HEMOSTASIS AND TRANSFUSION IN CARDIAC SURGERY

Daniela Filipescu, Ioana Marinica

Department of Cardiac Anesthesia & Intensive Care
Emergency Institute for Cardiovascular Diseases
Bucharest, Romania

INTRODUCTION

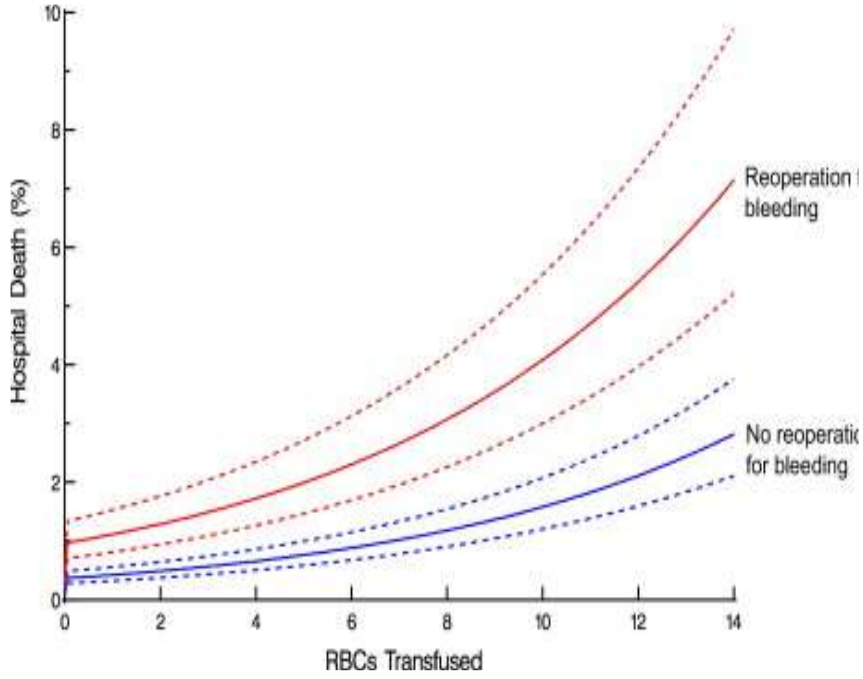
Bleeding is an important issue in cardiothoracic surgery.

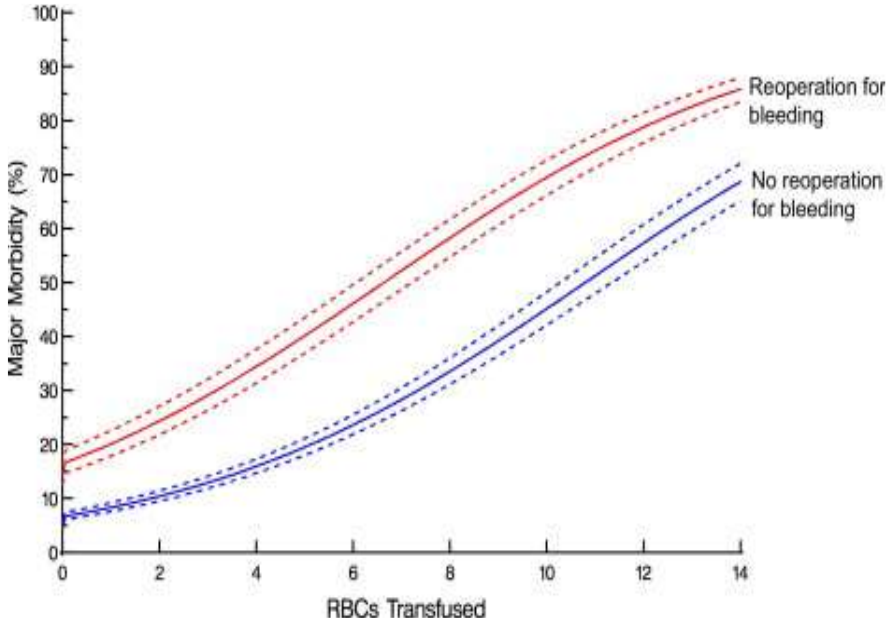
20% of all blood products are transfused in this clinical setting worldwide.

More than 25% of allogeneic blood transfusions have been considered inappropriate.

Both bleeding and allogeneic blood transfusion are associated with increased morbidity, mortality, and hospital costs.

The risk of bleeding and reoperation





Vivacqua A. et al.Ann Thorac Surg 2011;91:1780-1790

THE CARDIAC SURGERY PATIENT

HEMOSTATIC ABNORMALITIES IN THE CARDIAC SURGICAL PATIENT

Management of the patient taking preoperative antithrombotic drugs

Abnormalities acquired during cardiac surgery

ANTICOAGULATION FOR CPB
POINT OF CARE COAGULATION TEST
ASSESMENT OF POTENTIAL BLEEDING RISK
PHARMACOLOGICAL AGENTS
PERIOPERATIVE STRATEGY, MULTIMODAL APPROACH
PERIOPERATIVE BLEEDING GUIDELINES (ESA)

Management of the patient taking preoperative antiplatelet drugs

European Society of Anaesthesiology ESA

Recommendations

Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. ***A***

Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. ***A***

Multipple electrode aggregometry in cardiac surgery

The multipple electrode aggregometry (MEA) ADP test in patients under thienopyridine (ticlopidine or clopidogrel) undergoing cardiac surgery is associated with

postoperative bleeding and

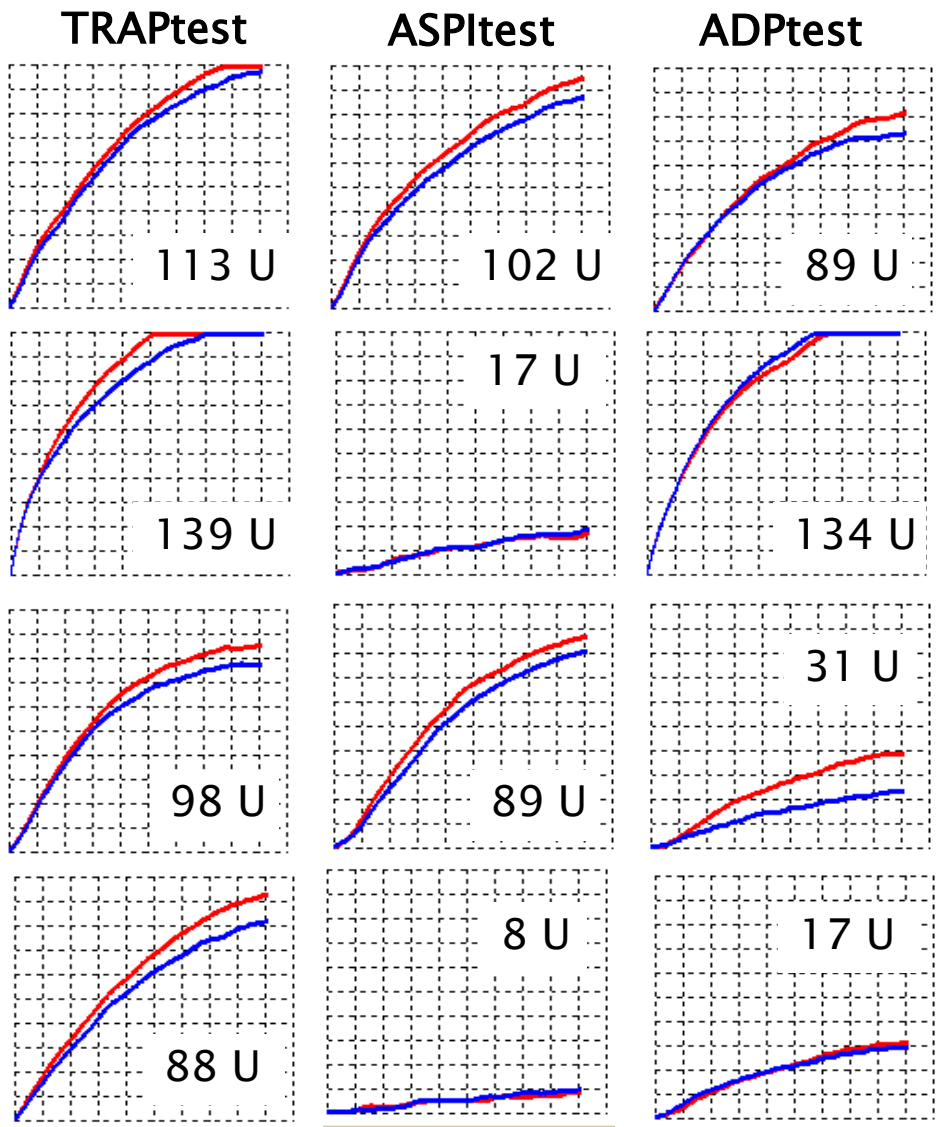
platelets transfusion

MEA provides en accurate preoperative prediction of postoperative bleeding.

Ranucci M et al. Ann Thorac Surg 2011;91:123-30

Multiplate Electrode Aggregometry (MEA)

test	activation	sensitivity
ASPItest	arachidonic acid: is converted to TXA2 by platelet-own cyclooxygenase	aspirin, IIb/IIIa antagonists
ADPtest	ADP: binds onto platelet ADP receptors	clopidogrel, IIb/IIIa antagonists
ADPtest HS	ADP + prostaglandin E1 (Prostaglandin is a natural inhibitor and enhances the sensitivity of the assay for clopidogrel)	clopidogrel, IIb/IIIa antagonists
TRAPtest	TRAP-6 (thrombin receptor activating peptide): TRAP-6 is a potent agonist which mimicks the platelet-activating action of thrombin	IIb/IIIa antagonists GpIIb/IIIa antagonists: Reopro ® (abciximab) Aggrastat ® (Tirofiban) Integrillin ® (Eptifibatid)



NORMAL RANGE: …

► **Multiplate tests**

Management of the patient taking preoperative anticoagulant drugs

Vitamin K antagonist

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADSS2 score >2, pts with recurrent VTE treated for <3 months, pts with mechanical valve). Day 5:last VKA dose; DAY 4 :no heparin; Days 2 and 3: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH, Day 1: hospitalization and INR measurements. Day 0: surgery

1C

We recommend that, in VKA treated pts undergoing procedure or developing a bleeding complication, PCC (25 IU FIX/kg) should be given.

1B

Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors.

Proposals of the Working Group on Perioperative Haemostasis (GIHP) - March 2013.

Dabigatran and rivaroxaban

In case of severe haemorrhage in a critical organ, it is proposed to reduce the effect of anticoagulant therapy using a nonspecific procoagulant drug (activated prothrombin concentrate, FEIBA, 30-50U/kg, or non-activated 4-factors prothrombin concentrates 50U/kg).

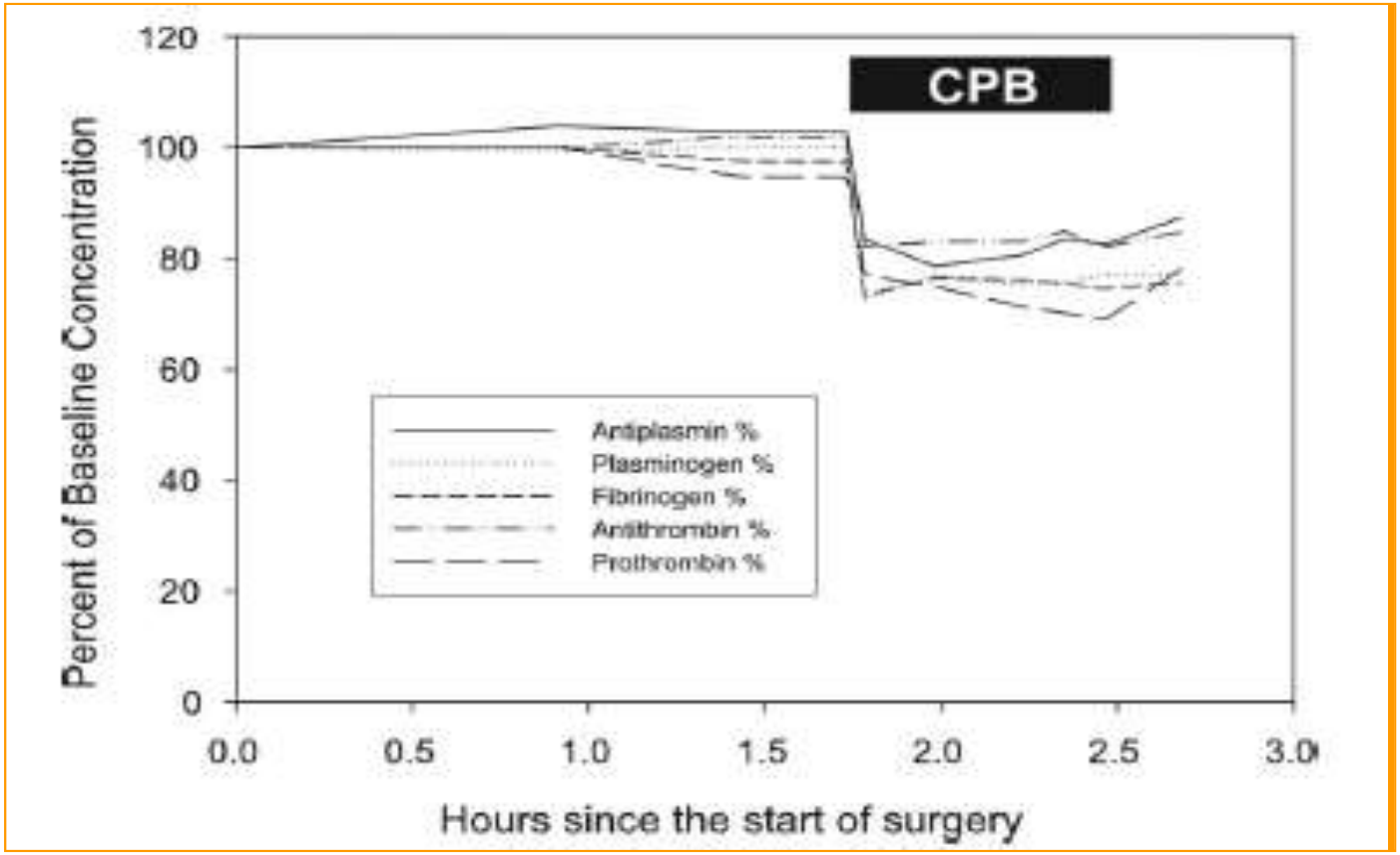
Pernod G, et al. Ann Fr Anesth Reanim. 2013 Aug 29

Abnormalities acquired during cardiac surgery with cardiopulmonary bypass

1. Hemodilution
2. Contact System
3. Fibrinolytic System
4. Inflammation
5. Platelets *thrombocytopenia*
   platelets dysfunction

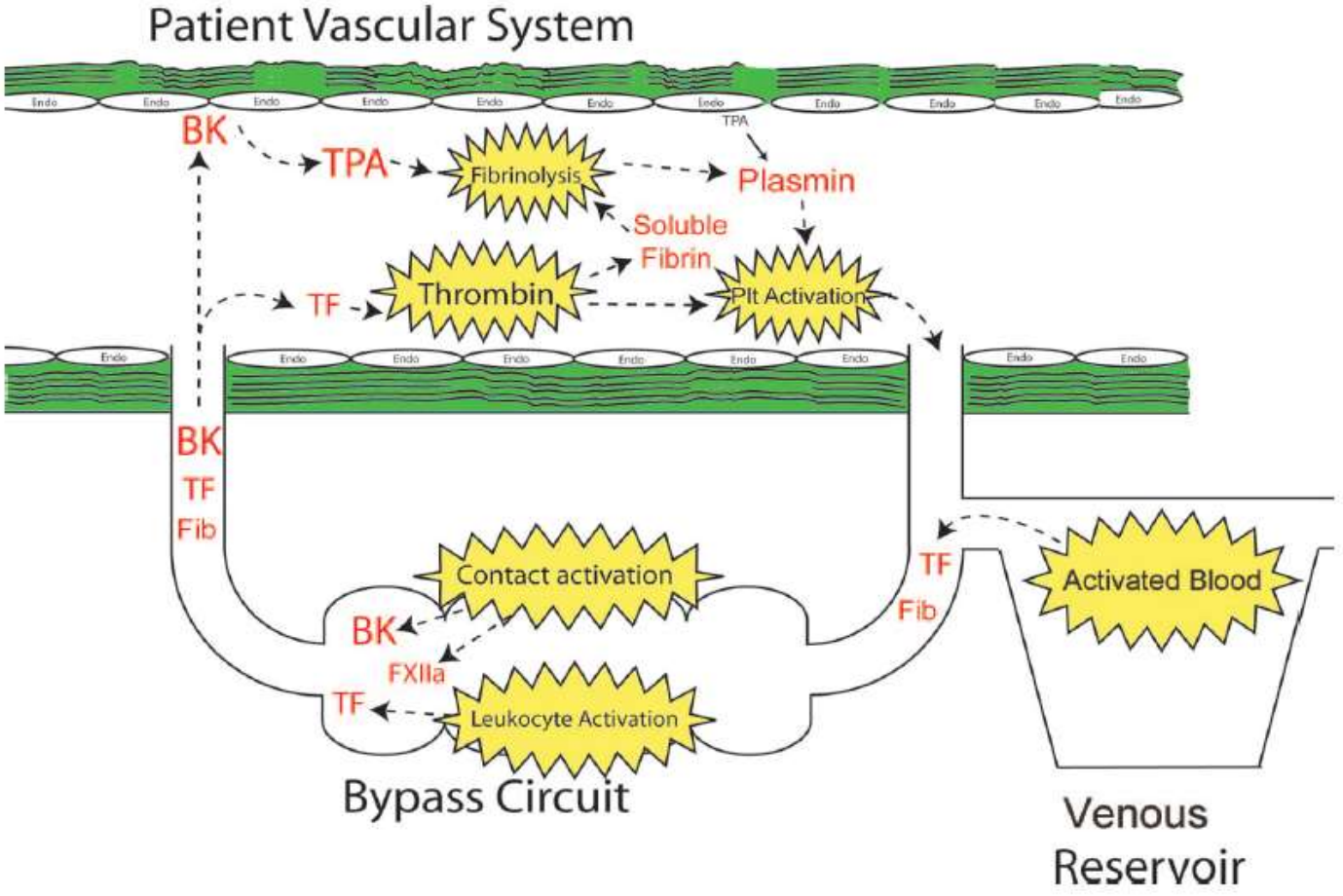
Effect of hemodilution on stable factor levels.

Priming fluid reduces all factors in blood including coagulation factors, inhibitors, and activation markers, by approximately 30%to 40%.



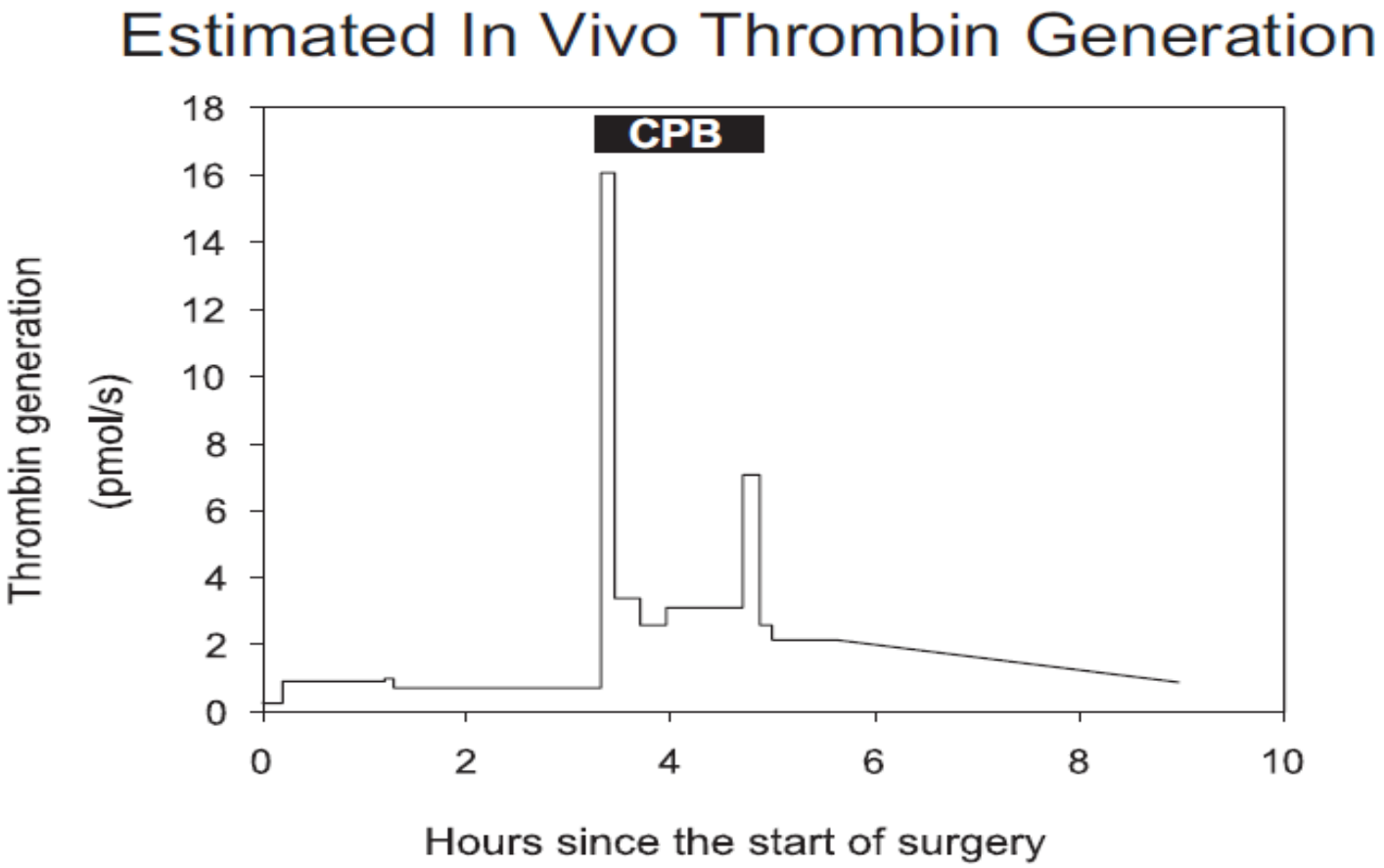
Chandler WL. J Cardiothorac Vasc Anesth 2005;19:459–67

Contact activation



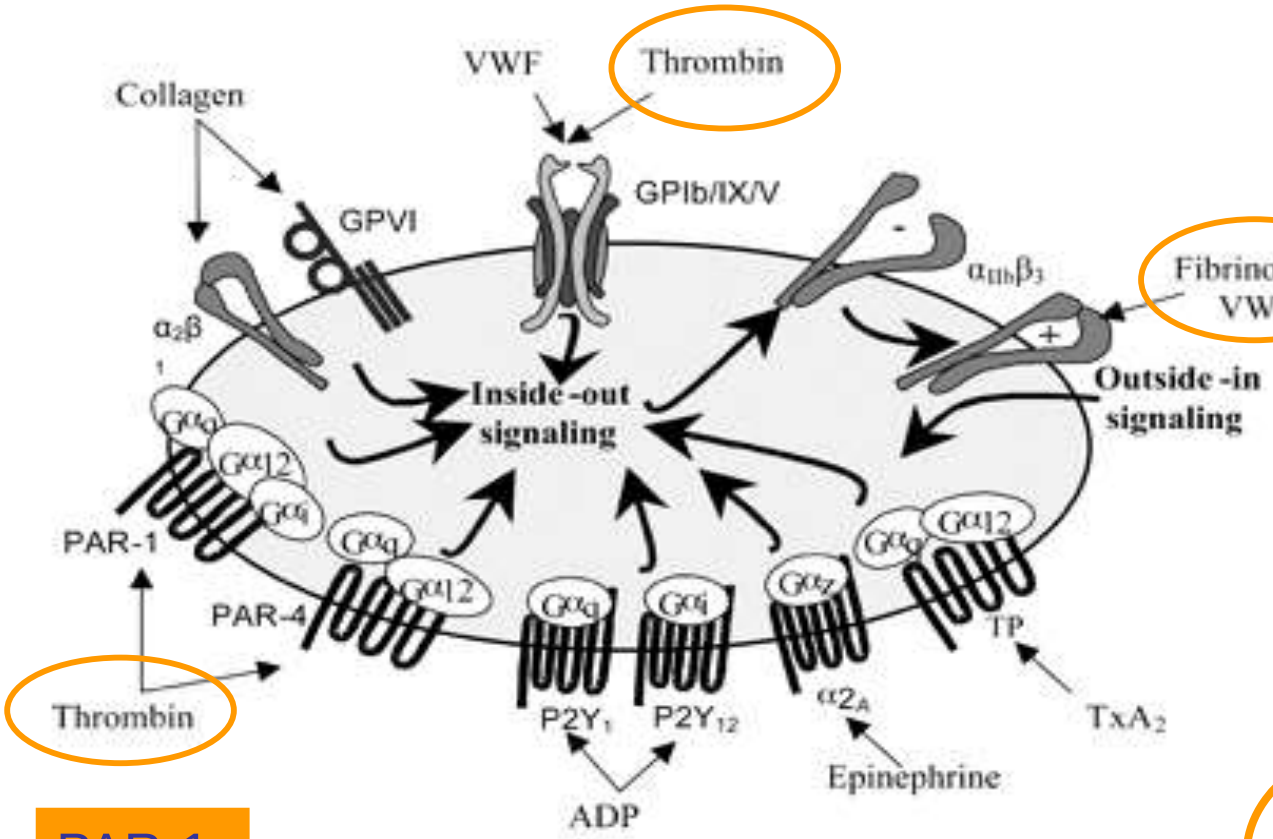
Thrombin Generation

Conventional CPB leads to substantial increases in thrombin activation markers, unrelated to the surgical wound itself.



Chandler WL, Velan T.Blood 2003;101:4355–4362.

Platelets activation – aggregation - release granule contents.



GPIIb/IIIa

PAR-1

PAR-4

plasmin

Protamine

Heparin

Major platelet receptor-ligand interaction

REDUCING ACTIVATION

Limiting Use of Cardiotomy Suction

Increasing Circuit Biocompatibility

Decreasing CPB Circuit Size

Off-Pump Coronary Artery Bypass

Heparin –suppress thrombin activation

Antifibrinolytics

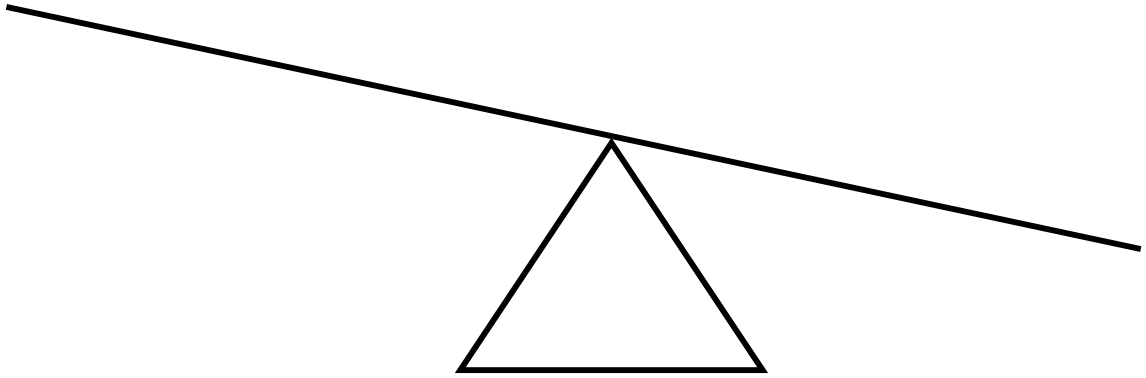
Tranexamic acid during CPB preserves platelet adenosine diphosphate levels
Aprotinin during CPB reduces platelet activation, preserves PAR1 function, and reduces platelet GPIb cleavage.

ANTICOAGULATION FOR CPB

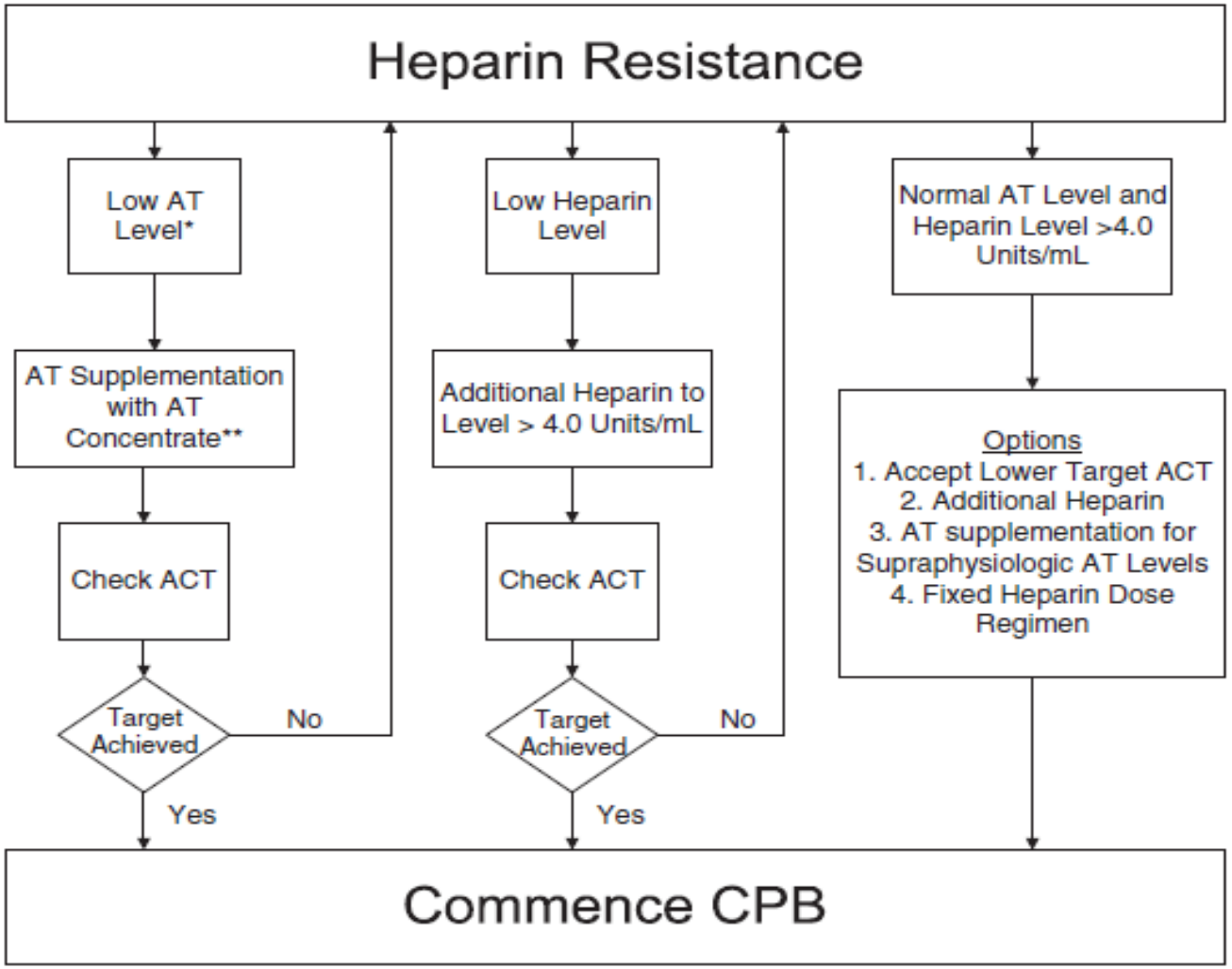
Large doses of heparin
Heparin resistance
Insufficient heparin

Unneutralized heparin
Heparin rebound
Protamine overdose

Heparin and Protamine Dosing



Bleeding diathesis



FFP as an alternative to AT concentrate -2 U FFP=500IU AT

Finley A, Anesth Analg 2013;116:1210–22)

POINT OF CARE COAGULATION TEST (POC)

Results must be timely as well as accurate

Bedside test utilize whole blood samples

Analysis the coagulation in its entire

POINT OF CARE COAGULATION TEST

1. Functional measures of coagulation or test that measures the intrinsec coagulation pathway

   Activating Clotting Time (ACT)

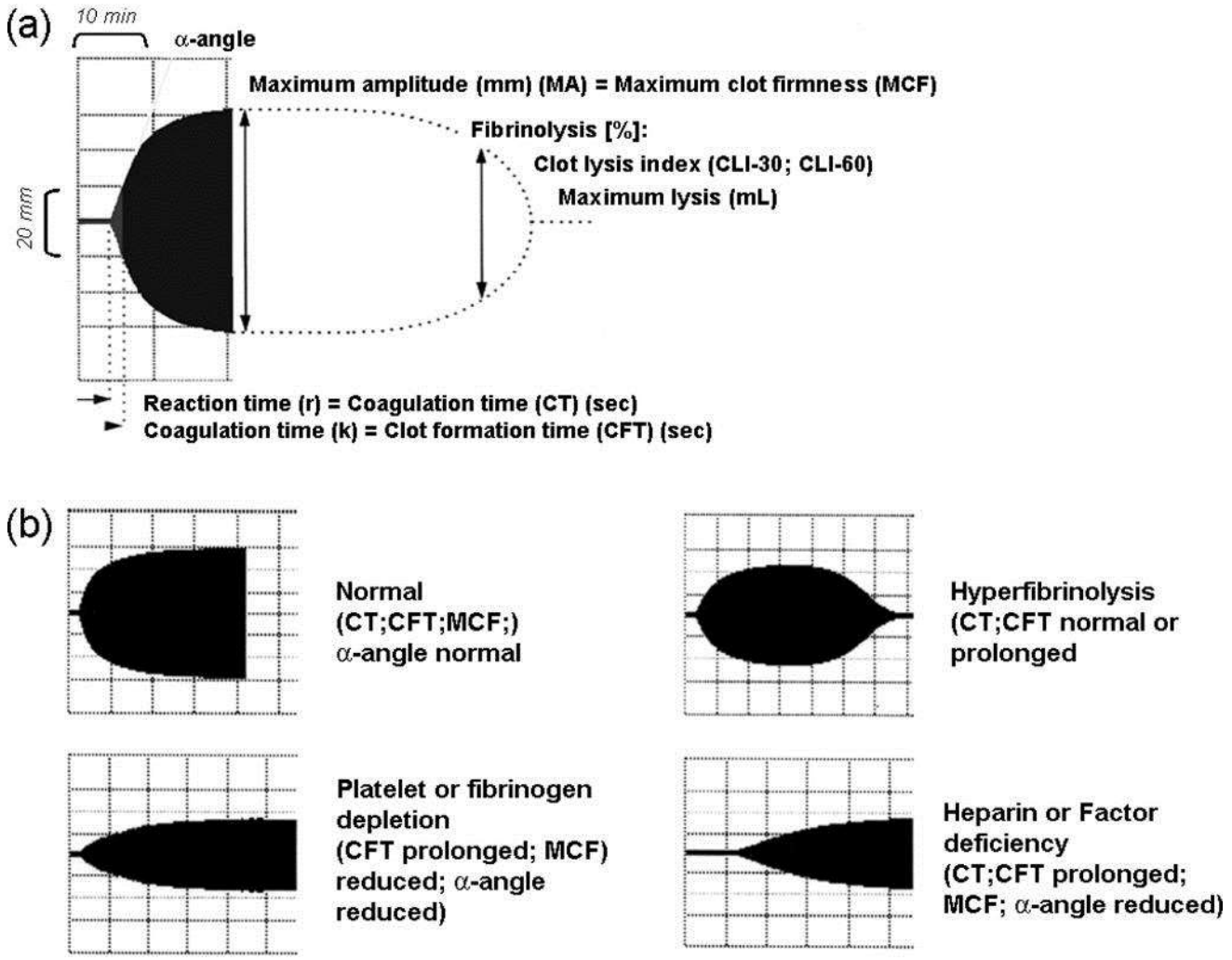
   High-dose thrombin time (HiTT)

2. Heparin Concentration Monitors + ACT

   Protamine titration method

3. Viscoelastic measures of coagulation (TEG, ROTEM)
4. Platelet function monitors

Thromboelastometry (ROTEM)



Spalding G. J. et al.; Eur J Cardiothorac Surg 2007;31:1052-1057

Assessment of potential bleeding risk

A structured patient interview or questionnaire before surgery or invasive procedures

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery

1C

Predictors of postoperative bleeding

1. **Advanced age (age > 70 years)**
2. **Small body size or preoperative anemia (low RBC volume)**
3. Anti-platelet & anti-thrombotic drugs
4. Prolonged operation (CPB time**)**
5. **Emergency operation or complex operation**
6. Other co-morbidities (CHF, COPD, HTN, PVD, renal failure)

Ferraris VA, et al. STS Guidelines. Ann Thorac Surg. 2005--2011

Pharmacological agents

Antifibrinolytic therapy

- **tranexamic acid and EACA**
- **aprotinine**

Fibrinogen concentrate

Prothrombin complex concentrate (PCC)

Desmopressine (DDAVP)

Recombinant activated factor VII (rFVIIa)

Factor XIII concentrate

The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery.

- retrospective single-center cohort study (2000-2008)
- 15,365 patients
- cardiac surgery with cardiopulmonary bypass
- aprotinin [6 x 10(6) U] or tranexamic acid (50-100 mg/kg)

Aprotinin tends to have a better risk-benefit profile than tranexamic acid in high-risk, but not low- to moderate-risk, patients. Its use in high-risk cases may therefore be warranted.

Karkouti K, et al
Anesth Analg. 2010 Jan 1;110(1):21-9.

Anti-fibrinolytics and tranexamic acid

We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high, medium and lower risk cardiovascular surgery. ***1A***

We recommend the consideration of tranexamic acid (20-25 mg/kg). ***1A***

Fibrinogen concentrate

We recommend plasma fibrinogen level <1.5–2.0 g/l^{-1} or ROTEM/TEG signs of functional fibrinogen deficit as triggers for fibrinogen substitution

1C

We recommend that fibrinogen concentrate infusion guided by point of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiac surgery.

1B

We suggest an initial fibrinogen concentrate dose of 25-50 mg/kg^{-1}

2C

Prothrombin complex concentrate (PCC)

We suggest that PCC (20-30 IU/kg) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients.

2C

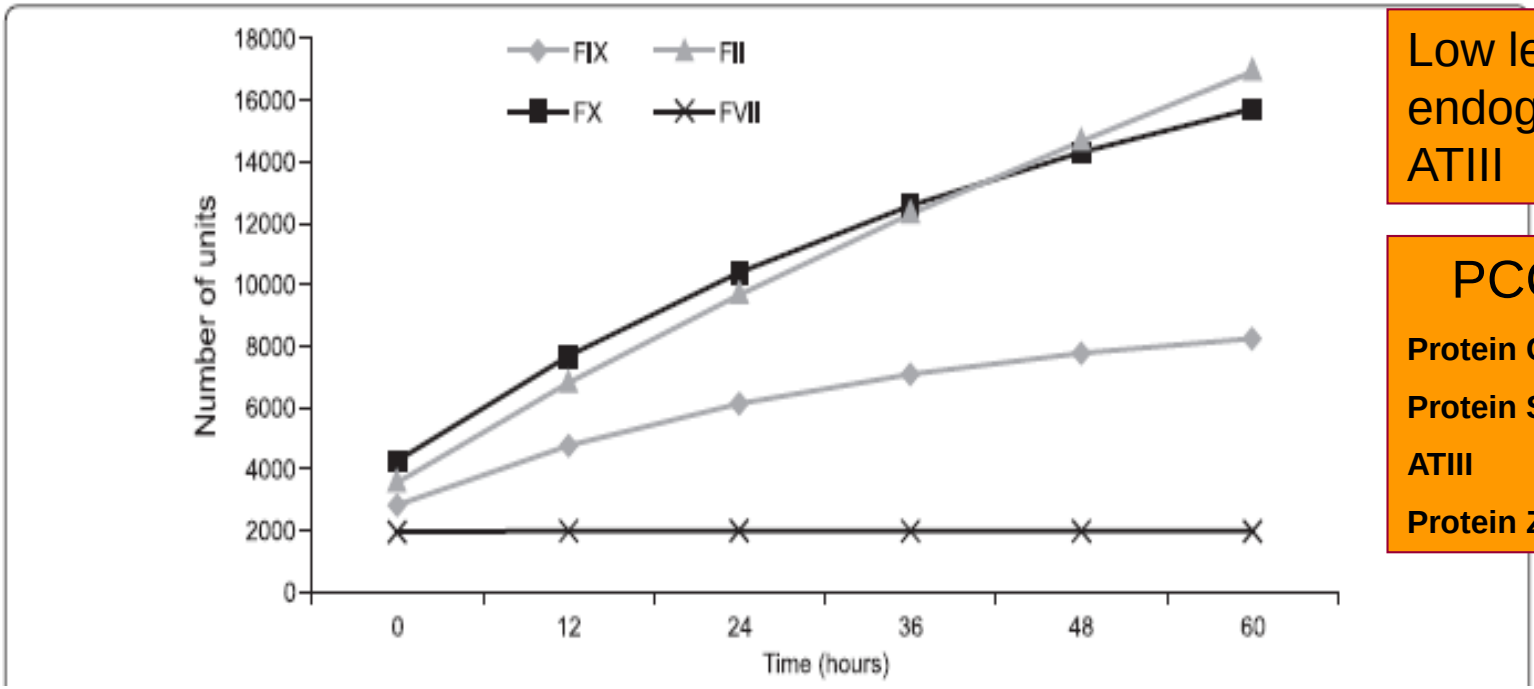
Sørensen *et al. Critical Care* 2011, 15:201
http://ccforum.com/content/15/1/201

CRITICAL CARE

REVIEW

Clinical review: Prothrombin complex concentrates - evaluation of safety and thrombogenicity

Benny Sørensen[1]*, Donat R Spahn[2], Petra Innerhofer[3], Michael Spannagl[4] and Rolf Rossaint[5]



Low levels of endogenous ATIII

PCC 4

Protein C

Protein S

ATIII

Protein Z

Recombinant factor VIIa (rFVIIa)

We suggest that off-label administration of rFVIIA can be considered for bleeding which cannot be stopped by conventional ,surgical or interventional radiological and/or when comprehensive coagulation therapy fails.

2C

Hypofibrinogenaemia, thrombocytopenia, hypothermia, acidosis and hyperfibrinolysis should be treated before rFVIIA.

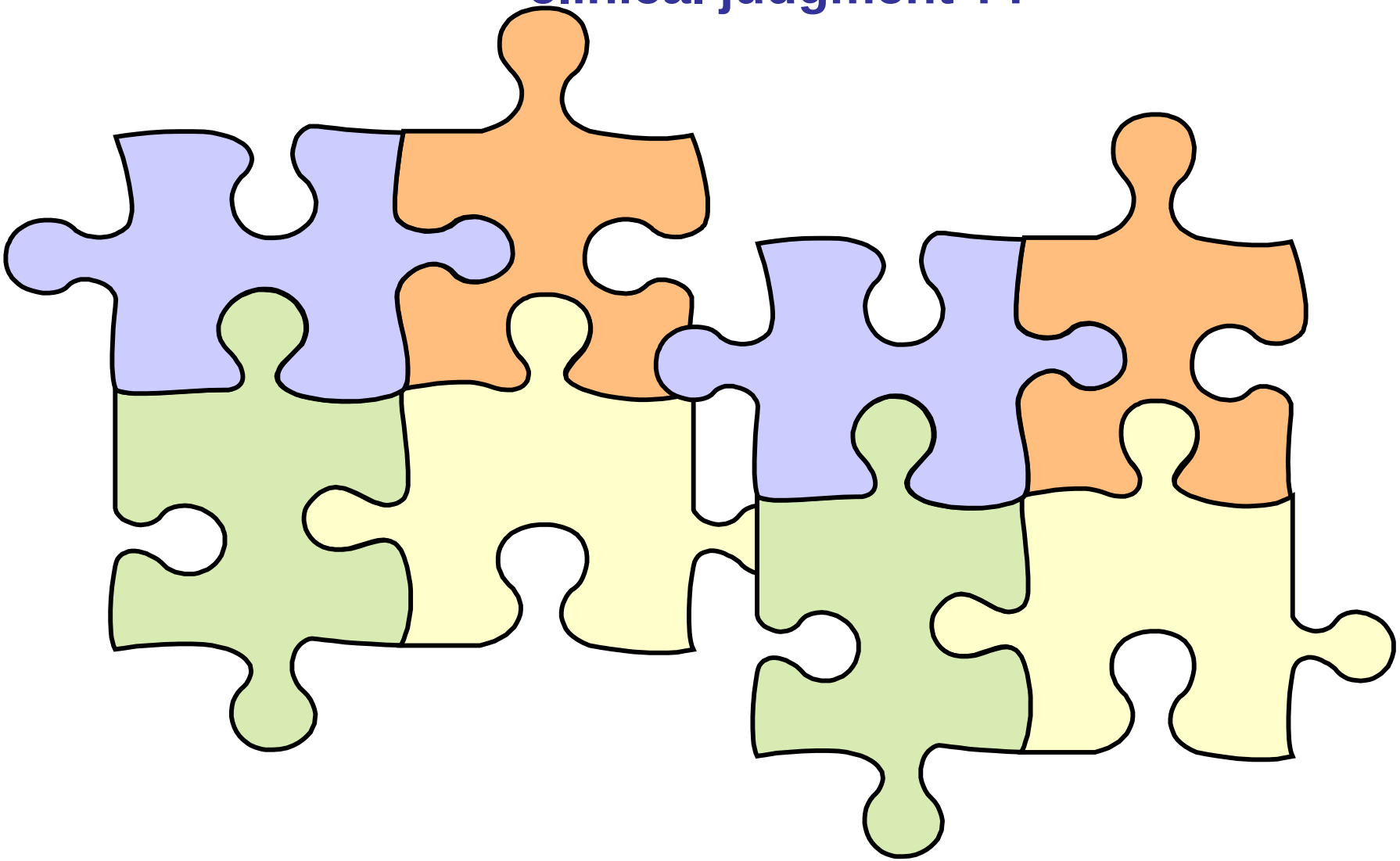
Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

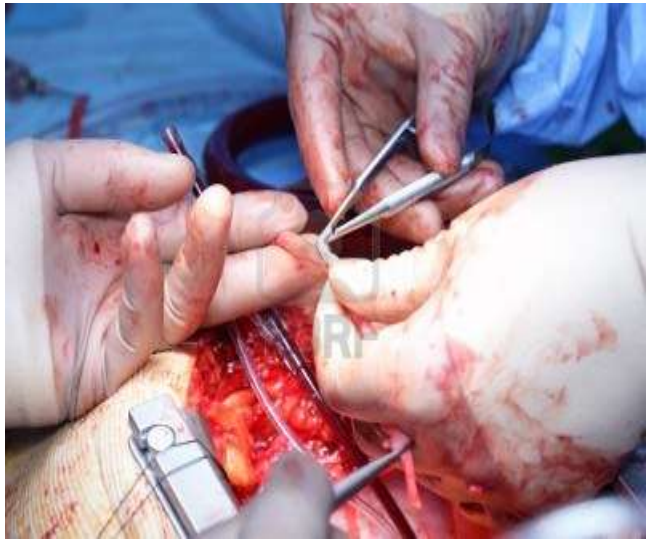
Table 3. Arterial Thromboembolic Events with a Rate Greater Than 0.5%.

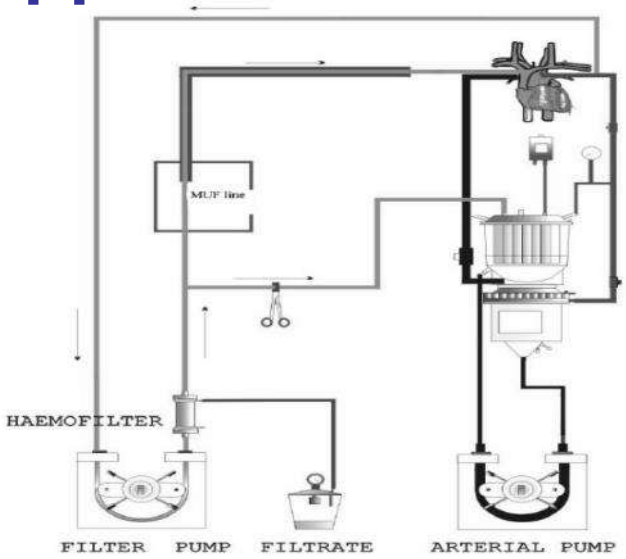
Variable	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)			
All arterial thromboembolic events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Coronary events	76 (2.9)	17 (1.1)	2.39 (1.39–4.09)	0.002
Acute coronary syndromes	57 (2.2)	11 (0.7)		
Increased troponin level	19 (0.7)	6 (0.4)		
Cerebrovascular events	45 (1.7)	20 (1.3)	1.27 (0.74–2.17)	0.39
Cerebral infarction	44 (1.7)	19 (1.2)		
Hemiparesis†	1 (<0.1)	1(<0.1)		

Intra-operative strategy clinical judgment ??



Intra-operative strategy multimodal approach





Reoperation causes

18,891 primary and repeat

1. coronary artery bypass grafting
2. valve
3. combined operations

Risk factors included:

- older age
- greater comorbidity
- aortic valve surgery
- longer myocardial ischemic
- cardiopulmonary bypass durations
- surgeon.

3.0% underwent reoperation for bleeding

Reoperation causes

- **technical factors (74%),**
- **coagulopathy (13%),**
- **both (10%)**
- **other (3.3%)**

Vivacqua A. et al.Ann Thorac Surg 2011;91:1780-1790

STS blood conservation revision

Cell-savage

Centrifugation of pump-salvaged blood, instead of direct infusion, is reasonable for minimizing post-CPB allogeneic red blood cell (RBC) transfusion. IIa (A)

Ultrafiltration

Use of modified ultrafiltration is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB 1A

Benefit of the use of conventional or zero balance ultrafiltration is not well established for blood conservation and reducing postoperative blood loss in adult cardiac operations.
IIb (A)

2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines

Ferraris A Ann of Thorac Surgery; 2011;91:944-82

Management of hemorrhage in cardiothoracic surgery.

Individualized goal-directed hemostatic therapy ("theranostic" approach)

POC transfusion and coagulation management algorithms

guided by 1. viscoelastic tests : TEG/ROTEM

2. POC platelet function tests:

whole blood impedance aggregometry (MEA)

based on first-line therapy with fibrinogen and prothrombin complex concentrate.

Görlinger K, et al. J Cardiothorac Vasc Anesth. 2013 Aug;27(4 Suppl):S20-34.

First-line therapy with coagulation factor concentrates combined with POC coagulation testing

Retrospective study - 3,865 pts. in cardiac surgery
High risk of bleeding or clinically relevant diffuse bleeding after protamine

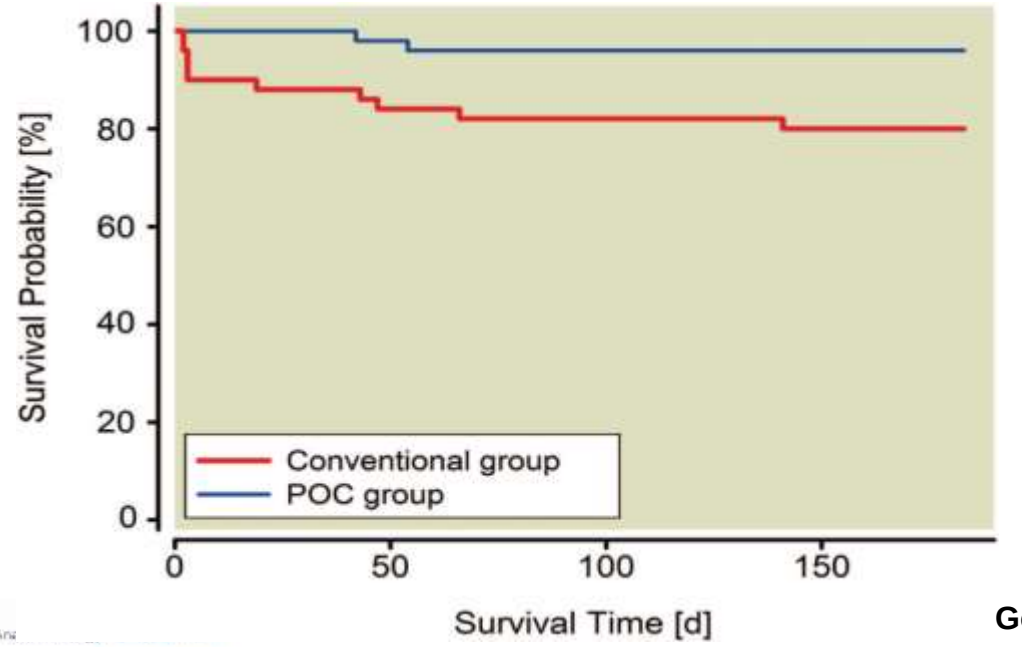
- **Decreased incidence of:**
  1. **Blood transfusion**
  2. **Thrombotic/thromboembolic events**
  3. **Reexploration**
- **Overall costs for allogeneic blood transfusion and factor concentrates per patient decreased by 6.5 %.**

Gorlinger K et al. Anesthesiology 2011

A Prospective, Randomized Clinical Trial of Efficacy in Coagulopathic Cardiac Surgery Patients

Haemostatic therapy algorithms with POC testing reduced:

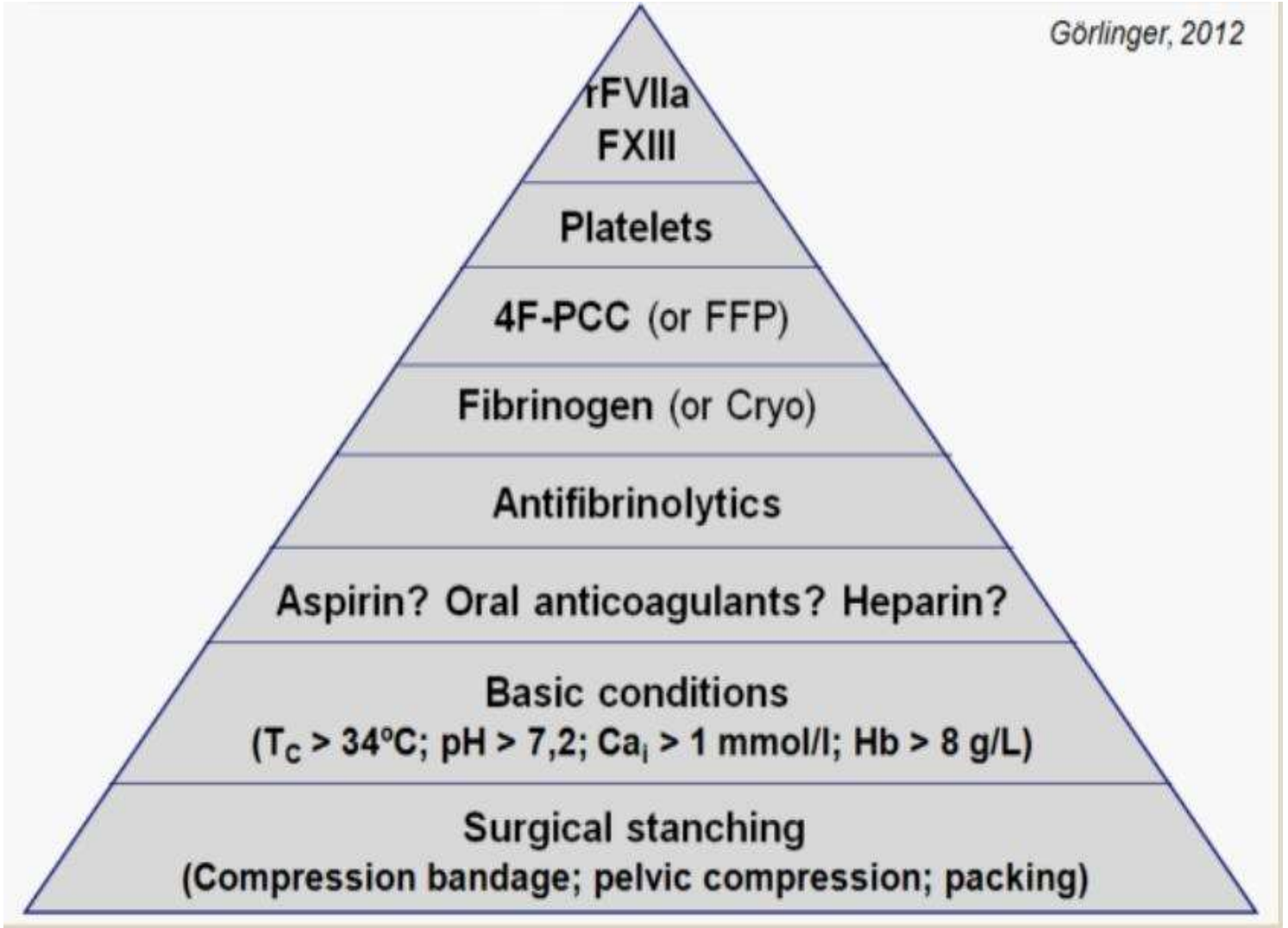
1. **the number transfused units of RBC, FFP, PC**
2. **costs of therapy**



First study showing improved survival !

Gorlinger K et al. Anesthesiology 2012

Principles of the POC - supported coagulation management algorithm



ROTEM-based Point-of-Care Coagulation Management in Patients with Acute Aortic Dissection

Retrospective study

Surgery for Acute type A aortic dissection

January to December 2012.

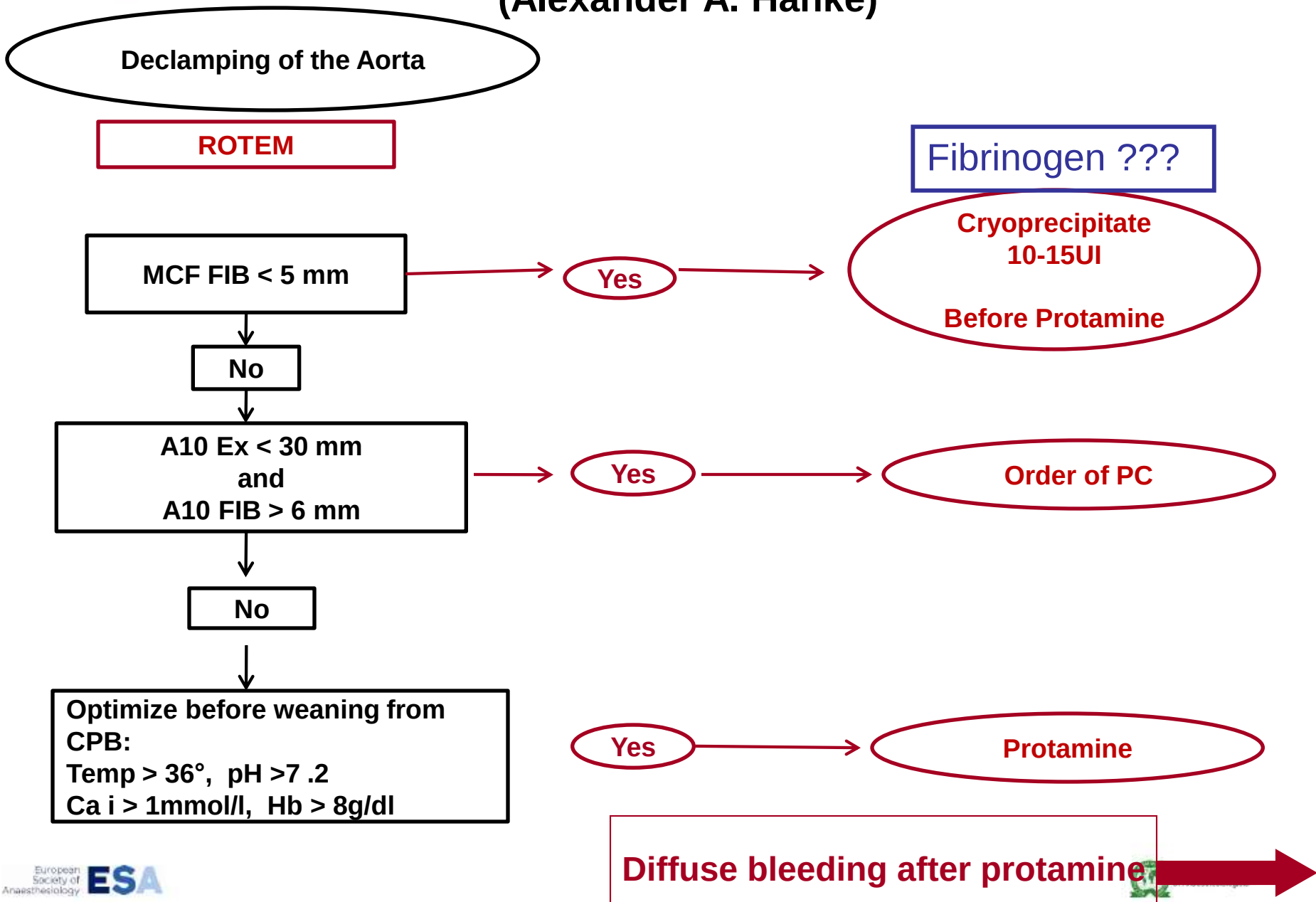
The same team of surgeons

Two different peri operative haemostatic therapies

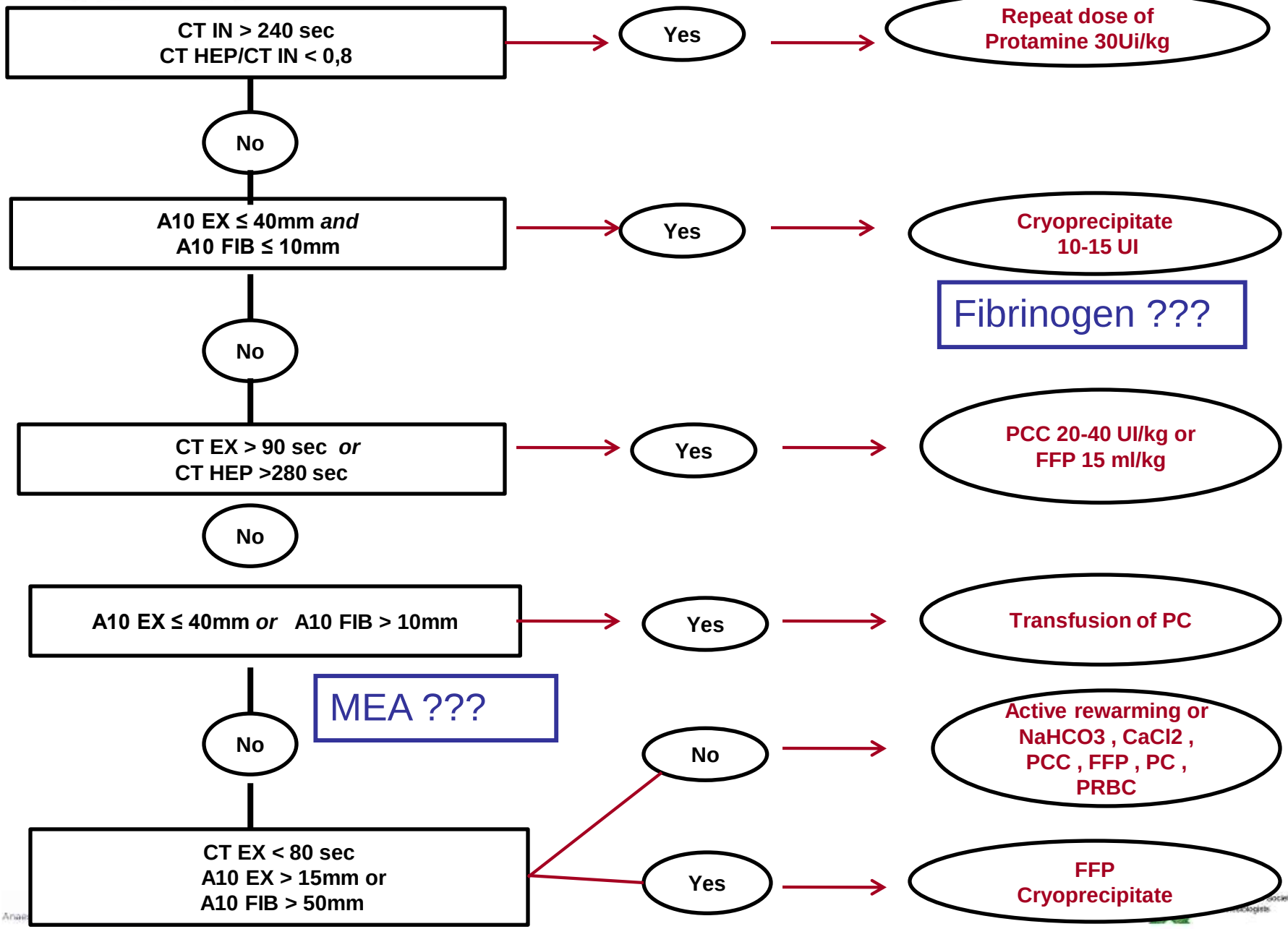
1. ROTEM- based Point-of-Care coagulation management-ROTEM group- RG
2. Usual care (standard) – UCG group

Daniela Filipescu, Ioana Marinica, Mihail Luchian,
Alina Paunescu, Simona Marin, Carmen Manofu
Depart. of Cardiac Anesthesia and Intensive Care Unit
Emergency Institute of Cardiovascular Diseases
"Prof. Dr. C. C. Iliescu"
Bucharest, Romania

Adapted hemostatic therapy algorithms (Alexander A. Hanke)

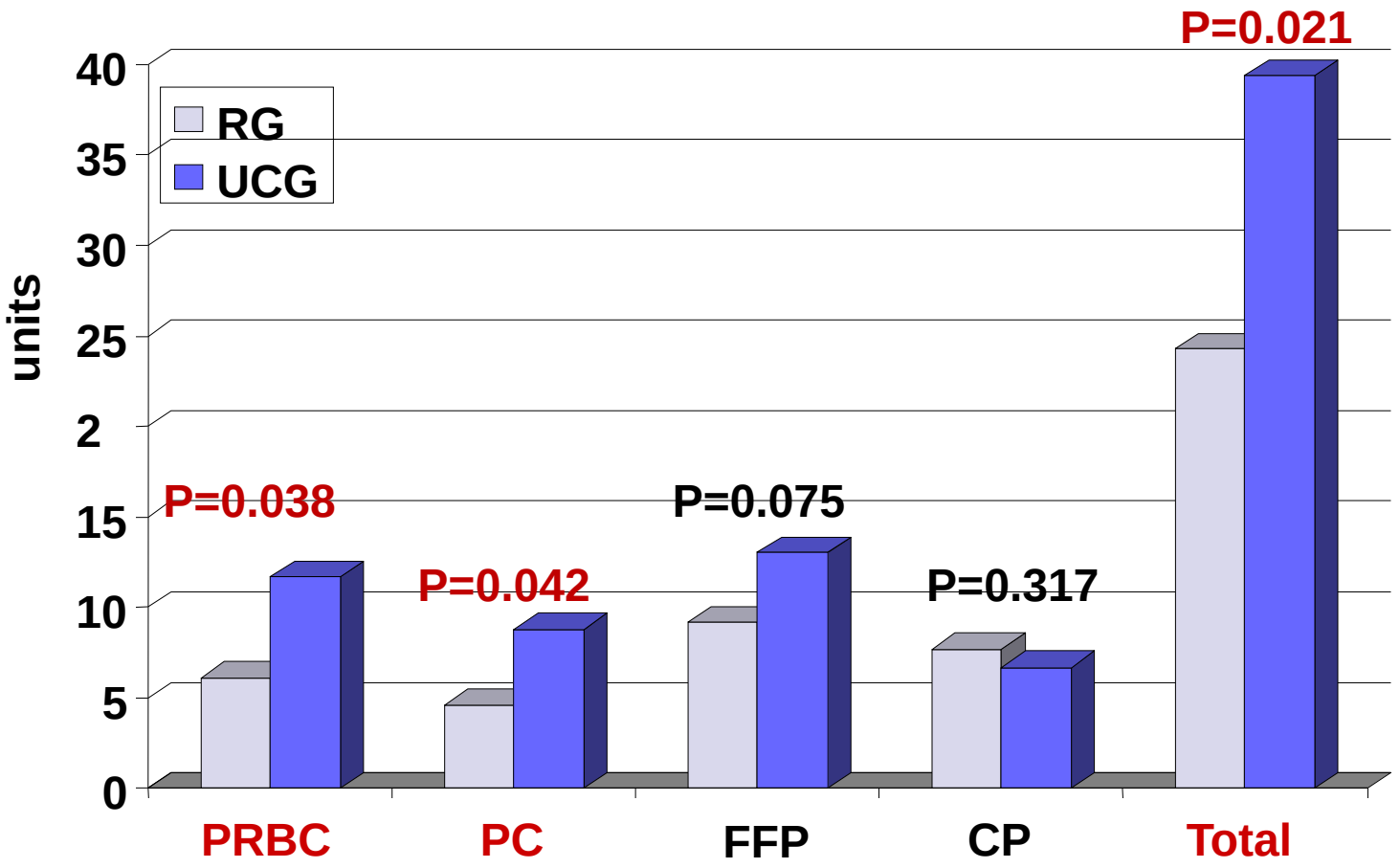


Repeat ROTEM after each intervention



Result (5)

Allogenic blood product exposure



PRBC packed red blood cells
PC platelet concentrates
FFP fresh frozen plasma
CP cryoprecipitate

European Society of Anaesthesiology 2012 Perioperative bleeding guidelines

Use of standardised haemostatic algorithms with intervention triggers measured using thrombelastography or thromboelastometry at the point-of-care may reduce transfusion requirements and perioperative blood loss in cardiovascular surgery


Thank You

CEEA

EJA

Eur J Anaesthesiol 2013; **30:**1–112

GUIDELINES

Management of severe perioperative bleeding

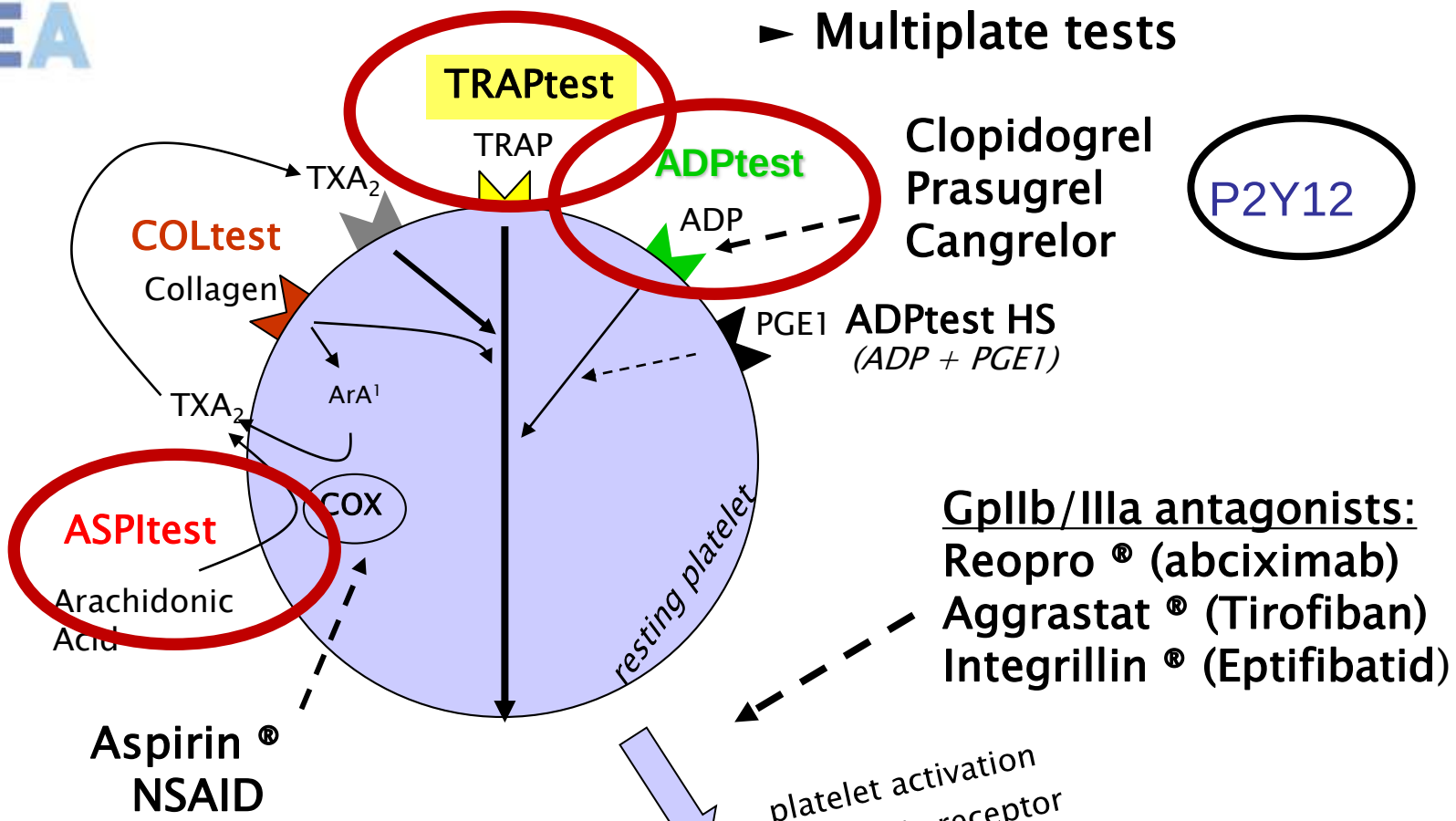
Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano, Edoardo De Robertis, Daniela C. Filipescu, Dietmar Fries, Klaus Görlinger, Thorsten Haas, Georgina Imberger, Matthias Jacob, Marcus Lancé, Juan Llau, Sue Mallett, Jens Meier, Niels Rahe-Meyer, Charles Marc Samama, Andrew Smith, Cristina Solomon, Philippe Van der Linden, Anne Juul Wikkelsø, Patrick Wouters and Piet Wyffels

European Society of Anaesthesiology ESA

World Federation of Societies of Anaesthesiologists

► Multiplate tests

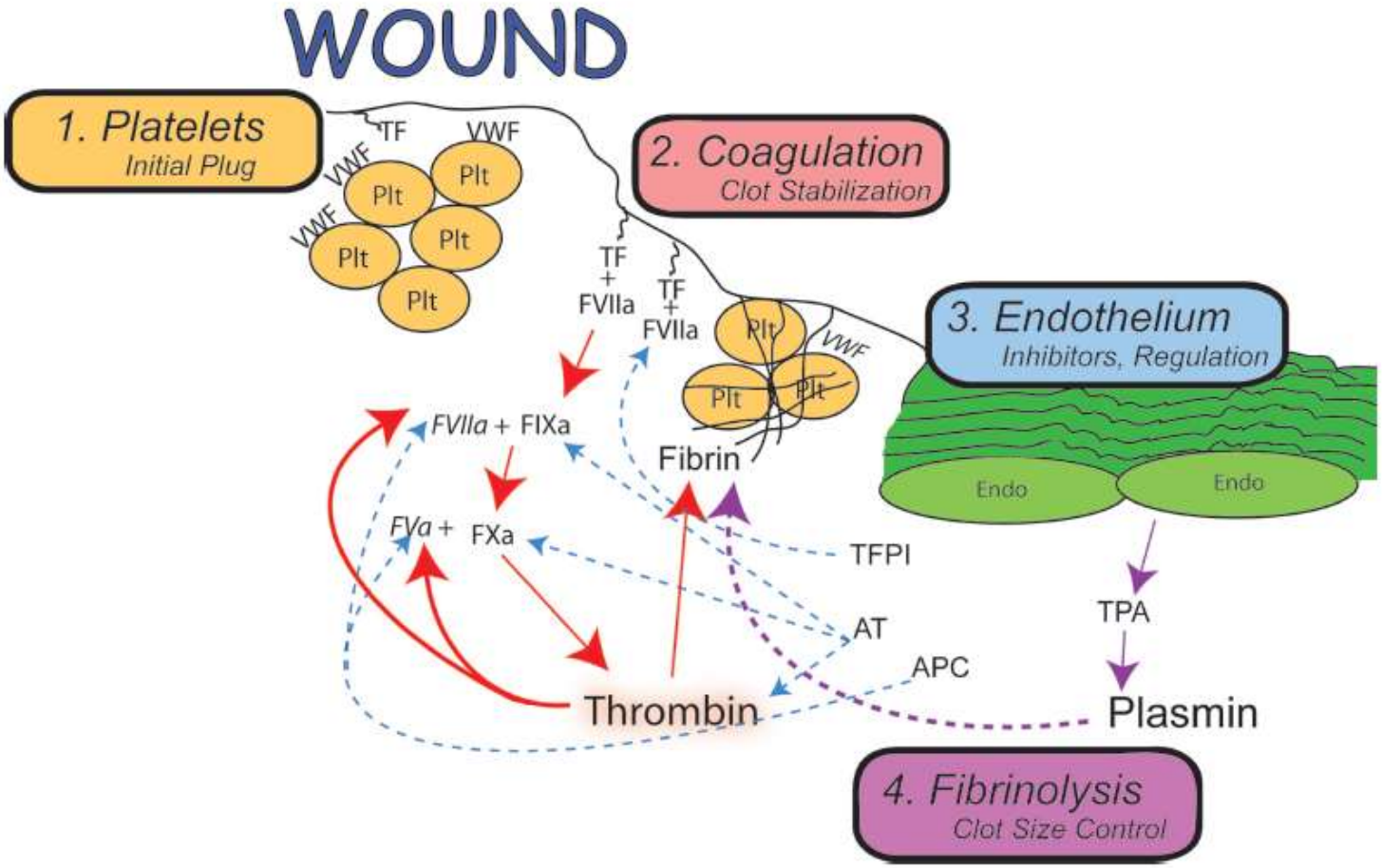


Clopidogrel
Prasugrel
Cangrelor

P2Y12

<u>GpIIb/IIIa antagonists:</u>
Reopro ® (abciximab)
Aggrastat ® (Tirofiban)
Integrillin ® (Eptifibatid)

Normal hemostasis



Prothrombin complex concentrate

Rapid reversal of coumarin effect

Patients with defective hepatic synthesis of coagulation factors

Improvement of coagulation in patients with massive blood loss

Patients with factor II or X inherited defects

Recombinant factor VIIa (rFVIIa)

Licensed only for use in:

- hemophiliacs with inhibitors to factor VIII or IX
- acquired hemophilia
- FVII deficiency
- Glanzmann thrombastenia refractory to platelets

Off-label use of rFVIIa

- Trauma
- Abdominal surgery
- Thoracic surgery
- Orthopedic surgery
- Hepatic procedures
- Cardiac surgery
- Non-surgical bleeding
- Acquired coagulopathies
- Obstetric hemorrhages

rFVIIa: efficacy in surgery

There is a significant effect of rFVIIa treatment in terms of reduction in the number of patients being exposed to allogeneic RBC transfusions, regardless of the dose applied (55.7% vs 67.6%)

In the subgroup analysis only patients receiving at least 50 µg/kg of rFVIIa, had a significant benefit (64.9% vs. 68.4%)

The cost benefit ratio is favorable only in patients who need a huge number of RBC units (> 40)

Ranucci M, et al. Arch Surg 2008;143:296