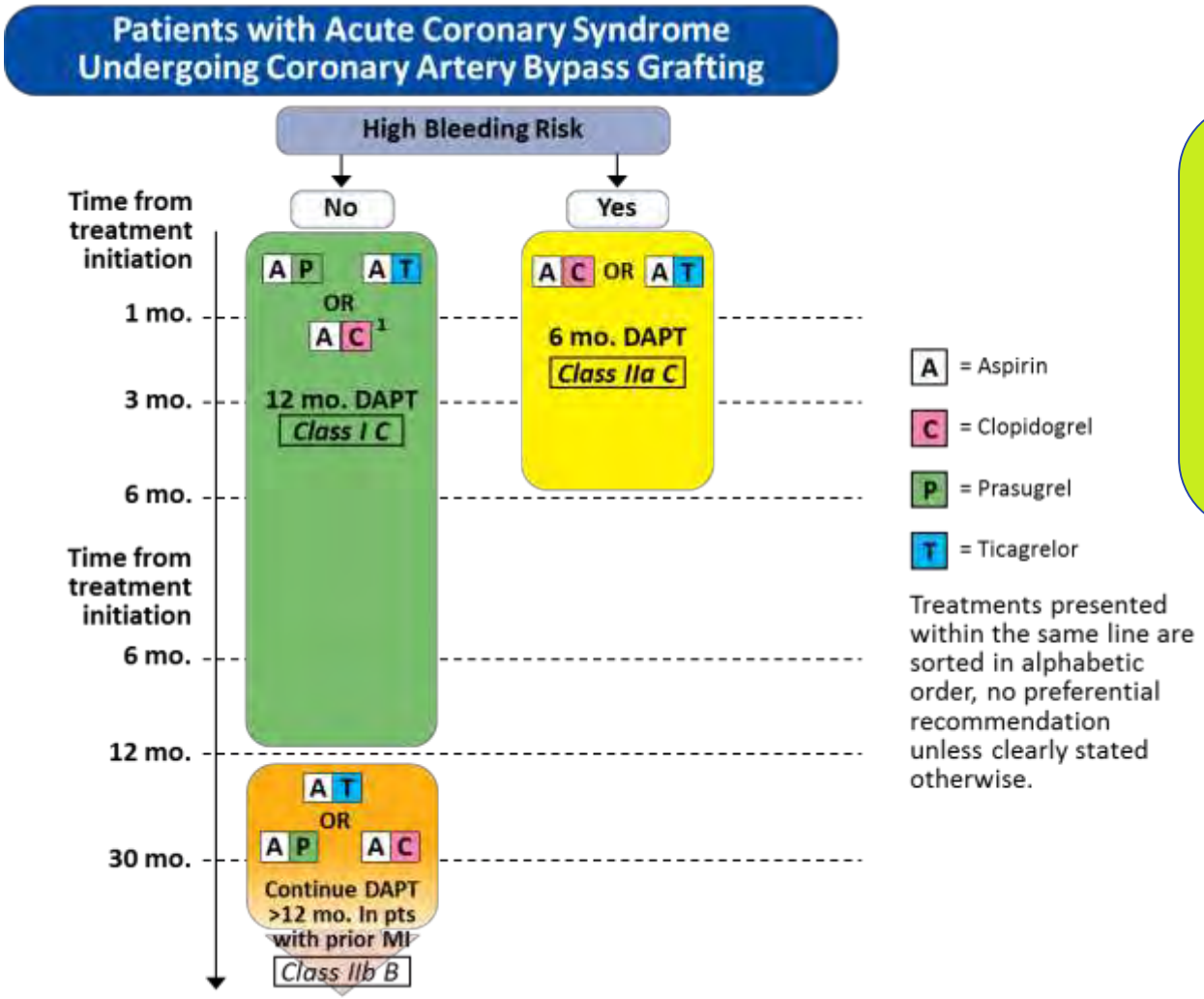
DAPT - Risikoevaluation

Eur Heart J. 2018 Jan 14;39(3):213-260.

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

DAPT – Aortokoronare Bypasschirurgie

Eur Heart J. 2018 Jan 14;39(3):213-260.



Keine Indikation für DAPT in Patienten mit stabiler KHK ausser eine Begleitindikation ist gegeben (z.B. PCI)

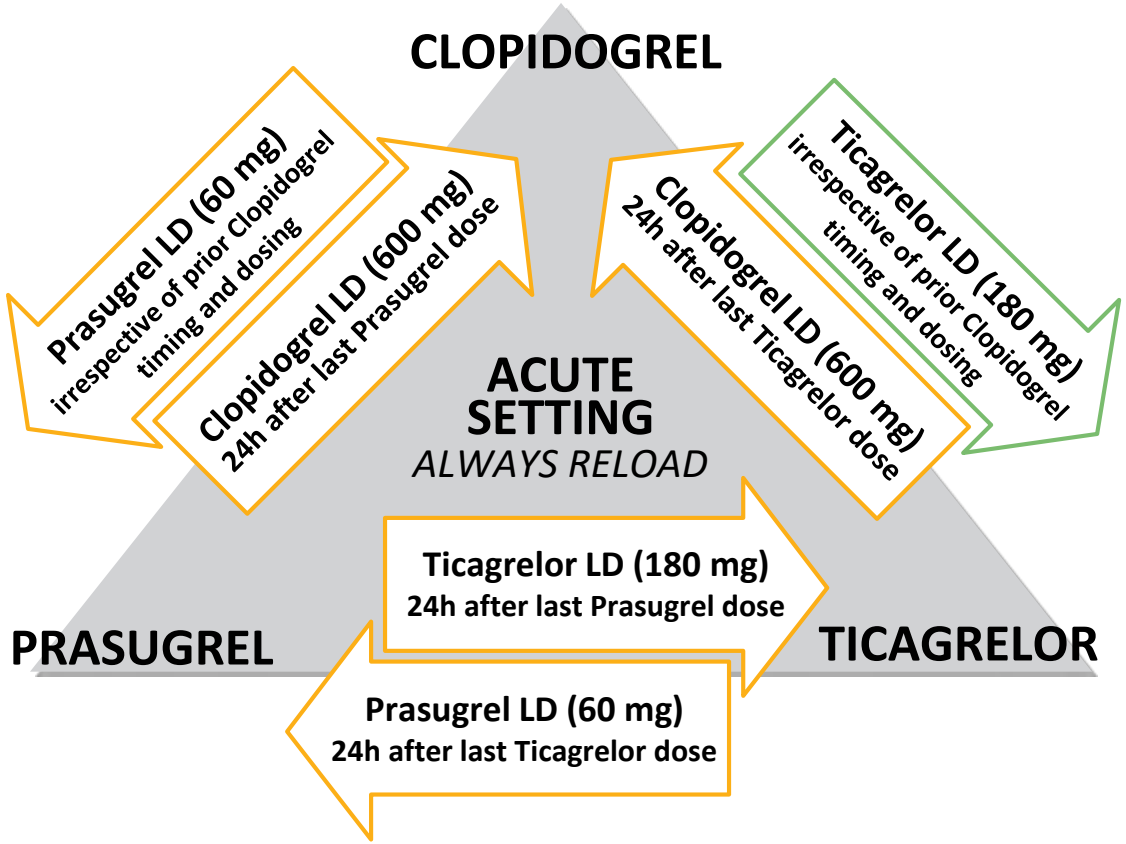
DAPT – Wechsel zwischen oralen $P2Y_{12}$-Inhibitoren

Eur Heart J. 2018 Jan 14;39(3):213-260.

Recommendations	Class	Level
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.	I	B
Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

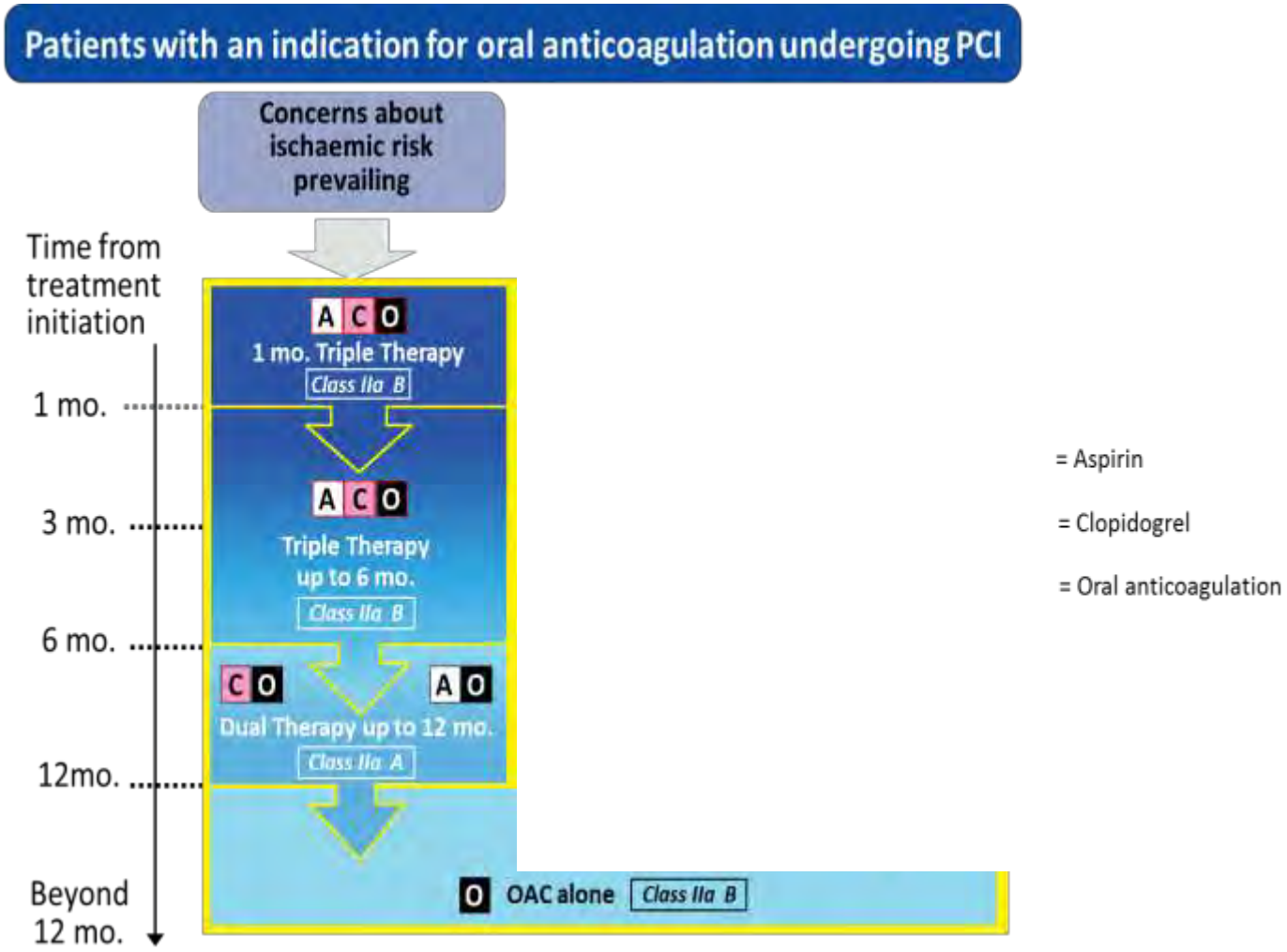
DAPT – Wechsel zwischen oralen $P2Y_{12}$-Inhibitoren

Eur Heart J. 2018 Jan 14;39(3):213-260.



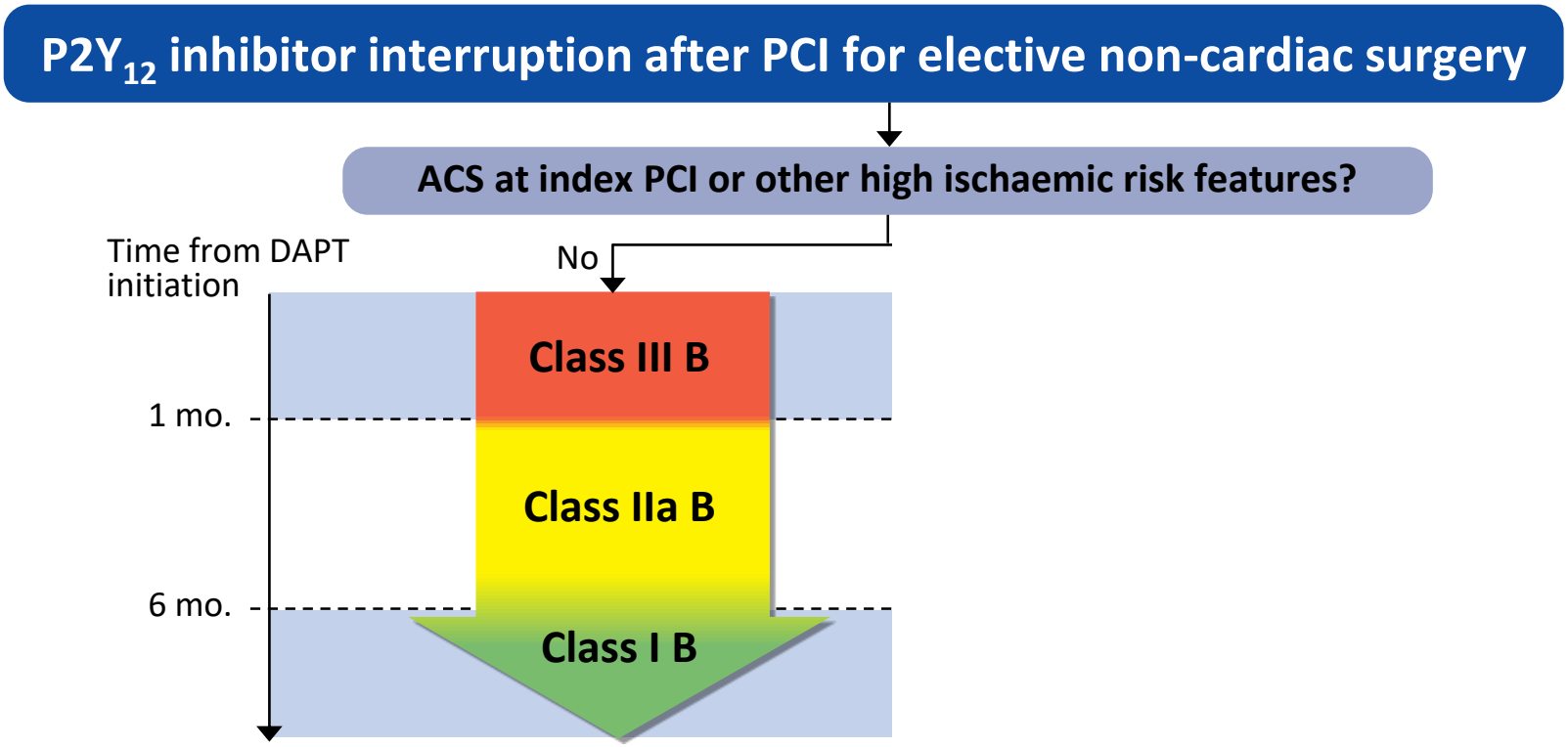
DAPT – Patienten mit oraler Antikoagulation

Eur Heart J. 2018 Jan 14;39(3):213-260.



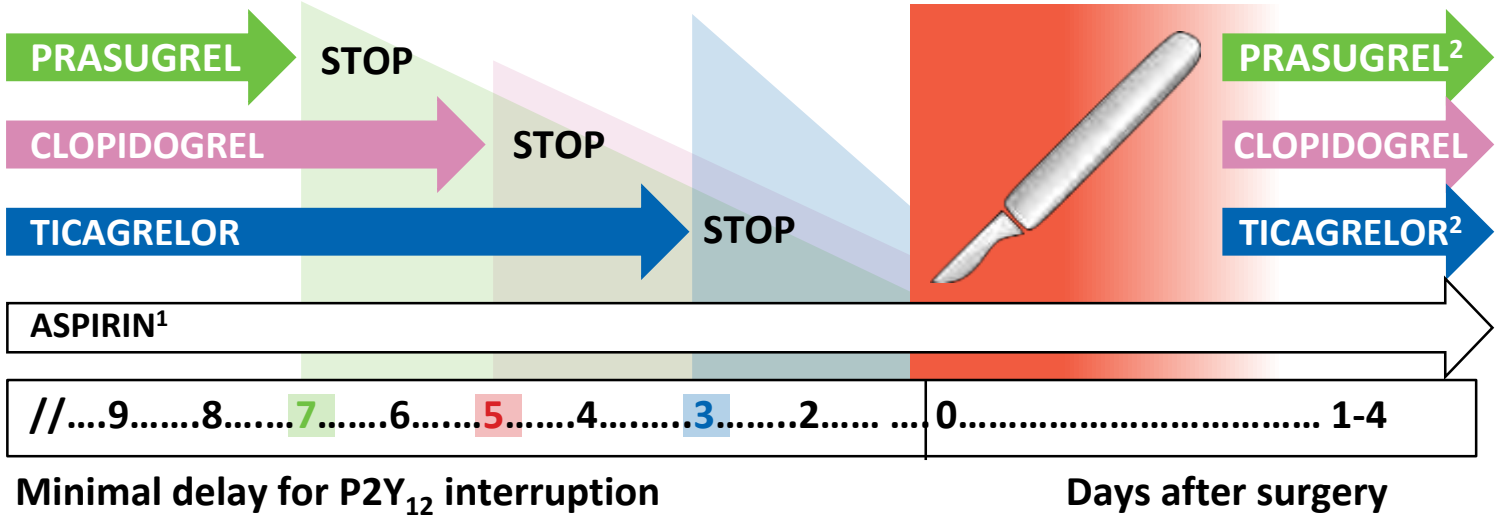
$P2Y_{12}$-Unterbrechung: elektive Operationen

Eur Heart J. 2018 Jan 14;39(3):213-260.



Zeitpunkt / Dauer $P2Y_{12}$-Unterbrechung: elektive Operationen

Eur Heart J. 2018 Jan 14;39(3):213-260.



= Expected average platelet function recovery

[1] Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

[2] In patients not requiring OAC.

$P2Y_{12}$-Unterbrechung: elektive Operationen

Eur Heart J. 2018 Jan 14;39(3):213-260.

Recommendations	Class	Level
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.	IIb	C

Cangrelor

Blutungen unter DAPT +/- OAK

Eur Heart J. 2018 Jan 14;39(3):213-260.

TRIVIAL BLEEDING

Any bleeding not requiring medical intervention or further evaluation

e.g. skin bruising or ecchimosis, self-resolving epistaxis, minimal conjunctival bleeding

- Continue DAPT.
- Consider OAC continuation or skip one single next pill.
- Reassure the patient.
- Identify and discuss with the patient possible preventive strategies.
- Counsel patient on the importance of drug-adherence.

Legend

DAPT management

OAC management

General recommendations

Blutungen unter DAPT +/- OAK

Eur Heart J. 2018 Jan 14;39(3):213-260.

MILD BLEEDING

Any bleeding that requires medical attention without requiring hospitalization

e.g. not self resolving epistaxis, moderate conjunctival bleeding, genitourinary or upper/lower gastrointestinal bleeding without significant blood loss, mild haemoptysis

- Continue DAPT.
- Consider shortening DAPT duration or switching to less potent $P2Y_{12}$ inhibitor (i.e.from ticagrelor/ prasugrel to clopidogrel), especially if recurrent bleeding occurs.
- In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC.
- Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm).
- Add PPI if not previously implemented.
- Counsel patient on the importance of drug-adherence.

Legend

DAPT management

OAC management

General recommendations

Blutungen unter DAPT +/- OAK

Eur Heart J. 2018 Jan 14;39(3):213-260.

LIFE-THREATENING BLEEDING

Any severe active bleeding putting patient's life immediately at risk

e.g. massive overt genitourinary, respiratory or upper/lower gastrointestinal bleeding, active intracranial, spinal or intraocular haemorrhage, or any bleeding causing haemodynamic instability.

Legend

DAPT management

OAC management

General recommendations

- Immediately discontinue all antithrombotic medications.
- Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the $P2Y_{12}$ inhibitor especially in case of upper GI bleeding.

- Stop and reverse OAC.

- Fluid replacement if hypotension.
- Consider RBC transfusion irrespective of HB values.
- Platelet transfusion.
- Consider i.v. PPI if GI bleeding occurred.
- Urgent surgical or endoscopic treatment of bleeding source if deemed possible.

Vielen Dank für Ihre Aufmerksamkeit

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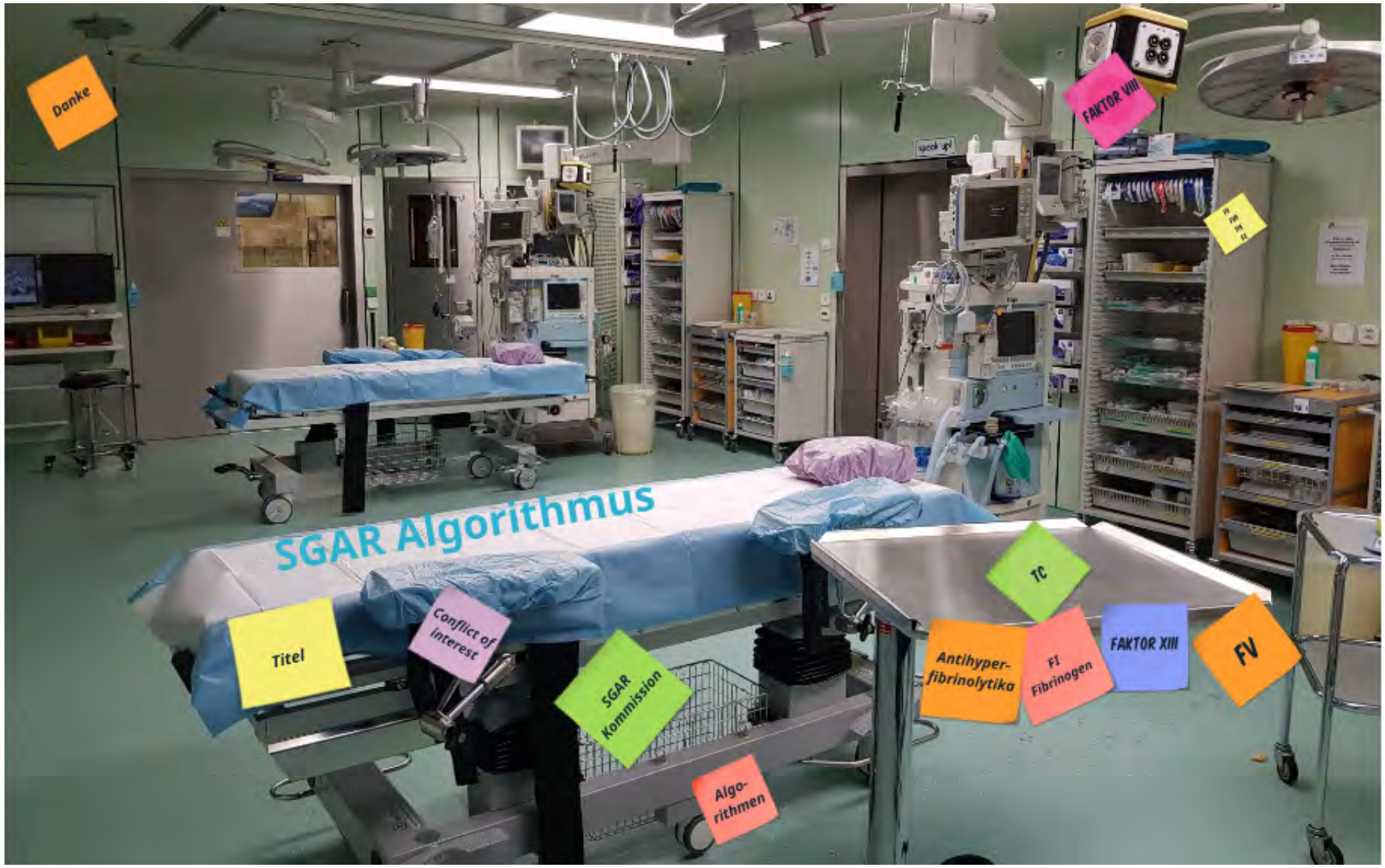
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FAKTOR VIII
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV

+41 44 255 41 91

Empfehlung bei massiver Blutung

der Kommission für perioperatives Blutprodukte- und Blutgerinnungsmanagement der SGAR

martin.brueesch@usz.ch


UND HIER SEHEN SIE NOCHMAL DAS SCHEMA DER BLUTGERINNUNG. DAS KENNEN SIE JA SCHON AUS DER VORKLINIK UND AUS DER KLINISCHEN CHEMIE. ERKLÄRT SICH VON ALLEINE, WÜRD ICH SAGEN.
WTF!
MENSA!
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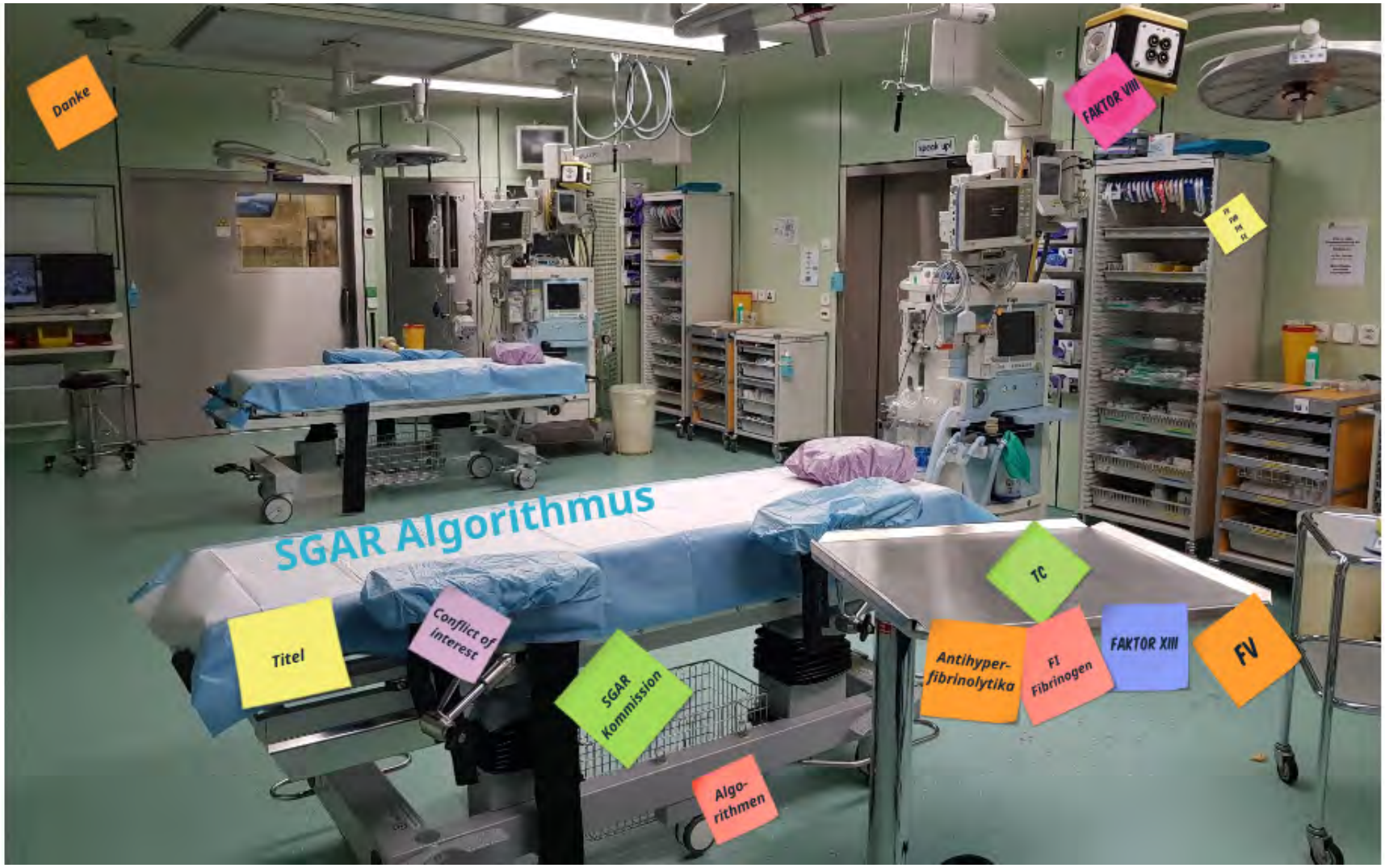
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SGAR Algorithmus
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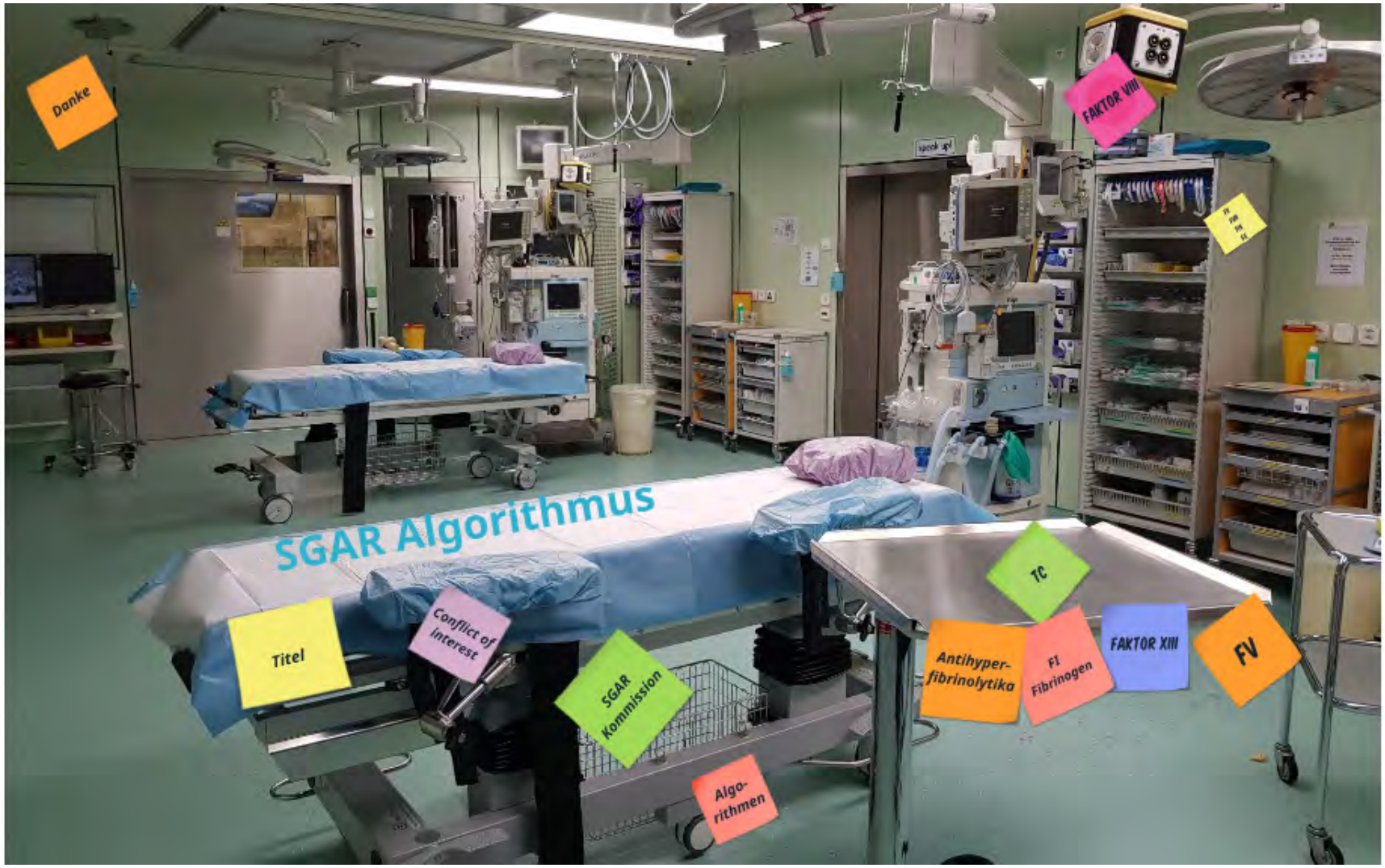
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV

CONFLICT OF INTEREST


Danke
FAKTOR VIII
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV

SGAR Kommission

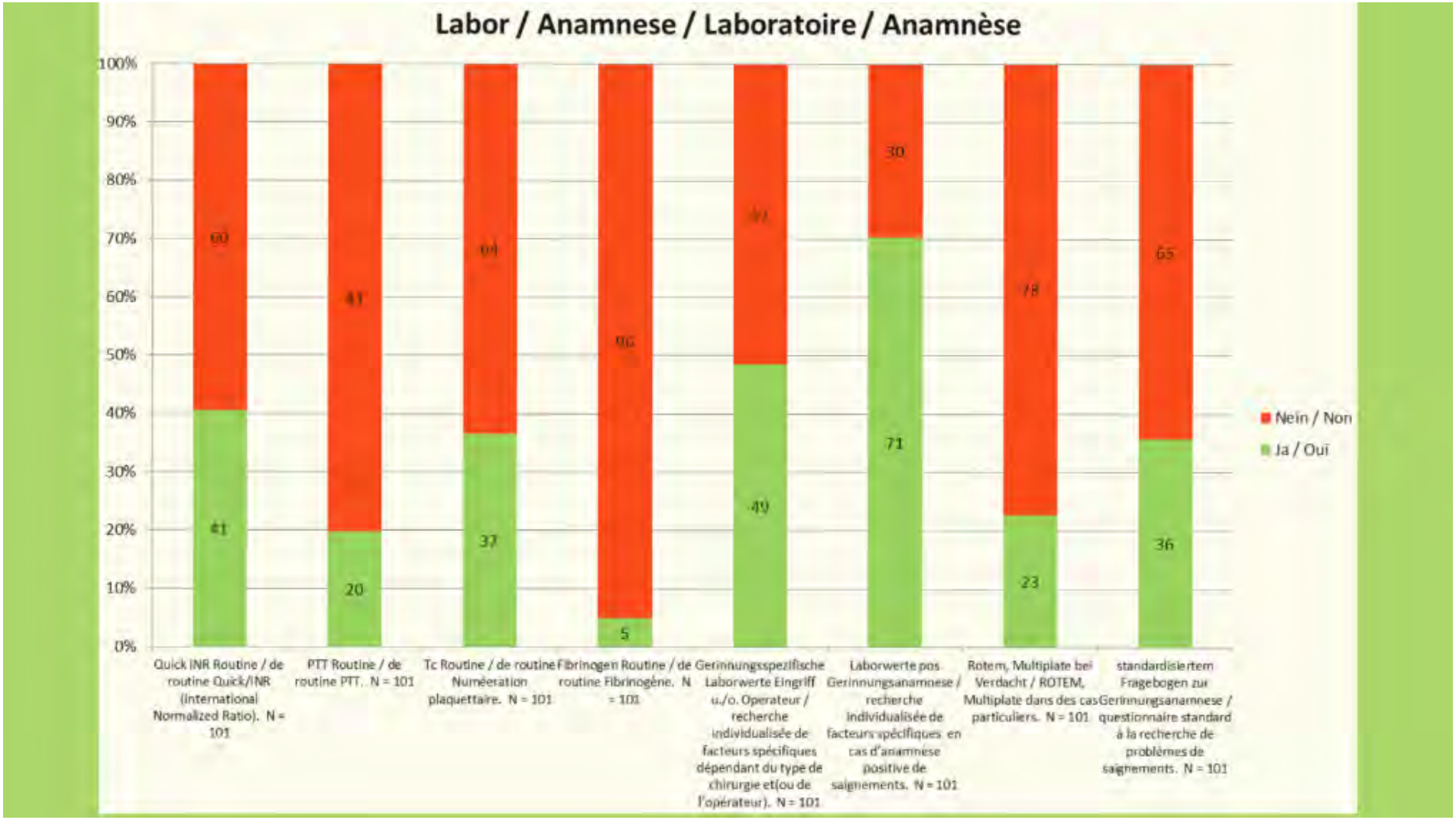
perioperatives Gerinnungs- und Blutproduktemanagement

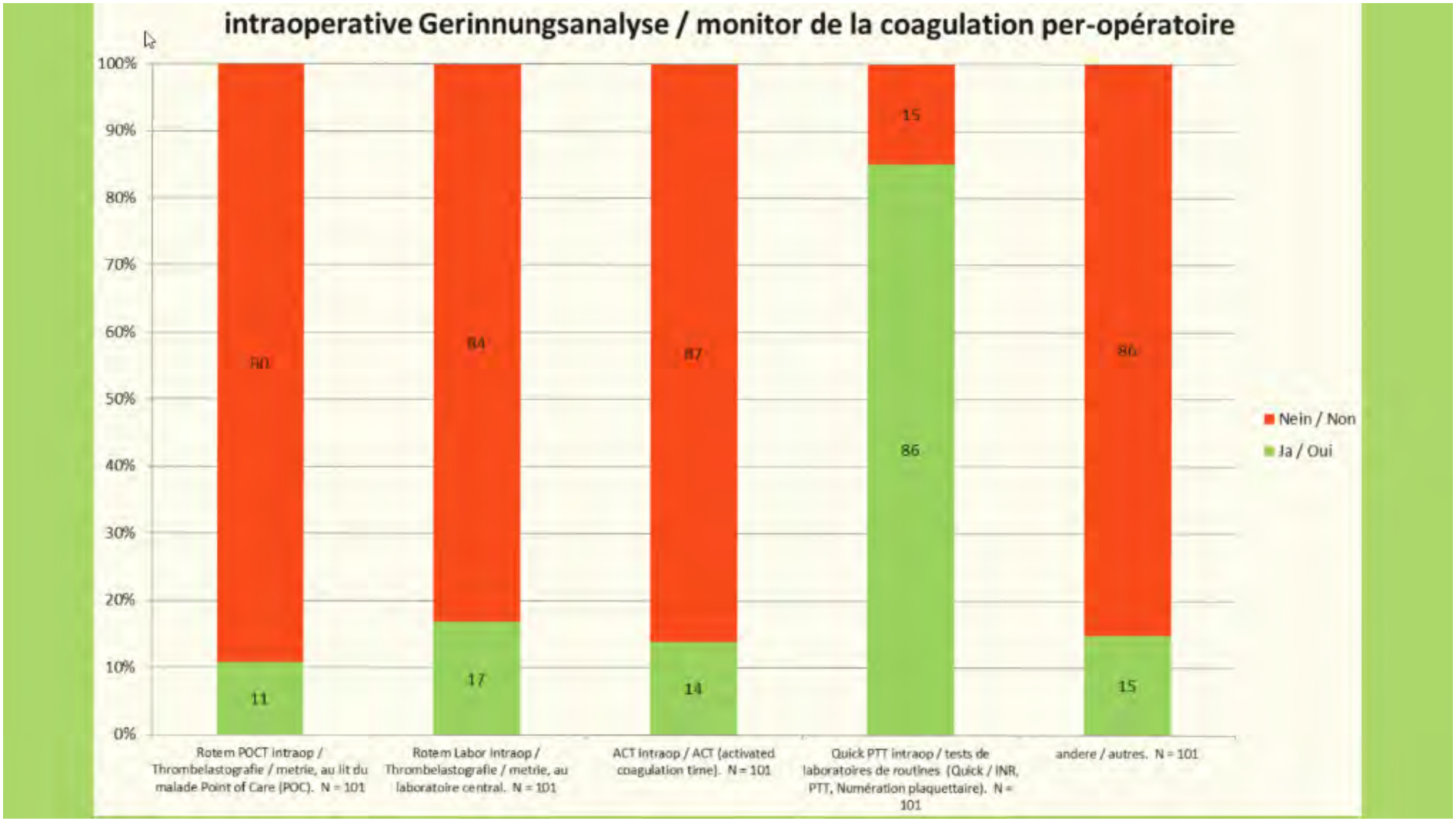
Auftrag:

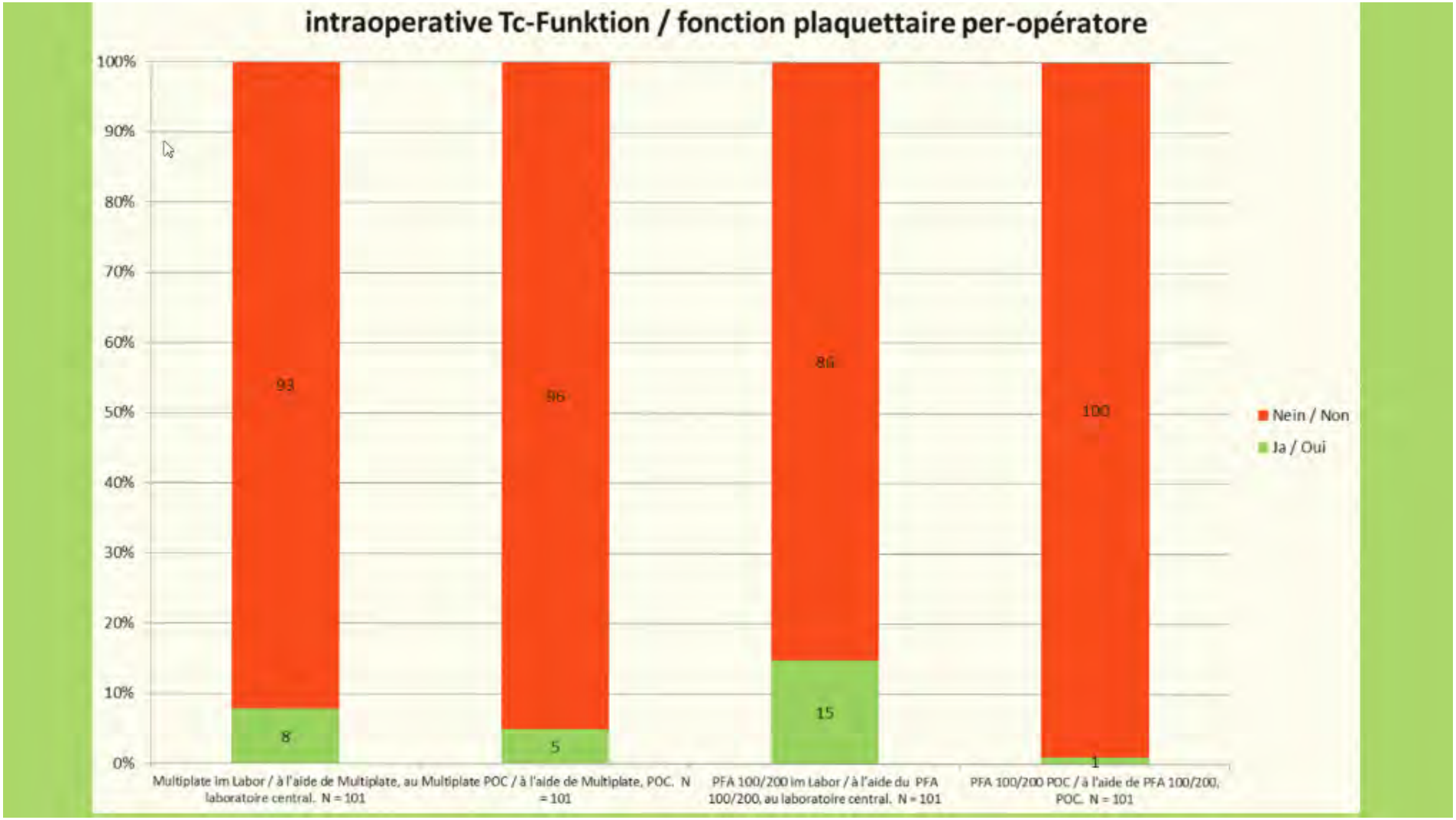
- Analyse der gegenwärtigen Praxis in der Schweiz
- Entwicklung von Standards und Empfehlungen
- Unterstützung der Mitglieder bei der Implementation der Standards und neuen Methoden
- Aufbau eines Lernzielkatalogs für die Weiterbildung gemäss dem neuen SGAR Weiterbildungsprogramm, Integration der Inhalte ins Weiterbildungsprogramm.

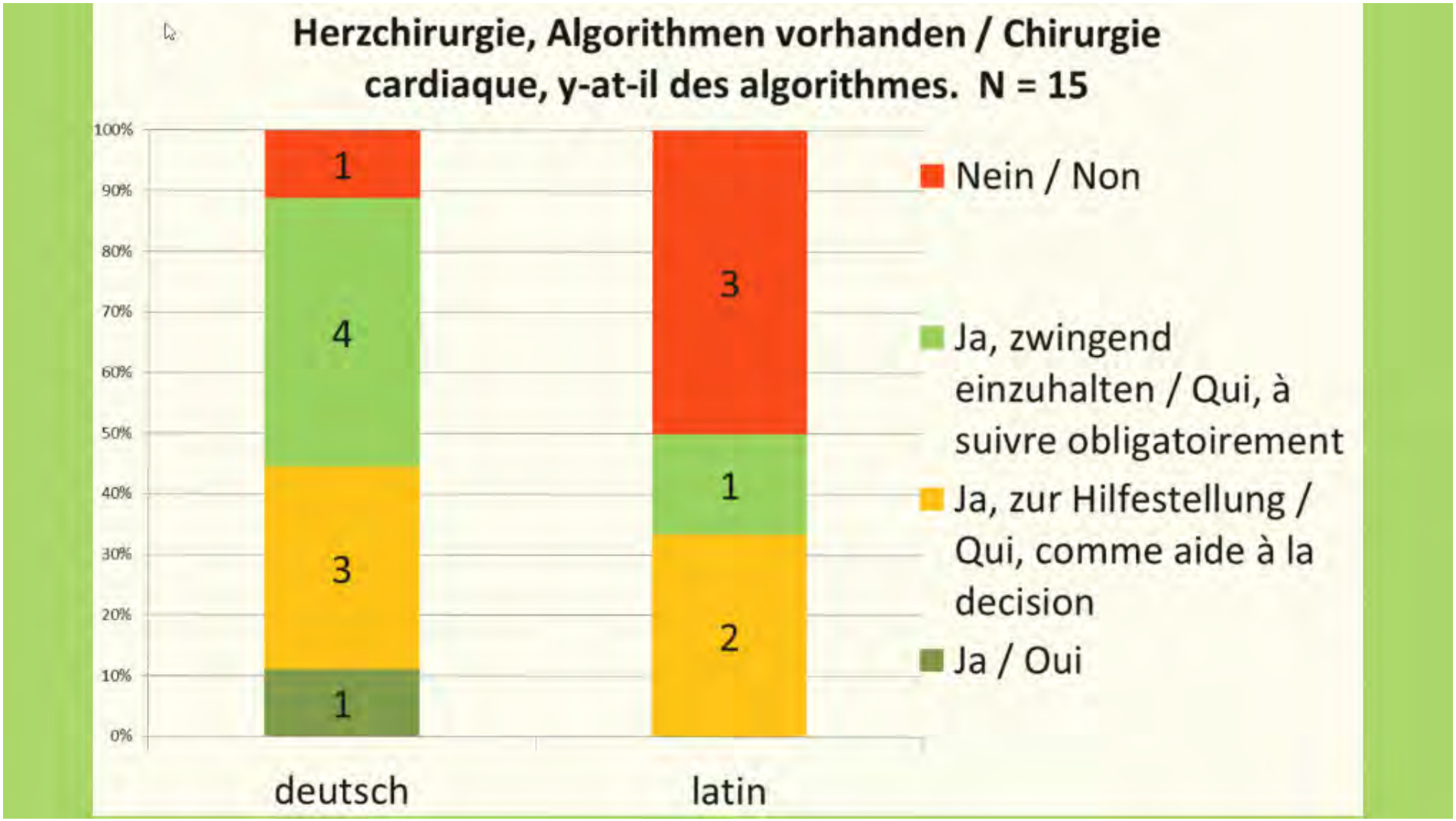
Mitglieder

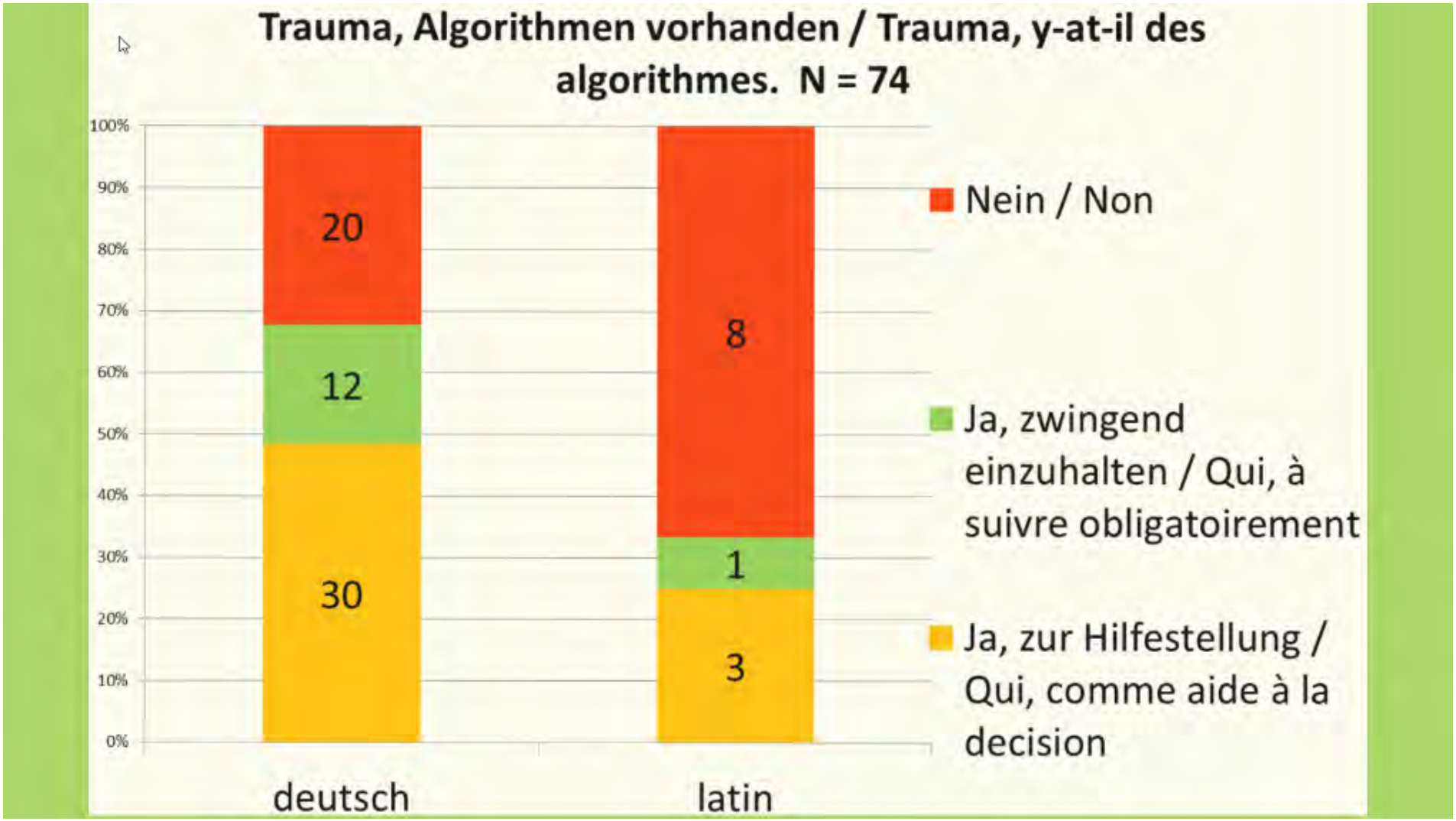
Lars Asmis
Daniel Bolliger
Martin Brüesch
Patricia Manndorff
Carlo Marcucci

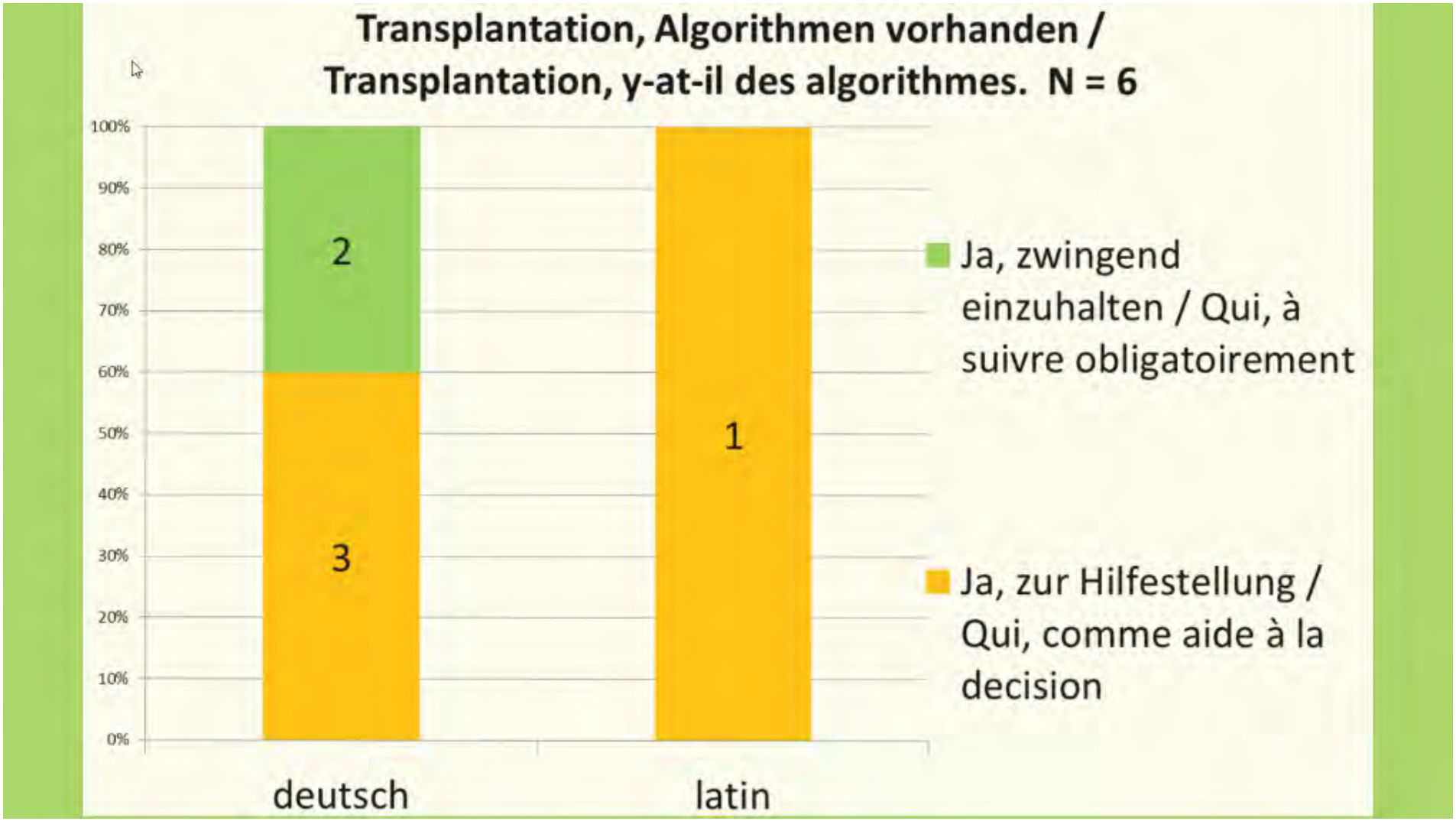

Labor / Anamnese / Laboratoire / Anamnèse
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
60
41
41
20
64
37
96
5
51
49
30
71
78
23
65
36
Nein / Non
Ja / Oui
Quick INR Routine / de routine Quick/INR (International Normalized Ratio). N = 101
PTT Routine / de routine PTT. N = 101
Tc Routine / de routine Numération plaquettaire. N = 101
Fibrinogen Routine / de routine Fibrinogène. N = 101
Gerinnungsspezifische Laborwerte Eingriff u./o. Operateur / recherche individualisée de facteurs spécifiques dépendant du type de chirurgie et(ou de l'opérateur). N = 101
Laborwerte pos Gerinnungsanamnese / recherche individualisée de facteurs spécifiques en cas d'anamnèse positive de saignements. N = 101
Rotem, Multiplate bei Verdacht / ROTEM, Multiplate dans des cas particuliers. N = 101
standardisiertem Fragebogen zur Gerinnungsanamnese / questionnaire standard à la recherche de problèmes de saignements. N = 101

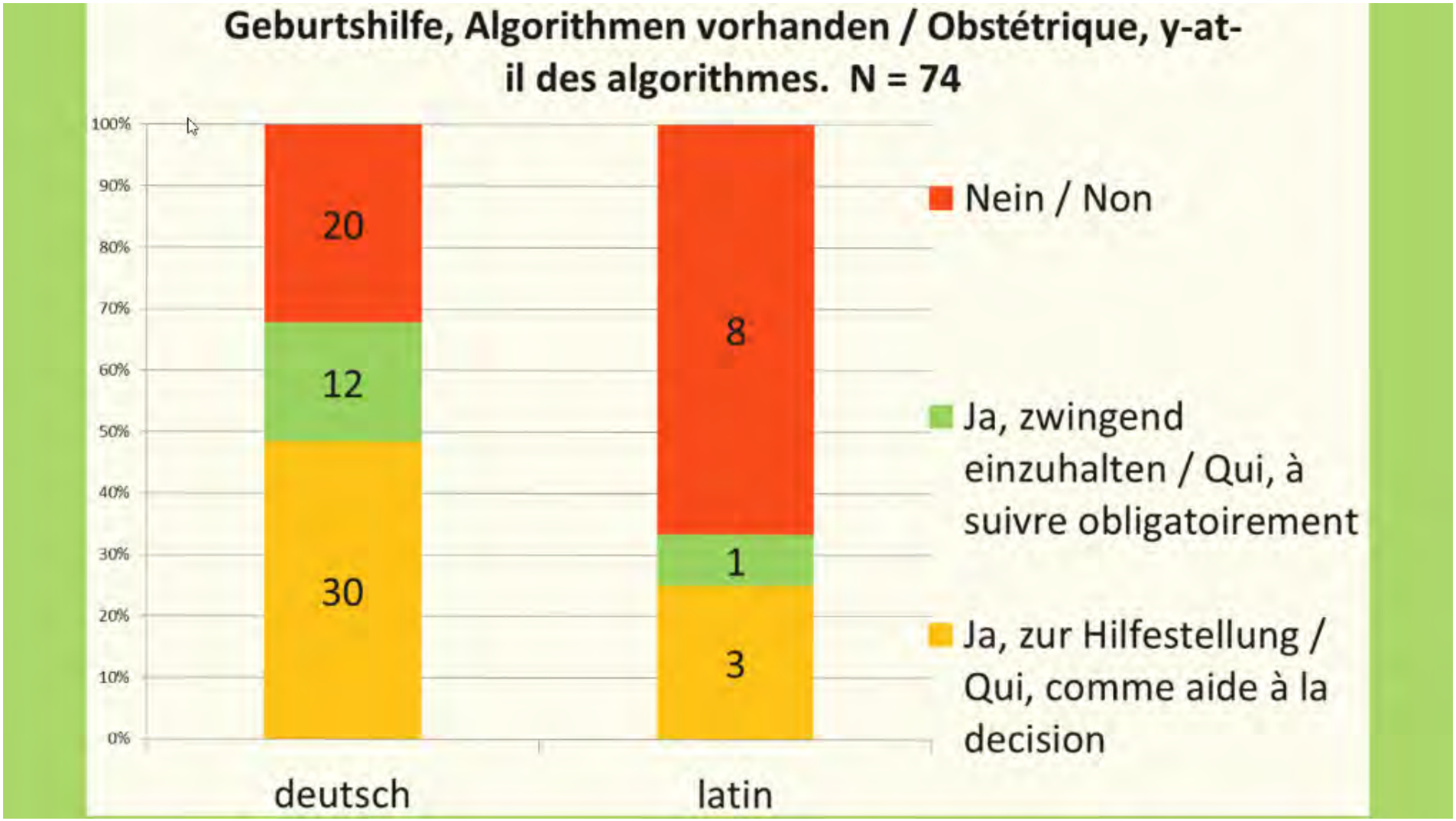

intraoperative Gerinnungsanalyse / monitor de la coagulation per-opératoire
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
90
84
87
15
86
11
17
14
86
15
Nein / Non
Ja / Oui
Rotem POCT intraop / Thrombelastografie / metrie, au lit du malade Point of Care (POC). N = 101
Rotem Labor intraop / Thrombelastografie / metrie, au laboratoire central. N = 101
ACT intraop / ACT (activated coagulation time). N = 101
Quick PTT intraop / tests de laboratoires de routines (Quick / INR, PTT, Numération plaquettaire). N = 101
andere / autres. N = 101

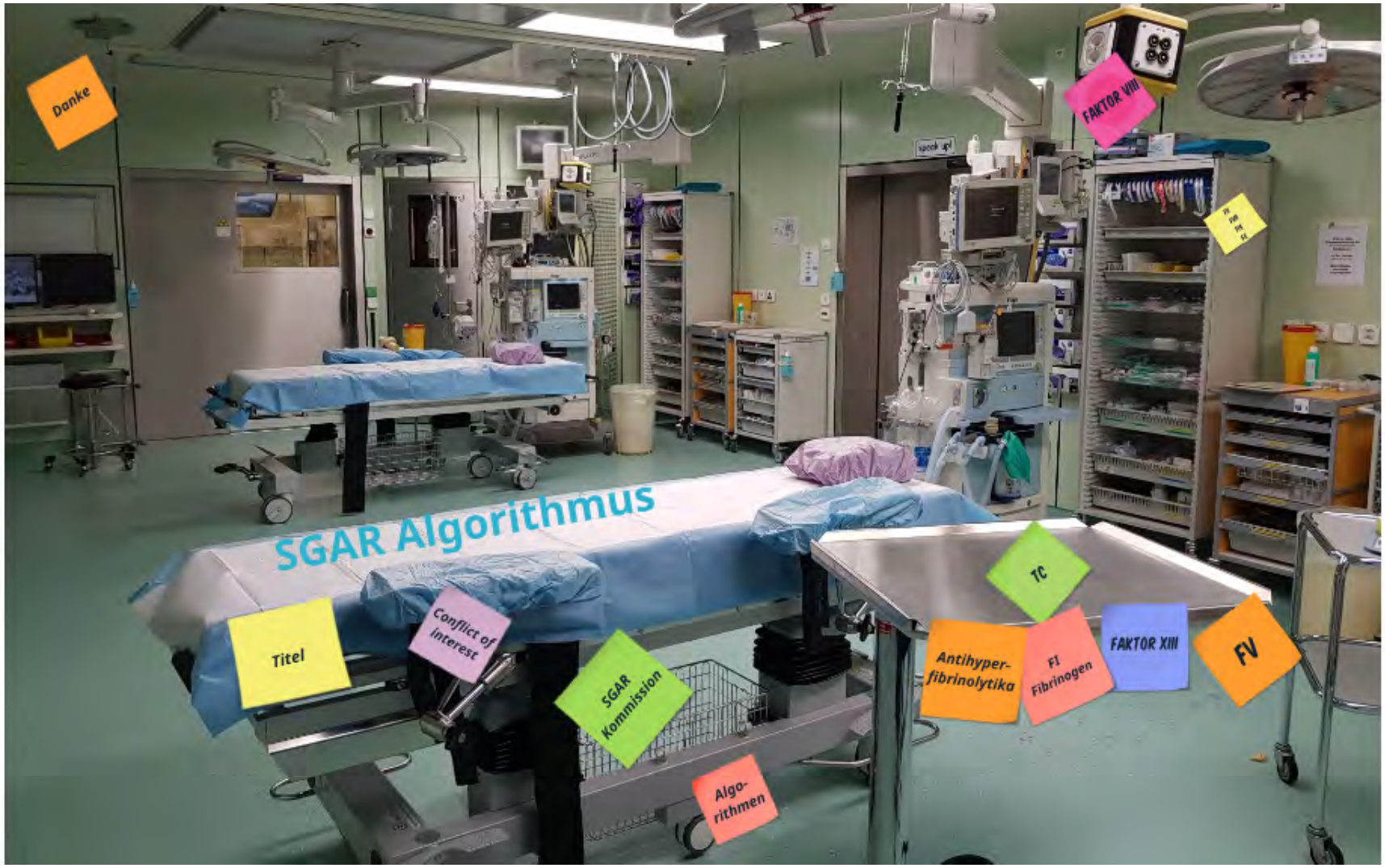

intraoperative Tc-Funktion / fonction plaquettaire per-opératore
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
93
8
96
5
86
15
100
1
Nein / Non
Ja / Oui
Multiplate im Labor / à l'aide de Multiplate, au laboratoire central. N = 101
Multiplate POC / à l'aide de Multiplate, POC. N = 101
PFA 100/200 im Labor / à l'aide du PFA 100/200, au laboratoire central. N = 101
PFA 100/200 POC / à l'aide de PFA 100/200, POC. N = 101


Herzchirurgie, Algorithmen vorhanden / Chirurgie cardiaque, y-at-il des algorithmes. N = 15
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
4
3
1
3
1
2
deutsch
latin
Nein / Non
Ja, zwingend einzuhalten / Qui, à suivre obligatoirement
Ja, zur Hilfestellung / Qui, comme aide à la decision
Ja / Oui


Trauma, Algorithmen vorhanden / Trauma, y-at-il des algorithmes. N = 74
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
20
12
30
8
1
3
deutsch
latin
Nein / Non
Ja, zwingend einzuhalten / Qui, à suivre obligatoirement
Ja, zur Hilfestellung / Qui, comme aide à la decision


Transplantation, Algorithmen vorhanden /
Transplantation, y-at-il des algorithmes. N = 6
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2
3
1
deutsch
latin
Ja, zwingend einzuhalten / Qui, à suivre obligatoirement
Ja, zur Hilfestellung / Qui, comme aide à la decision


Geburtshilfe, Algorithmen vorhanden / Obstétrique, y-at-il des algorithmes. N = 74
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
20
12
30
8
1
3
deutsch
latin
Nein / Non
Ja, zwingend einzuhalten / Qui, à suivre obligatoirement
Ja, zur Hilfestellung / Qui, comme aide à la decision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FV

gynécologie suisse

POSTPARTALE BLUTUNG | Handlungsalgorithmus

nach vaginaler Geburt oder in der postoperativen Überwachungsphase nach Sectio caesarea

© 2012: PPH-KONSENSUS – Gruppe (D-A-CH)

	Klinische Symptome	allgemeine/operative Massnahmen		Medikamente
	Dauer max. 30 min nach Diagnosestellung	HINZUZIEHEN: Oberarzt (Facharzt Geburtshilfe) INFORMATION Anästhesie		
STEP 1	• vaginale Blutung >500 ml nach vaginaler Geburt 1000 ml nach Sectio caesarea CAVE: Unterschätzung (Messsystem!) • Patientin kreislaufstabil	• 2 iv-Zugänge (mindestens 1 großlumiger) • Kreuzprobe / Notfallrator / DFS bereitstellen • Volumengabe (z.B. Kristalloide / Kolloide) • Blase katheterisieren • Blutverlust messen • rasche Abklärung der Blutungsursache (4T's): – Uterustonus (Bonus-Atonie?) – Plazentainspektion (Exsue-Plazentarest?) – Speculumeinstellung (Trauma-Geburtskanal?) – Gerinnung (Thrombin-Laborwerte?) • Uteruskompression - Ultraschall	P A R A L L E L	• OXYTOCIN 3-5 IE (1 Amp.) als Kurzinfusion und 40 IE in 30 min (Infusion/Perfusor) ODER • CARBETOCIN (off label use) 100 µg (1 Amp.) in 100 ml NaCl 0,9% als Kurzinfusion bei starker persistierender Blutung STEP 2 bei minimal persistierender Blutung evtl.: • MISOPROSTOL (off label use) 800 µg (4 Tbl. à 200 µg) rektal
	Dauer max. weitere 30 min (= 60 min nach Diagnosestellung)	HINZUZIEHEN: Anästhesie / Hebamme(n) OP-Team / ORGANISATION OP-Saal / TRANSFUSIONSMEDIZIN überbrücken		
STEP 2	• anhaltend schwere Blutung • Patientin kreislaufstabil	• OP-Vorbereitung • Ausschluss Uterusruptur: • Nachtastung / Ultraschall • bei V. a. Plazentarest (nach US oder Inspektion): • manuelle Nachlösung • ggf. Curettage (US-Kontrolle)		Bestellung FFP / EK / TK (Venflon und in den Kreissaal/OP bringen lassen) • SULTROPIN 500 µg (1 Amp.; max. 3 Amp. pro 24 h) nur über Infusomat/Perfusor • 2 g TRANEXAMSÄURE i.v. vor Fibrinogengabe Bei persistierender schwerer Blutung (ca. 1500 ml Gesamtblutverlust): • FIBRINOGEN 2–4 g • FFP / TK erwägen
	TRANSFUSIONSMEDIZIN übernehmen / HINZUZIEHEN: Oberarzt Anästhesie INFORMATION der bestmöglichen personellen Expertise			
STEP 3	• therapierefraktäre schwere Blutung und kreislaufstabile Patientin oder • hämorrhagischer Schock ZIEL: • hämodynamische Stabilisierung (temporäre) Blutungsstop • Optimierung von Gerinnung und • Erythrozytenkonzentration • Organisation von STEP 4	CAVUMTAMPONADE BALLONTAMPONADE • Ballonanlegung unter Ultraschallkontrolle • ausreichendes Auffüllen des Ballons (Sulprostonzusatz) • leichten Zug applizieren • alternativ Streifentamponade BLUTUNGSSTOP • Intervallbeobachtung • BALLON ENTFERNEN nach 12–24 Std. ggf. nach Transfer in Zentrum PERSISTIERENDE oder ERNEUTE BLUTUNG (Blutung bei liegendem Ballon oder nach Entblockade) • ggf. erneute Ballonapplikation („bridging") • obligat STEP 4		ZIELWERTE/ZIEL • Hämoglobin > 8–10 g/dl (5–6,2 mmol/l) • Thrombozyten > 50 Gpt/l • RR systolisch > 90 mmHg • pH > 7,2 • Temperatur > 35° C • Calcium > 0,8 mmol/l
	HINZUZIEHEN der bestmöglichen personellen Expertise			
STEP 4	• persistierende Blutung	Definitive Versorgung / chirurgische Therapie KREISLAUFINSTABILITÄT BLUTSTILLUNG ↓ Laparotomie / Gefäßklemmen / Kompression STABILISIERUNG Kreislauf / Temperatur / Gerinnung eventuell rekomb. Faktor VIIa		KREISLAUFSTABILITÄT DEFINITIVE CHIRURGISCHE THERAPIE Kompressionsnähte Gefäßligaturen Hysterektomie EMBOLISATION

Transfusionsregime

rekombinanter Faktor VIIa (off label use !)

Voraussetzungen

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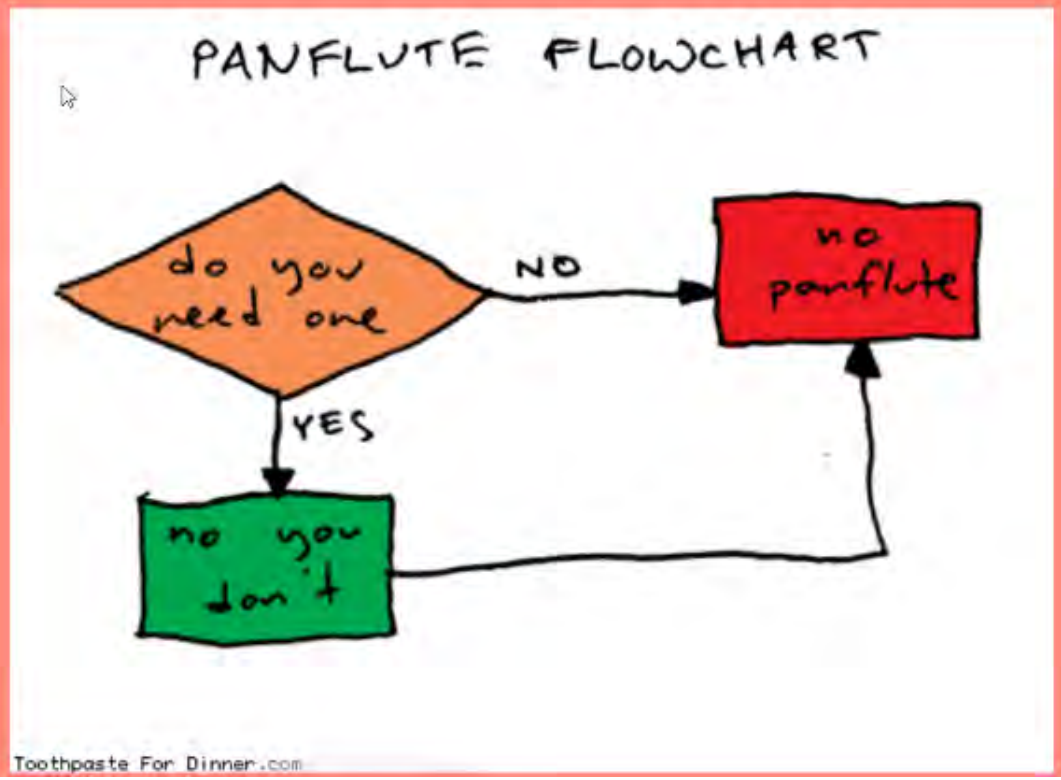
Inselspital
CH-3010 Bern
E-mail: [redacted]

Telefon: +41 / 31 / 632 11 03
Telefax: +41 / 31 / 632 11 05

Ein Algorithmus ist eine eindeutige Handlungsvorschrift zur Lösung eines Problems oder einer Klasse von Problemen.



FIXES VERHÄLTNIS VON EC, FFP UND TC

KOMPONENTENTHERAPIE NACH LABORWERTEN

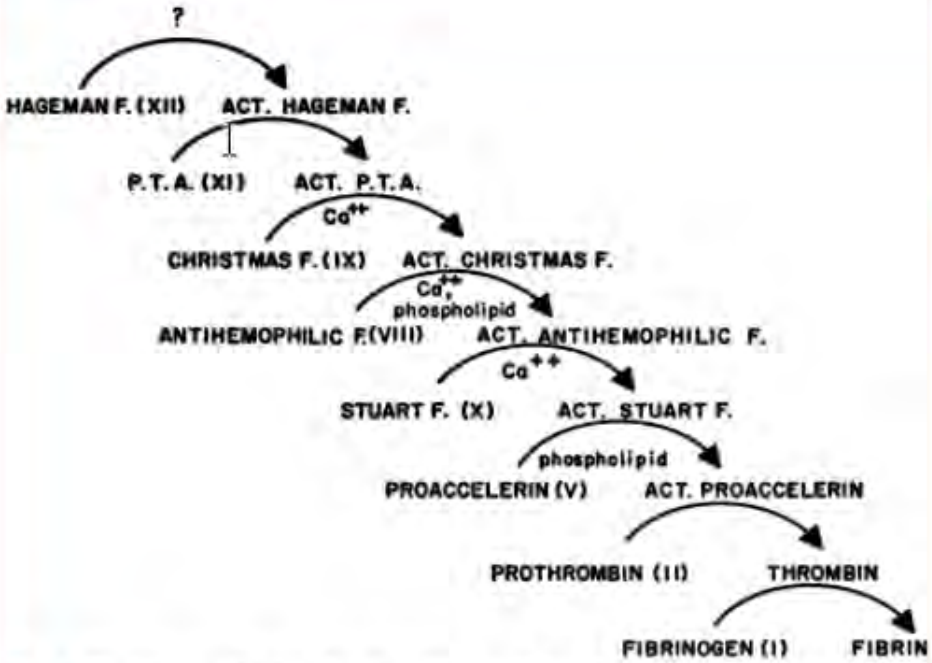


Fig. 1. Tentative mechanisms for the initiation of blood clotting in mammalian plasma in the intrinsic system. Abbreviations: F., factor; Act., activated; P.T.A., plasma thromboplastin antecedent. The term "Act. Proaccelerin" is probably a misnomer but was used in this figure instead of accelerin or prothrombin converting principle. Accelerin refers to a thrombin-modified form of proaccelerin; prothrombin converting principle, a term we have used elsewhere, does not identify the precursor of this enzyme. Hageman factor, Christmas factor, and Stuart factor are clotting factors named after the patients who were among the first observed in which the clotting deficiency was seen. This scheme does not represent all views held on the mechanism of blood coagulation (*32*).

Waterfall Sequence for Intrinsic Blood Clotting

Earl W. Davie[1], Oscar D. Ratnoff[2]
+ See all authors and affiliations

Science 18 Sep 1964:
Vol. 145, Issue 3638, pp. 1310-1312
DOI: 10.1126/science.145.3638.1310

Hemostatic Factors and Replacement of Major Blood Loss with Plasma-Poor Red Cell Concentrates

Seppo T. Hiippala, MD, Gunnar J. Myllylä, MD, and Elina M. Vahtera, PhD

Department of Anesthesiology, Helsinki University Central Hospital, and Finnish Red Cross Blood Transfusion Service, Helsinki, Finland

Table 1. Critical Level of Hemostatic Factors and the Inversely Predicted Corresponding Blood Loss (95% Confidence Interval) as Percent of Calculated Blood Volume

Hemostatic factor	Critical level	Blood loss (%)
Platelets	$50 \times 10^3/mm^3$	230 (169–294)
Fibrinogen	1.0 g/L	142 (117–169)
Prothrombin	20	201 (160–244)
Factor V	25	229 (167–300)
Factor VII	20	236 (198–277)

For prothrombin, factor V, and factor VII, the critical level is expressed as percent of normal activity. (Edmunds LH, Salzman EW. Hemostatic problems, transfusion therapy, and cardiopulmonary bypass in surgical patients. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis: basic principles and clinical practice. Philadelphia: JB Lippincott, 1994:956–68).

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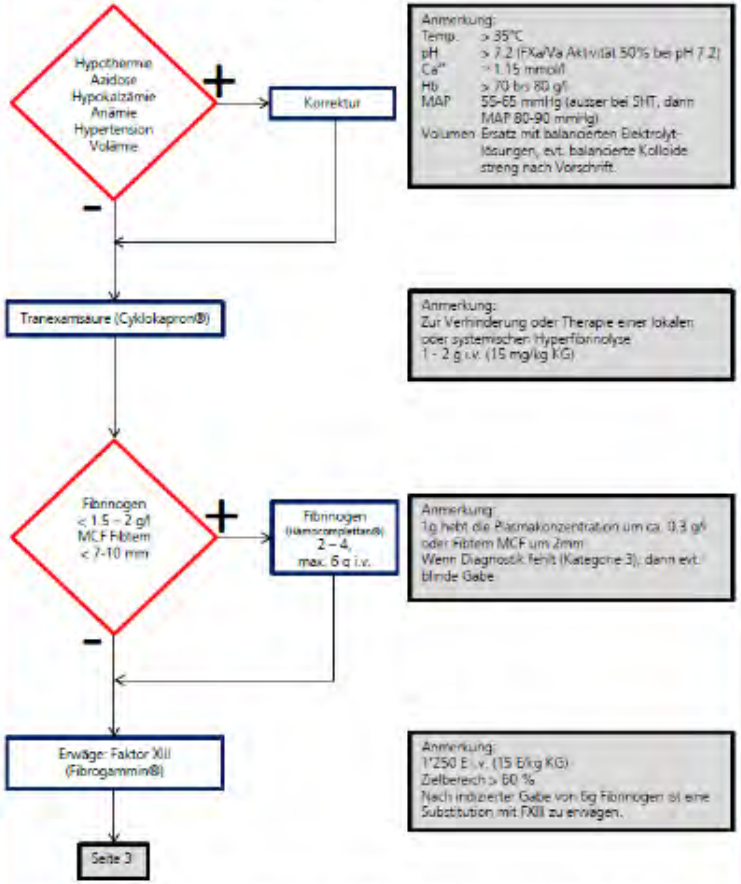
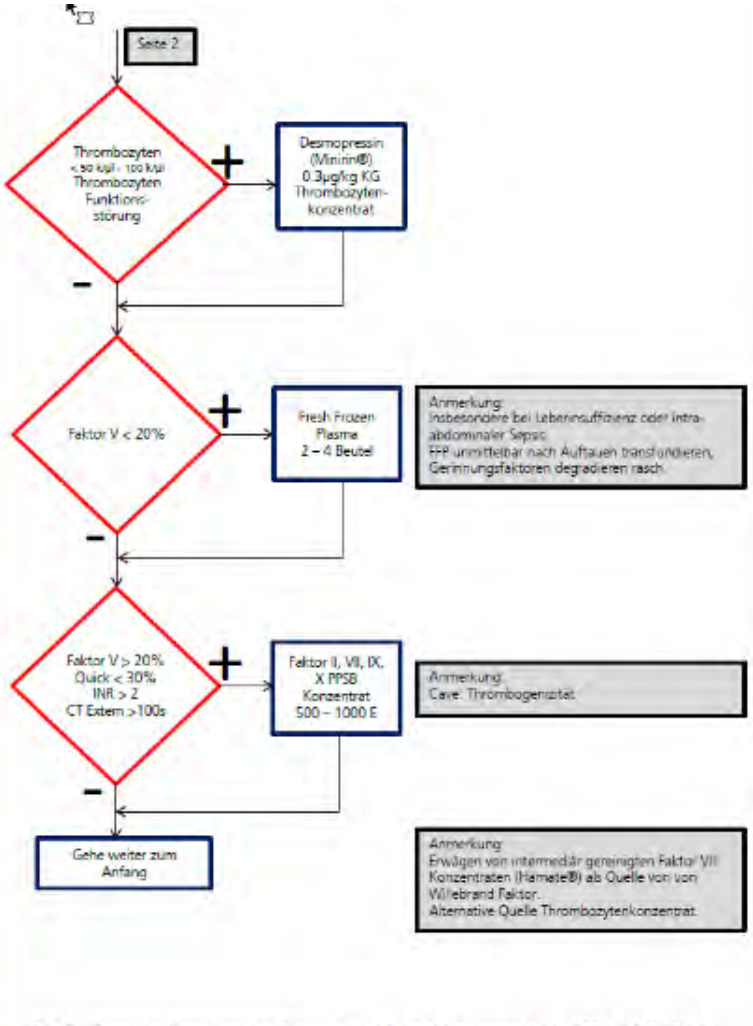
Accession: 00000539-199508000-00026

Algorithmus zur Transfusion von Blutprodukten und zur Blutgerinnungstherapie bei massiver Blutung

Bedingung: persistierende koagulopathische Blutung





UniversitätsSpital Zürich

Institut für Anästhesiologie
Klinik für Hämatologie

Algorithmus zur Transfusion von Blut- und Blutprodukten bei massiver Blutung

Bei allen Patientinnen und Patienten, welche nach diesem Algorithmus behandelt werden, wird ein **Gerinnungsstatus*** (Hb, Tc, INR, aPTT, Fibrinogen, Faktor V, Faktor XIII) gemacht bei Eintritt in diese Behandlung, vor und 30 min nach jeder Gabe von F XIII (**Fibrogammin®**) und rekombinantem F VIIa (**NovoSeven®**) sowie am Ende der Operation.
Nebst dem üblichen Schockraumlabor wird bei SHT, Polytrauma, Thoraxtrauma, schwerer Blutung / hämorrhagischem Schock auch Faktor V und Faktor XIII mitbestimmt.
Wenn bekannt ist, dass ein Patient mit einem Xa Hemmer (Rivaroxaban, Apixaban, Edoxaban) oder einem IIa Hemmer (Dabigatran) behandelt wird, wird der entsprechende Plasmaspiegel bestimmt.

WICHTIG (siehe Tabelle 1 im Anhang)
Ein auffallend hoher INR-Wert weist auf die Einnahme eines Vit-K Antagonisten hin.
Eine anti Xa Aktivität weist auf Behandlung mit Heparin oder einen Xa Hemmers hin.
Eine auffallend hohe Thrombinzeit weist auf die Einnahme eines IIa Hemmers hin.

Diagnostik	Intervention
Präoperative Anamnese 1. Medikamente mit Einfluss auf Blutgerinnung • Thrombozyten-Aggregationshemmer (Acetylsalicylsäure, Clopidogrel, Prasugrel, Ticagrelor) • Heparin • OAK (Vitamin-K Antagonisten, Rivaroxaban, Apixaban, Edoxaban, Dabigatran) 2. Verdacht auf HIT I	**ROTEM (EXTEM, INTEM, FIBTEM, APTEM)** präoperativ • HTPL, Lungen-TPL, Leber-TPL • Herz- und grosse Gefässchirurgie • Spezielle Tumorchirurgie (Wirbelsäule, Sarkomoperationen) • Eintritt Schockraum (bei SHT, Polytrauma, Thoraxtrauma, hämorrhagischer Schock) • Leberinsuffizienz und intra-abdominale Sepsis • Tangentiale Exzision bei grossflächigen Verbrennungen **Multiplate** bei Tc-Hemmern, wenn möglich
Blutverlust ≥ 50 % und diffuse Blutung	
ROTEM (**EXTEM, INTEM, FIBTEM, APTEM, HEPTEM** bei Hinweis auf Heparinwirkung!)	1. **Korrigiere (Zielwert)** • Hypothermie (Temperatur ≥ 35.0° C) • Hypokalziämie (Ca^{++} ≥ 1.15 mmol/l) • Azidose • Anämie (Hämatokrit ≥ 0.21) • Hypertension (MAP 55 - 65 mmHg) • (Ausnahme SHT, dann MAP 80 - 90 mmHg) **Volumenersatz: Ringerfundin®** und **Physiogel balanced®** 2. Tranexamsäure (**Cyklokapron®**) zur Verhinderung einer lokalen Hyperfibrinolyse: 1g i.v. (15 mg/kg KG)

* Bei ungültiger Faktor V Messung bitte aus Labor-logistischen Gründen keine anderen Einzel-Faktoren anfordern, sonst verzögert sich die Faktor V Messung um mindestens 48 Std.
† AEL 2009 Ref. Referenzhandbuch 6 - 12, Referenzbereich cCa^{++}: 1.15 - 1.28 mmol/l; 2.30 - 2.56 meq/L

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Diagnostik	Intervention
MCF FIBTEM ≤ 7 mm	Fibrinogen (**Haemocomplettan®**) 2 – 4 g, max 6 g i.v.
INTEM (CT u. CFT verlängert) und **HEPTEM** normal u./o. ACT pathologisch, Heparinase-ACT normal)	**Protaminsulfat** 1 : 1 zu verabreichter Heparindosis **Volumenersatz: Ringerfundin® und Physiogel balanced®**
EXTEM / INTEM: Abfall der MCF nach Erreichen des Maximums **APTEM**: normal = systemische Hyperfibrinolyse	Tranexamsäure (**Cyklokapron®**) • Bolus: 1 g i.v. (15 mg/kg KG)
Fortdauernde, diffuse Blutung	
EXTEM / INTEM MCF < 40 mm • CT EXTEM / INTEM normal • MCF FIBTEM ≤ 7 mm • HKT ≥ 0.21	Nach total 6 g Fibrinogen: Faktor XIII (**Fibrogammin®**) 15 E/kg KG i.v. Bei persistierendem FIBTEM ≤ 7 mm weiter Fibrinogen und **Backup informieren**
EXTEM / INTEM MCF < 40 mm • MCF FIBTEM > 7 mm • Tc ≥ 50 000/µl (≥ 100 000/µl in der Herzchirurgie und bei SHT) • Tc-Funktionsstörung (Tc-Hemmer, Multiplate)	**Thrombozytenkonzentrat** Desmopressin (**Minirin®**) **0.3 µg/kg KG**
Gerinnungsstatus* vor jeder Gabe von F XIII (Hb, Tc, Quick, aPTT, Fibrinogen, Faktor V, Faktor XIII)	Faktor XIII: Zielbereich ≥ 60 % (**Fibrogammin®**) Faktor V: Zielbereich ≥ 20 %, insbesondere bei Leberinsuffizienz oder intra-abdominaler Sepsis (**2-4 Beutel FFP**) **Volumenersatz: Ringerfundin® und Physiogel balanced®**
Fortdauernde Blutung	
Quick < 30% und Faktor V > 20% oder EXTEM / INTEM: CT, CFT verlängert	Faktor II, VII, IX, X-Konzentrat (**Beriplex®P/N 500**) 1000 bis 2000 E, abhängig vom Patientengewicht.
Bei Massivtransfusion	
	Ziel Hämoglobin 70g/l
Bei fortdauernder massiver diffuser Blutung und	
• behandelter Azidose • behandelter Hypothermie • Ausschluss Hypokalziämie • Hematokrit ≥ 0.21 • Ausschluss DIC • Fibrinogen substituiert • Thrombozyten ≥ 50 000/µl (≥ 100 000/µl in der Herzchirurgie und bei SHT)	Rekombinanter Faktor VIIa (**NovoSeven®**) Initial 60 µg/kg KG i.v. 2 mg für 30-50 kg/KG 4 mg für 51-100 kg/KG 6 mg für >100 kg/KG Es werden keine halben Ampullen verabreicht. Bei initialem Ansprechen aber nicht vollständigem Stopp oder Wiederauftreten der Blutung: Wiederholungsdosis von 60 µg/kg KG i.v. nach 2 – 4 h. **Wird ausschliesslich vom Backup verordnet!**

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ANHANG

Abkürzungen
CT Clotting Time
CFT Clot Formation Time (bei Beginn Gerinnung bis zu Gerinnselfestigkeit von 20 mm)
MCF Maximum Clot Firmness
ML Maximum Lysis (normale Stabilität des Gerinnsels, wenn ML < 15 % innerhalb 1 h)

Limitationen des ROTEM point of care testing
- keine Detektion von Acetylsalicylsäure, Clopidogrel, Prasugrel, Ticagrelor
- keine Detektion des von Willebrand Syndroms
- geringe Sensitivität für Glykoprotein IIb/IIIa Rezeptorantagonisten, wie Abciximab (Reopro®)
- geringe Sensitivität für Fondaparinux, niedermolekulares Heparin, Organan und Pentasaccharid
- geringe Sensitivität für OAK (Vit-K Antagonisten, Xa-Hemmer und IIa Hemmer)

Tabelle 1 Labortest Gerinnungshemmer

Antikoagulans	INR	aPTT (s)	Thrombinzeit (s)	Anti FXa (U/ml)
Vitamin K Antagonisten	↑	(↑)	Keine Veränderung	Keine Veränderung
Unfraktioniertes Heparin	Keine Veränderung (*)	↑	↑	↑
Low molecular weight heparin	Keine Veränderung (*)	(↑)	(↑)	↑
Rivaroxaban, Apixaban Edoxaban	(↑)	↑↑↑	Keine Veränderung	↑
Dabigatran	(↑)	↑	↑↑	Keine Veränderung

(*) Kann bei sehr hoher Heparinkonzentration

Sensitive Testist grau hinterlegt

PAT 1 Perioperatives Anämie- und Transfusionsmanagement am USZ

Verbindlicher Inhalt

Weisung zum Einsatz von Blutprodukten am USZ
Ärztliche Direktion
August 2017

Hb-Transfusionsgrenzen

Hb < 60 g/l	Gesunde Gebärende [27]
Hb < 70 g/l	Patienten ohne wesentliche Begleiterkrankung (siehe Hb > 70 g/dl) [28]
Hb < 80 g/l	SaO2 < 90 % (trotz optimierter Beatmung) Schädel-Hirn-Trauma [29] (kann mit multimodalem Neuro-Monitoring auf < 70 g/l angepasst werden) Freie Lappenplastik [30] Schwere koronare Herzkrankheit [31,32] Herzinsuffizienz [31,32] Karotisstenose > 70 % Alter > 80 Jahre [31,32]
Hb < 90 g/l	Instabile koronare Herzkrankheit Schwere, massive katecholaminbedürftige Herzinsuffizienz

Wichtig:

- Ein tiefer Hämoglobin-Wert alleine stellt nicht in jedem Fall eine zwingende Indikation zur Erythrozyten-Transfusion dar.
- Bei einem Hb > 90 g/l besteht in der Regel **keine** Indikation zur Erythrozyten-Transfusion.

Empfehlung bei massiver Blutung

Kategorisierung der Institutionen:

1. Maximalversorgung: (Traumazentren, Herzchirurgie und Chirurgie der grossen Gefässe, Transplantationschirurgie, Leberchirurgie, komplexe Wirbelsäulenchirurgie und intrakranielle Chirurgie, Verbrennungszentren).
2. Intermediäre Versorgung: Geburtshilfe, primäre Traumaversorgung.
3. Minimalanforderung: alle anderen.

Institutionen der Kategorie 3 verlegen blutende Patienten grosszügig in Kategorie 2 und 1.
Empfehlung: Absprache über Verlegungsprozess, evt. Standard Operating Procedure (SOP).

Institutionen der Kategorie 2 verlegen blutende Patienten in Kategorie 1, wenn chirurgische Blutung oder koagulopathische Blutung mit eigenen Mitteln voraussichtlich nicht behoben werden können.
Empfehlung: Absprache über Verlegungsprozess, evt. Standard Operating Procedure (SOP).

Vorgehen bei potentiellem Blutverlust von > 500ml

Gerinnungsanamnese bestehend aus:
1. Blutungsanamnese
2. Familienanamnese
3. Thromboseanamnese
4. Medikamentenanamnese

Empfohlene Laborbestimmungen:
Hb, Tc, Quick, aPTT, Fibrinogen, Thrombinzeit.

Zusätzliche empfohlene Laborbestimmungen für Kategorie 1, wünschbar für Kategorie 2:
Viskoelastische Methoden (Thrombelastometrie, Thrombelastografie), point of care oder zentral rund um die Uhr.
Plättchenfunktionstests, point of care oder zentral rund um die Uhr.
D-Dimere, Faktor V, Faktor XIII, Anti Xa Aktivität (in IU/ml oder µg/L) rund um die Uhr.
Bei bekannter Therapie mit einem Xa Hemmer (Rivaroxaban, Apixaban, Edoxaban) oder einem IIa Hemmer (Dabigatran) kann der entsprechende Plasmaspiegel bestimmt werden.

Ein auffallend tiefer Quick-Wert kann z.B. auf die Einnahme eine Vit-K Antagonisten hinweisen. Gleiches gilt für eine anti Xa Aktivität für die Behandlung mit Heparin oder eines Xa Hemmers. IIa Hemmer führen zu einer verlängerten Thrombinzeit.

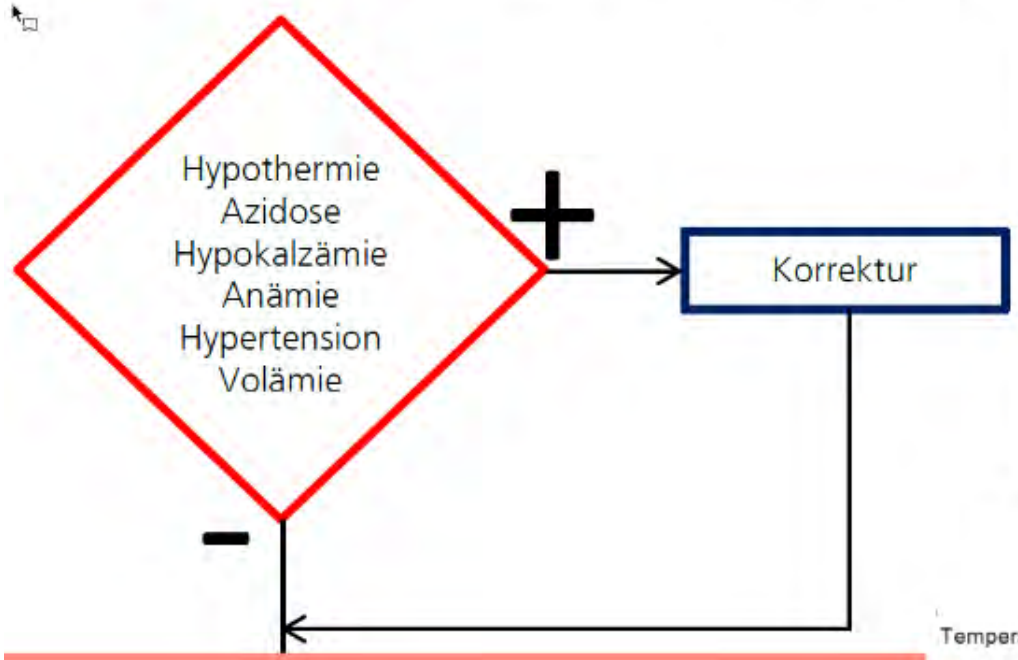
Unter Berücksichtigung der Antikoagulationsindikation soll bei persistierender Blutung die Antikoagulation teilweise oder ganz aufgehoben werden. Besonderer Beachtung gilt im Verlauf der thromboembolischen Prophylaxe.

Vitamin K Antagonisten:	4 Faktoren Konzentrate = Prothrombinkomplex-Konzentrat = PPSB
IIa Hemmer:	Idarucizumab = Praxbind®
Xa Hemmer:	PPSB bis spezifischer Antagonist verfügbar
Heparin:	Protaminsulfat
Antiplatelet Therapie:	Desmopressin = Minirin® Thrombozytentransfusion (vorhandene Plasmaspiegel von Thrombozytenaggregationshemmern und deren Metabolite beeinflussen transfundierte Thrombozyten ebenfalls)

Erwäge bei jedem Schritt die Verlegung des Patienten in eine höhergradige Institution.

Algorithmus zur Transfusion von Blutprodukten und zur Blutgerinnungstherapie bei massiver Blutung

Bedingung: persistierende koagulopathische Blutung

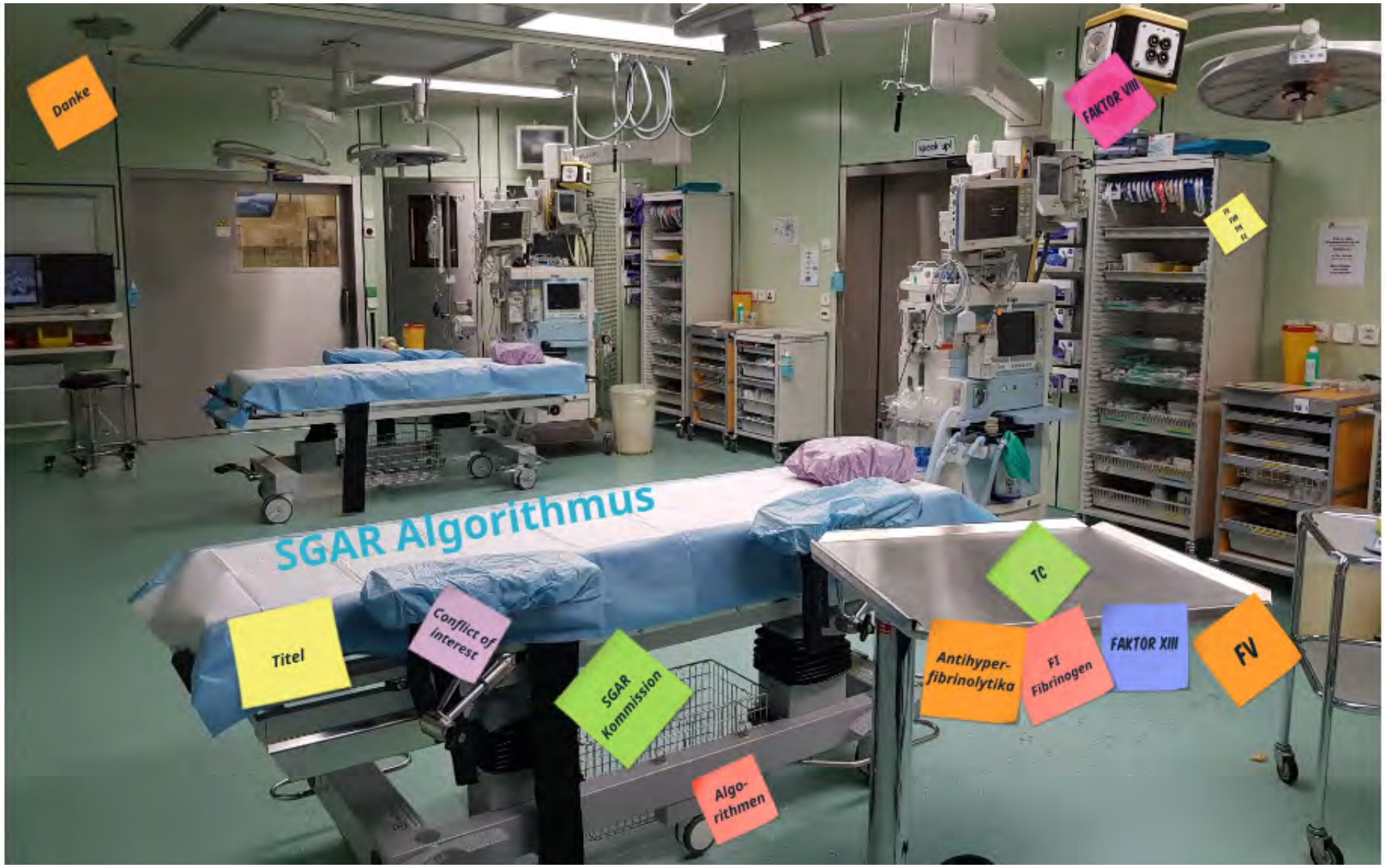


Anmerkung:

Temp.	> 35°C
pH	> 7.2 (FXa/Va Aktivität 50% bei pH 7.2)
Ca^{2+}	> 1.15 mmol/l
Hb	> 70 bis 80 g/l
MAP	55-65 mmHg (ausser bei SHT, dann MAP 80-90 mmHg)
Volumen	Ersatz mit balancierten Elektrolyt-lösungen, evt. balancierte Kolloide streng nach Vorschrift.

Temperatur:

Mehrfach wurde gewünscht, den Zielwert auf 35 Grad heraufzusetzen. Wir haben dies in den Algorithmus aufgenommen.


Danke
FAKTOR VIII
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV

Serinproteinaseninhibitor

Lysinanalogen

Utako Okamoto

Antihyper-fibrinolytika

- CRASH II
- Woman Trial
- und noch viele mehr
- Stein
- und ausser dem

Tranexamsäure (Cyklokapron®)

Anmerkung:
Zur Verhinderung oder Therapie einer lokalen oder systemischen Hyperfibrinolyse
1 - 2 g i.v. (15 mg/kg KG)

Corticosteroid Randomisation after severe Headtrauma

CRASH2

Limitationen

CRASH2

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**

Lancet 2011; 377: 1096–101

Published Online
March 24, 2011
DOI:10.1016/S0140-6736(11)60278-X

Verbluten

BMJ

BMJ 2012;345:e5839 doi: 10.1136/bmj.e5839 (Published 11 September 2012)

RESEARCH

Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial

OPEN ACCESS

Ian Roberts *professor*[1], Pablo Perel *senior clinical lecturer*[1], David Prieto-Merino *lecturer, medical statistics*[1], Haleema Shakur *senior lecturer in clinical trials*[1], Tim Coats *professor*[2], Beverley J Hunt *professor*[3], Fiona Lecky *professor*[4], Karim Brohi *professor*[5], Keith Willett *professor*[6], on behalf of the CRASH-2 collaborators.

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

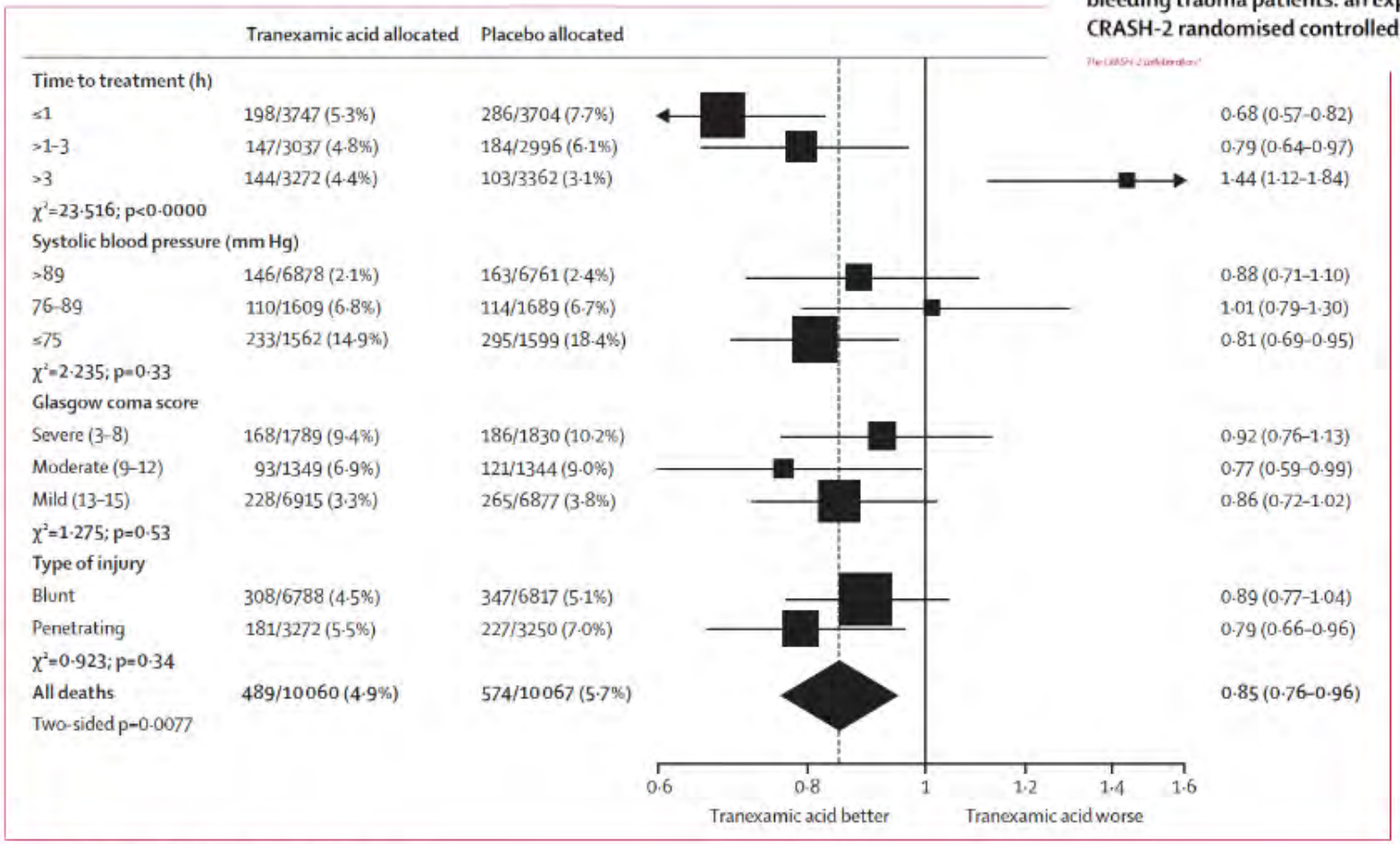


Figure 1: Mortality due to bleeding by subgroups

Figures

Risk of death at baseline	No of patients (%) Tranexamic acid	Placebo	Odds ratio (95% CI)	Odds ratio (95% CI)
<6%	33/2487 (1%)	40/2353 (2%)		0.78 (0.49 to 1.23)
6-20%	223/2682 (8%)	266/2713 (10%)		0.83 (0.70 to 1.00)
21-50%	281/908 (31%)	337/940 (36%)		0.80 (0.69 to 0.94)
>50%	392/607 (65%)	410/583 (70%)		0.77 (0.68 to 0.87)
All	929/6684 (14%)	1053/6589 (16%)		0.85 (0.78 to 0.93)

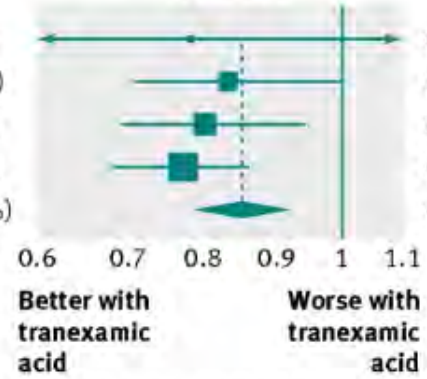


Fig 1 Deaths from all causes in patients with traumatic bleeding according to treatment with tranexamic acid (P=0.96 for heterogeneity)


BMJ

RESEARCH

Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial

Risk of death at baseline	No of patients (%) Tranexamic acid	Placebo	Odds ratio (95% CI)	Odds ratio (95% CI)
<6%	14/2487 (1%)	16/2353 (1%)		0.83 (0.40 to 1.96)
6-20%	38/2682 (1%)	50/2713 (2%)		0.77 (0.50 to 1.17)
21-50%	29/908 (3%)	52/940 (6%)		0.56 (0.36 to 0.89)
>50%	17/607 (3%)	22/583 (4%)		0.73 (0.39 to 1.38)
All	98/6684 (1%)	140/6589 (2%)		0.69 (0.53 to 0.89)

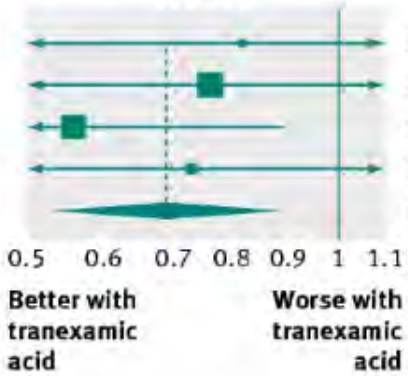


Fig 3 Fatal and non-fatal thrombotic events in patients with traumatic bleeding according to treatment with tranexamic acid (P=0.74 for heterogeneity)

Limitationen

WOMAN Trial

The WOMAN (World Maternal Antifibrinolytic) Trial

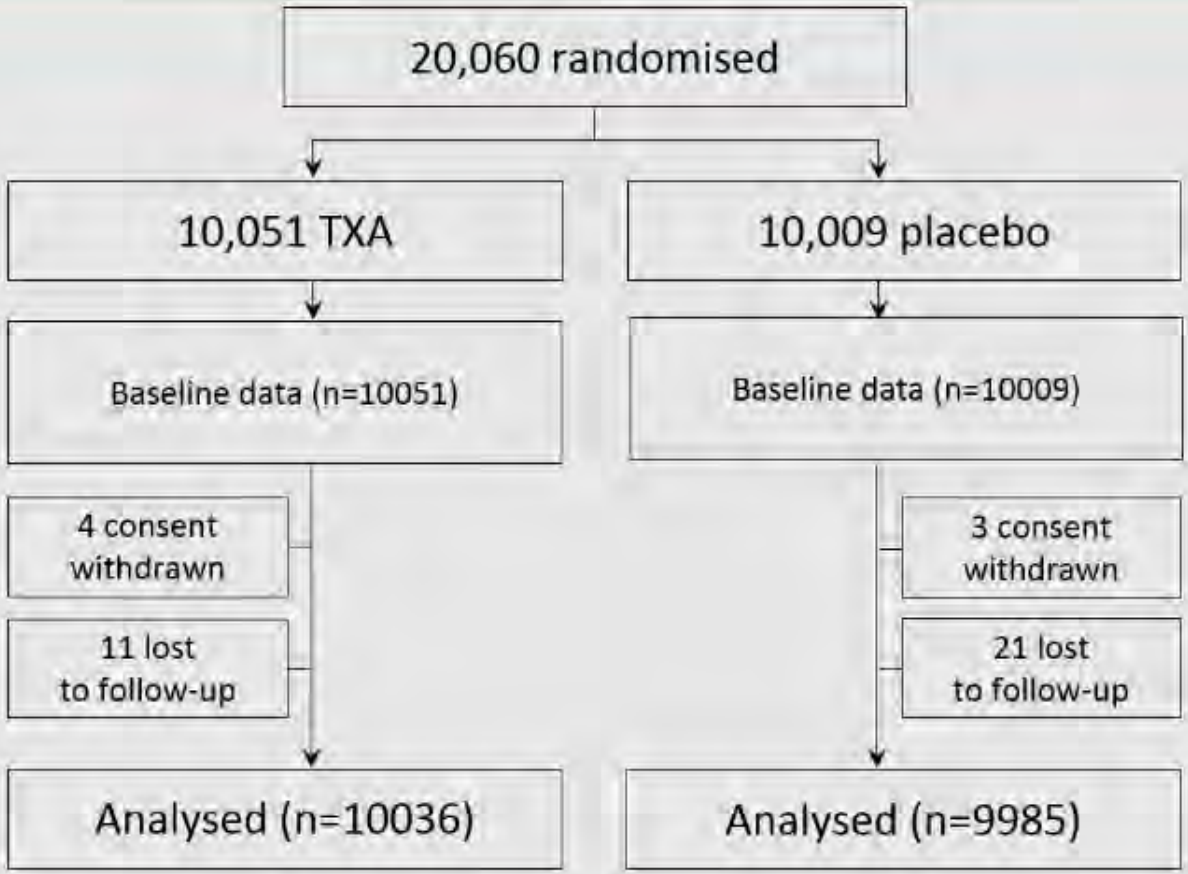
Lancet 2017; 389: 2105–16
Published Online
April 26, 2017
http://dx.doi.org/10.1016/
S0140-6736(17)30638-4

Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

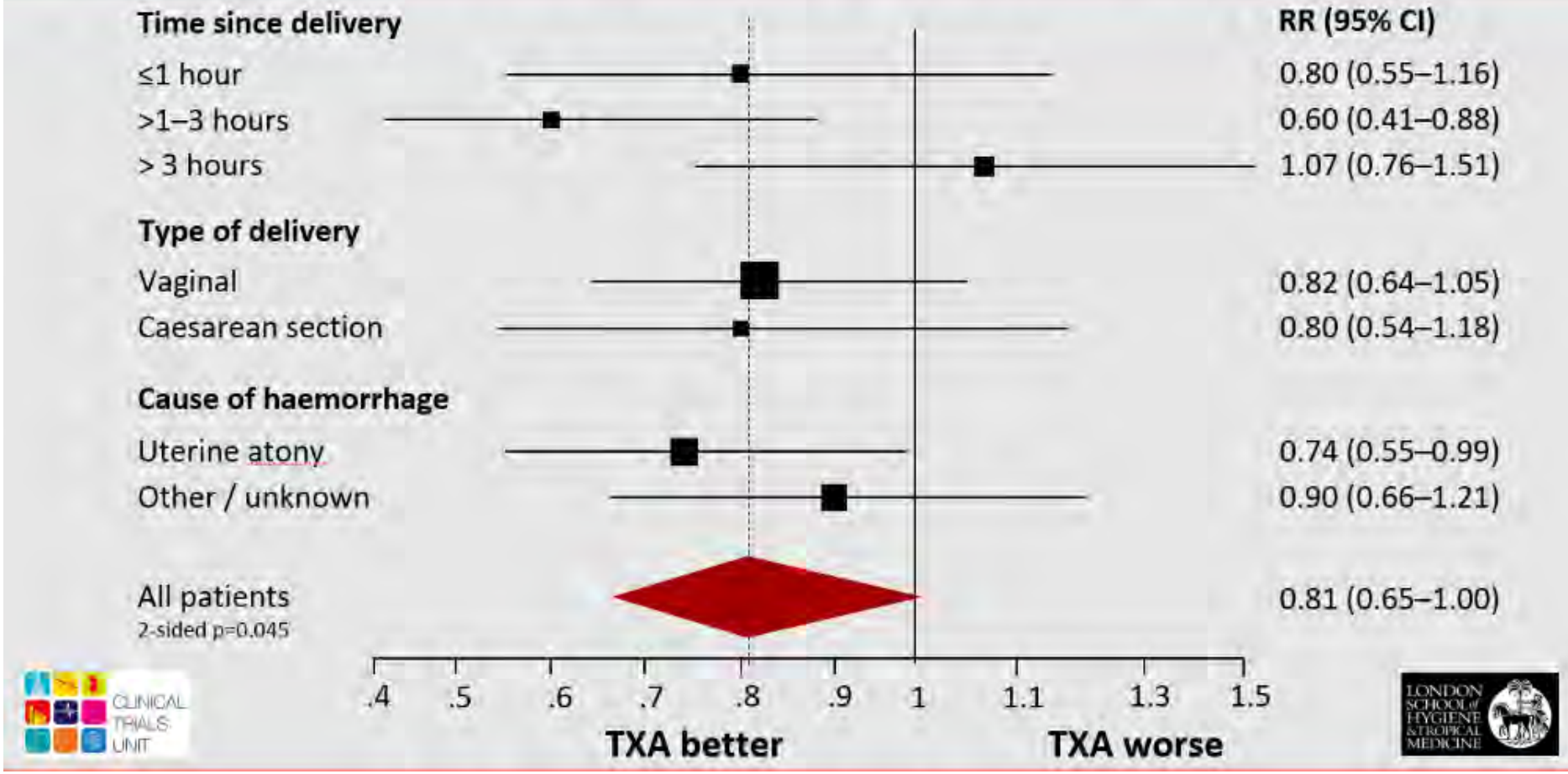
*WOMAN Trial Collaborators**

Methods In this randomised, double-blind, placebo-controlled trial, we recruited women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries. We randomly assigned women to receive either 1 g intravenous tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given. Patients were assigned by selection of a numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Participants, care givers, and those assessing outcomes were masked to allocation. We originally planned to enrol 15 000 women with a composite primary endpoint of death from all-causes or hysterectomy within 42 days of giving birth. However, during the trial it became apparent that the decision to conduct a hysterectomy was often made at the same time as randomisation. Although tranexamic acid could influence the risk of death in these cases, it could not affect the risk of hysterectomy. We therefore increased the sample size from 15 000 to 20 000 women in order to estimate the effect of tranexamic acid on the risk of death from post-partum haemorrhage. All analyses were done on an intention-to-treat basis. This trial is registered with ISRCTN76912190 (Dec 8, 2008); ClinicalTrials.gov, number NCT00872469; and PACTR201007000192283.

The WOMAN trial



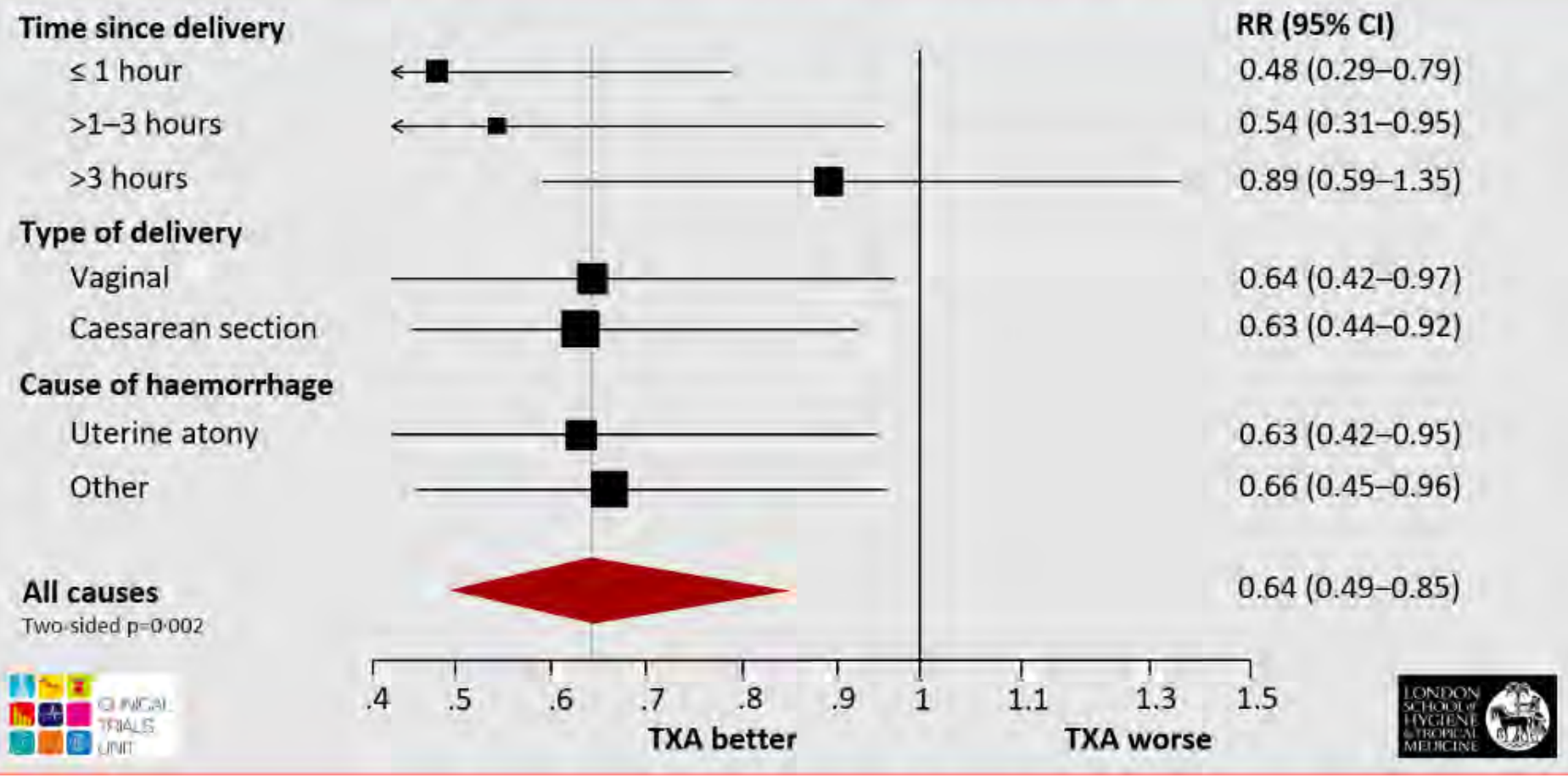
Effect of TXA on death due to bleeding: subgroups



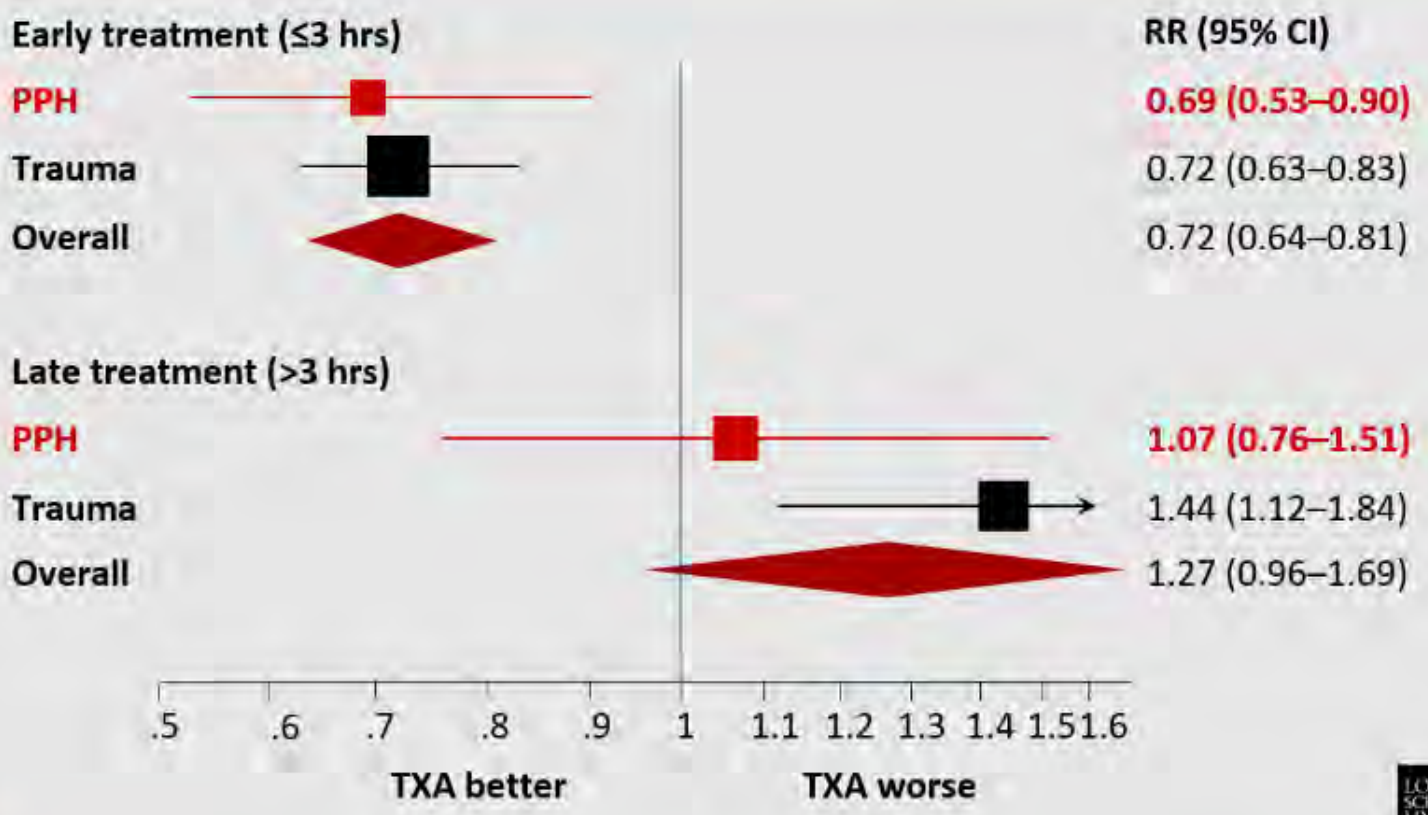
Hysterectomy

Outcome	TXA (N=10036) n (%)	Placebo (N=9985) n (%)	Risk ratio (95% CI)	P-value
Hysterectomy (all causes)	358 (3.6)	351 (3.5)	1.02 (0.88–1.17)	0.84
Hysterectomy (bleeding)	283 (2.8)	295 (3.0)	0.95 (0.81–1.12)	0.57

Laparotomy for bleeding



Death due to bleeding



Tranexamsäure in PPH

- 1/5 Reduktion von Tod durch Verbluten über alles
- 1/3 Reduktion von Tod durch Verbluten bei Gabe innerhalb von 3 Stunden
- Kein Effekt auf andere Todesursachen
- Keine Reduktion von Hysterektomie Häufigkeit
- 35% Reduktion von Laparatomie wegen Blutung
- Kein Hinweis für Nebenwirkungen

www.womantrial.lshtm.ac.uk

und noch viele mehr

Matters

Arch Surg. 2012;147(2):113-119. Published online October 17, 2011. doi:10.1001/archsurg.2011.287

ONLINE FIRST

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

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

Resultate

Design: Retrospective observational study comparing TXA administration with no TXA in patients receiving at least 1 unit of packed red blood cells. A subgroup of patients receiving massive transfusion (≥10 units of packed red blood cells) was also examined. Univariate and multivariate regression analyses were used to identify parameters associated with survival. Kaplan-Meier life tables were used to report survival.

Resultate

ONLINE FIRST

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

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

Table 1. Demographic Data, Mechanism of Injury, Injury Severity, Physiology, and Transfusion Requirement for Overall and Massive Transfusion Groups

	Overall (N=896)			Massive Transfusion (n=231)		
Variable	TXA (n=293)	No TXA (n=603)	*P* Value[a]	TXA (n=125)	No TXA (n=196)	*P* Value[a]
Demographic data						
Age, mean (SD), y	24.9 (9.6)	23.1 (10.1)	.12	23.8 (7.7)	22.9 (9.2)	.46
Male, %	97.3	94.2	**.04**	98.4	96.9	.49
Host national, No. (%)	116 (39.6)	261 (43.3)	.29	39 (31.2)	65 (33.2)	.71
NATO military	177 (60.4)	342 (56.7)		86 (68.8)	131 (66.8)	
Mechanism of injury, %						
GSW	25.3	36.7	**<.001**	24.0	32.1	.14
Explosion	74.7	62.4		76.0	66.8	
Injury severity						
ISS, mean (SD)	25.2 (16.6)	22.5 (18.5)	**<.001**	26.1 (17.1)	25.2 (20.5)	.11
AIS score ≥3, %						
Head	9.9	13.4	.13	9.6	13.8	.26
Chest	22.2	22.2	.99	21.6	23.0	.78
Abdomen	14.7	16.4	.50	13.6	21.0	.06
Extremity	66.6	47.3	**<.001**	68.0	51.0	**.003**
RTS, mean (SD)	5.53 (2.14)	6.04 (2.69)	**.01**	5.58 (2.21)	5.74 (2.88)	.21
Admission physiology, %						
GCS score ≤8	63.3	35.6	**<.001**	64.1	39.3	**<.001**
SBP ≤90 mm Hg	22.8	13.8	**.003**	20.4	18.2	.67
24-h Transfusion, mean (SD), units						
PRBCs	11.8 (12.1)	9.8 (13.1)	**<.001**	21.0 (12.8)	22.5 (15.9)	.47
FFP	10.3 (10.8)	8.6 (11.7)	**<.001**	18.4 (11.5)	19.6 (14.3)	.67
Platelets	1.6 (2.2)	1.4 (2.7)	**.001**	3.2 (2.4)	3.6 (3.6)	.84
Cryoprecipitate	1.6 (2.7)	0.5 (1.3)	**<.001**	1.6 (2.6)	0.7 (1.6)	**<.001**
Miscellaneous						
Time in ED, mean (SD), min	36 (25)	56 (55)	**<.001**	39 (27)	52 (57)	.39
Time in OR, mean (SD), min	170 (121)	115 (74)	**<.001**	180 (126)	113 (74)	**<.001**
Lowest body temperature, mean (SD), °C	36.1 (1.1)	36.4 (0.9)	**.04**	36.5 (0.8)	36.3 (0.9)	.28
Pulmonary embolism, No. (%)	8 (2.7)	2 (0.3)	**.001**	4 (3.2)	0	**.01**
Deep venous thrombosis, No. (%)	7 (2.4)	1 (0.2)	**.001**	2 (1.6)	1 (0.5)	.32

Resultate

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

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

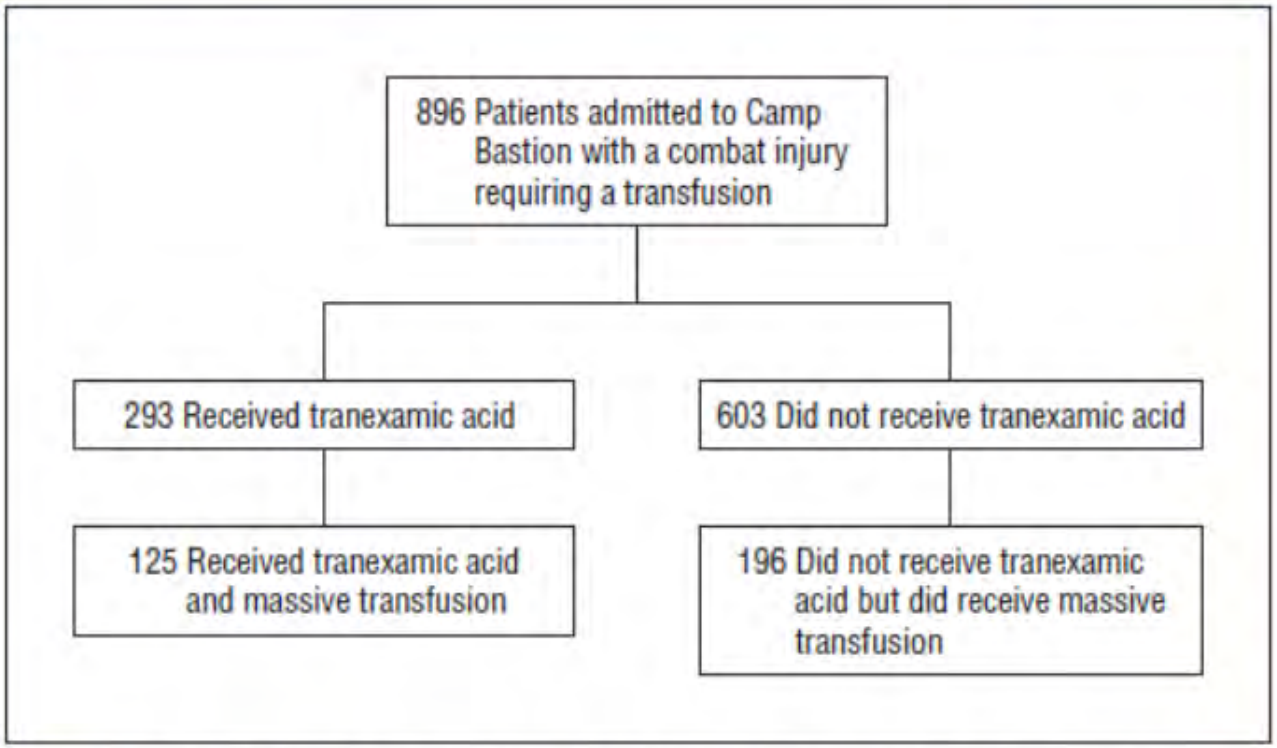

Figure 1. Study profile illustrating the overall cohort and study groups.

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

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

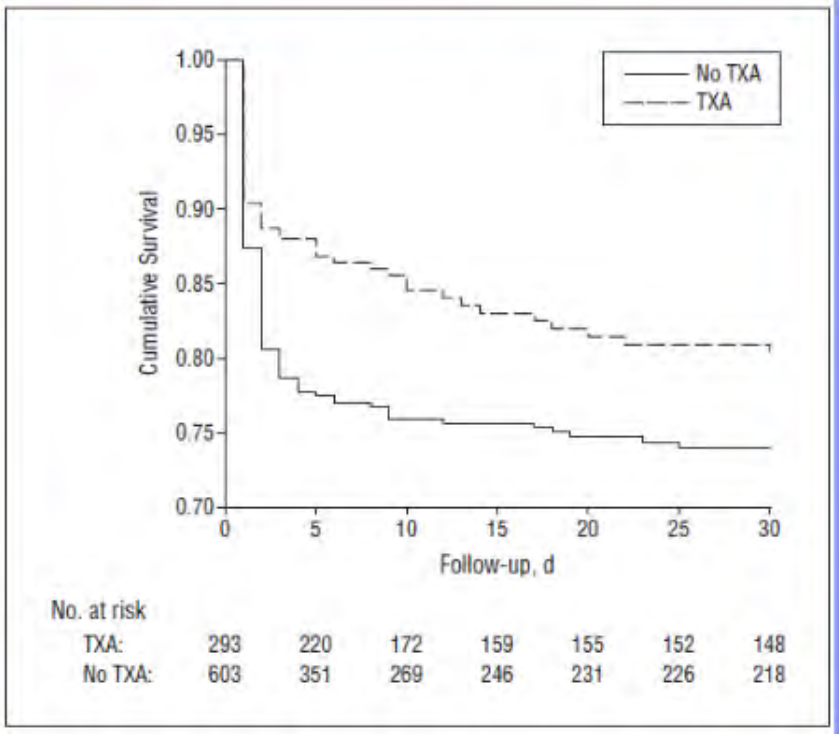

Figure 3. Kaplan-Meier survival curve of the overall cohort, including patients receiving tranexamic acid (TXA) vs no TXA. *P*=.006, Mantel-Cox log-rank test.

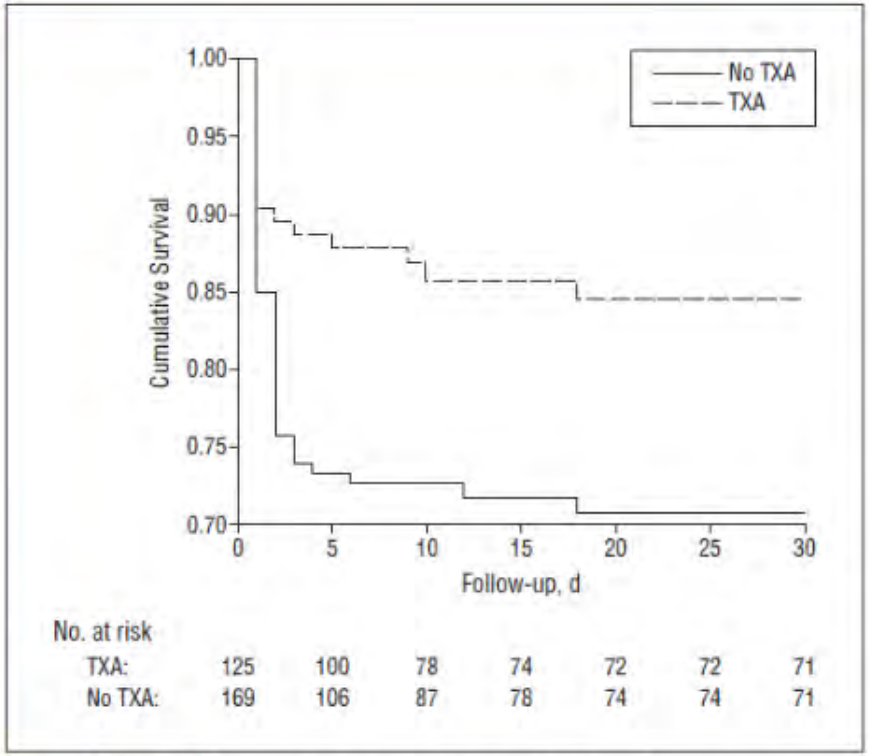

Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. *P*=.004, Mantel-Cox log-rank test.

Farrow

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 1458–1470 1458

SYSTEMATIC REVIEW

A systematic review of tranexamic acid in hip fracture surgery

Correspondence Mr Luke S. Farrow, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK. Tel.: +44 034 5456 6000; Fax: +44 1224 552180; E-mail: luke.farrow@nhs.net

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PROSPERO Registration: CRD42016036806

Keywords bleeding, hip fracture, meta-analysis, orthopaedics, systematic review, tranexamic acid

Resultate

Resultate

SYSTEMATIC REVIEW

A systematic review of tranexamic acid in hip fracture surgery

L. S. Farrow et al.

Study or Subgroup	TXA Events	TXA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Emara 2014	1	20	7	20	4.1%	0.14 [0.02, 1.06]
Lee 2015	5	84	35	187	11.6%	0.32 [0.13, 0.78]
Mohib 2015	9	50	21	50	14.6%	0.43 [0.22, 0.84]
Sadeghi 2007	12	32	20	35	16.7%	0.66 [0.39, 1.12]
Tengberg 2016	27	33	33	39	20.8%	0.97 [0.78, 1.19]
Vijay 2013	7	45	18	45	13.3%	0.39 [0.18, 0.84]
Zufferey 2010	24	57	32	53	18.9%	0.70 [0.48, 1.01]
Total (95% CI)		**321**		**429**	**100.0%**	**0.54 [0.35, 0.85]**
Total events	85		166			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 27.89$, $df = 6$ ($P < 0.0001$); $I^2 = 78\%$

Test for overall effect: $Z = 2.65$ ($P = 0.008$)

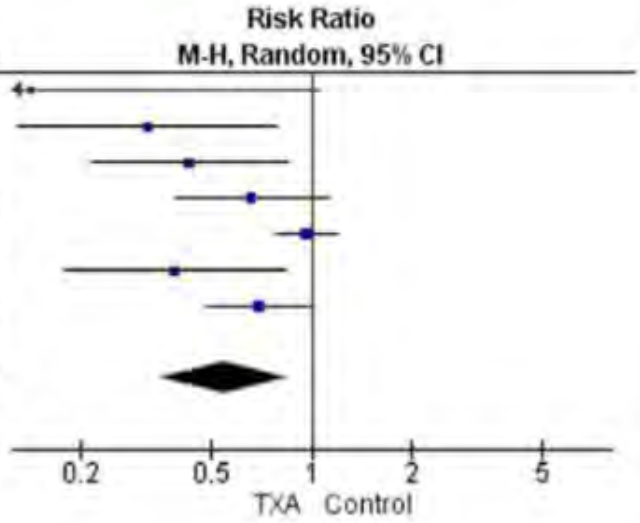


Figure 2

Forest-plot of TXA versus control for requirement for blood transfusion

Resultate

SYSTEMATIC REVIEW

A systematic review of tranexamic acid in hip fracture surgery

Study or Subgroup	TXA Mean	TXA SD	TXA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Emara 2014	10.5	1.5	20	9	1.1	20	13.6%	1.50 [0.68, 2.32]
Lee 2015	11.1	1.6	84	10.6	1.4	185	28.4%	0.50 [0.10, 0.90]
Mohib 2015	10.2	2.4	50	8.9	2.4	50	11.1%	1.30 [0.36, 2.24]
Sadeghi 2007	10.1	1.4	32	8.9	2.1	35	12.9%	1.20 [0.35, 2.05]
Tengberg 2016	10.5	9.4	33	10.5	15.3	39	0.4%	0.00 [-5.77, 5.77]
Vijay 2013	10.1	1	45	9.6	0.08	45	33.6%	0.50 [0.21, 0.79]
Total (95% CI)			**264**			**374**	**100.0%**	**0.81 [0.45, 1.18]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.23$, df = 5 (P = 0.10); $I^2 = 46\%$

Test for overall effect: Z = 4.39 (P < 0.0001)

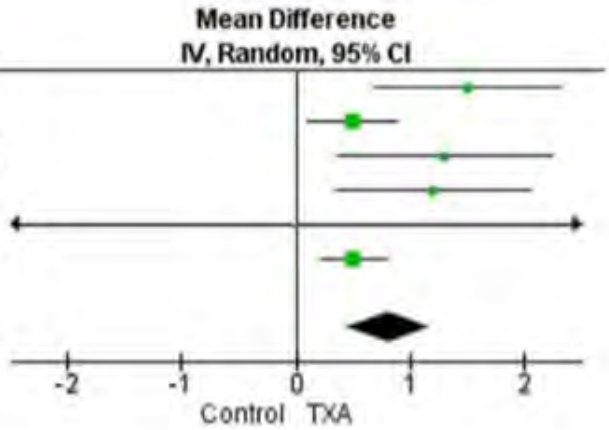


Figure 4

Forest-plot of TXA versus control for post-operative haemoglobin

Resultate

SYSTEMATIC REVIEW

A systematic review of tranexamic acid in hip fracture surgery

Study or Subgroup	TXA Events	TXA Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Emara 2014	6	20	1	20	3.3%	0.25 [0.03, 0.47]
Lee 2015	1	84	4	187	25.9%	-0.01 [-0.04, 0.02]
Mohib 2015	0	50	0	50	24.2%	0.00 [-0.04, 0.04]
Tengberg 2016	0	33	2	39	13.7%	-0.05 [-0.14, 0.03]
Vijay 2013	0	45	0	45	23.2%	0.00 [-0.04, 0.04]
Zufferey 2010	9	57	3	53	9.7%	0.10 [-0.01, 0.21]
Total (95% CI)		**289**		**394**	**100.0%**	**0.01 [-0.03, 0.05]**
Total events	16		10			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.81$, df = 5 (P = 0.007); $I^2 = 68\%$

Test for overall effect: Z = 0.39 (P = 0.69)

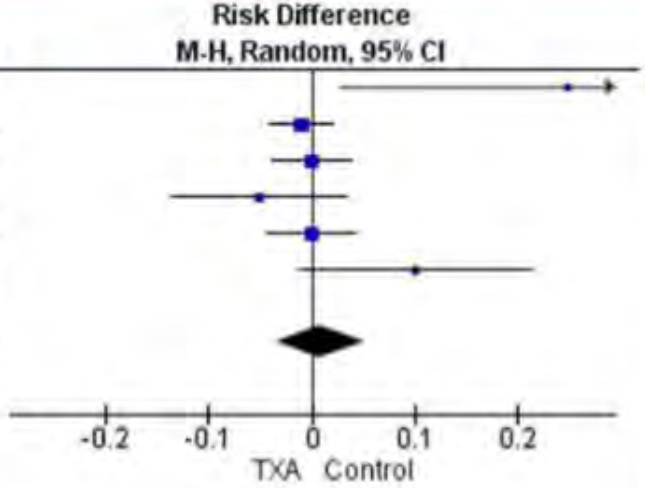


Figure 5

Forest-plot of TXA versus control for thromboembolic events

Trauma

Section Editor: Richard P. Dutton

The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients

Philipp Stein, MD,*† Jan-Dirk Studt, MD,‡ Roland Albrecht, MD,† Stefan Müller, MD,§‖ Dieter von Ow, MD,‖¶ Simon Fischer, MD,# Burkhardt Seifert, PhD,** Sergio Mariotti, MD,§‖ Donat R. Spahn, MD, FRCA,* and Oliver M. Theusinger, MD*

BACKGROUND: There is limited data on prehospital administration of tranexamic acid (TXA) in civilian trauma. The aim of this study was to evaluate changes in coagulation after severe trauma from on-scene to the hospital after TXA application in comparison to a previous study without TXA.
METHODS: The study protocol was registered at ClinicalTrials.gov (NCT02354885). A prospective, multicenter, observational study investigating coagulation status in 70 trauma patients receiving TXA (1 g intravenously) on-scene versus a control group of 38 patients previously published without TXA. To account for potential differences in patient and trauma epidemiology, crystalloid and colloidal resuscitation fluid, 2 propensity score matched groups (n = 24 per group) were created. Measurements included ROTEM, standard coagulation tests and blood gas analyses on-scene and emergency department admission. Presented values are mean and [standard deviation], and difference in means and 95% confidence intervals.
RESULTS: Patient epidemiology was not different between groups. Coagulation assays on-scene were comparable between the TXA and C. Prehospital hyperfibrinolysis was blunted in all 4 patients in the TXA group. Viscoelastic FIBTEM maximum clot firmness (MCF), representing functional fibrinogen levels, did not change from on-scene to the emergency department in the TXA group, whereas MCF decreased −3.7 [1.8] mm in the control group. Decrease of MCF was significantly reduced in the TXA group in EXTEM by 9.2 (7.2–11.2) mm ($P < .001$) and INTEM by 6.8 (4.7–9.0) mm ($P < .001$) in favor of the TXA group. Production of fibrinogen fragments (represented by D-dimers) was significantly lower in the TXA group compared to group C.
CONCLUSIONS: Early prehospital administration of TXA leads to clot stabilization and a reduction of fibrinolytic activity, causing a decrease in fibrin degradation products buildup (D-dimer).
(Anesth Analg 2018;126:522–9)

KEY POINTS

- **Question:** Are there changes in coagulation after severe trauma from on-scene to the hospital after tranexamic acid (TXA) application in comparison to a previous study without TXA?
- **Findings:** Early prehospital administration of TXA leads to clot stabilization and a reduction of fibrinolytic activity, causing a decrease in fibrin degradation products buildup (D-dimer).
- **Meaning:** Emergency medical services should use TXA in the preclinical setting to improve coagulation in severe trauma patients.

Anesthesia & Analgesia
Issue: Volume 126(2), February 2018, p 522–529

Publication Type: [Trauma: Original Clinical Research Report]
DOI: 10.1213/ANE.0000000000002708
ISSN: 0003-2999
Accession: 00000539-201802000-00027

Resultate

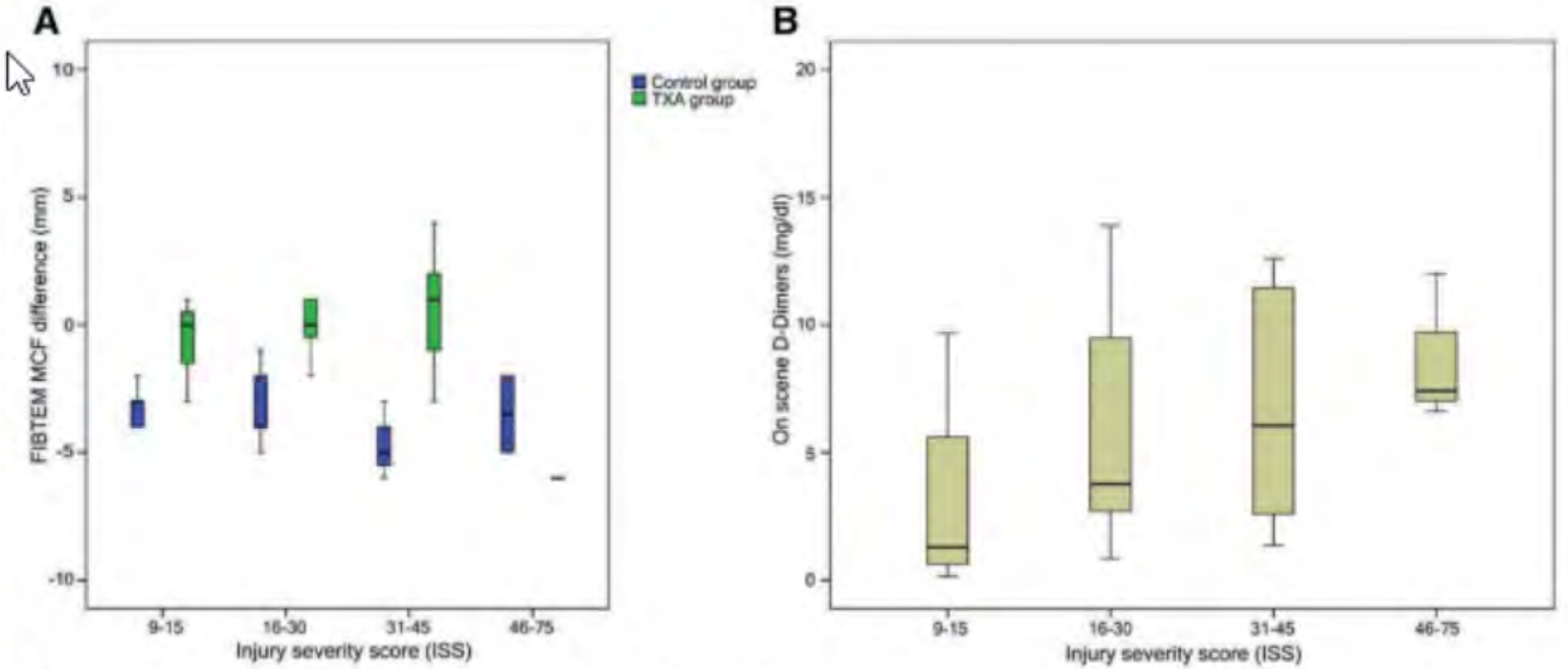
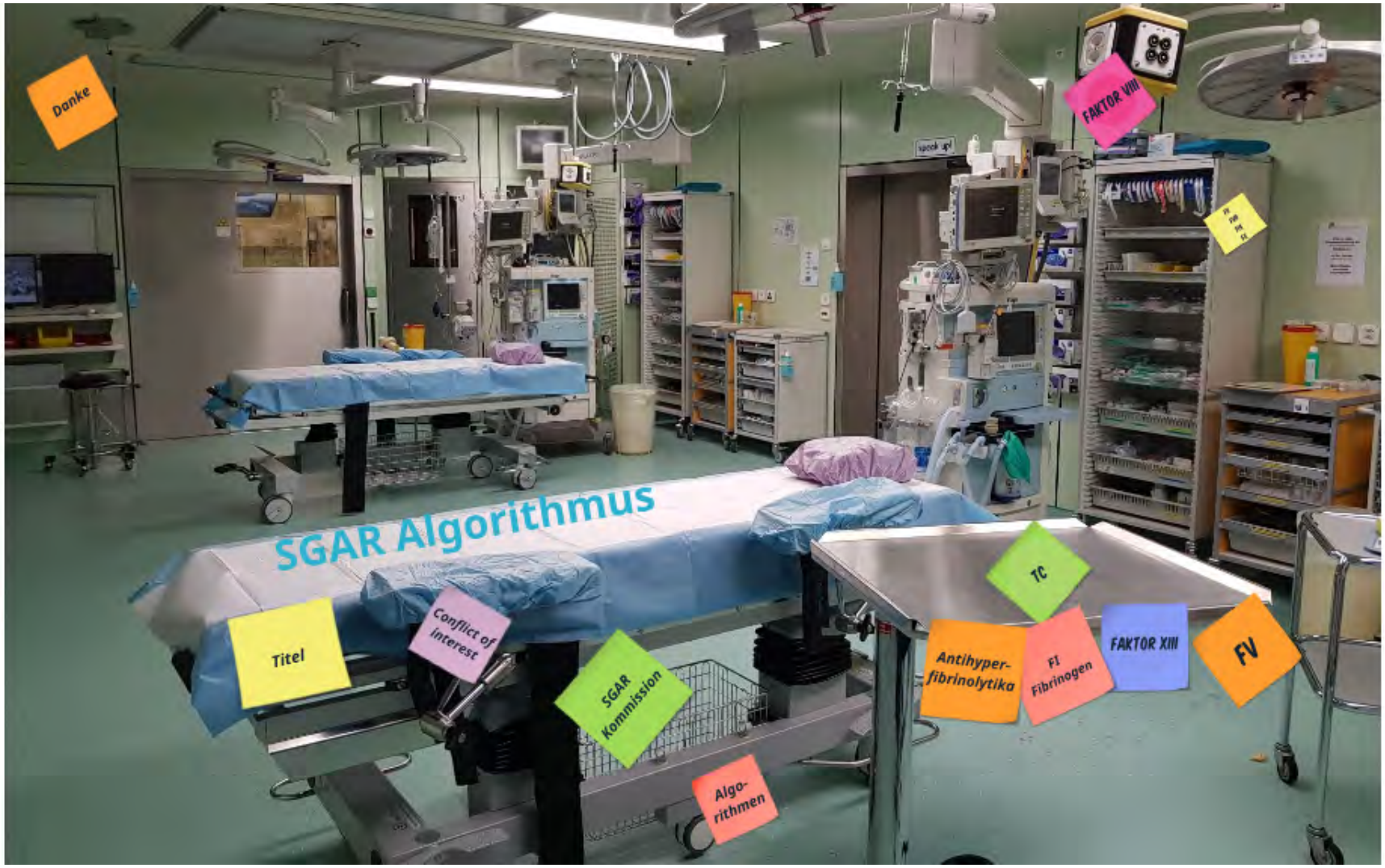
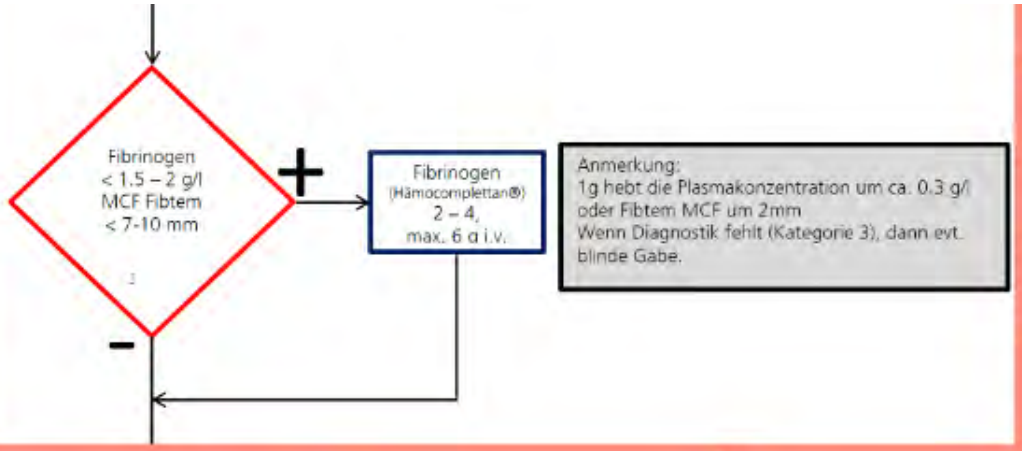


Figure 2. A, Changes of maximum clot firmness (MCF) FIBTEM between on-scene and the emergency department regarding injury severity score. FIBTEM MCF differences between on-scene and the emergency department (ED) between the groups tranexamic acid (TXA) and control (C) are displayed in regard to ISS. B, On-scene D-dimers in regard to ISS. On-scene fibrinogen fragments (represented by D-dimer levels) increase with injury severity.

Tranexamsäure:

Nach erstem Durchlauf durch den Algorithmus und persistierender koagulopathischer Blutung beginnt man wieder vorne. Damit kommt die nächste Dosis Tranexamsäure. Das Crash2-Studienprotokoll beinhaltet einen Bolus mit anschliessender kontinuierlicher Gabe. In der Praxis wird die kontinuierliche Gabe häufig nicht mehr gegeben, da Bolus alleine zum Stopp der Hyperfibrinolyse ausreicht.


Danke
FAKTOR VIII
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV



Innerhofer

Solomon

FI FIBRINOGEN

- Akutphaseprotein
- Adhäsivprotein
- Blutviskosität
- Geschwindigkeit der Fibrinbildung von Thrombin abhängig
- Leicht fällbar
- 1.6 - 4 g/L
- in der Leber synthetisiert
- Hämocomplettan (R)
- Unerwünschte Wirkung

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

Hans Innerhofer, Dietmar Fries, Markus Mitterer, Nicole Innerhofer, Daniel van Laer, Tobias Hell, Gottfried Fischer, Stefan Schmid, Barbara Fraessdorf, Ingo R Lorenz, Mathias Strohle, Verena Fastner, Susanne Trubsbach, Helmut Ruda, Benedikt Treml, Dieter Wally, Benjamin Treml, Agnes Meyr, Christof Kastenholz, Olga Oswald

THE LANCET
Haematology
Volume 4, Issue 6, June 2017, Pages e258–e271

Findings Between March 3, 2012, and Feb 20, 2016, 100 out of 292 screened patients were included and randomly allocated to FFP (n=48) and CFC (n=52). Six patients (four in the FFP group and two in the CFC group) discontinued treatment because of overlooked exclusion criteria or a major protocol deviation with loss of follow-up. 44 patients in the FFP group and 50 patients in the CFC group were included in the final interim analysis. The study was terminated early for futility and safety reasons because of the high proportion of patients in the FFP group who required rescue therapy compared with those in the CFC group (23 [52%] in the FFP group *vs* two [4%] in the CFC group; odds ratio [OR] 25·34 [95% CI 5·47–240·03], p<0·0001) and increased needed for massive transfusion (13 [30%] in the FFP group *vs* six [12%] in the CFC group; OR 3·04 [0·95–10·87], p=0·042) in the FFP group. Multiple organ failure occurred in 29 (66%) patients in the FFP group and in 25 (50%) patients in the CFC group (OR 1·92 [95% CI 0·78–4·86], p=0·15).

Interpretation Our results underline the importance of early and effective fibrinogen supplementation for severe clotting failure in multiple trauma. The available sample size in our study appears sufficient to make some conclusions that first-line CFC is superior to FFP.

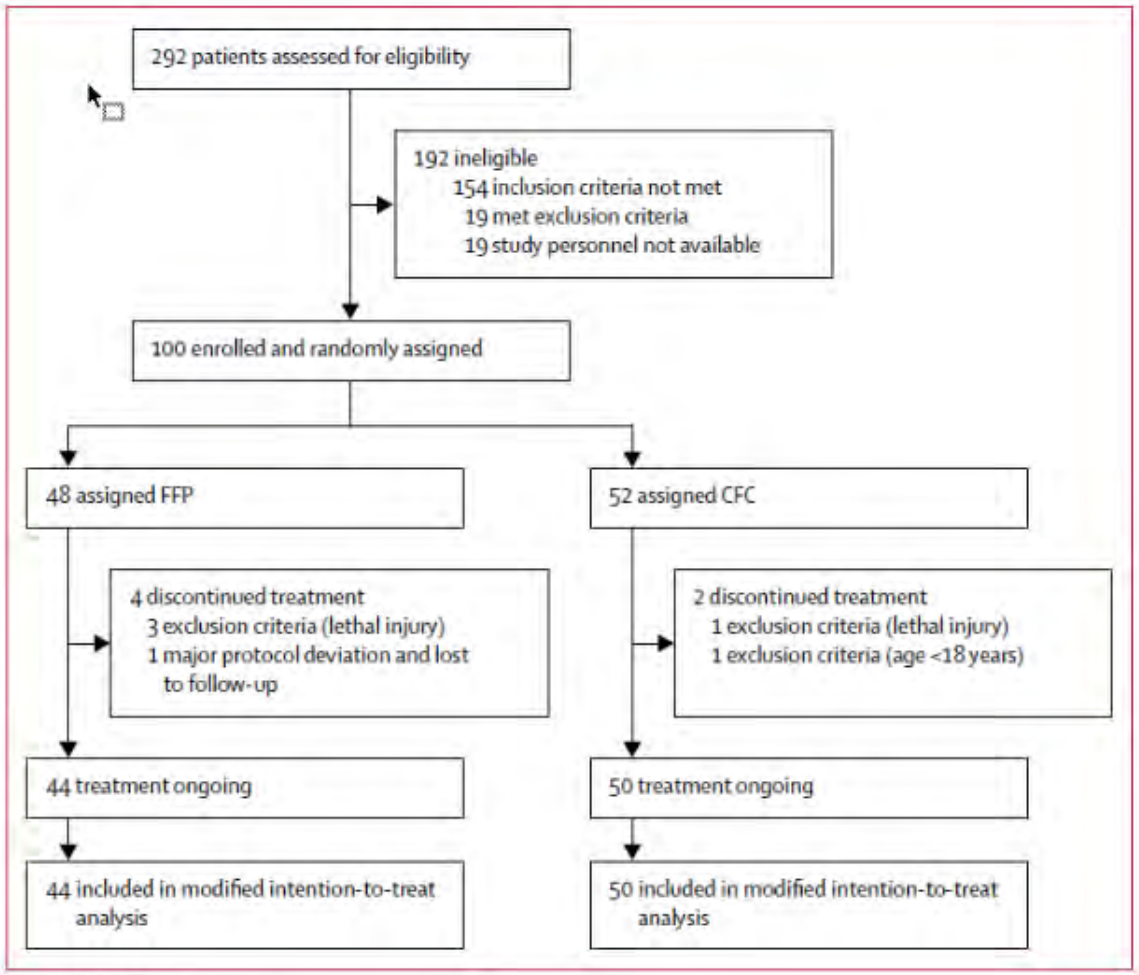


Figure 1: **Trial profile**
FFP=fresh frozen plasma. CFC=coagulation factor concentrates.

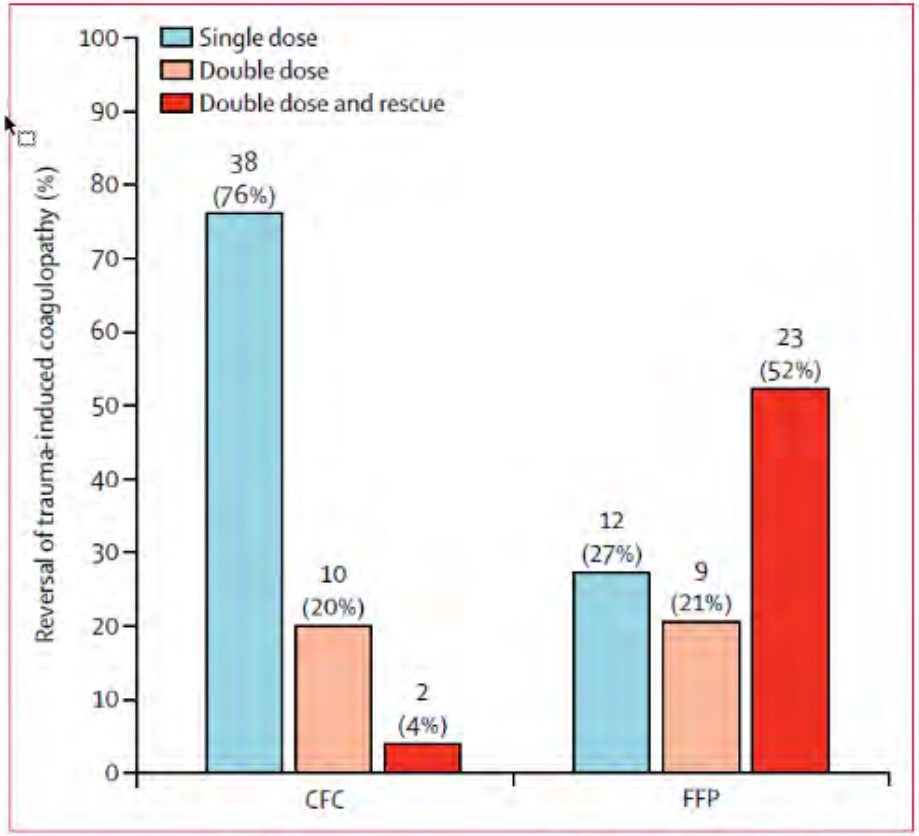


Figure 3: **Percentage of patients with reversal of coagulopathy after either single-dose or double-dose study drug administration during the first therapy loop, and percentage of patients needing double-dose and rescue medication during the first 24 h in the intention-to-treat population**
CFC=coagulation factor concentrates. FFP=fresh frozen plasma.

Article in Thrombosis and Haemostasis · March 2014
DOI: 10.1160/TH13-12-0997 · Source: PubMed

Fibrinogen measurement in cardiac surgery with cardiopulmonary bypass: Analysis of repeatability and agreement of Clauss method within and between six different laboratories

Cristina Solomon[1,2,3]; Ekaterina Baryshnikova[4]; Armando Tripodi[5]; Christoph J. Schlimp[3]; Herbert Schöchl[3,6]; Janne Cadamuro[7]; Dag Winstedt[8]; Lars Asmis[9]; Marco Ranucci[4]

[1]Department of Anesthesiology and Intensive Care, Salzburg University Hospital, SALK, Salzburg, Austria; [2]CSL Behring, Marburg, Germany; [3]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology and AUVA Research Centre, Vienna, Austria; [4]Department of Cardiothoracic and Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, Milan, Italy; [5]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Clinical Sciences and Community Health, Università degli Studi di Milano and IRCCS Cà Granda Maggiore Hospital Foundation, Milan, Italy; [6]Department of Anesthesiology and Intensive Care, AUVA Trauma Hospital of Salzburg, Austria; [7]Department of Laboratory Medicine, University Hospital of Salzburg, Salzburg, Austria; [8]Department of Anaesthesiology and Intensive Care, Skåne University Hospital and Lund University, Lund, Sweden; [9]Unilabs, Coagulation Laboratory of Unilabs, Zurich, Switzerland

Summary

Plasma fibrinogen concentration is important for coagulopathy assessment, and is most commonly measured using the Clauss method. Several factors, including device type and reagent, have been shown to affect results. The study objective was to evaluate performance and repeatability of the Clauss method and to assess differences between measurements performed during and after cardiopulmonary bypass (CPB), by testing plasma samples from patients undergoing cardiac surgery with CPB. Samples were collected from 30 patients before surgery, approximately 20 minutes before weaning from CPB, and 5 minutes after CPB and protamine. Fibrinogen concentration was determined using the Clauss method at six quality-controlled specialised laboratories, according to accredited standard operating procedures. Regarding within-centre agreement for Clauss measurement, mean differences between duplicate measurements were between 0.00 g/l and 0.15 g/l, with intervals for 95% limits of agreement for mean Bland-Altman differences up to 1.3 g/l. Regarding between-centre agreement, some mean differences between pairs of centres were above 0.5 g/l. Differences of up to ~2 g/l were observed with individual samples. Increased variability was observed between centres, with inter-class correlation values below 0.5 suggesting only fair agreement. There were no significant differences in fibrinogen concentration before weaning from CPB and after CPB for most centres and methods. In conclusion, considerable differences exist between Clauss-based plasma fibrinogen measured using different detection methods. Nevertheless, the similarity between measurements shortly before weaning from CPB and after CPB within centres suggests that on-pump measurements could provide an early estimation of fibrinogen deficit after CPB and thus guidance for haemostatic therapy.

Keywords

Blood coagulation tests, clinical laboratory techniques, fibrinogen, nephelometry and turbidimetry, patient care management

Resultate

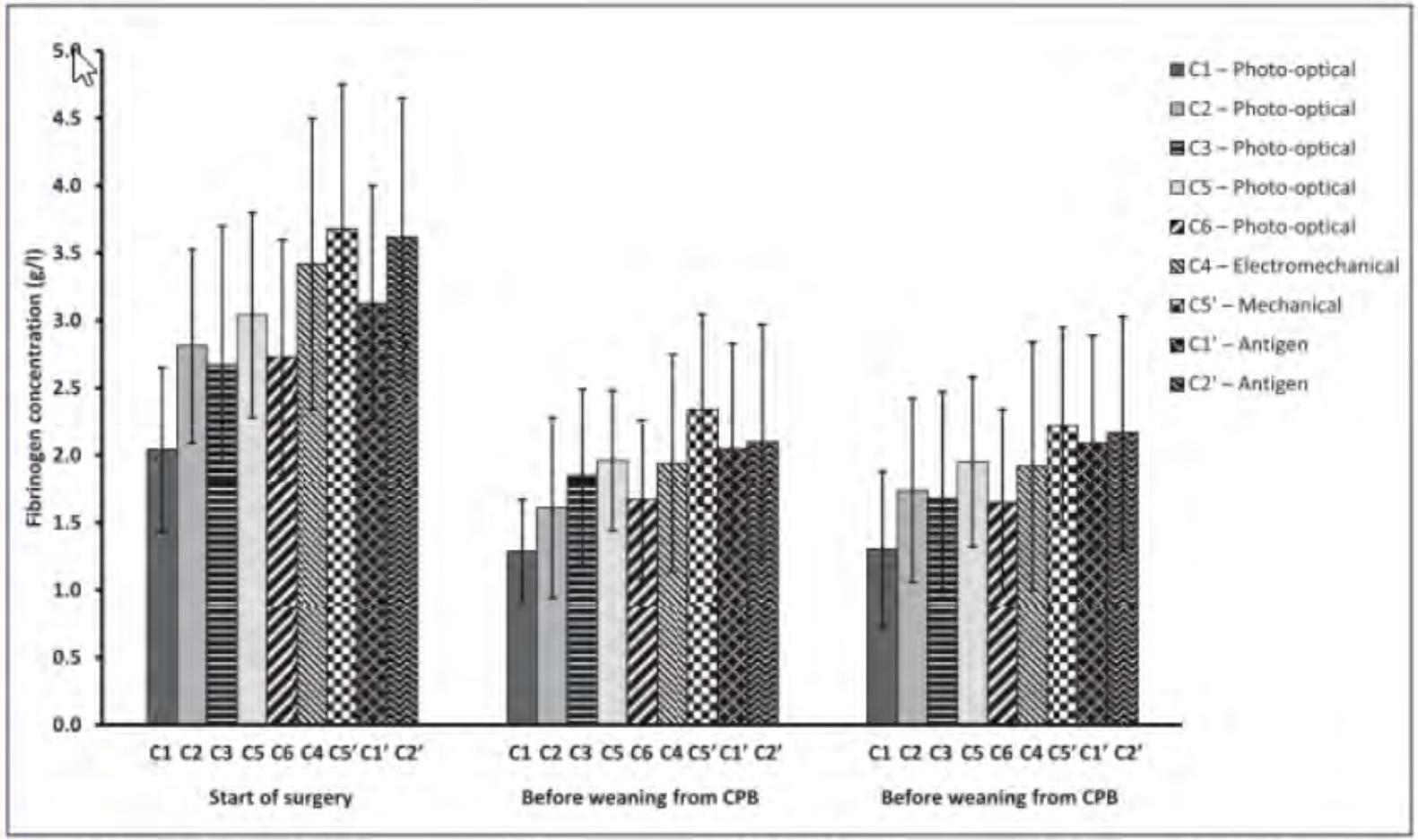
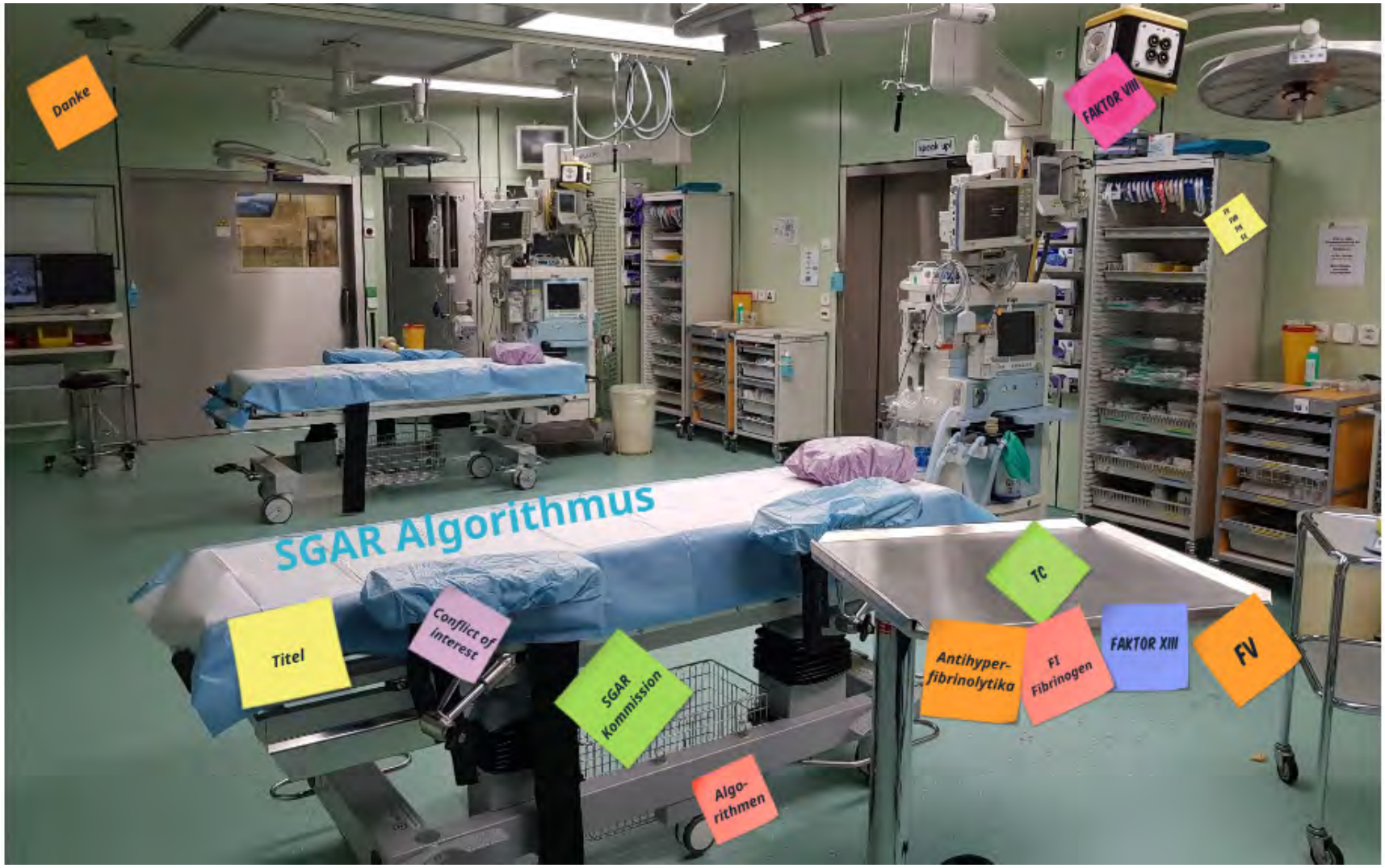


Figure 1: Mean (SD) values of fibrinogen concentration measurements obtained from the same set of plasma samples at each centre and each time point. CPB, cardiopulmonary bypass; SD, standard deviation. Fibrinogen concentration measurements are the mean of the first measurement for each plasma sample from each centre. The number assigned to each centre is independent of the order listed in *Methods*. C, centre.


Danke
FAKTOR VIII
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV

FXIII
Laki-Lorand Faktor

Transglutaminase
Quervernetzung
14-28 mg/L
70 -140%
Halbwertszeit 7d
Bestimmung

Anmerkung:
1'250 E i.v. (15 E/kg KG)
Zielbereich > 60 %
Nach indizierter Gabe von 6g Fibrinogen ist eine Substitution mit FXIII zu erwägen.

multi-functional

Networker:
Fibrin-Fibrin
Antiplasmin-Fibrin
Bakterien-Fibrinogen
Thrombospondin-Endothel (Angiogenese / Neovascularisation
Leukozyten Extrazelluläre Matrix

Faktor XIII:

Aus Sicht des Wirkungsprinzips macht die Gabe Sinn (Stabilisierung und Antihyperfibrinolyse) ist allerdings auch mit Kosten verbunden. Die Expertenmeinungen zur Gabe und zum Zeitpunkt der Gabe sind nicht vollständig kongruent. Deshalb «Gabe erwägen».

Thrombosis and Haemostasis

Coagulation factor XIII: a multifunctional transglutaminase with clinical potential in a range of conditions

Gerhard Dickneite[1]; Heiko Herwald[2]; Wolfgang Korte[3]; Yannick Allanore[4]; Christopher P. Denton[5]; Marco Matucci Cerinic[6]

[1]Preclinical Research & Development, CSL Behring GmbH, Marburg, Germany; [2]Department of Clinical Sciences, Lund University, Lund, Sweden; [3]Centre for Laboratory Medicine and Haemostasis and Haemophilia Centre, St Gallen, Switzerland; [4]Department of Rheumatology A, Paris Descartes University, APHP, Hôpital Cochin, Paris, France; [5]Centre for Rheumatology, UCL Medical School, Royal Free Campus, London, UK; [6]Department of Experimental and Clinical Medicine, Careggi Hospital (AOUC), University of Florence, Florence, Italy

http://dx.doi.org/10.1160/TH14-07-0625
Thromb Haemost 2015; 113: 686–697

Summary

Coagulation factor XIII (FXIII), a plasma transglutaminase, is best known as the final enzyme in the coagulation cascade, where it is responsible for cross-linking of fibrin. However, a growing body of evidence has demonstrated that FXIII targets a wide range of additional substrates that have important roles in health and disease. These include antifibrinolytic proteins, with cross-linking of α_2-antiplasmin to fibrin, and potentially fibrinogen, being the principal mechanism(s) whereby plasmin-mediated clot degradation is minimised. FXIII also acts on endothelial cell VEGFR-2 and $\alpha_v\beta_3$ integrin, which ultimately leads to downregulation of the antiangiogenic protein thrombospondin-1, promoting angiogenesis and neovascularisation. Under infectious disease conditions, FXIII cross-links bacterial surface proteins to fibrinogen, resulting in immobilisation and killing, while during wound healing, FXIII induces cross-linking of the provisional matrix. The latter process has been shown to influence the interaction of leukocytes with the provisional extracellular matrix and promote wound healing. Through these actions, there are good rationales for evaluating the therapeutic potential of FXIII in diseases in which tissue repair is dysregulated or perturbed, including systemic sclerosis (scleroderma), invasive bacterial infections, and tissue repair, for instance healing of venous leg ulcers or myocardial injuries. Adequate levels of FXIII are also required in patients undergoing surgery to prevent or treat perioperative bleeding, and its augmentation in patients with/at risk for perioperative bleeding may also have potential clinical benefit. While there are preclinical and/or clinical data to support the use of FXIII in a range of settings, further clinical evaluation in these underexplored applications is warranted.

Keywords

Coagulation, factor XIII, infection, scleroderma, wound healing

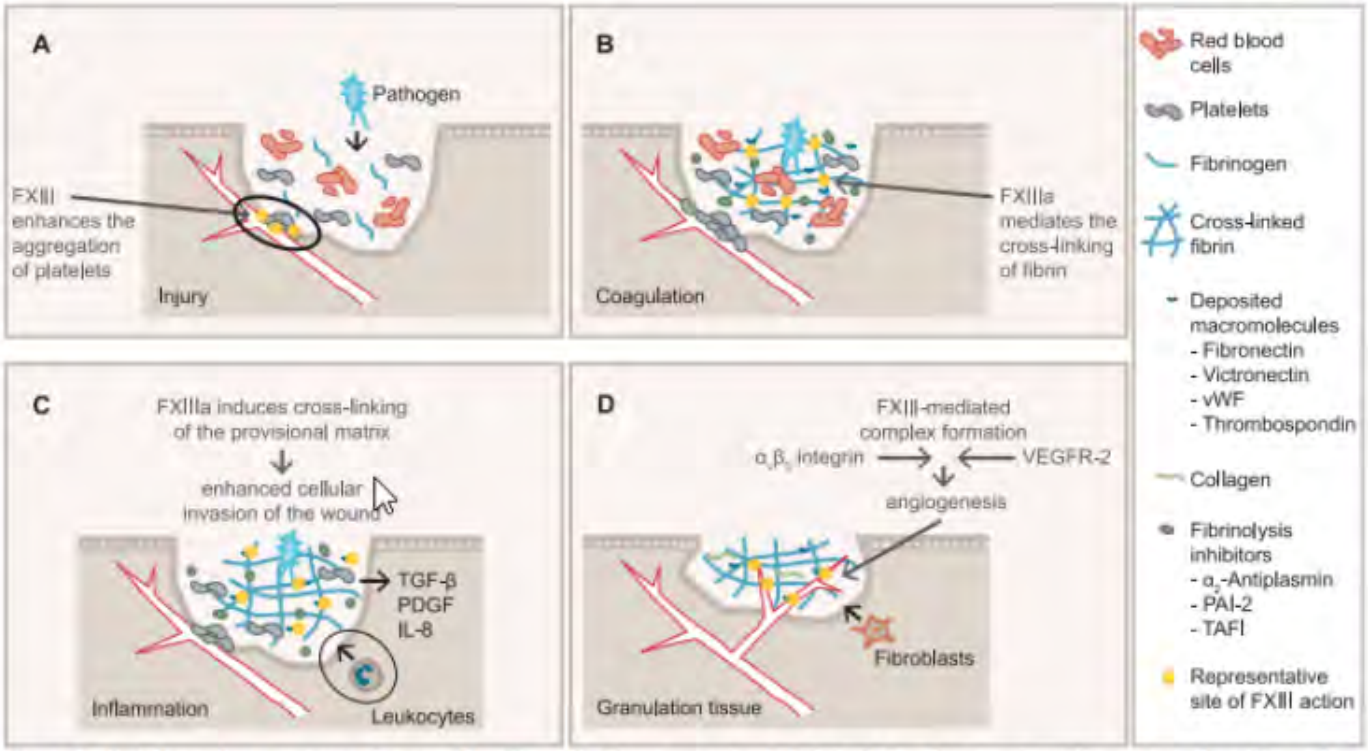
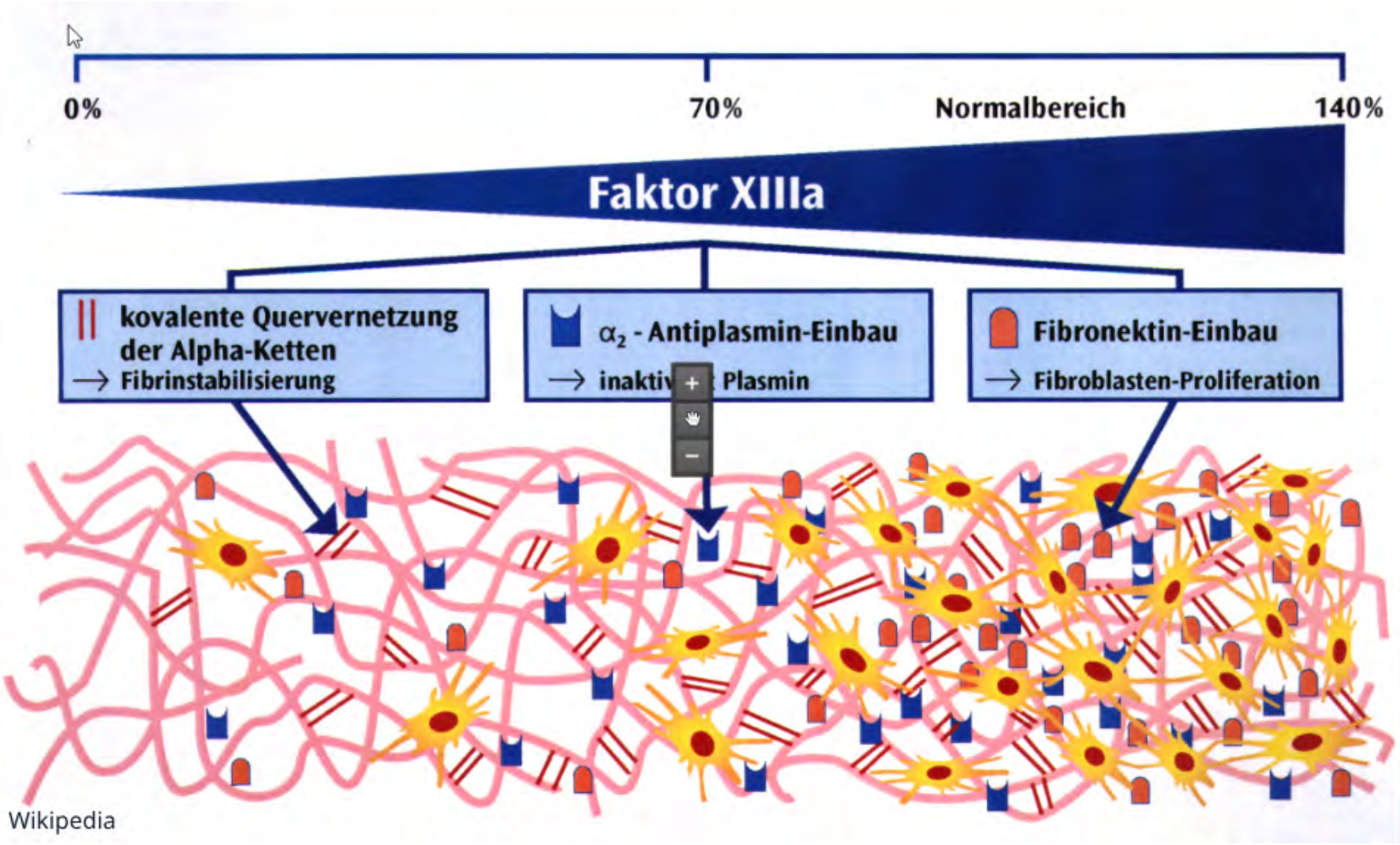


Figure 5: FXIII-dependent processes in wound healing (52). Plasma FXIII plays a role in wound healing through a number of mechanisms: A) Plasma FXIII enhances aggregation of platelets to the endothelium at the site of injury; B) FXIIIa promotes the cross-linking of fibrin, thus increasing the integrity and tensile strength of the clot. FXIIIa also mediates incorporation of pathogens, structural macromolecules and fibrinolysis inhibitors into the fibrin clot; C) FXIIIa-induced cross-linking of the provisional matrix enables the infiltration of leukocytes, which interact with the matrix via integrins; D) Cross-linked macromolecules facilitate the invasion of fibroblasts and endothelial cells into the wound, enabling collagen deposition and angiogenesis. FXIII mediates the formation of a complex between $\alpha_9\beta_1$ integrin and VEGFR-2 on endothelial cells. This complex formation results in the activation of both receptors and the upregulation of downstream angiogenic signalling pathways (shown in Figure 2). FXIIIa, activated FXIII; IL-8, interleukin-8; PAI-2, plasminogen activator inhibitor-2; PDGF, platelet-derived growth factor; TAFI, thrombin-activatable fibrinolysis inhibitor; TGF-β, transforming growth factor-β; VEGFR-2, vascular endothelial growth factor receptor 2; vWF, von Willebrand factor.


0%
70%
Normalbereich
140%
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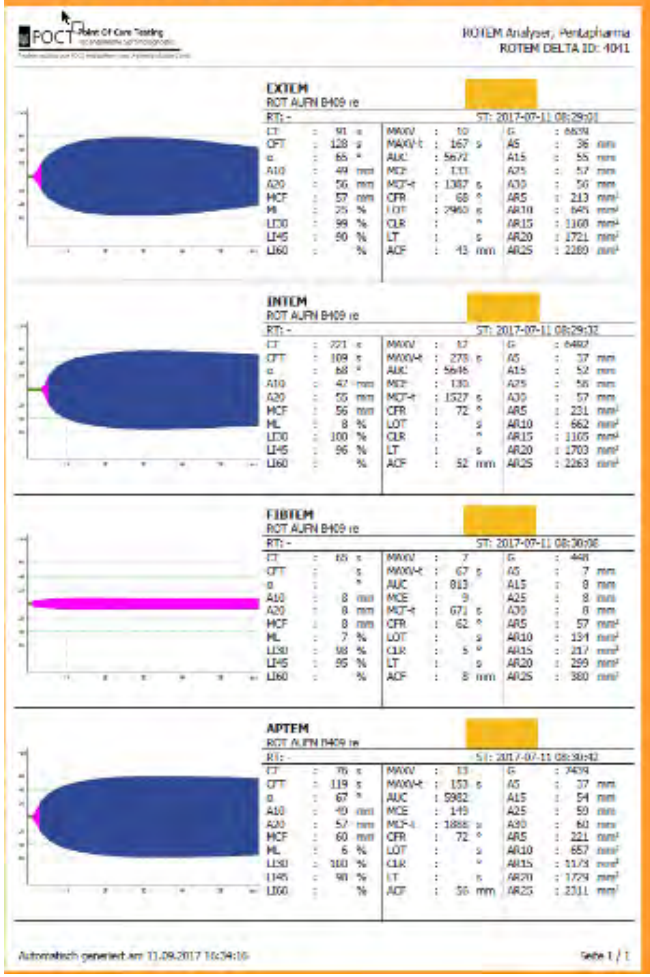
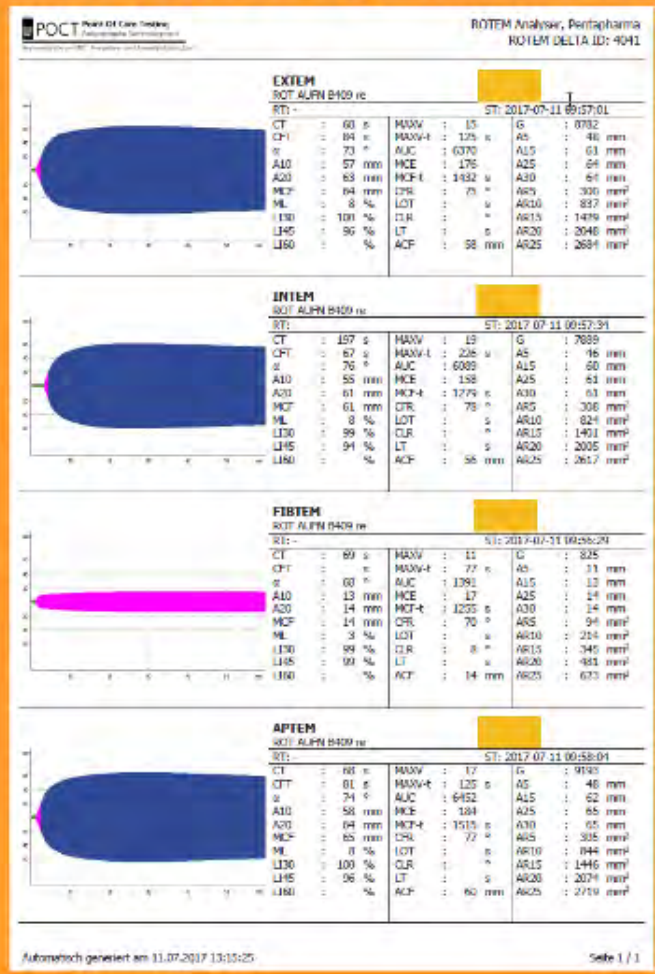
→ Fibrinstabilisierung
α2 - Antiplasmin-Einbau
→ inaktiv Plasmin
Fibronektin-Einbau
→ Fibroblasten-Proliferation

Wikipedia

Faktor XIII Mangel <10%

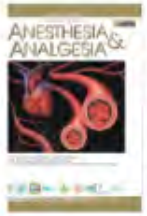


nach 2000IE Fibrogammin >80%



Factor XIII and Tranexamic Acid But Not Recombinant Factor VIIa Attenuate Tissue Plasminogen Activator–Induced Hyperfibrinolysis in Human Whole Blood

Daniel Dirkmann, Dr. med., Klaus Görlinger, Dr. med., Caroline Gisbertz, Fabian Dusse, Dr. med., and Jürgen Peters, Prof. Dr. med.



Anesthesia & Analgesia
Issue: Volume 114(6), June 2012, p 1182–1188

Publication Type: [Cardiovascular Anesthesiology: Research Reports]
DOI: 10.1213/ANE.0b013e31823b6683
ISSN: 0003-2999
Accession: 00000539-201206000-00010

BACKGROUND: Hyperfibrinolysis is a pathological state that often results in depletion of coagulation factors and platelets and can contribute to bleeding. Factor XIII (FXIII) and thrombin activatable fibrinolysis inhibitor have key roles in protecting clots against fibrinolysis. We tested the hypotheses that FXIII concentrate, prothrombin complex concentrate (PCC), recombinant factor VIIa (rFVIIa), and tranexamic acid (TA) inhibit fibrinolysis to different degrees, and that platelets contribute to antifibrinolysis.

METHODS: Hyperfibrinolysis was induced by addition of recombinant tissue plasminogen activator (r-tPA) (final concentration: 100 ng · mL^{-1}) to citrated whole blood obtained from 13 healthy volunteers. To assess inhibition of fibrinolysis, we added to the assays FXIII-A_2B_2 (0.42 U · mL^{-1}), PCC (0.42 U · mL^{-1}), rFVIIa (final concentration: 1.6 μg · mL^{-1}), TA (final concentration: 0.33 mg · mL^{-1}), or saline. Coagulation was analyzed by rotational thromboelastometry (ROTEM®) using the clot lysis index (CLI) after 45 and 60 minutes in extrinsically activated assays, with (FIBTEM®) and without (EXTEM®) inhibition of platelet function by cytochalasin D.

RESULTS: After r-tPA–evoked fibrinolysis (CLI45: median 78%; 72/85.5, 25th/75th percentile), FXIII (90%; 82.5/96, $P = 0.025$), PCC (89%; 74/91, $P = 0.0465$), and TA (94%; 92/96, $P = 0.001$) but not rFVIIa (79%; 72/86.5, $P = 1.0$) significantly attenuated the decrease in CLI. Similarly, CLI60 increased only with FXIII (66%; 33/90.5, $P = 0.017$) and TA (90%; 89/92, $P = 0.001$) compared with r-tPA alone (21%; 7/59). After abolition of platelet function by cytochalasin D, only TA (95%; 89/97.5, $P = 0.0025$) and PCC (84%; 70.5/90, $P = 0.0305$) but not FXIII or rFVIIa significantly increased CLI45 and CLI60 (TA: 89%; 84.5/96, $P = 0.01$ and PCC: 55%; 29.5/60, $P = 0.0405$) compared with r-tPA alone (CLI45: 59%; 40.5/72.5 and CLI60: 10%; 0/30).

CONCLUSION: In thromboelastometric assays using whole blood, only TA, FXIII, and PCC significantly inhibited r-tPA–evoked hyperfibrinolysis whereas rFVIIa had no effect. We also found that the effects of exogenous FXIII were dependent on the presence of functional platelets. (Anesth Analg 2012;114:1182–8)

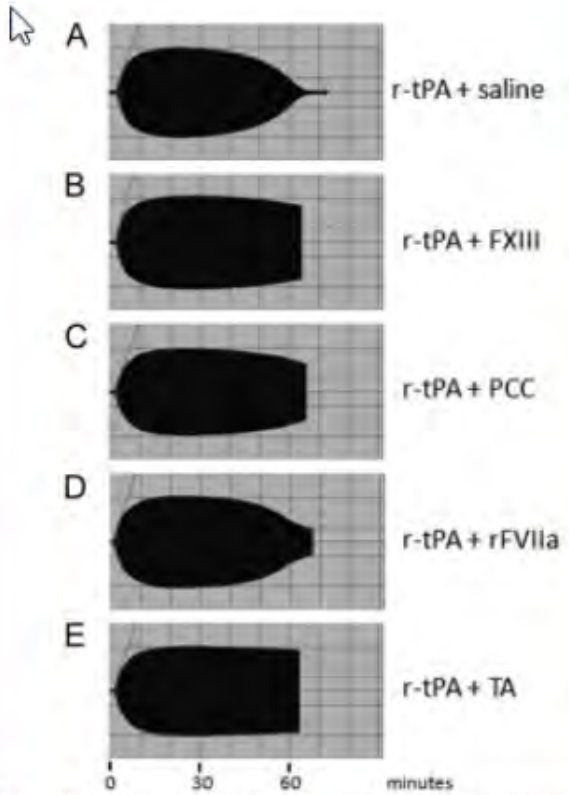
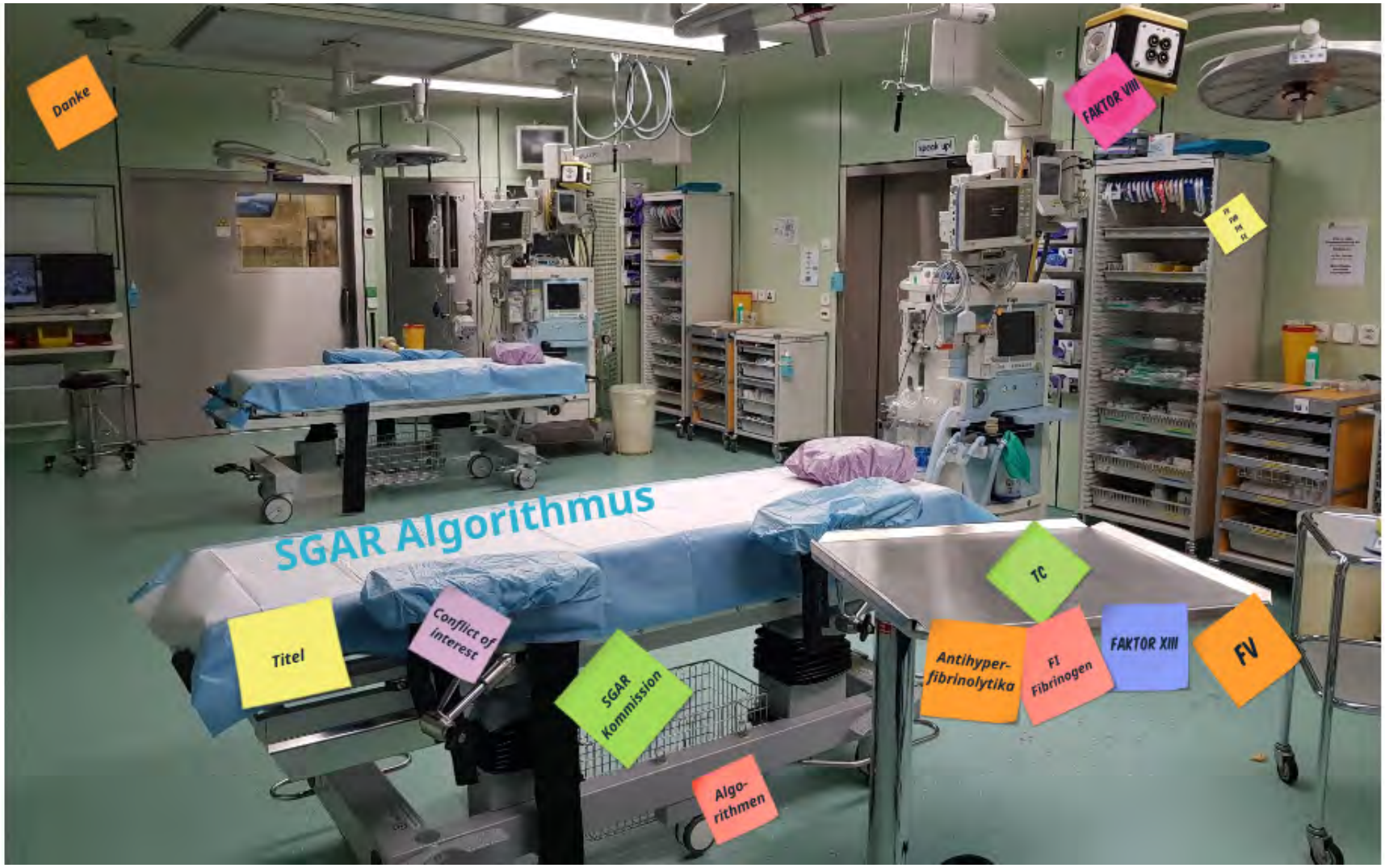


Figure 2. Representative ROTEM® recordings demonstrating the effects of administration of coagulation factor concentrates on recombinant tissue plasminogen activator (*r*-tPA)-induced hyperfibrinolysis in extrinsically activated assays. A, Saline control. B, Factor XIII (FXIII) concentrate (final concentration: 0.42 U · mL^{-1}). C, Prothrombin complex concentrate (PCC) (0.42 U · mL^{-1}). D, Recombinant factor VIIa (rFVIIa) (1.6 μg · mL^{-1}). E, Tranexamic acid (TA) (0.33 mg · mL^{-1}) delivered in equal volumes.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FI Fibrinogen
FAKTOR XIII
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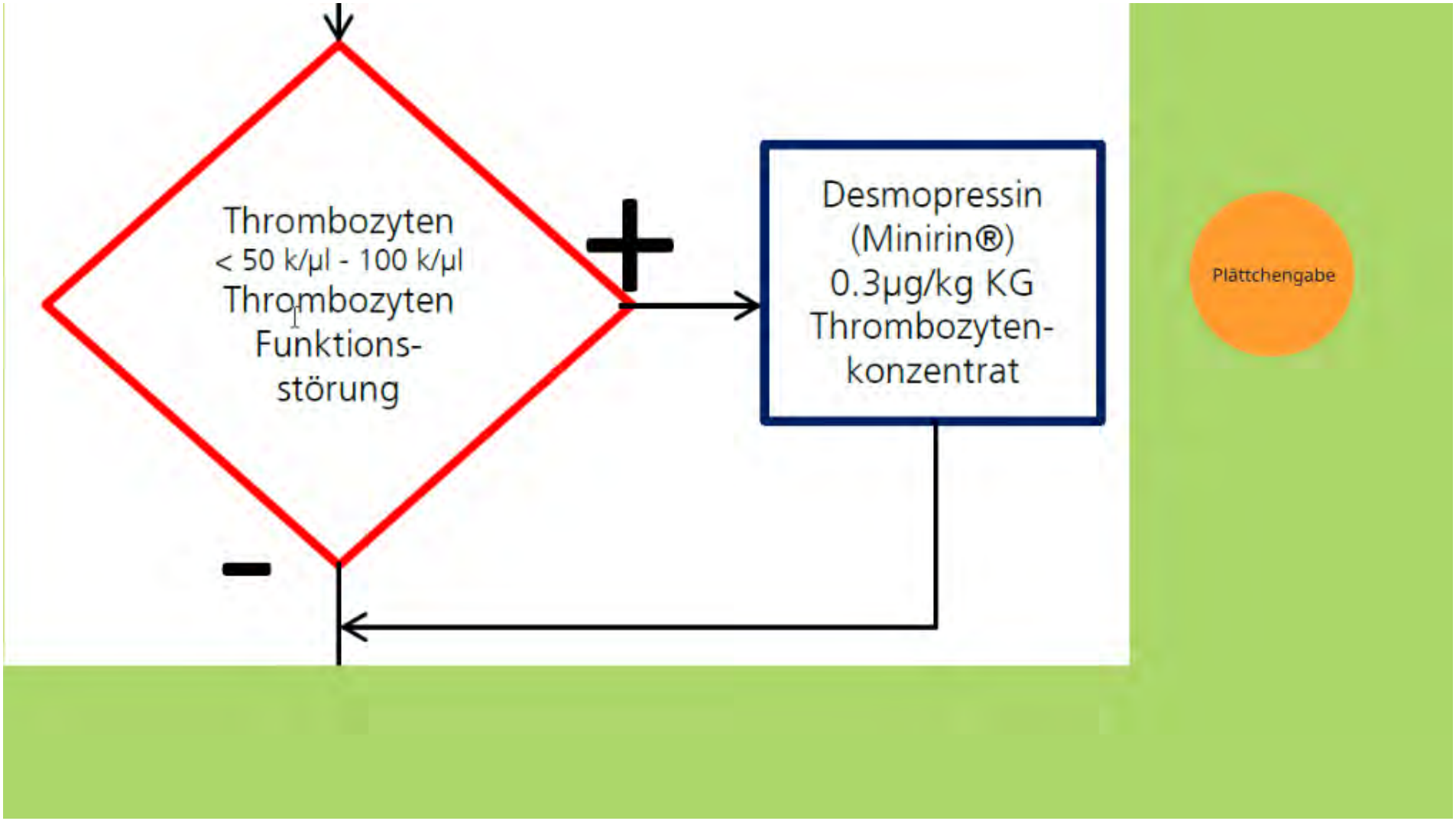
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Plättchengabe

neurocritical care society Neurocrit Care (2016) 24:6–46
DOI 10.1007/s12028-015-0222-x

CrossMark

REVIEW ARTICLE

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine

Jennifer A. Frontera[1] · John J. Lewin III[2] · Alejandro A. Rabinstein[3] · Imo P. Aisiku[4] · Anne W. Alexandrov[5,6] · Aaron M. Cook[7] · Gregory J. del Zoppo[8] · Monisha A. Kumar[9] · Ellinor I. B. Peerschke[10] · Michael F. Stiefel[11] · Jeanne S Teitelbaum[12] · Katja E. Wartenberg[13] · Cindy L. Zerfoss[14]

Published online: 29 December 2015

(2) We suggest *against* platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will *not* undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (Conditional recommendation, low-quality evidence)

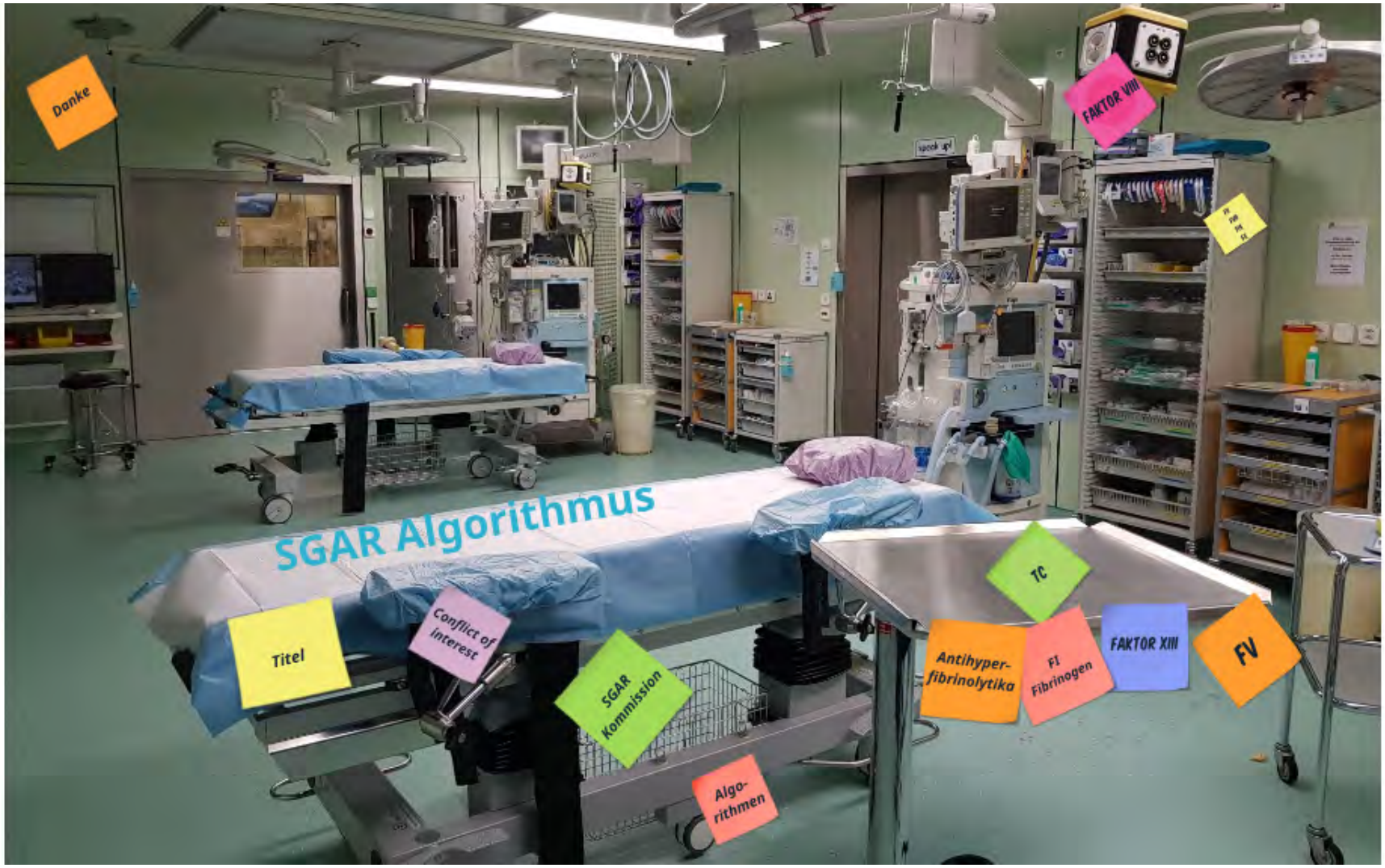
(3) We suggest platelet transfusion for patients with aspirin- or ADP inhibitor- associated intracranial hemorrhage who will undergo a neurosurgical procedure. (Conditional recommendation, moderate quality of evidence)

(a) We recommend platelet function testing prior to platelet transfusion if possible. (Strong recommendation, moderate quality evidence)

(b) When platelet function testing is not readily available, empiric platelet transfusion may be reasonable. (Conditional recommendation, low-quality evidence)

(c) We recommend against platelet transfusion for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance. (Strong recommendation, moderate quality evidence)

(6) We suggest consideration of a single dose of desmopressin (DDAVP) in intracranial hemorrhage (0.4 mcg/kg IV) associated with aspirin/COX-1 inhibitors or ADP receptor inhibitors. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (Conditional recommendation, low-quality evidence)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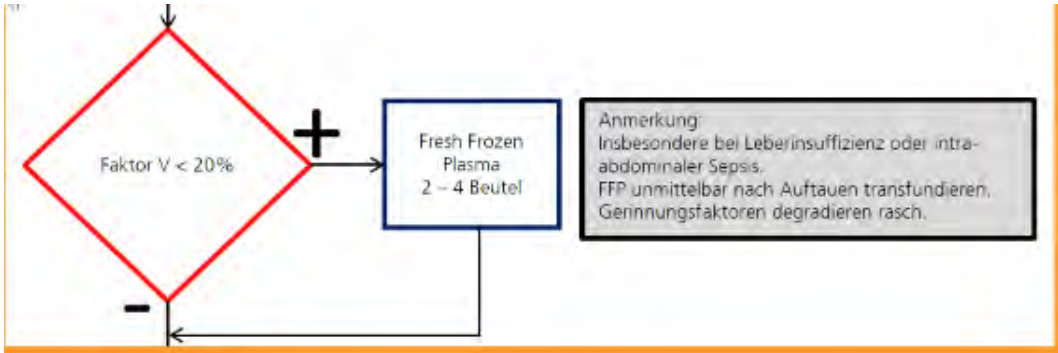
SGAR Algorithmus
Titel
Conflict of interest
SGAR Kommission
Algo-rithmen
TC
Antihyper-fibrinolytika
FI Fibrinogen
FAKTOR XIII
FV


Faktor V < 20%
+
Fresh Frozen Plasma 2 – 4 Beutel
Anmerkung:
Insbesondere bei Leberinsuffizienz oder intra-abdominaler Sepsis.
FFP unmittelbar nach Auftauen transfundieren.
Gerinnungsfaktoren degradieren rasch.
-
FV
FV Leiden
Therapie



FV

FV Leiden

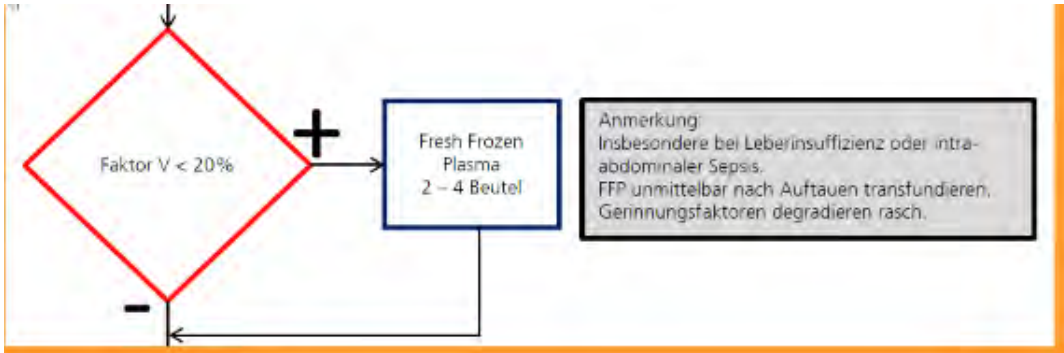
Mangel

International Normalized Ratio

aktivierte Partielle Thromboplastin zeiT

Thrombin zeiT

Therapie



FV

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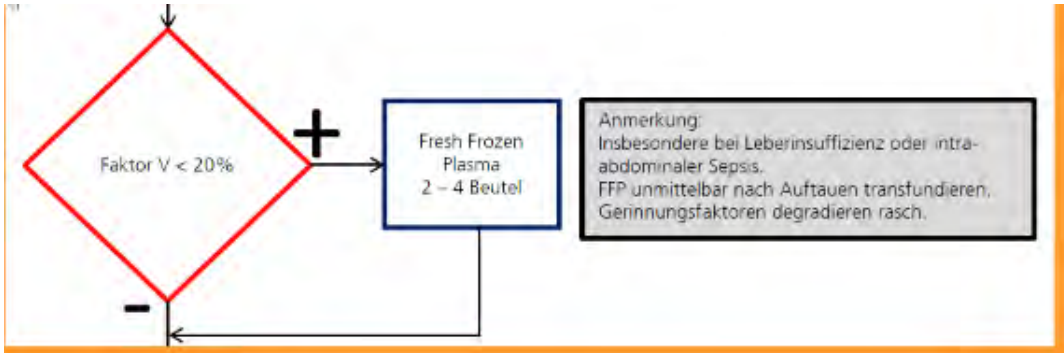


FV

FV Leiden

Mangel

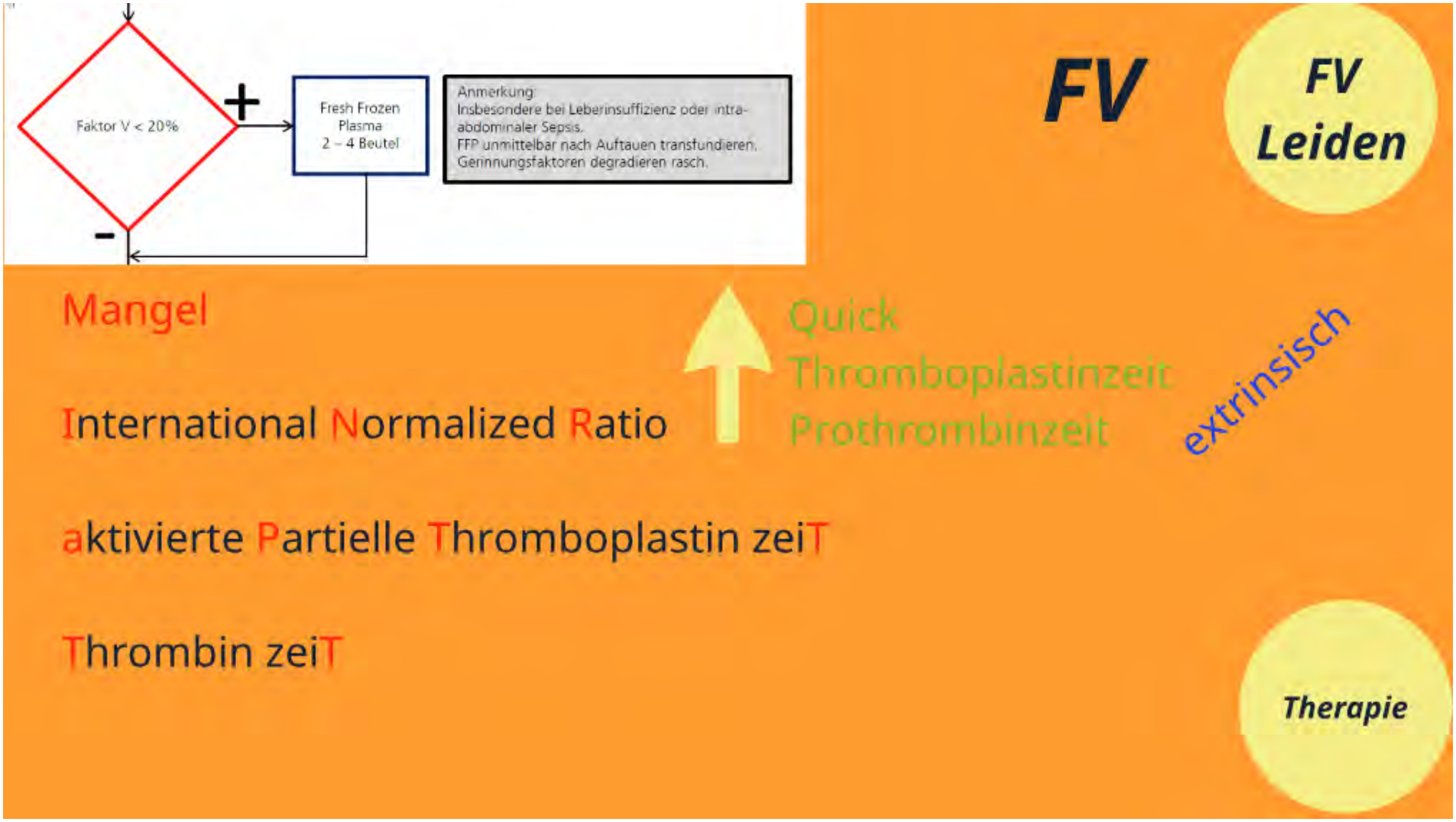
International Normalized Ratio

aktivierte Partielle Thromboplastin zeiT

Thrombin zeiT

Quick
Thromboplastinzeit
Prothrombinzeit

Therapie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Thrombin zeiT
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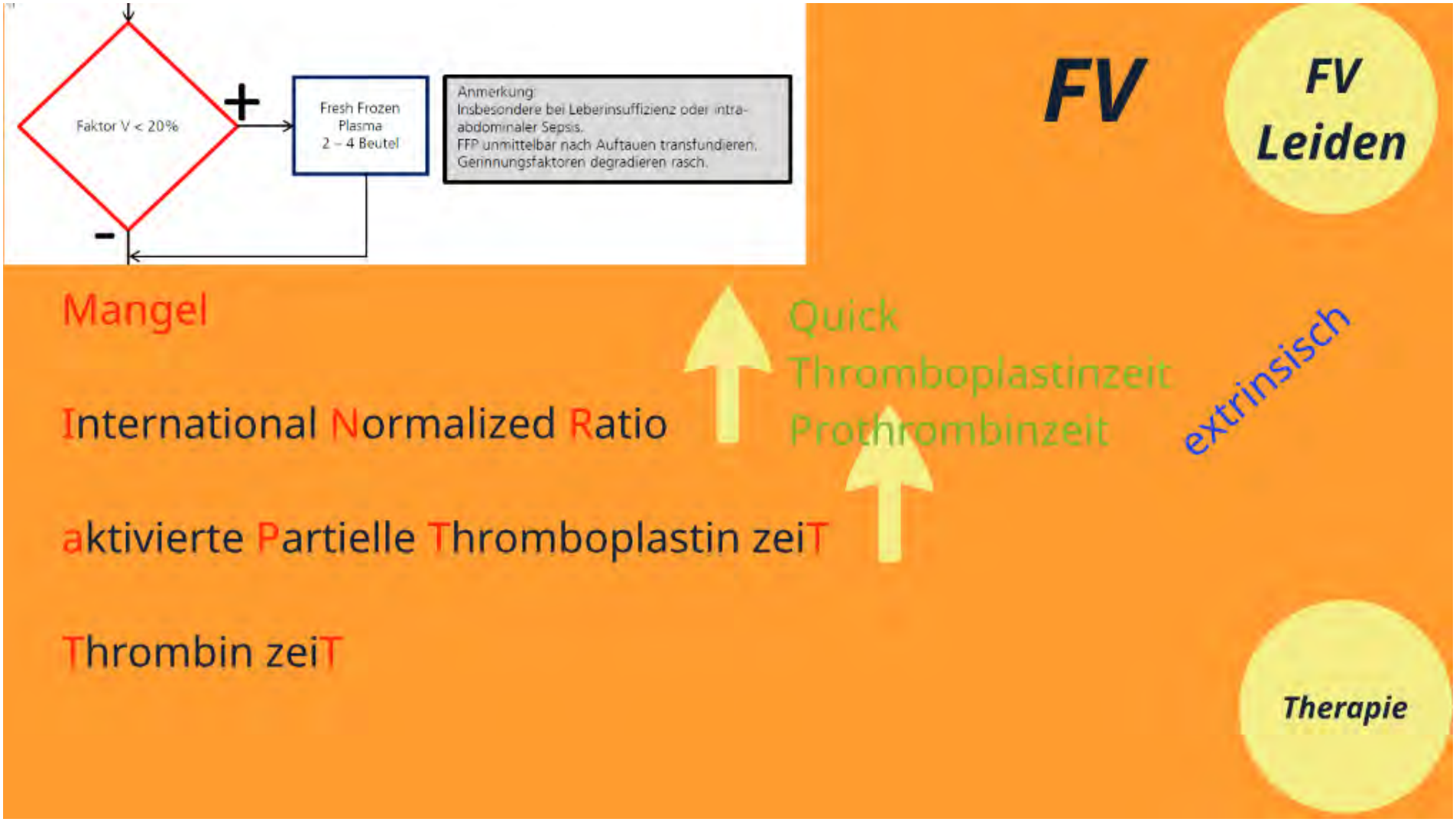
Prothrombinzeit
extrinsisch
Therapie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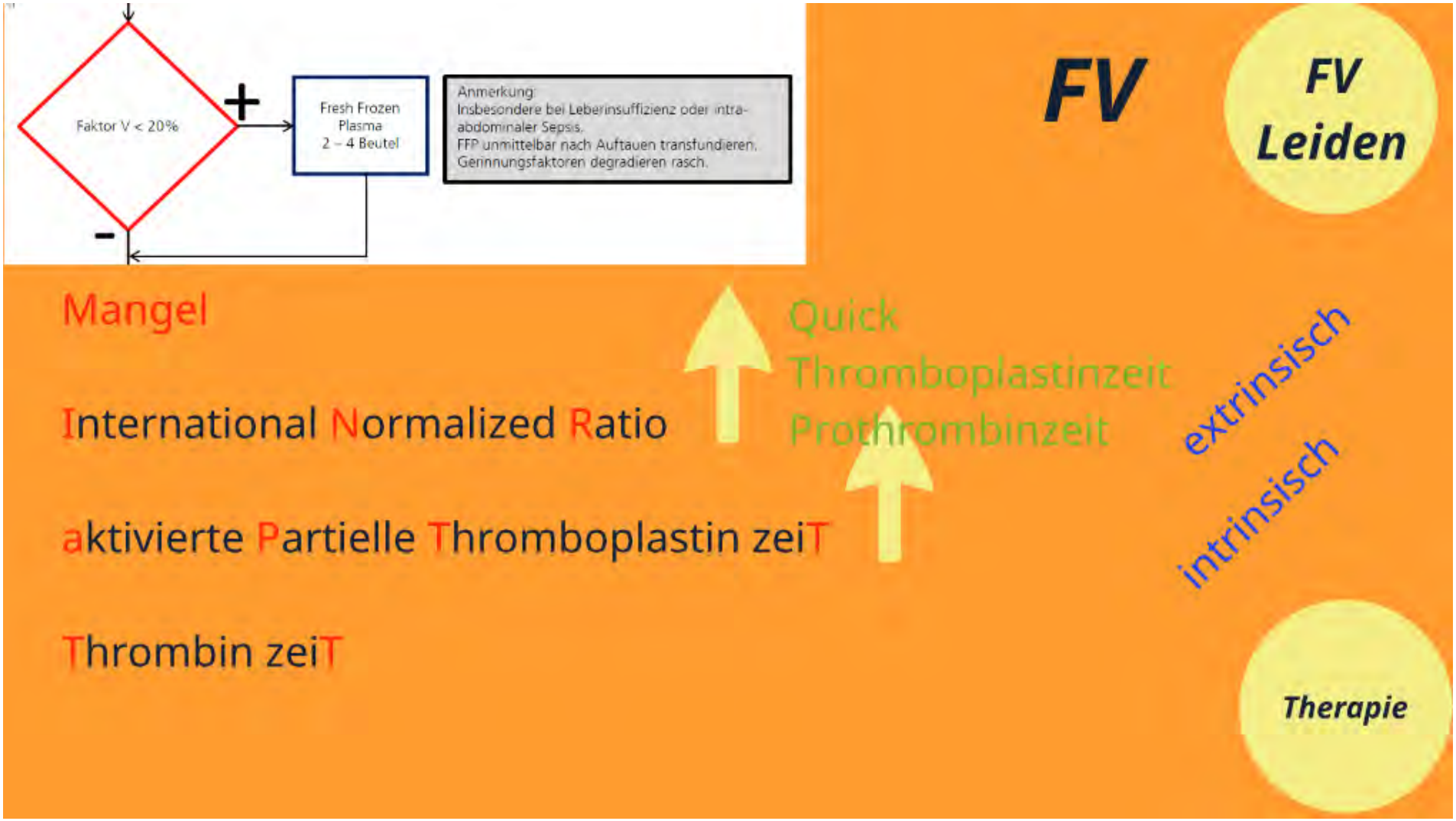
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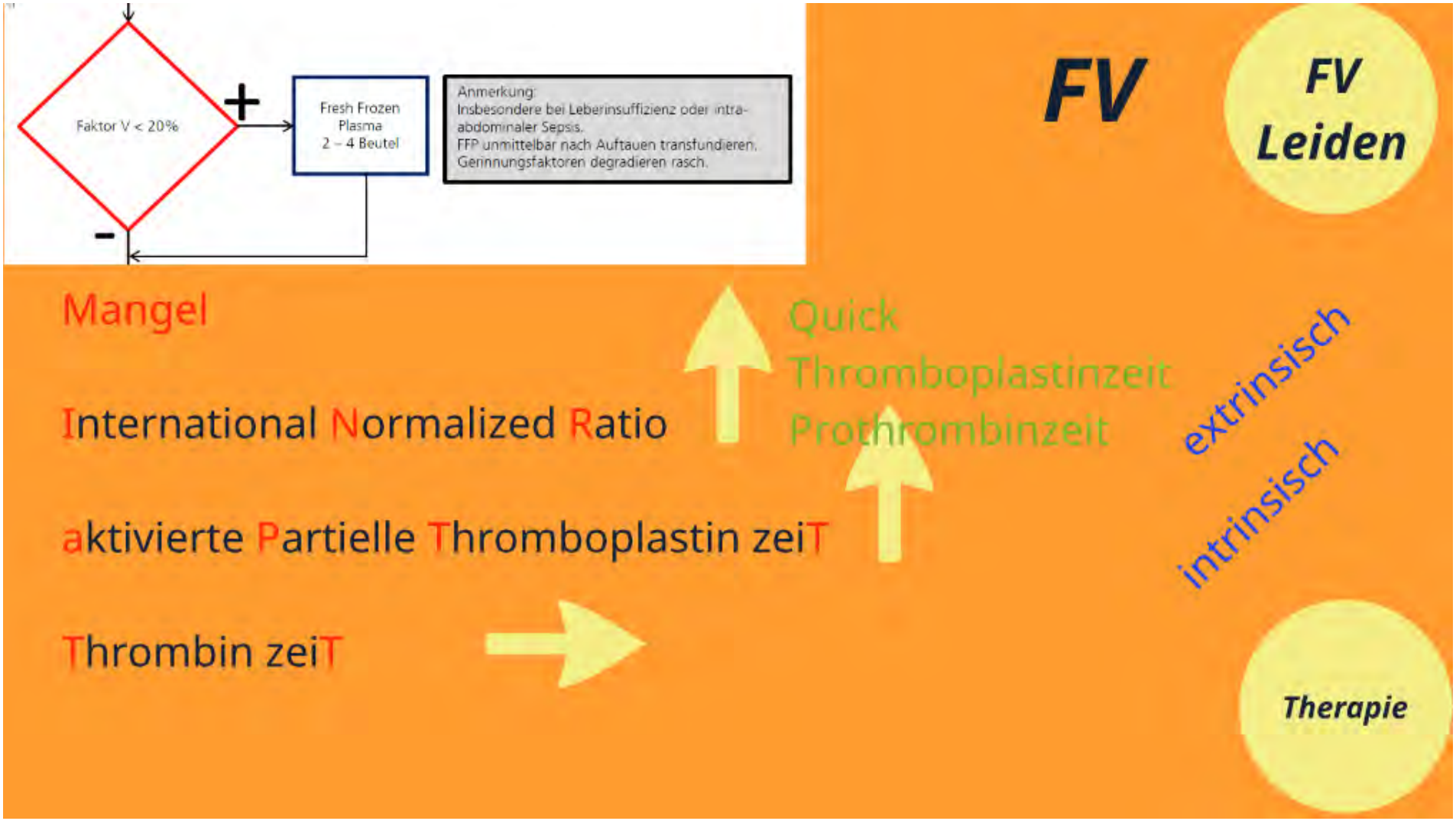
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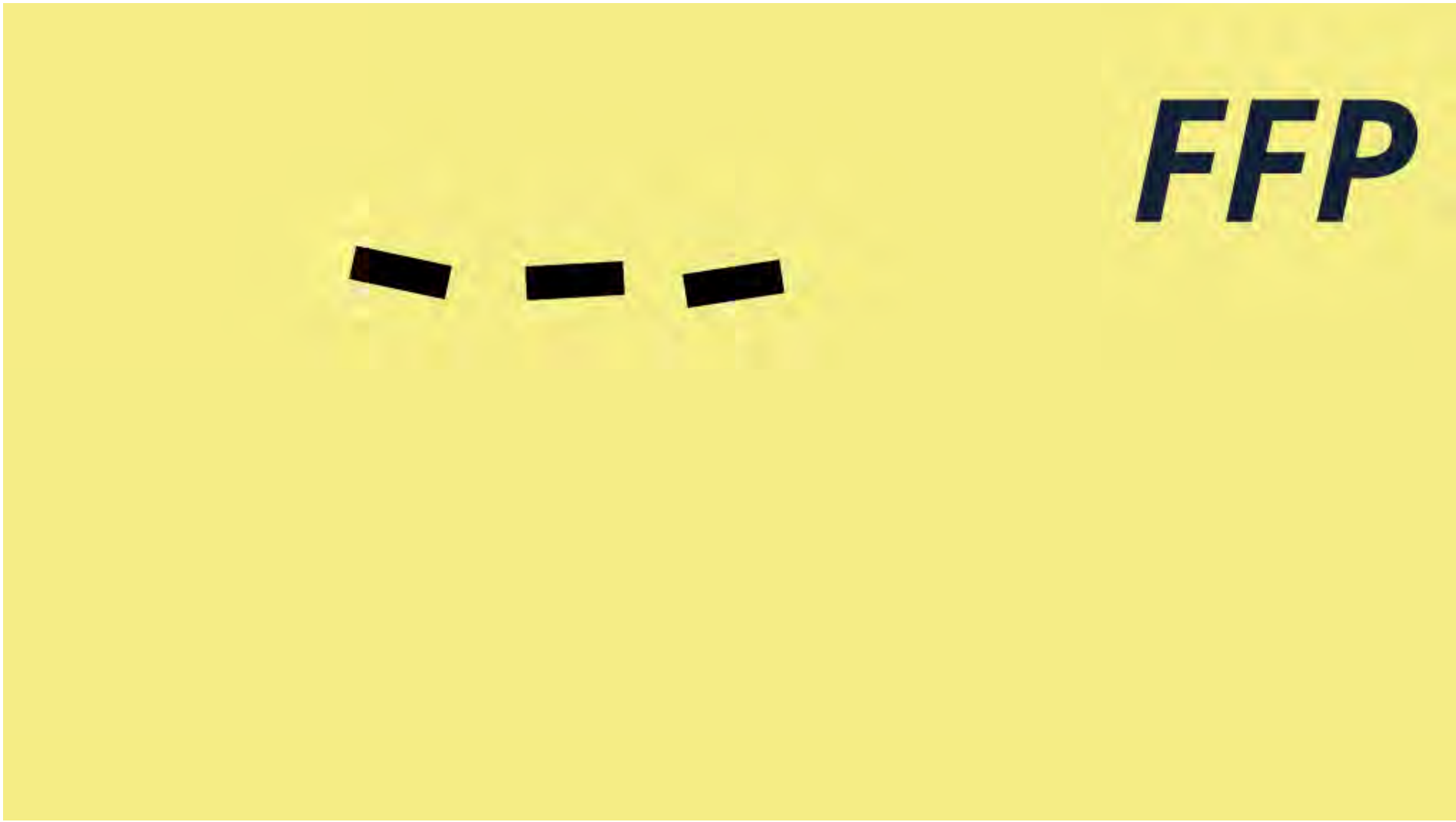
intrinsisch
Therapie

G1691 Mutation = APCR

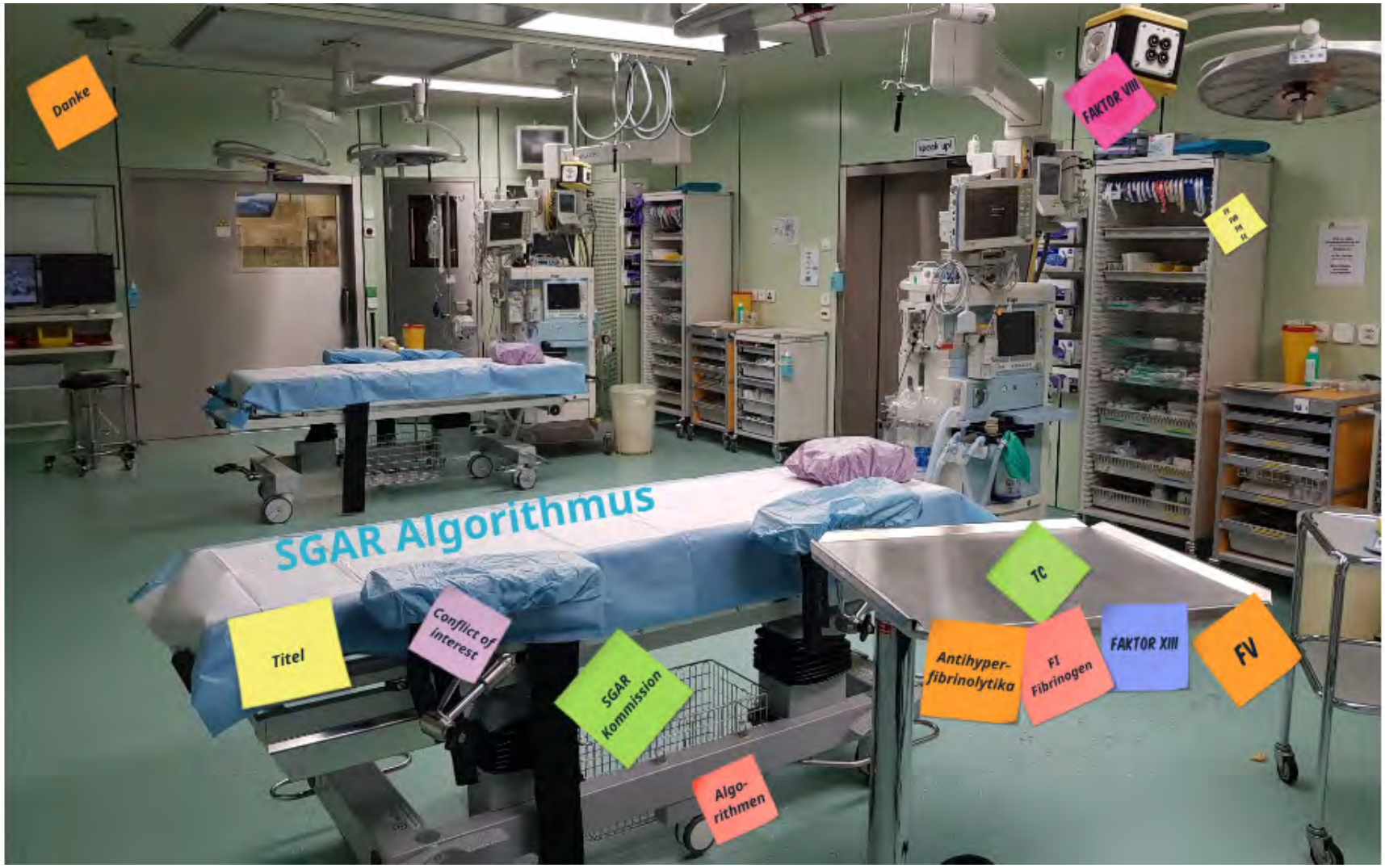
Faktor V Leiden

7% heterozygot / Risiko x7

homozygot Risiko x50 - x100


FFP


FFP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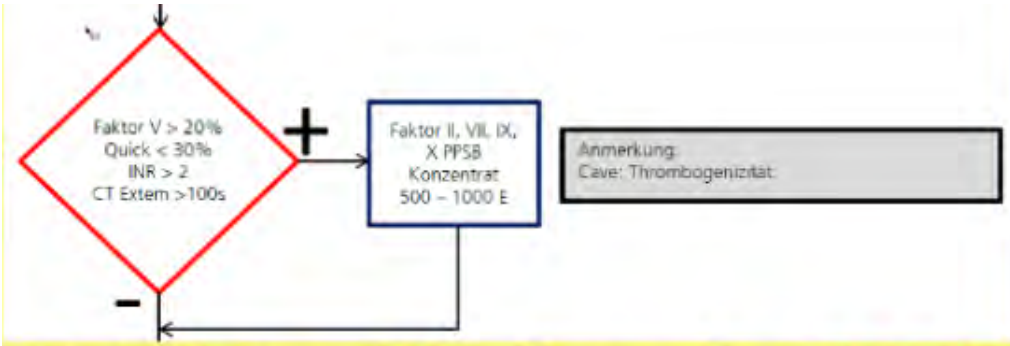

PPSB
PCC

FVII

FX

Prothrombin Komplex PPSB oder PCC (Vitamin K abhängige Faktoren):

- **Faktor II (Prothrombin)**
- **Faktor VII (Proconvertin)**
- **Faktor IX (Christmas Faktor, Hämophilie B)**
- **Faktor X (Stuart-Prower-Faktor)**

PPSB Faktorenkonzentrate:

Beriplex®
Prothromblex®
Octaplex®

PPSB
auf Faktor IX standardisiert
Heparin / AT
Reversierung von Vit. K Antagonisten

Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal

A systematic review and meta-analysis

Received: April 4, 2016
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Thromb Haemost 2016; 116: 879–890
Supplementary Material to this article is available online at www.thrombosis-online.com.

Chatree Chai-Adisaksopha[1,2]; Christopher Hillis[1,3]; Deborah M. Siegal[1]; Ron Movilla[1]; Nancy Heddle[1]; Alfonso Iorio[1,2]; Mark Crowther[1,2]

[1]Department of Medicine, McMaster University, Canada; [2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada; [3]Department of Oncology, McMaster University, Canada

Summary

Urgent reversal of warfarin is required for patients who experience major bleeding or require urgent surgery. Treatment options include the combination of vitamin K and coagulation factor replacement with either prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP). However, the optimal reversal strategy is unclear based on clinically relevant outcomes. We searched in MEDLINE, EMBASE and Cochrane library to December 2015. Thirteen studies (5 randomised studies and 8 observational studies) were included. PCC use was associated with a significant reduction in all-cause mortality compared to FFP (OR= 0.56, 95 % CI; 0.37–0.84, p=0.006). A higher proportion of patients receiving PCC achieved haemostasis compared to those receiving FFP, but this was not statistically significant (OR 2.00, 95 % CI; 0.85–4.68). PCC use was more likely to achieve normalisation of international normalised ratio (INR) (OR 10.80, 95 % CI; 6.12–19.07) and resulted in a shorter time to INR correction (mean difference –6.50 hours, 95 %CI; –9.75 to –3.24). Red blood cell transfusion was not statistically different between the two groups (OR 0.88, 95 % CI: 0.53–1.43). Patients receiving PCC had a lower risk of post-transfusion volume overload compared to FFP (OR 0.27, 95 % CI; 0.13–0.58). There was no statistically significant difference in the risk of thromboembolism following administration of PCC or FFP (OR 0.91, 95 % CI; 0.44–1.89). In conclusion, as compared to FFP, the use of PCC for warfarin reversal was associated with a significant reduction in all-cause mortality, more rapid INR reduction, and less volume overload without an increased risk of thromboembolic events.

Keywords

Factor concentrates, haemorrhage, warfarin, mortality, plasma

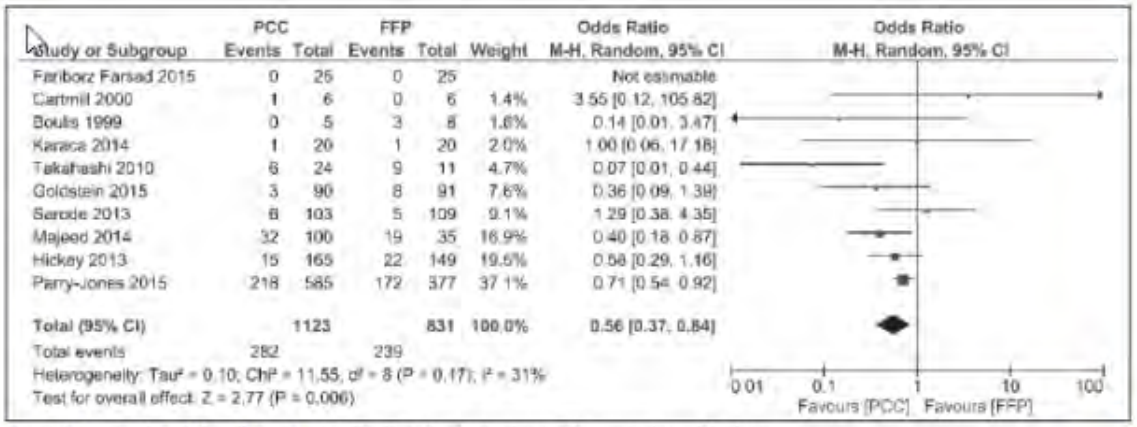

Figure 2: Forest plot of the all-cause mortality in patients receiving PCC comparing with plasma.

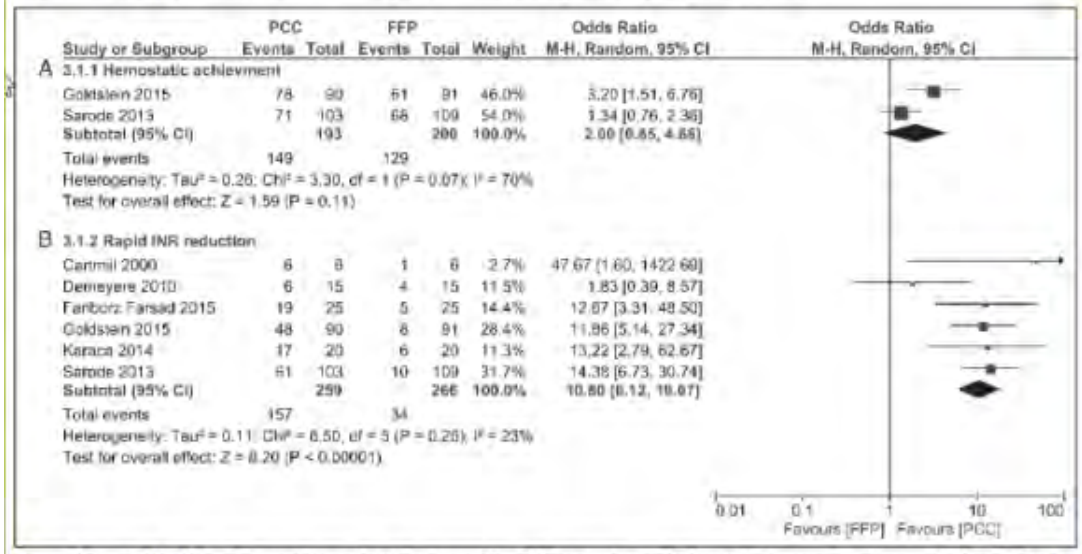

Figure 3: Forest plot of the efficacy outcomes in patients receiving PCC comparing with plasma. A) Haemostatic achievement, B) Rapid INR reduction.

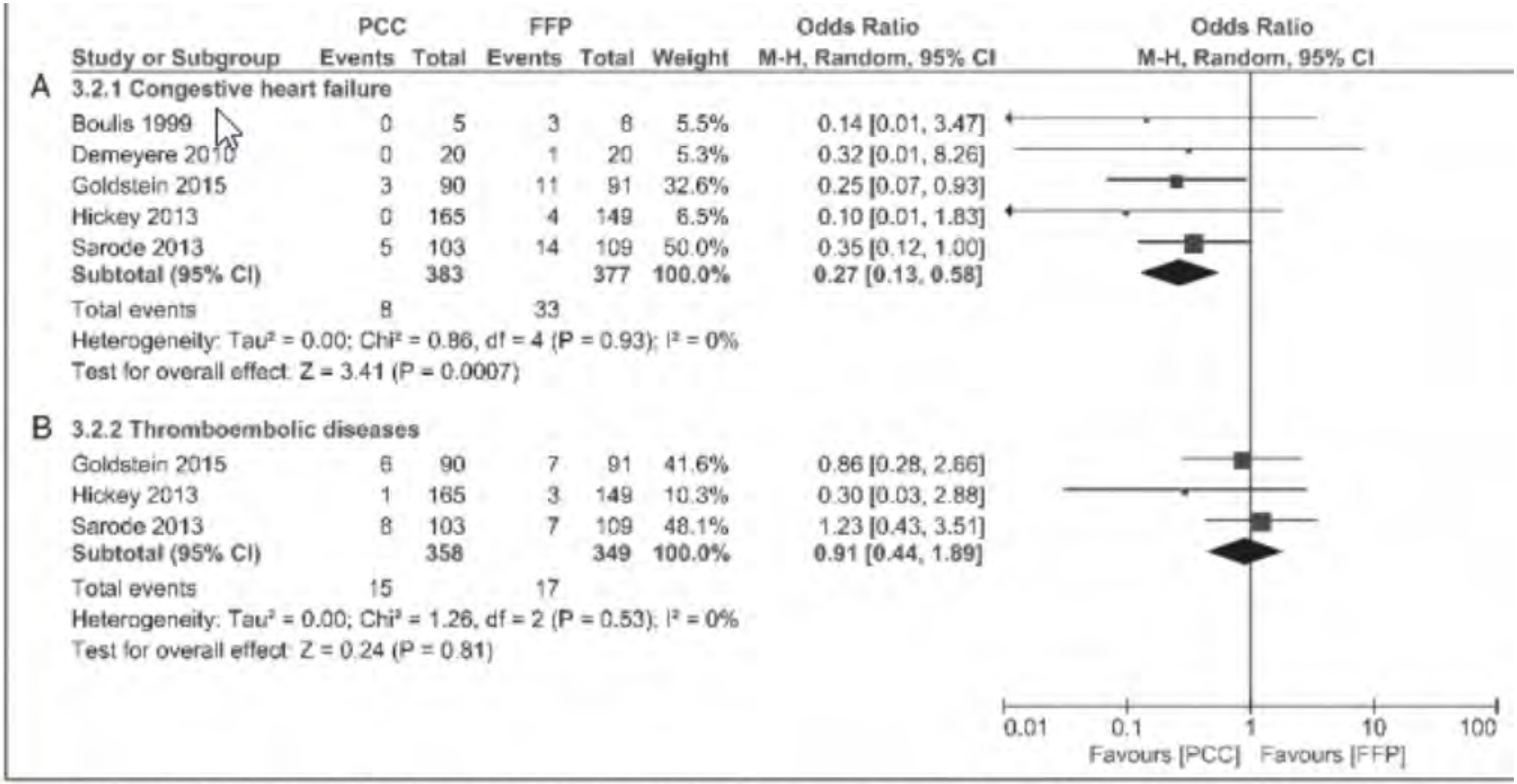

Figure 5: Forest plot of the safety outcomes in patients receiving PCC comparing with plasma. A) Congestive heart failure, B) Thromboembolic diseases.

Pharmacotherapeutic group

Antihaemorrhagics

Therapeutic indication

NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda units (BU);
- in patients with congenital haemophilia who are expected to have a high anamnestic response to factor-VIII or factor-IX administration;
- in patients with acquired haemophilia;
- in patients with congenital factor-VII deficiency;
- in patients with Glanzmann's thrombasthenia with antibodies to platelet glycoprotein (GP) IIb-IIIa and / or human leucocyte antigens (HLA), and with past or present refractoriness to platelet transfusions.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

VII

NovoSeven
eptacog alfa (activated)

Thromboembolic events - arterial and venous

When NovoSeven is administered to patients outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (see table: Vascular disorders) (5.6% in patients treated with NovoSeven versus 3.0% in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo-controlled trials conducted outside current approved indications in various clinical settings, each of these having distinct patient characteristics and hence different underlying risk profiles.

Safety and efficacy of NovoSeven have not been established outside the approved indications and therefore NovoSeven should not be used.

Thromboembolic events may lead to cardiac arrest.

Targeting factor Xa and thrombin: impact on coagulation and beyond

Charles T. Esmon

Howard Hughes Medical Institute, Coagulation Biology Laboratory, Oklahoma Medical Research Foundation, and Departments of Pathology and Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Summary

Great advances have been made in recent years in understanding the haemostatic system and the molecular and cellular basis of thrombus formation. Although directly targeting factor Xa or thrombin (factor IIa) for effective anticoagulation is now well established, evidence has emerged suggesting that factor Xa and thrombin are involved in other physiological and pathophysiological cellular processes, including inflammation. These non-haemostatic activities of factor Xa and thrombin are predominantly mediated via the activation of proteinase-activated receptors. Studies have indicated a potential role of coagulation proteins (including factor Xa and thrombin) in the progression of disease conditions such as atherothrombosis. Preclinical studies have provided evidence for the effects of direct factor Xa or direct thrombin inhibition beyond anticoagulation, including anti-inflammatory activities and atherosclerotic plaque stabilisation. In this article, the non-haemostatic activities of factor Xa and thrombin and the effects of direct inhibition of these coagulation factors on these activities are summarised. In addition, the potential roles of factor Xa and thrombin in atherosclerosis and atherothrombosis are explored and the cardiovascular profiles of rivaroxaban, apixaban and dabigatran etexilate observed in phase III clinical studies are discussed.

Keywords

Atherothrombosis, coagulation factors, proteinase-activated receptors (PAR), thrombin

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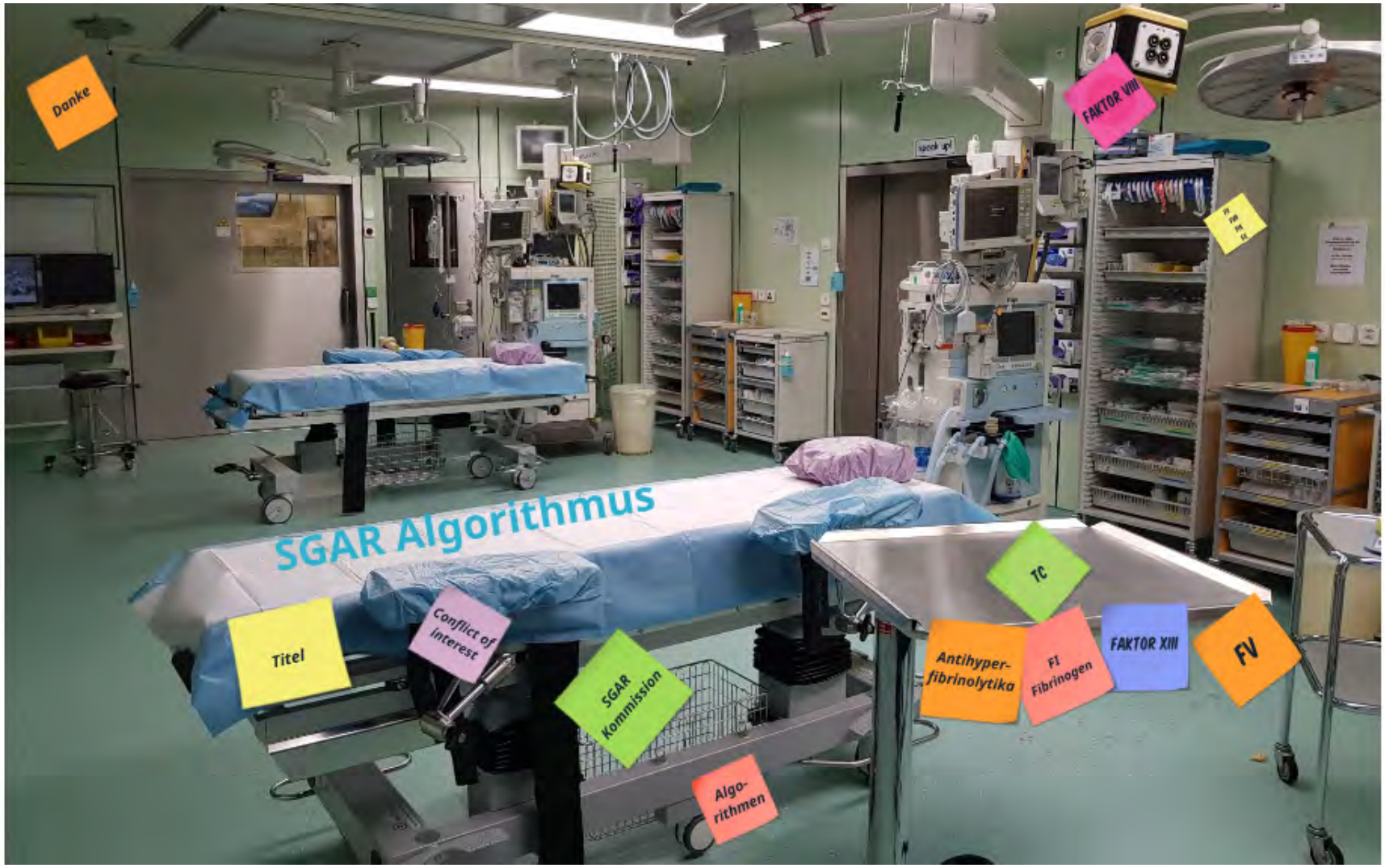
Table 1: Cardiovascular profiles of rivaroxaban, apixaban and dabigatran in phase III clinical studies of stroke prevention in patients with atrial fibrillation and of treatment of venous thromboembolism.

Stroke prevention in patients with AF				Treatment of VTE			
ROCKET AF(47)	Rivaroxaban	Warfarin	Hazard ratio (95% CI)	EINSTEIN DVT (60)	Rivaroxaban	SOC†	
Incidence of MI	0.9%	1.1%	0.81 (0.63–1.06); p=0.121	Incidence of ACS	0.3%	0.1%	
				EINSTEIN PE (61)			
				Incidence of ACS	0.6%	0.9%	
RE-LY	Dabigatran	Warfarin	Relative risk (95% CI)	RE-COVER (63)	Dabigatran	Warfarin	
Incidence of MI	110 mg 0.72%	0.53%	1.35 (0.98–1.87); p=0.07	Incidence of MI	0.3%	0.2%	p=0.69
(first publication) (62)	150 mg 0.74%		1.38 (1.00–1.91); p=0.048	RE-MEDY (64)			
			Hazard ratio (95% CI)	Incidence of ACS	0.9%	0.2%	p=0.02
Incidence of MI	110 mg 0.82%	0.64%	1.29 (0.96–1.75); p=0.09				
(Further analysis) (52)	150 mg 0.81%		1.27 (0.94–1.71); p=0.12				
ARISTOTLE	Apixaban	Warfarin	Hazard ratio (95% CI)				
Incidence of MI (65)	0.53%	0.61%	0.88 (0.66–1.17); p=0.37				

†SOC, standard of care = subcutaneous enoxaparin followed by either warfarin or acenocoumarol. ACS, acute coronary syndrome; AF, atrial fibrillation; MI, myocardial infarction; PE, pulmonary embolism.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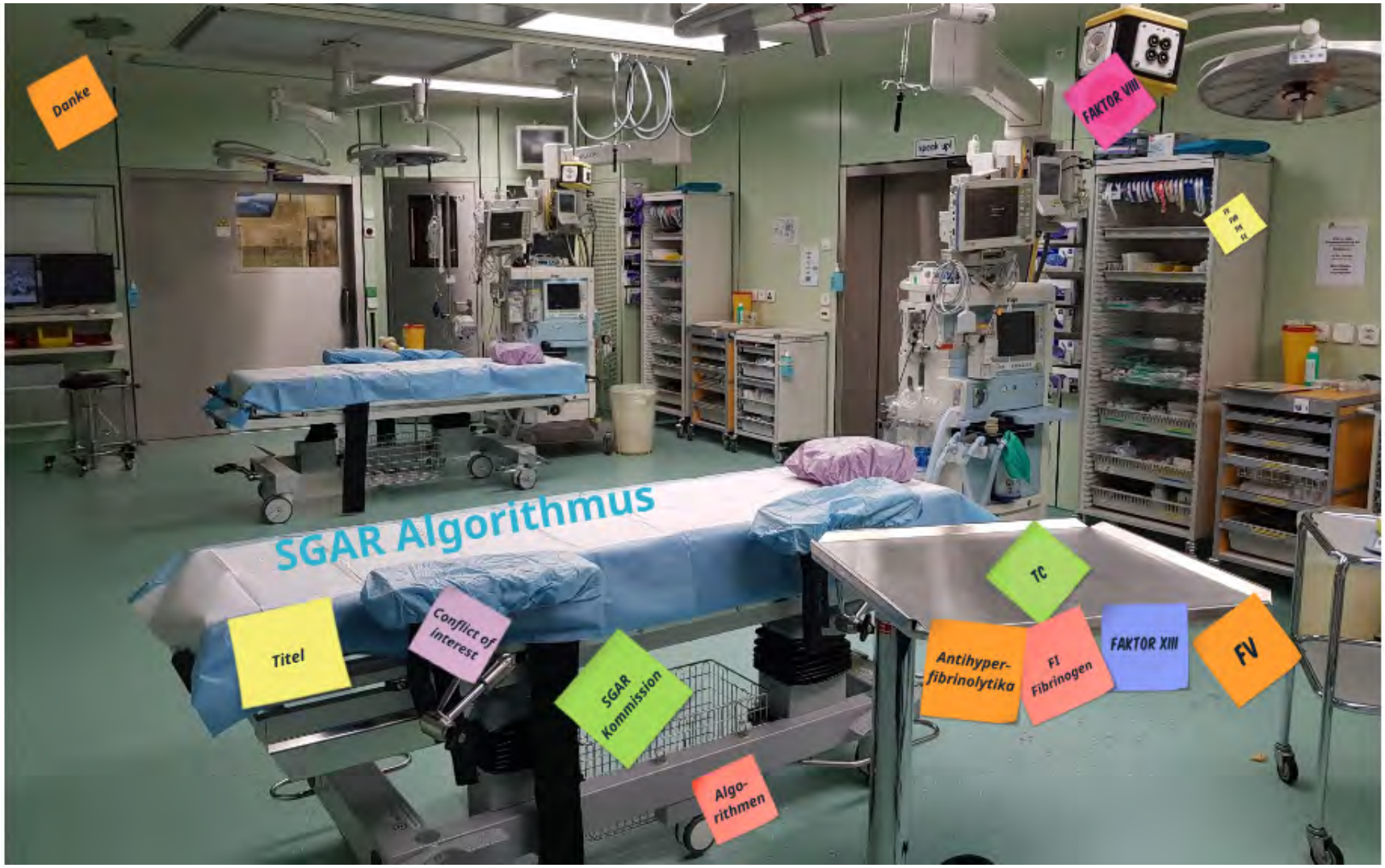
Gehe weiter zum Anfang

Anmerkung:
Erwägen von intermediär gereinigten Faktor VIII Konzentraten (Hämate®) als Quelle von von Willebrand Faktor.
Alternative Quelle Thrombozytenkonzentrat.

Hochgereinigt / Intermediär gereinigt
Rekombinant / Porcine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http://www.sgar-ssar.ch/fileadmin/user_upload/Dokumente/AG_Gerinnungs-Blutproduktemanagement/Standard_Algorithmus_22032017.pdf

Zusammenfassung

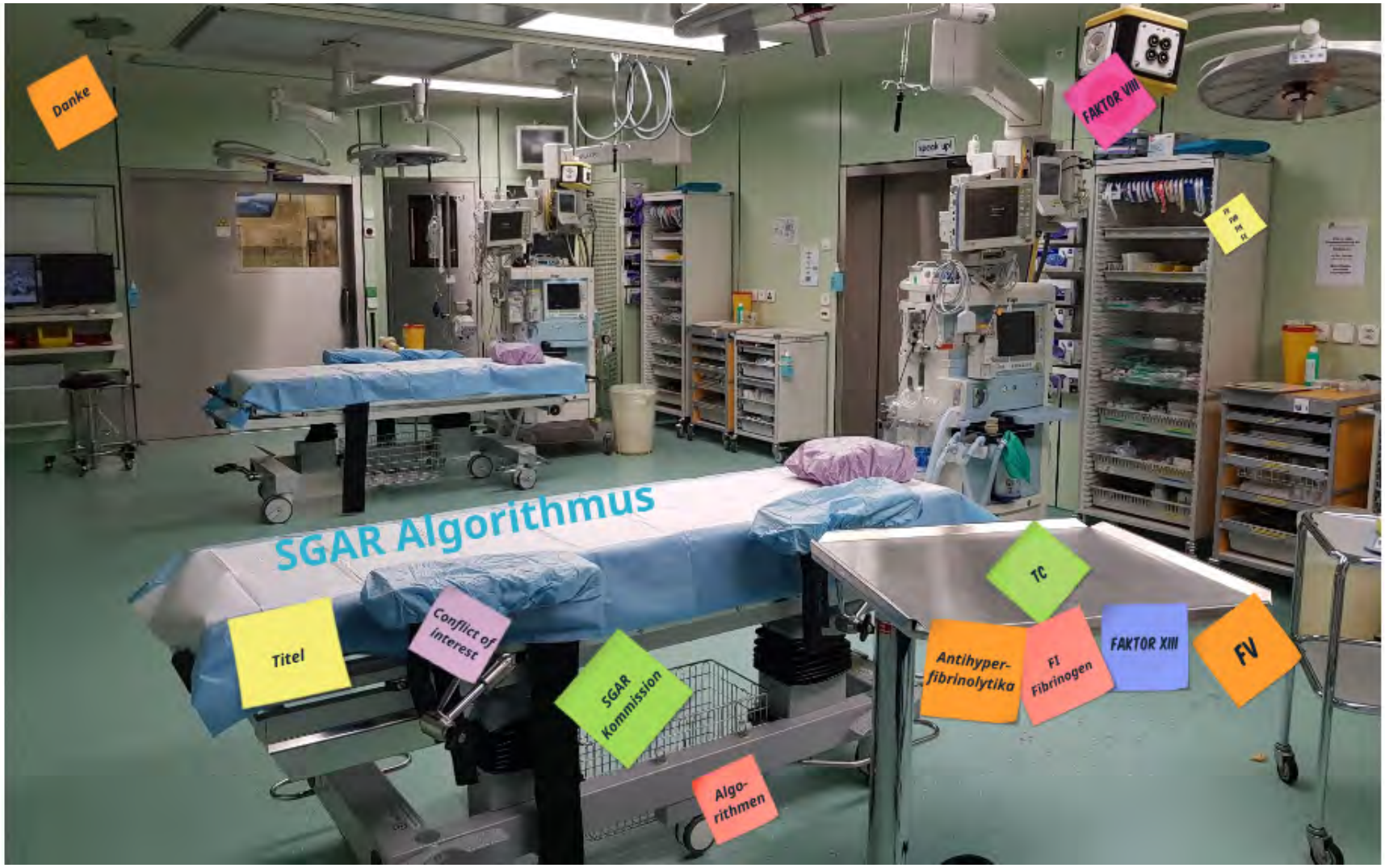
verbindlicher Transfusionsalgorithmus

wann, was, wieviel

chirurgische Blutung stoppen

POCT gesteuerte Komponententherapie

1. Imprägnieren
    a) TXA
2. Restituieren
    a) Tc Funktion
    b) AK
    c) vWF
3. Löcher stopfen
    a) Fibrinogen
    b) FXIII
    c) FV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