



XXIV Congresso Nazionale

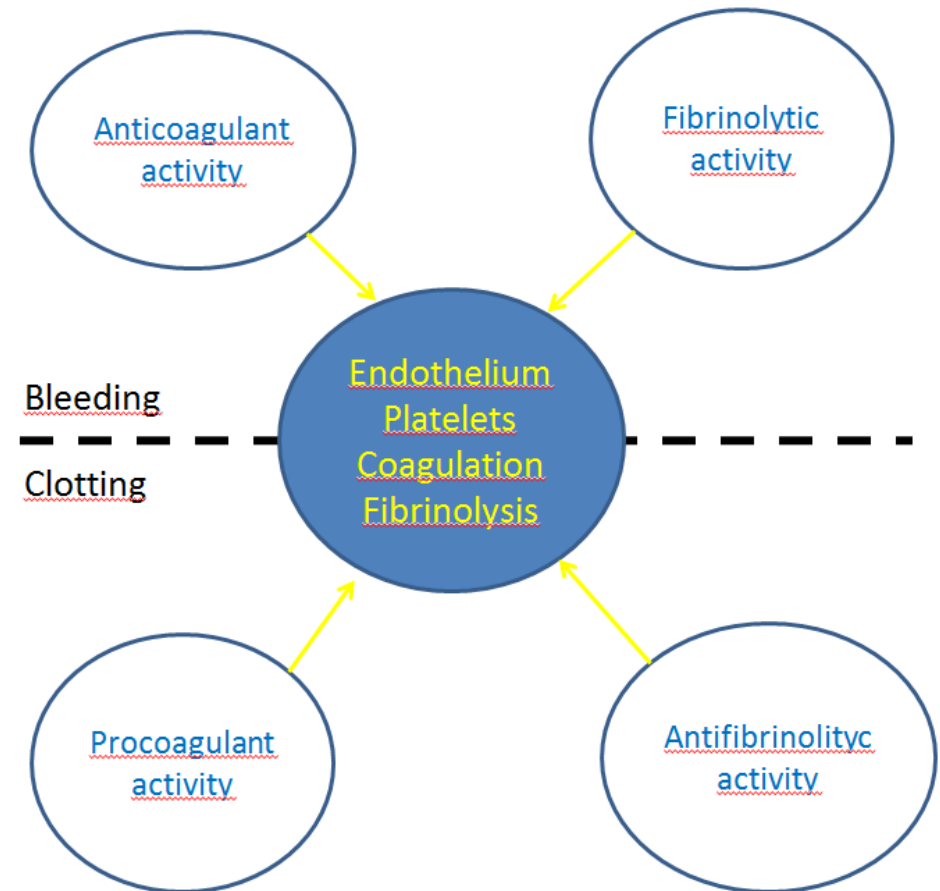
*Abano Terme (PD),
9-12 novembre 2016*

Sessione Educazionale 4 : *“Gestione del paziente emorragico”*

**Dubbi e certezze nella gestione delle
emorragie con metodiche point-of-care**

P. Simioni
Università di Padova

- ✓ Vascular phase
- ✓ Platelet phase
- ✓ Coagulation phase
- ✓ Fibrinolytic phase

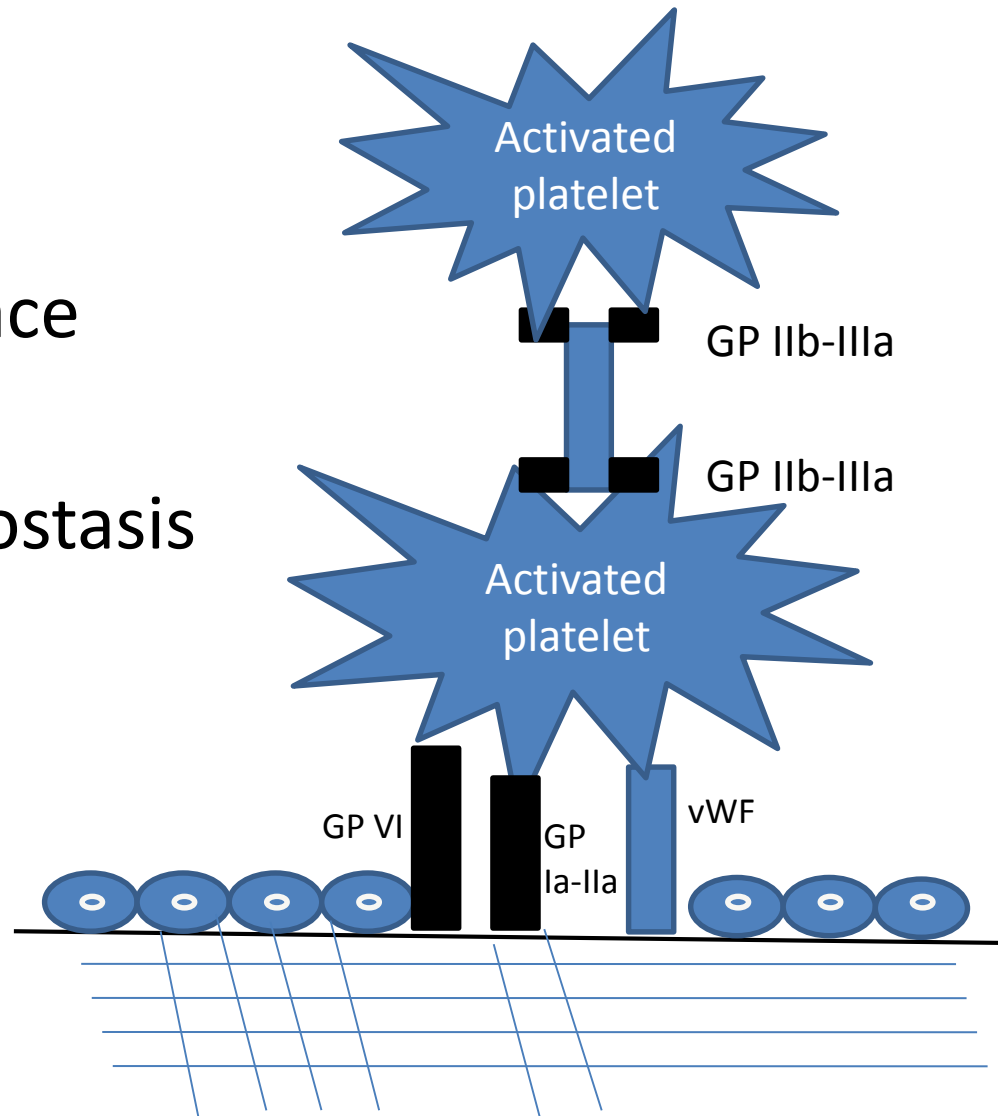


Blood vessels

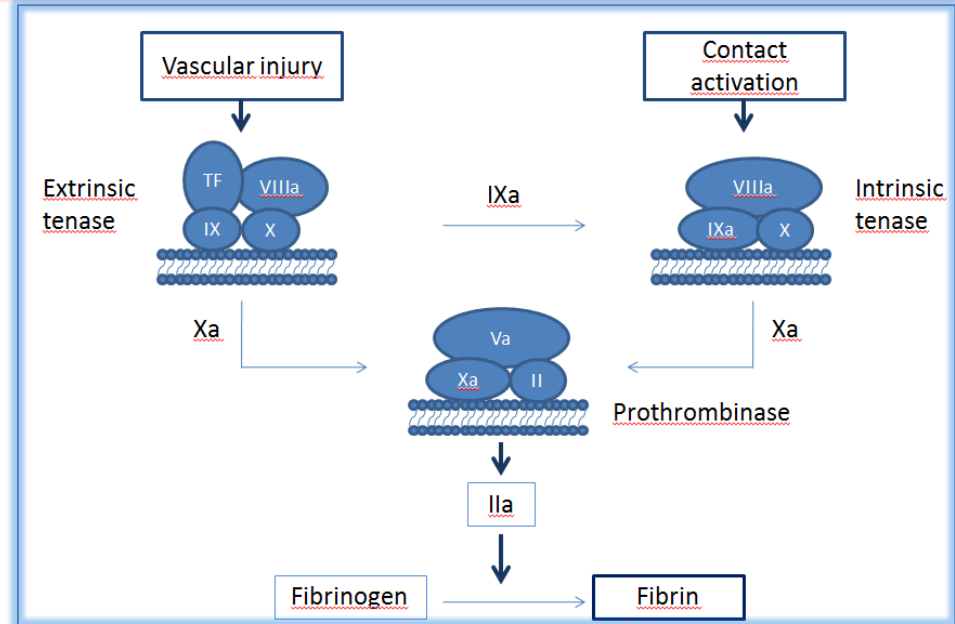
- ✓ Endothelial cells
- ✓ Sub-endothelial surface

Platelets: primary hemostasis

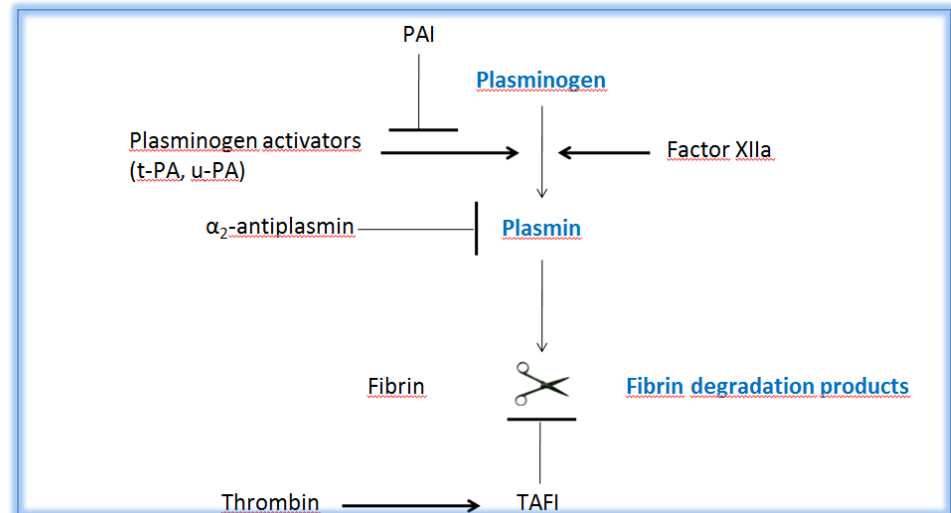
- ✓ Platelet membrane
- ✓ Platelet granules



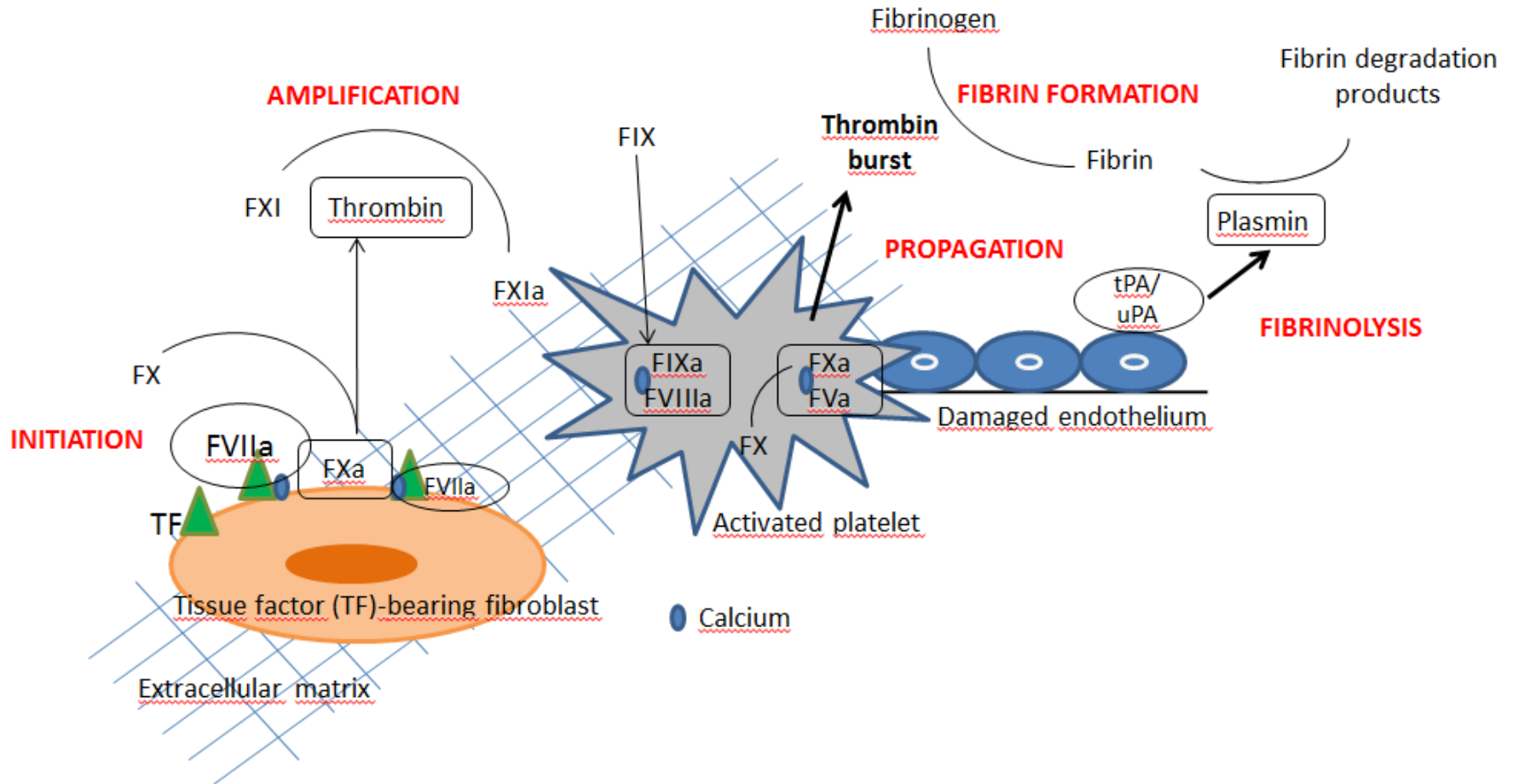
✓ Coagulation factors



✓ Fibrinolytic pathway



hemostasis



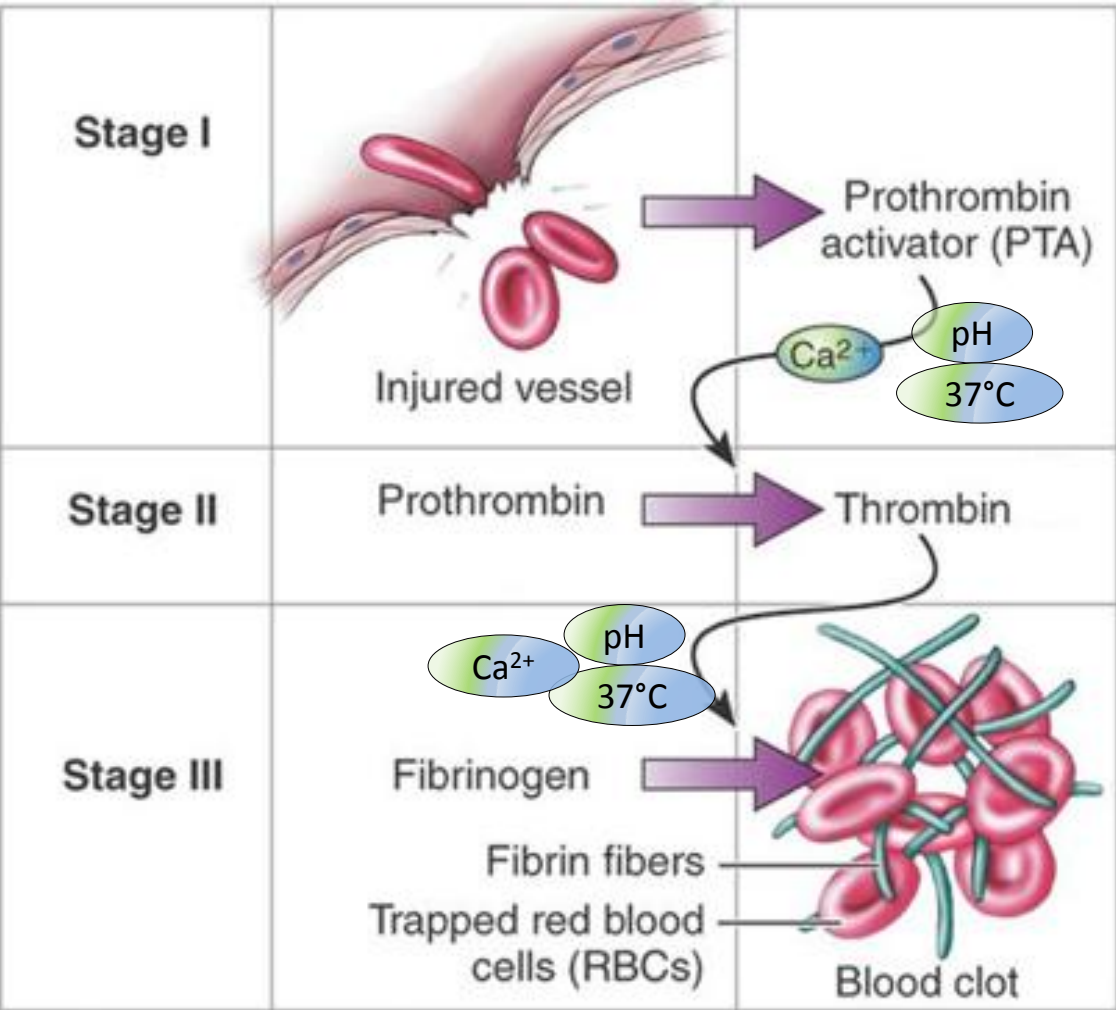


hemostasis



DEPENDENT UPON:

- ✓ Vessel Wall Integrity
- ✓ Adequate Numbers of Platelets
- ✓ Proper Functioning Platelets
- ✓ Adequate Levels of Clotting Factors
- ✓ Proper Function of Fibrinolytic Pathway



- ✓ Endothelial and sub-endothelial surface
- ✓ Platelet membrane and granules
- ✓ Tissue factor
- ✓ Contact activation

- ✓ Thrombin

- ✓ Fibrinogen
- ✓ Factor XIII
- ✓ Fibrinolysis



coagulation testing



- ✓ Prothrombin Time
- ✓ Activated partial thromboplastin time (aPTT)
- ✓ Thrombin Time (Thrombin added to plasma, & time to clot measured)
- ✓ Fibrinogen
- ✓ Platelet Count
- ✓ D-dimer

Primary Hemostasis

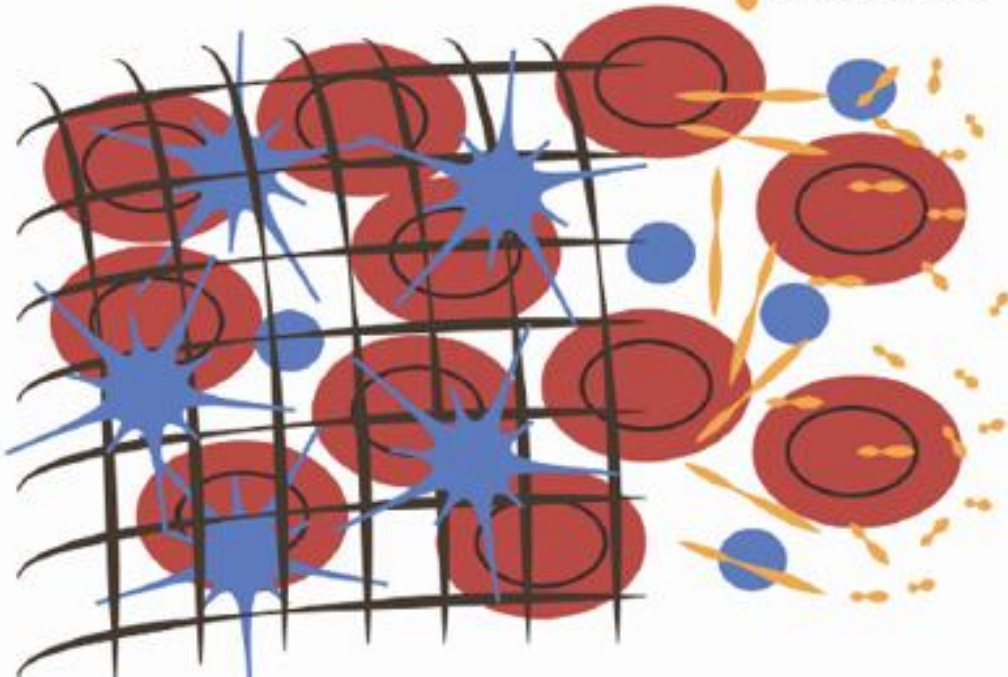
Activated platelets and thrombin burst. Measured by platelet count, vWF, platelet function analysis, and bleeding time.

Coagulation: Intrinsic and Extrinsic Pathways

Builds the fibrin mesh. Measured by PT/INR, aPTT and specific factor levels.

Fibrinolysis

Controls propagation of the fibrin mesh and dissolves clot when hemostasis is achieved. Measured by fibrinogen level, protein C and S levels, antithrombin III level, euglobulin lysis time, and anticoagulant levels (PAI-1, TAFI).



- The number of platelets does not reflect the quality of platelet function
- Platelet function does not play a role in coagulation test
- PT/aPTT only evaluate the initiation of the clotting process
- Relatively long response time
- No tests explore fibrinolysis
- Poor predictive power for bleeding during or after surgery
- Cannot assess the effect of hypothermia on hemostasis

The long turn-around-time of the conventional coagulation assay and the need of tests looking at the patient's overall hemostatic capacity, has prompted the development of 'global assays' including point-of-care tests (POCTs) which allow for a quick bedside analysis of the patient's coagulation condition.

- ✓ Viscoelastic assays
- ✓ Platelet function assays



**Targets of POC coagulation management:
Time saving (Time is Life!)**



Viscoelastic tests of hemostasis



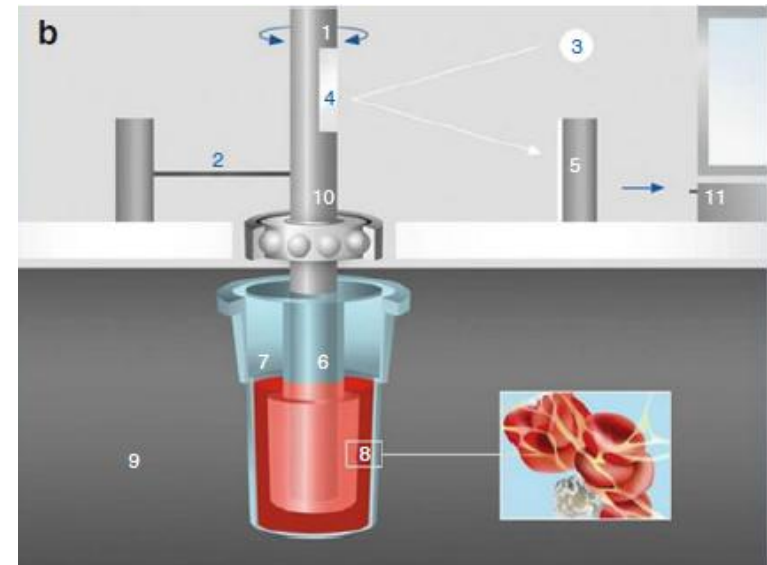
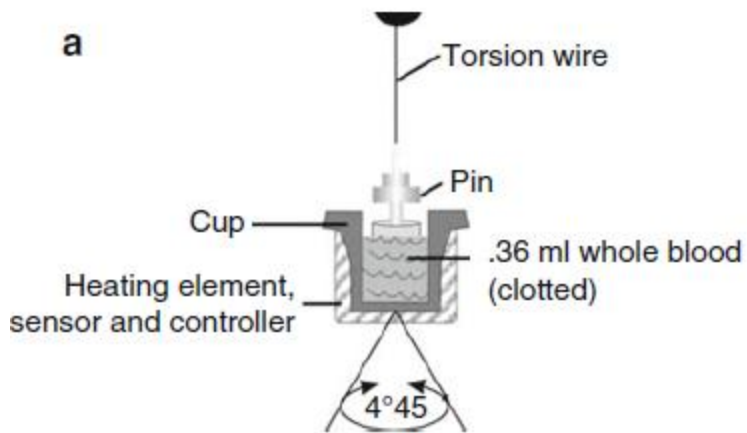
- Thrombelastography was first described by Hartert (1948).
- The viscoelastic changes that occur during coagulation were recorded, providing a graphical representation of the fibrin polymerization process as well as the overall clot strength.
- Thrombelastograph (TEG[®]) or thromboelastogram (ROTEM[®]) enable a complete evaluation of the process of clot initiation, formation and stability, using whole blood or plasma.
- The advantage that the TEG[®]/ROTEM[®] offers is its bedside capability to deliver within 30 min a representation of the sum of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system.



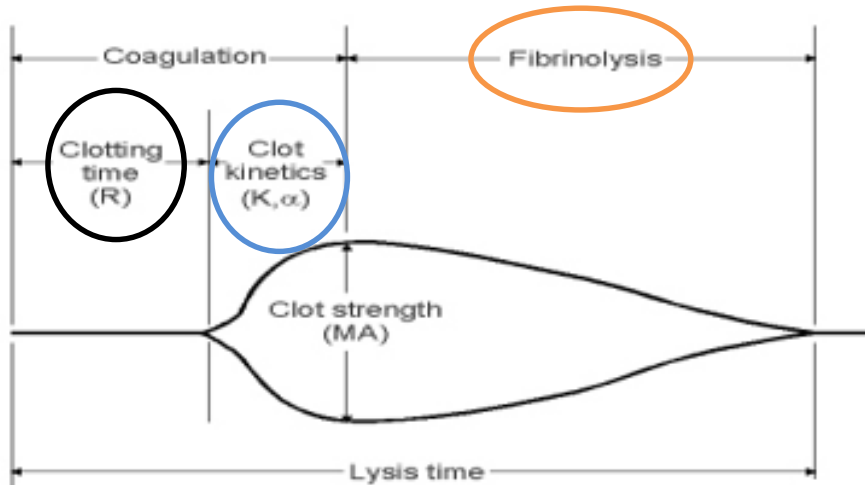
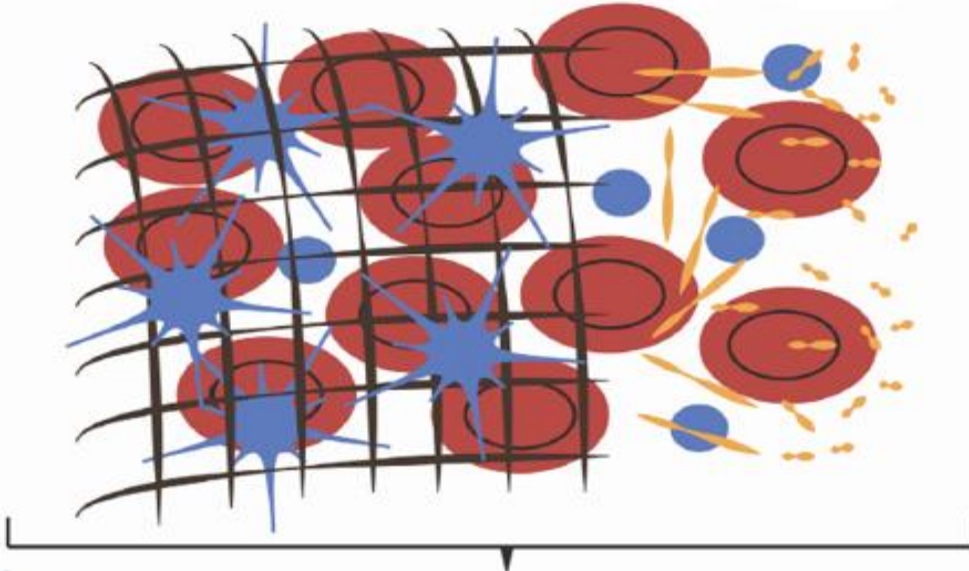
TEG®

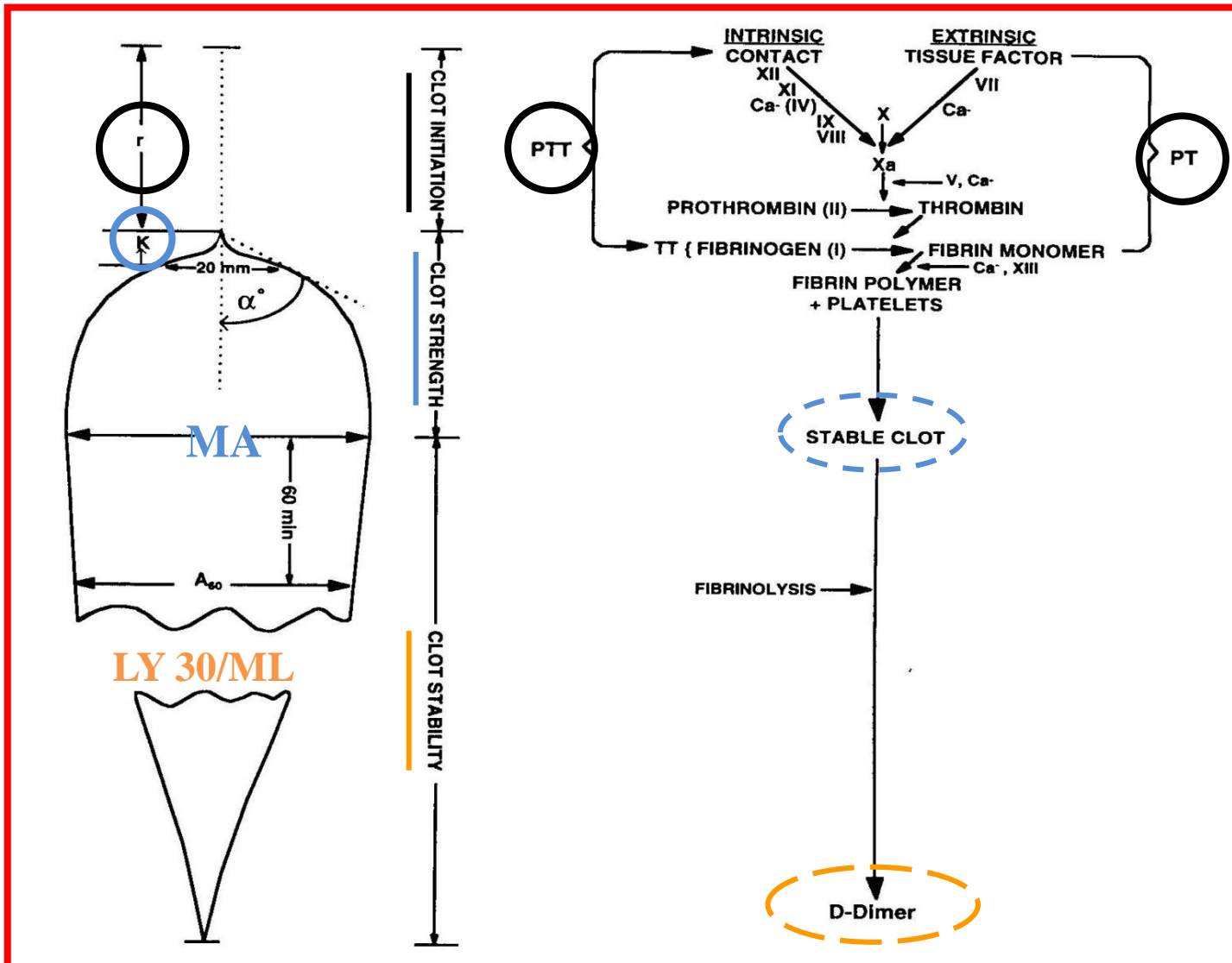


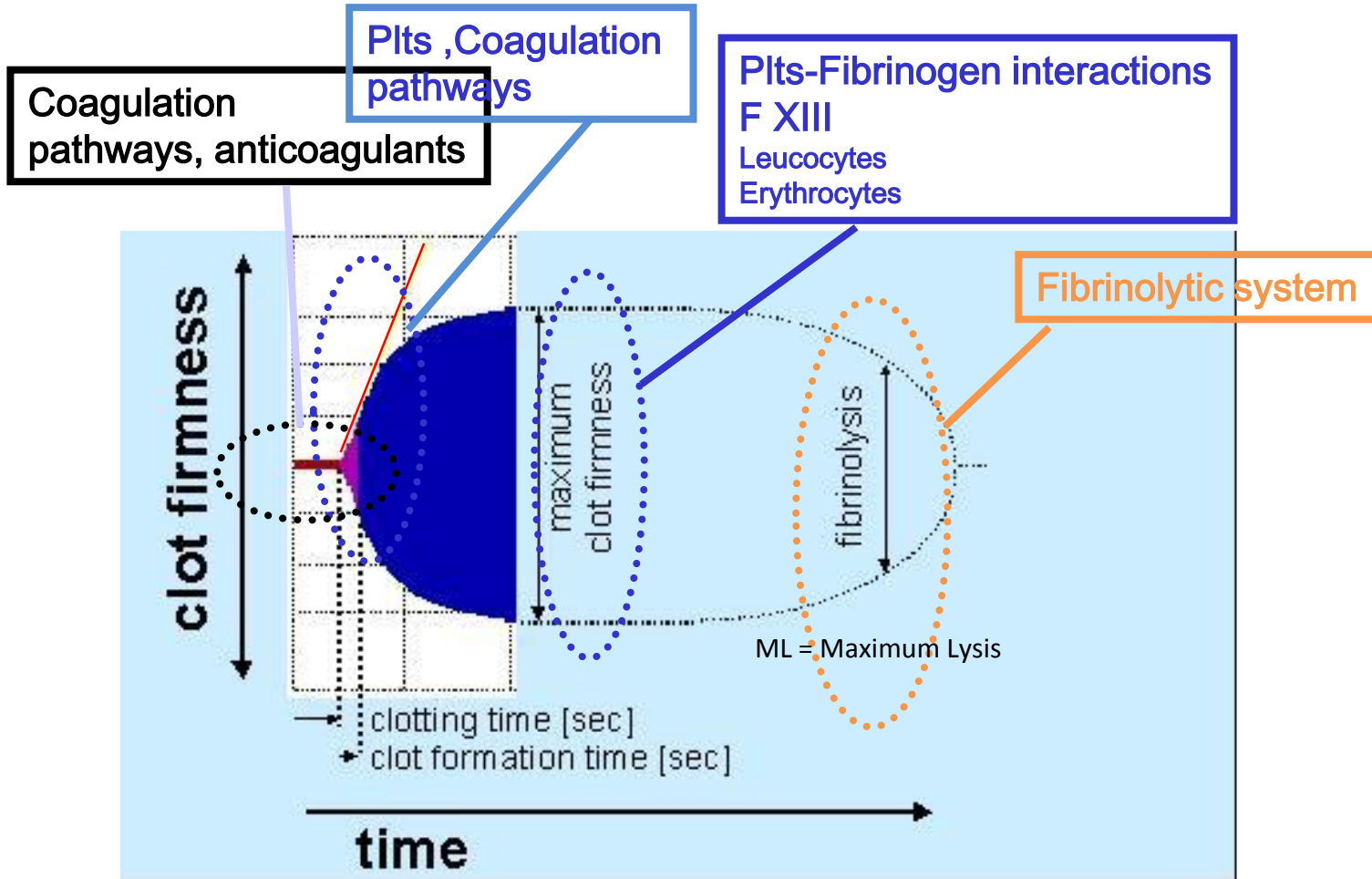
ROTEM®



Viscoelastic tests of hemostasis

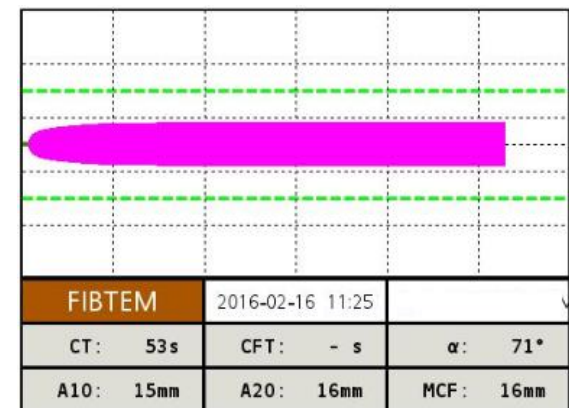
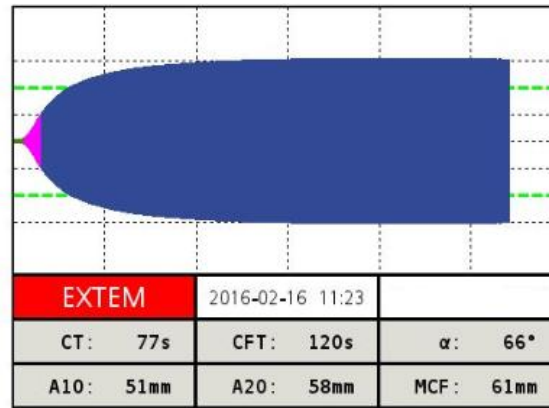
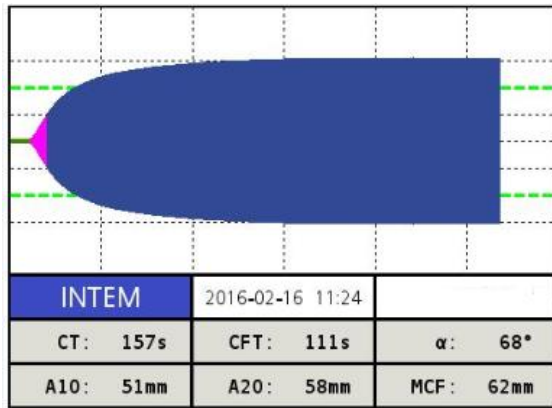




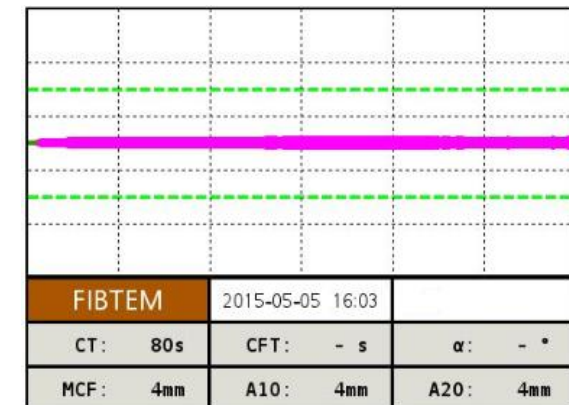
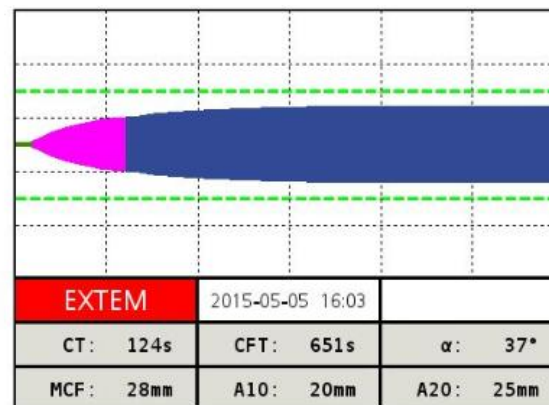
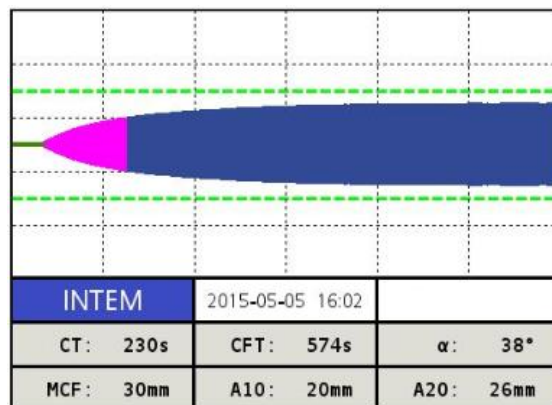


Examples of (A) normal and (B) hypocoagulable ROTEM profile.

A



B



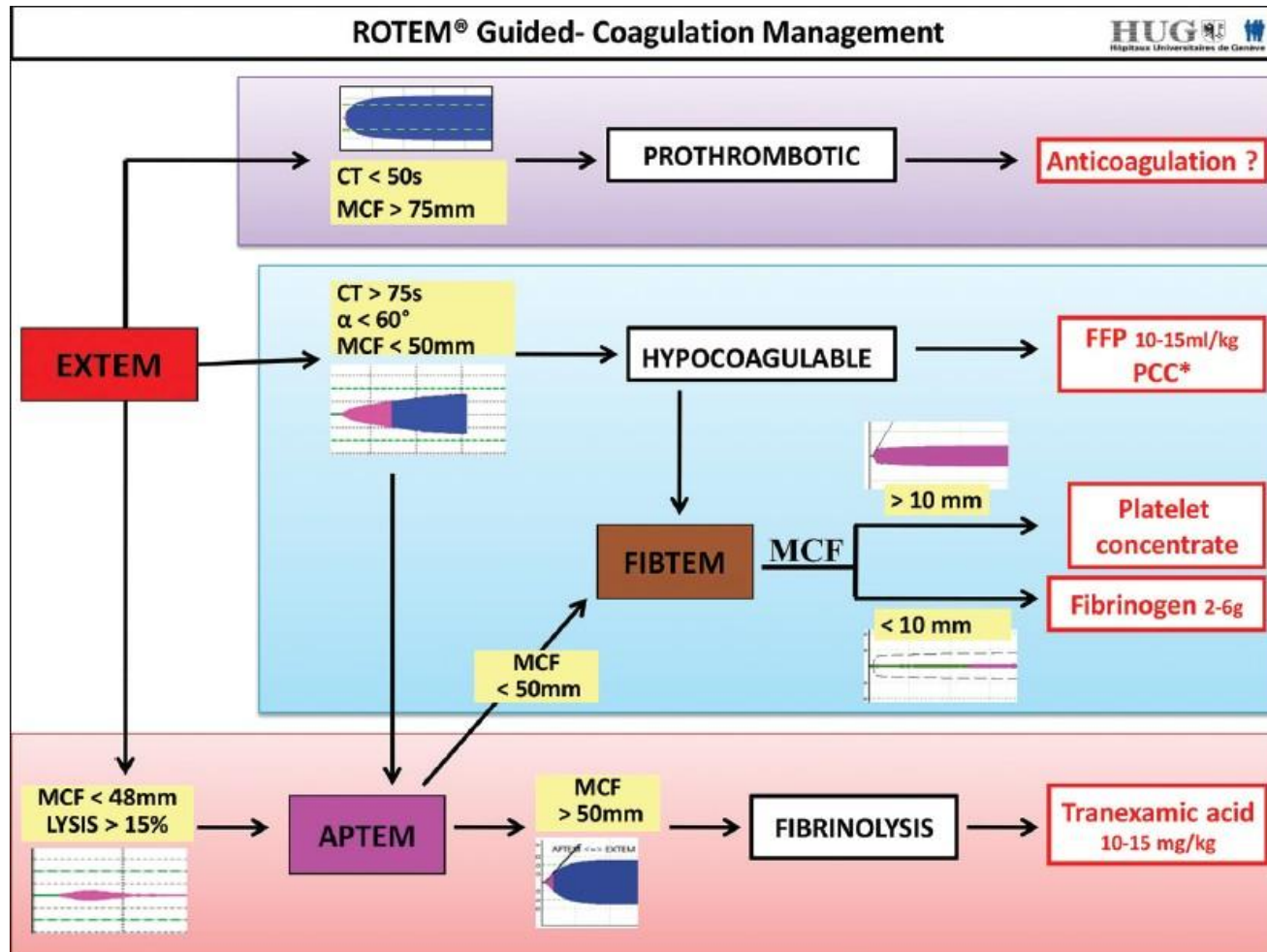


Viscoelastic tests of hemostasis



Current general advantages and disadvantages of viscoelastic point-of-care tests

Advantages	Disadvantages
Bedside	No information on primary hemostasis
Rapid, automated, and easy to perform (ROTEM® does not require pipetting)	No sensitivity for von Willebrand disease
Whole blood, no requirements for sample preparation	No information for antiplatelet drugs (aspirin/clopidogrel/anti GPIIb/IIIa)
Low sample volume (pediatric cups are also available)	No sensitivity for LMWH, fondaparinux, oral anticoagulants
Quick results (5 minutes after the start)	High inter-laboratory variability
Global and dynamic evaluation of coagulation process	Lacking of external quality control assessment
Different comparative analyses with multiple reagents and channels	No validated reference ranges for specific population
Rapid evaluation of the effects of replacement therapy	Reagents are quite expensive



As the assessment of platelet function plays a crucial role in the management of severe bleeding, a masterful ability to perform platelet function assays in a timely and efficient manner is mandatory.

Indeed, the growing number of patients on antiplatelet drugs with the correlated increased bleeding risk, mainly during trauma or surgical procedures, has prompted the use of platelet function POCTs in perioperative settings to predict hemorrhages and manage prohemostatic therapies.

Platelet POCTs devices are based on different operating systems but the driving principle remains the same.



Plateletworks®



VerifyNow®



Multiplate®



PFA100®



ROTEM platelet®

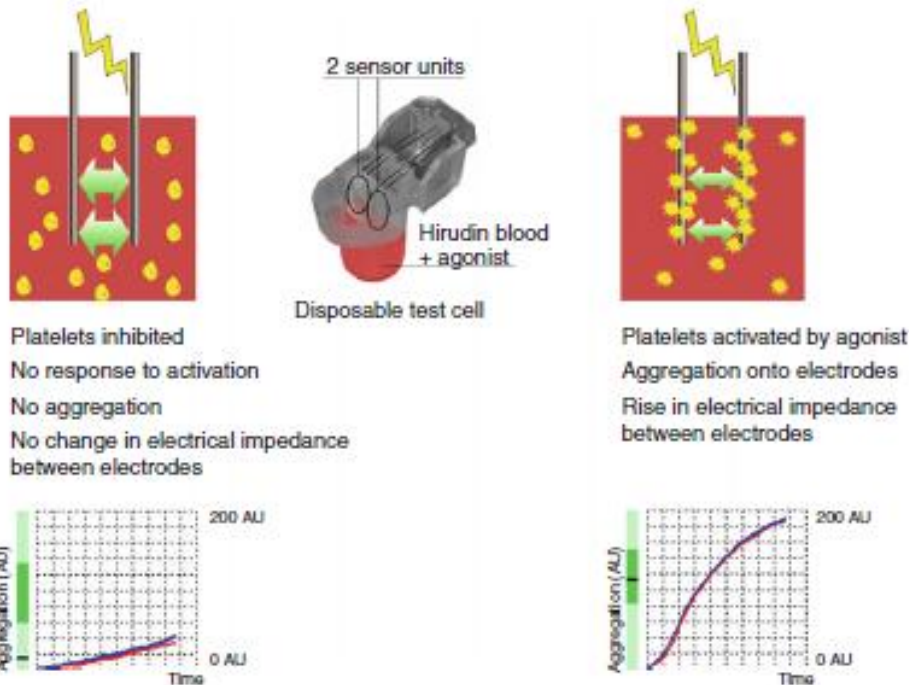
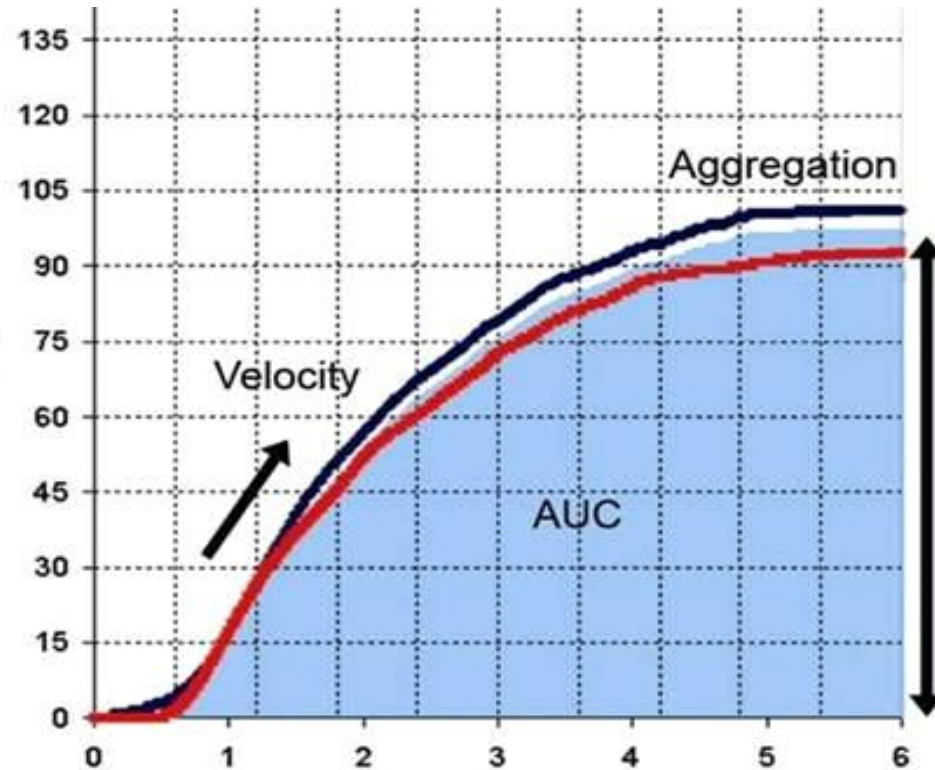
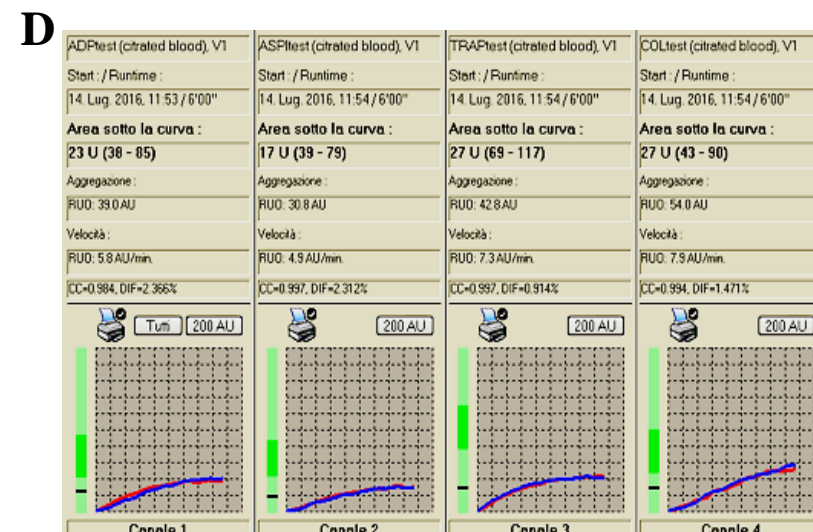
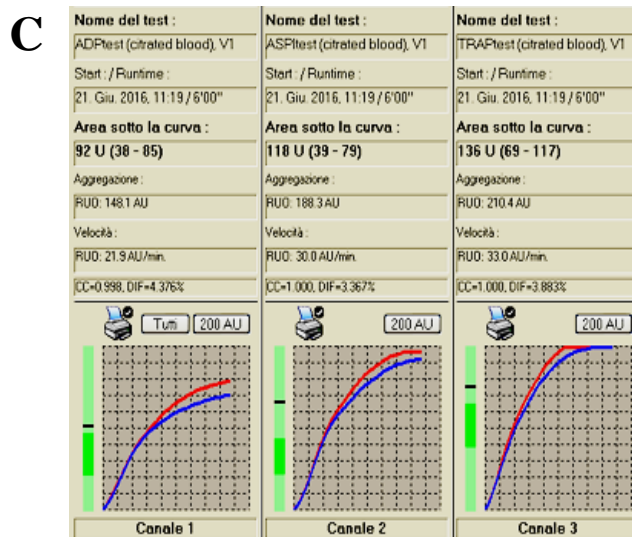
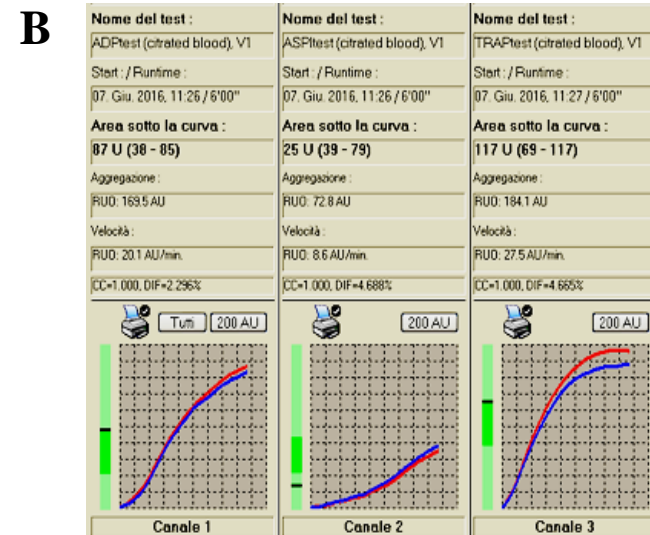
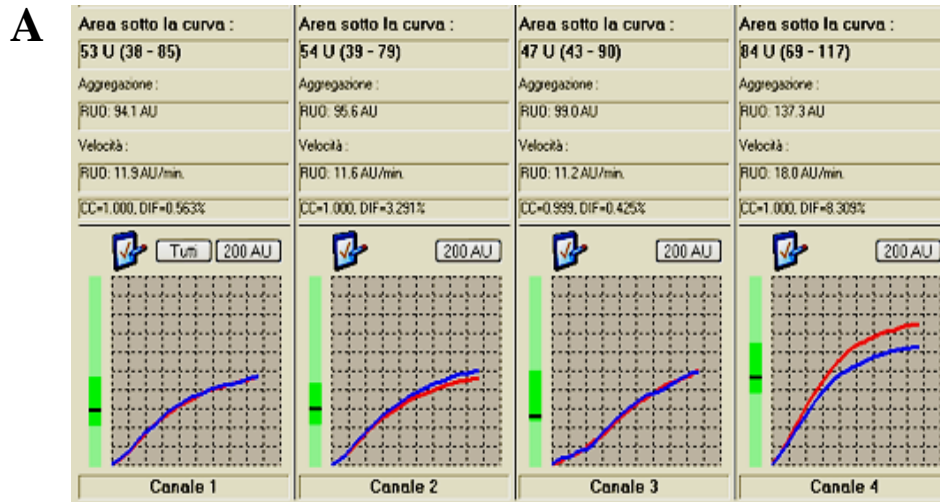


Fig. 4.4 Working mechanism of impedance aggregometry Multiplate®. AU aggregation units



Examples of multiple electrode aggregometry (MULTIPLATE) platelet aggregation profiles: A: normal profile; B: subject taking aspirin; C: hyperaggregation profile; D: hypoaggregation profile.

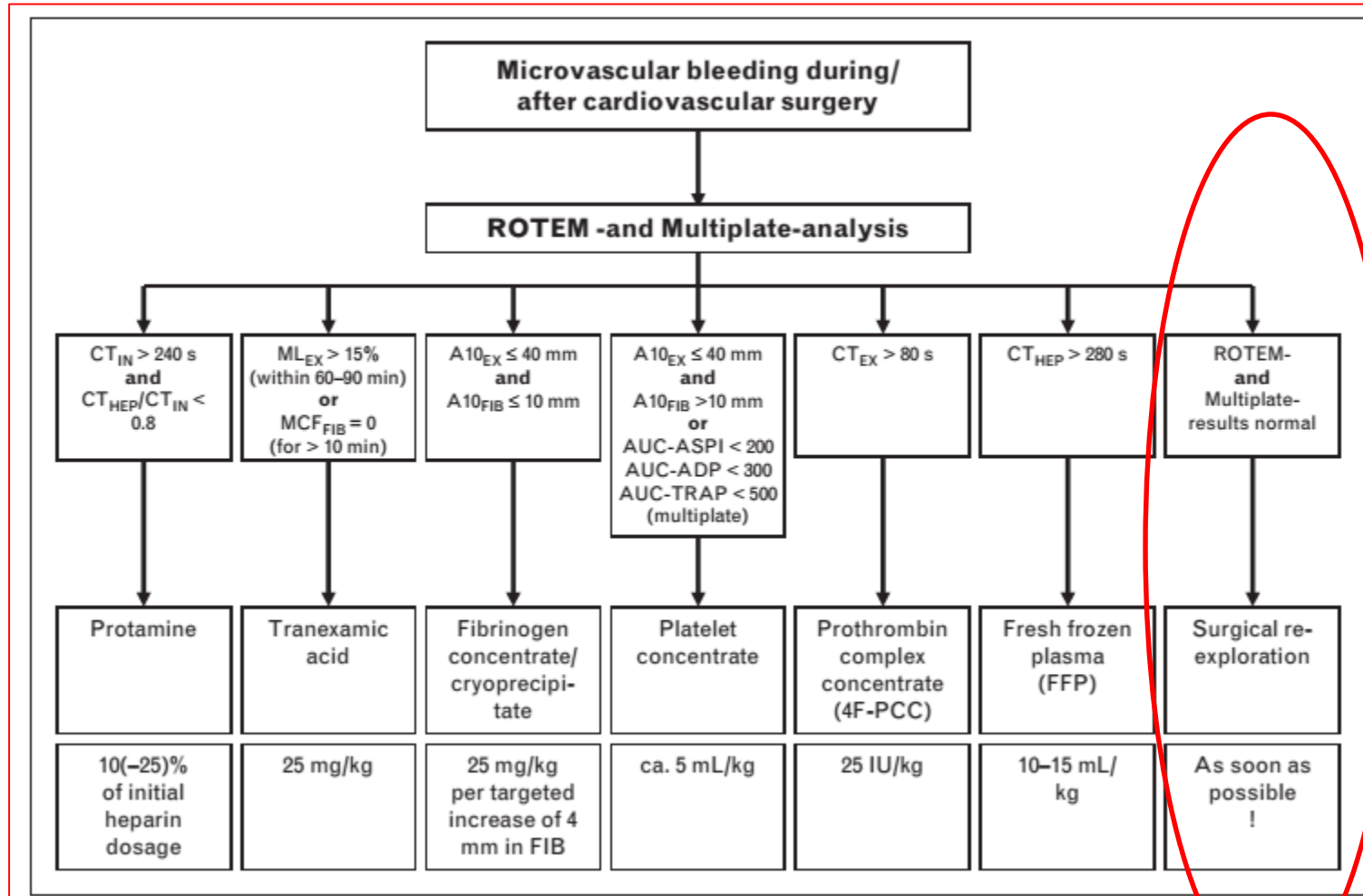


The aim of patient blood management is to preoperatively identify patients at risk and offer individualized therapy to decrease the likelihood of transfusion, thereby improving outcome, reducing side effects and overall costs.

Table 13.1 The basics of patient blood management

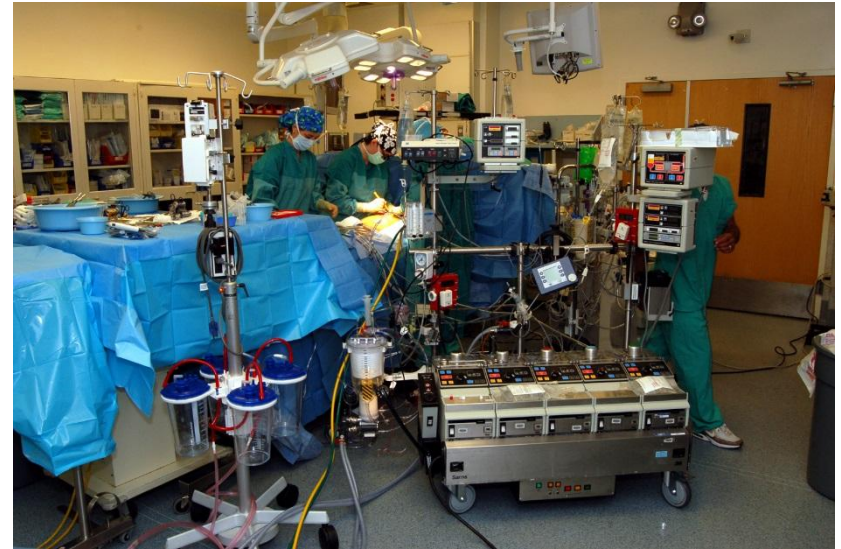
Patient blood management	
→	<i>Detect and correct preoperative anemia and iron deficiency</i>
	Iron (i.v.) + ESA perioperatively
→	<i>Reduce perioperative RBC loss</i>
	Meticulous surgical technique
	Acute normovolemic hemodilution
	Cell salvage and re-transfusion
	Avoidance of coagulopathy with an individualized, goal-directed coagulation algorithm and the use of antifibrinolytics and factor concentrates
	Low CVP, no hypertension, normothermia
→	<i>Harness and optimize physiological reserve of anemia</i>
	Tolerate low hemoglobin values
	Administer high FiO_2
	Minimize metabolic demand

ESA erythropoiesis stimulating agent, CVP central venous pressure, FiO_2 inspired oxygen fraction



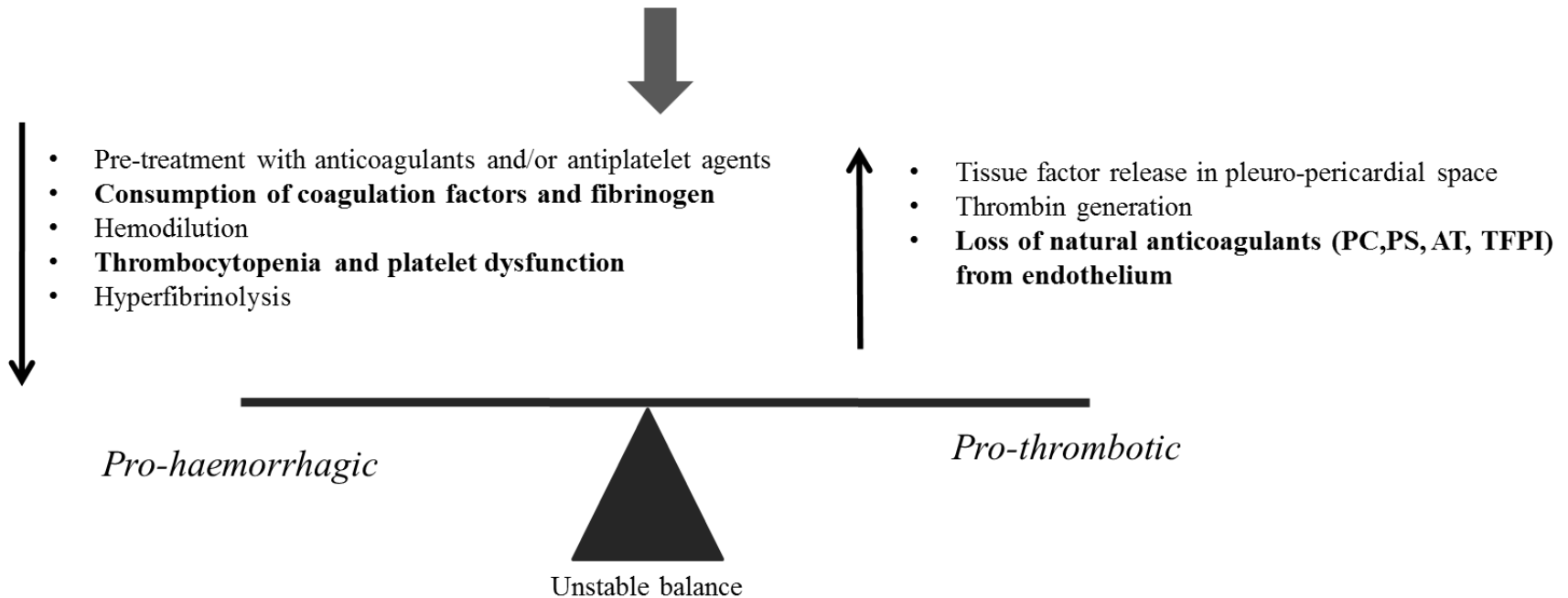
	Complications	Author	Year
RBCs	▪Viral transmission	Epstein and Homberg	2010
	▪Postoperative infections	Amato and Pescatori	2006
	▪TRALI	Rana et al.	2006
		Khan et al.	2007
		Chaiwat et al.	2009
	▪Multiorgan failure/thromboembolic events/myocardial infarction	Moore et al.	1997
	▪Renal dysfunction	Rogers et al.	2006
	▪Sepsis	Ferraris et al.	2012
	▪Alzheimer's disease	Morales et al.	2011
	▪Non Hodgkin Lymphoma/LLC	De Calignon et al. Castillo et al.	2012 2010
FFPs	Allergic reaction	Dara et al.	2005
	TRALI-TACO	Buddeberg et al.	2008
	Infections	Toy et al.	2005
Platelets	Infections	Norda et al.	2006

- ✓ Cardiac Surgery
- ✓ Liver transplantation
- ✓ Trauma
- ✓ Post-partum Hemorrhage (PPH)



Coagulopathy in cardiac surgery

Surgical damage to tissues, cardiopulmonary by-pass circuits, heparin, protamin



Guideline on antiplatelet and anticoagulation management in cardiac surgery

Joel Dunning^a, Michel Versteegh^b, Alessandro Fabbri^c, Alain Pavie^d,
Philippe Kolh^e, Ulf Lockowandt^f, Samer A.M. Nashef^{g,*}
on behalf of the EACTS Audit and Guidelines Committee

Recommendation:

Thromboelastography may be used to guide transfusion in the postoperative period and studies have demonstrated a reduction in blood and blood product usage if used in conjunction with a treatment algorithm. Further studies are required before thromboelastography can be recommended as the standard of care for postoperative transfusion management.

(Grade B recommendation based on level 2b studies)

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www.elsevier.com/locate/ejcts

Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

- 1.1 The ROTEM system and the TEG system are recommended to help detect, manage and monitor haemostasis during and after cardiac surgery.
- 1.3 Healthcare professionals using the ROTEM system and the TEG system during cardiac surgery should have appropriate training and experience with these devices.

Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion (Review)



Cochrane Database of Systematic Reviews

Main results

We included nine RCTs with a total of 776 participants; only one trial had a low risk of bias. We found two ongoing trials but were unable to retrieve any data from them. Compared with standard treatment, TEG or ROTEM showed no statistically significant effect on overall mortality (3.78% versus 5.11%, RR 0.77, 95% CI 0.35 to 1.72; $I^2 = 0\%$) but only five trials provided data on mortality. Our analyses demonstrated a statistically significant effect of TEG or ROTEM on the amount of bleeding (MD -85.05 ml, 95% CI -140.68 to -29.42; $I^2 = 26\%$) but failed to show any statistically significant effect on other predefined outcomes.

Authors' conclusions

There is an absence of evidence that TEG or ROTEM improves morbidity or mortality in patients with severe bleeding. Application of a TEG or ROTEM guided transfusion strategy seems to reduce the amount of bleeding but whether this has implications for the clinical condition of patients is still uncertain. More research is needed.

POCTs use in cardiac surgery significantly reduces overall transfusion rates, even though evidence of a clear association between POCTs and reduced blood losses and reduced morbidity/mortality has not been well established.

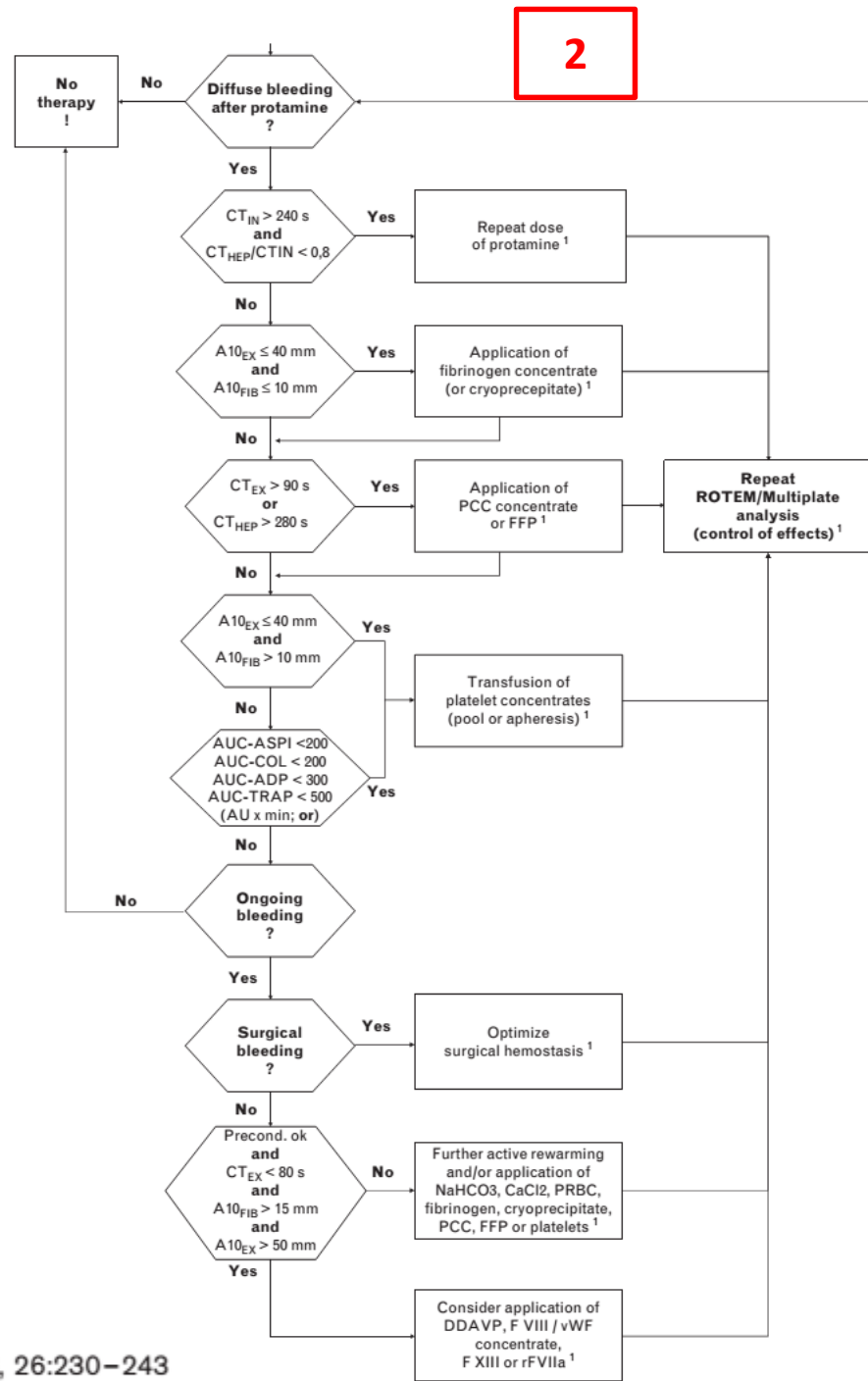
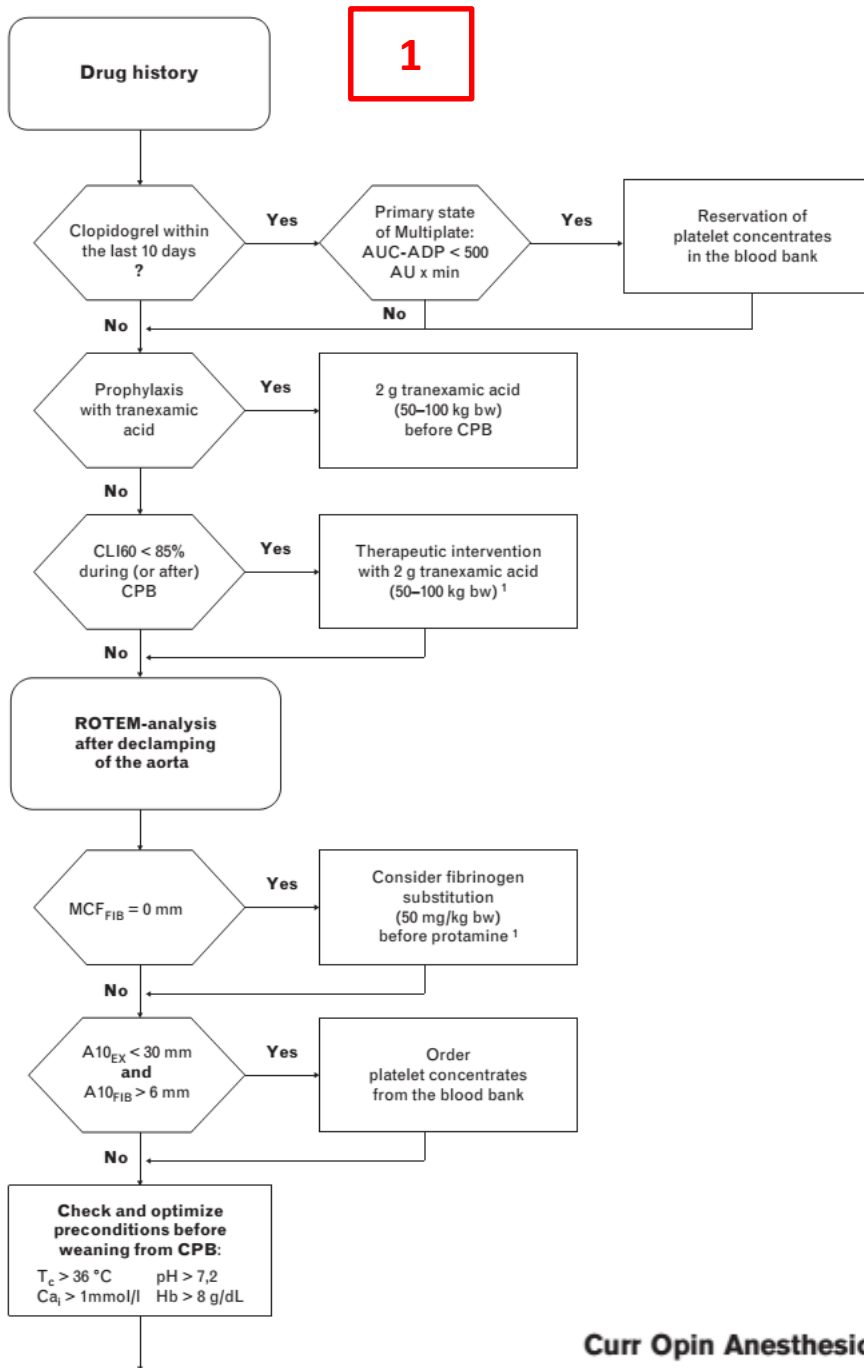
Despite a positive global recommendation by NICE (2014) on the monitoring of hemostasis with POCTs in cardiothoracic surgery, a universally applicable transfusion algorithm including optimal thresholds for the viscoelastic and platelet test parameters, timing and relationship with conventional laboratory assays is not available yet

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

We recommend the use of standardised haemostatic algorithms with predefined intervention triggers.

1A



Coagulopathy during liver transplantation

Marked portal hypertension, MELD/Child-Pugh, type of liver disease, quality of donor liver, experience of the transplantation team, length of cold ischemia time



- **Consumption of clotting factors**
- **Consumption of fibrinogen**
- **Thrombocytopenia and platelet consumption**
- Changes in production and clearance of clotting factors during OLTs phases
- Hyperfibrinolysis during anhepatic and reperfusion phases (increased tPA and reduced antifibrinolytic proteins)
- Hemodilution
- Acidosis, hypothermia, hypocalcemia, citrate toxicity
- Heparin-like effect from damaged ischemic graft endothelium

- **Increased levels of FVIII and vWF**
- **Reduced plasma levels of natural anticoagulants (PC,PS, AT, TFPI)**
- Hypofibrinolysis (high levels of PAI-1 and reduced levels of plasminogen)



Pro-haemorrhagic

Pro-thrombotic

Unstable balance

Thromboelastography-Guided Transfusion Decreases Intraoperative Blood Transfusion During Orthotopic Liver Transplantation: Randomized Clinical Trial

Transplantation Proceedings, 42, 2590–2593 (2010)

S.-C. Wang, J.-F. Shieh, K.-Y. Chang, Y.-C. Chu, C.-S. Liu, C.-C. Loong, K.-H. Chan, S. Mandell, and M.-Y. Tsou

Table 3. Perioperative Data*

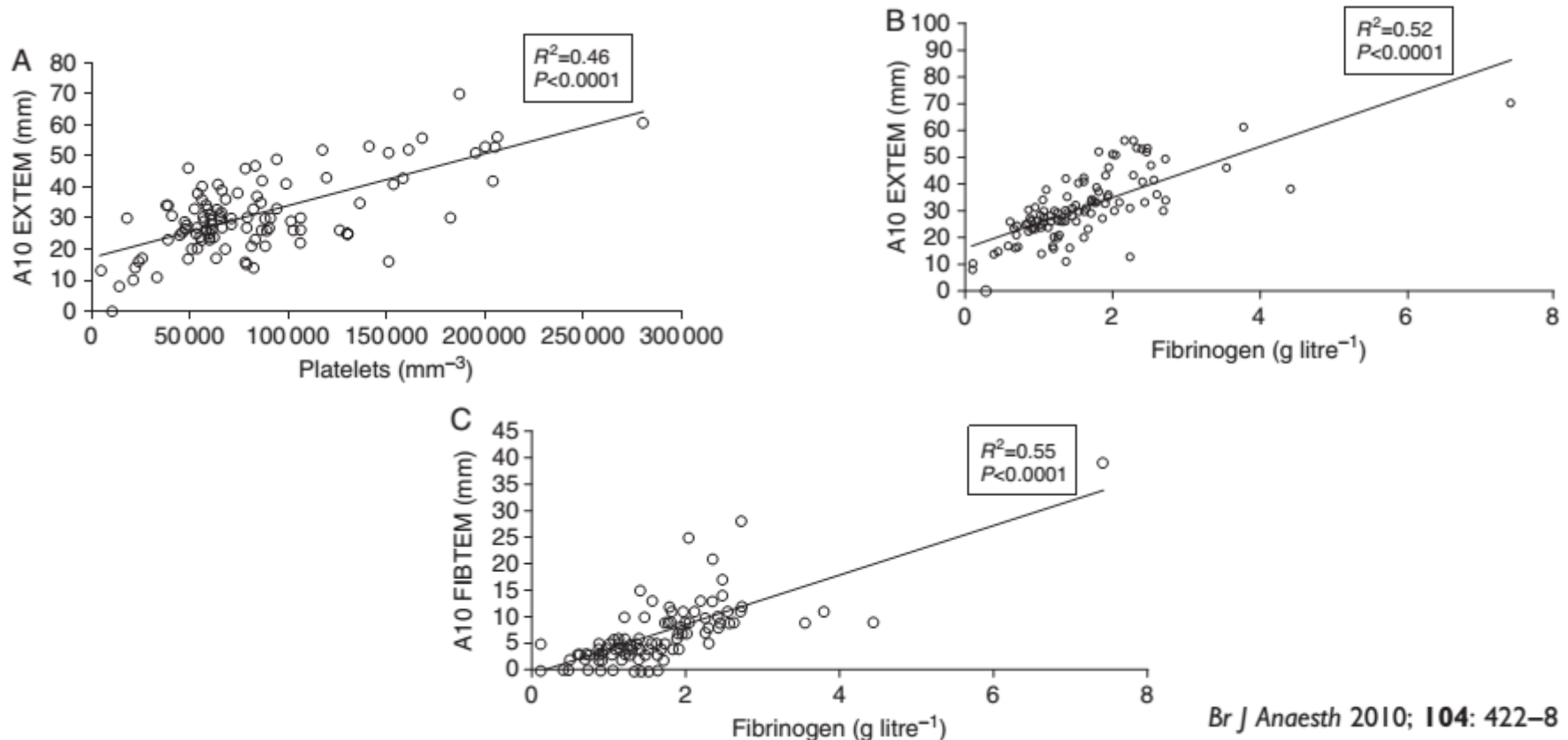
Variable	Control Group	TEG Group
Intake		
Blood product		
Total transfusion, mL	6587.1 (3254.6)	4937.1 (2038.2)
Fresh-frozen plasma, U	21.5 (12.7)	12.8 (7.0) [†]
Cryoprecipitate, U	15.6 (9.5)	13.0 (10.3)
Platelet concentrates, U	30.1 (18.5)	27.3 (13.9)
Whole blood, U	1.4 (2.5)	0.3 (1.1)
Packed RBCs, U	16.7 (12.8)	14.2 (7.1)
IV fluid		
Fluid total, mL	10053.8 (4966.8)	9198.0 (4546.9)
HAES, mL	214.3 (544.7)	150.0 (231.2)
Albumin, mL	664.3 (474.9)	829.2 (588.7)
Output		
Blood loss, mL	6348.0 (3704.1)	4775.7 (4264.7)
Urine output, mL	2139.3 (1208.0)	2312.9 (1491.5)

Material and Methods. Twenty-eight patients undergoing OLTs were recruited over 2 years. Patients were randomized into 2 groups: those monitored during surgery using point-of-care TEG analysis, and those monitored using standard laboratory measures of blood coagulation.

Conclusion. Thromboelastography-guided transfusion decreases transfusion of FFP in patients undergoing orthotopic liver transplantation, but does not affect 3-year survival.

Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation

S. Roulet^{1*}, J. Pillot¹, G. Freyburger², M. Biais¹, A. Quinart¹, A. Rault³, P. Revel¹
and F. Sztark¹





Methods to decrease blood loss and transfusion requirements for liver transplantation (Protocol)

Gurusamy KS, Davidson BR



THE COCHRANE
COLLABORATION®

- ✓ A Cochrane review which included 33 trials involving 1913 patients concluded that thromboelastography groups may potentially reduce blood loss and transfusion requirements during liver transplantation.
- ✓ Evidence is based on clinical trials that are small sized and with high risk of bias (only 2 trials assessed the outcome of thromboelastography-versus non thromboelastography-driven, 31 vs 31 patients).
- ✓ Only a borderline significant lower allogeneic blood transfusion requirement in POCTs driven-group. There were no significant differences in the blood losses, hospital or intensive care unit stay and mortality in the comparison.

In end-stage liver disease, viscoelastic tests have shown a better correlation with the bleeding tendency than classical coagulation tests and have been proven to adequately predict severe thrombocytopenia and hypofibrinogenemia.

ESA Guidelines recommend perioperative coagulation monitoring using ROTEM/TEG for a targeted management of coagulopathy during liver transplantation with a grade 1C. Implementation of TEG/ROTEM-based transfusion and coagulation management algorithms can reduce transfusion rates and transfusion-associated costs.

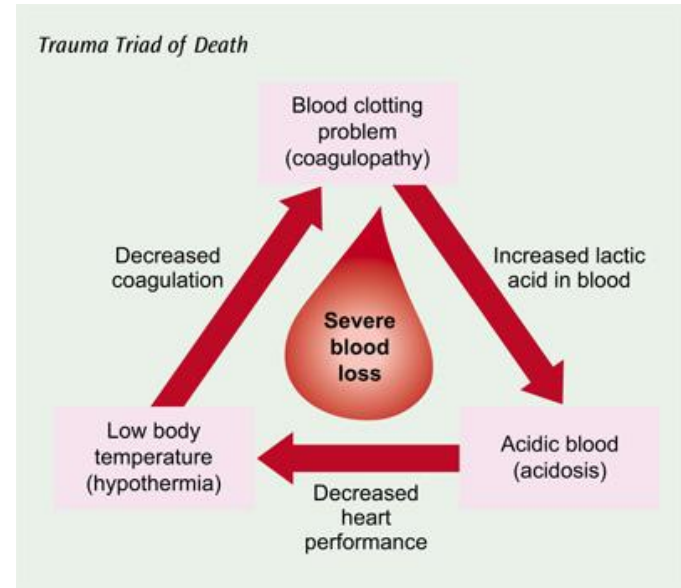
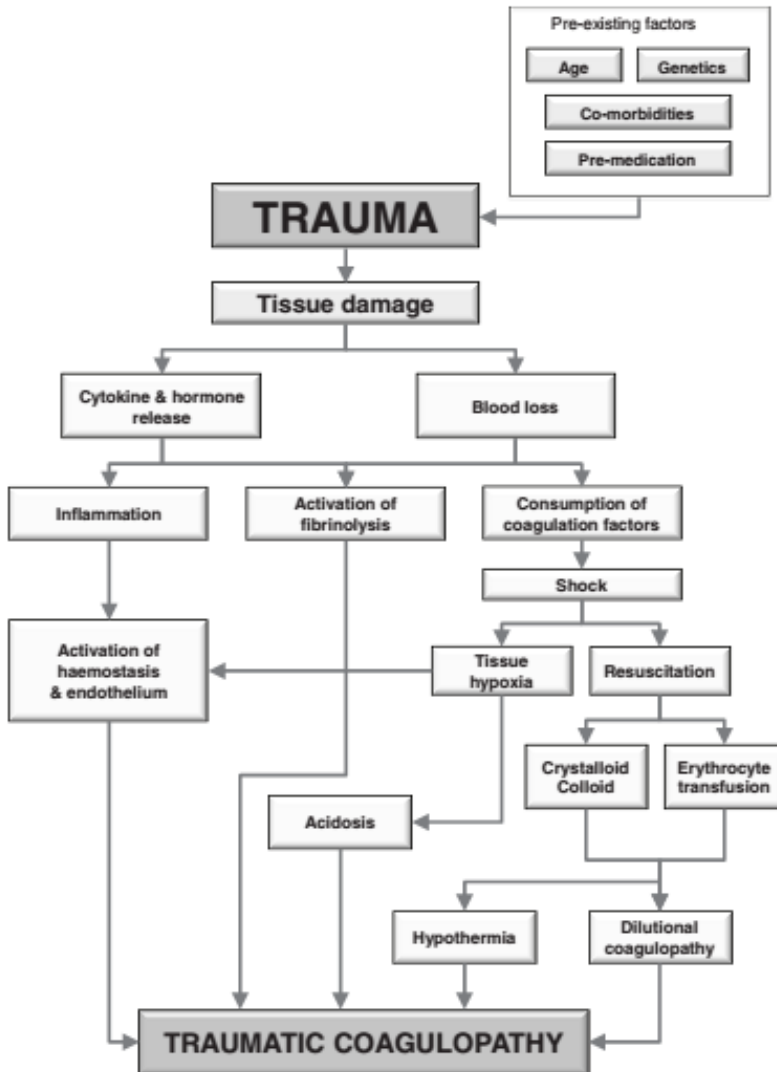
Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

We recommend the use of perioperative coagulation monitoring using ROTEM/TEG for targeted management of coagulopathy. **1C**

Point of care platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs. **C**

Coagulopathy in trauma



Trauma-induced coagulopathy: impact of the early coagulation support protocol on blood product consumption, mortality and costs

Nardi *et al. Critical Care* (2015) 19:83

Table 1 Main characteristics of the two treatment strategies^a

Treatment strategies	Standard treatment (2011)	Early coagulation support (2013)
Fluid resuscitation	Crystalloids and colloids	Crystalloids only
Fluid treatment strategy	Permissive hypotension, relative fluid restriction (except in TBI patients)	Permissive hypotension, relative fluid restriction (except in TBI patients)
Tranexamic acid	1 g + 1 g 8-hr infusion	1 g + 1 g 8-hr infusion
Initial coagulation support	"Initial" plasma at high level (>1:2) plasma:PRBC ratio	Fibrinogen 2 g
Treatment of uncontrolled bleeding	Plasma:PRBC ratio (>1:2) Keep PTL >100,000	Goal-directed treatment (including plasma:PRBC >1:2 if indicated)
Coagulation monitoring	Traditional: INR, aPTT, PTL, fibrinogen (von Clauss method)	Viscoelastic POC

The ECS protocol must be considered as part of a comprehensive damage resuscitation control strategy.

The introduction of the ECS protocol in two Italian trauma centers was associated with a marked reduction in blood product consumption, reaching statistical significance for plasma and PTL, and with a non-significant trend toward a reduction in early and 28-day mortality. The overall costs of transfusion and coagulation support (including POC tests) decreased by 23%

RESEARCH

Open Access

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



Rolf Rossaint¹, Bertil Bouillon², Vladimir Cerny^{3,4,5,6}, Timothy J. Coats⁷, Jacques Duranteau⁸, Enrique Fernández-Mondéjar⁹, Daniela Filipescu¹⁰, Beverley J. Hunt¹¹, Radko Komadina¹², Giuseppe Nardi¹³, Edmund A. M. Neugebauer¹⁴, Yves Ozier¹⁵, Louis Riddez¹⁶, Arthur Schultz¹⁷, Jean-Louis Vincent¹⁸ and Donat R. Spahn^{19*}

Coagulation monitoring

Recommendation 12 We recommend that routine practice include the early and repeated monitoring of coagulation, using either a traditional laboratory determination [prothrombin time (PT), activated partial thromboplastin time (APTT) platelet counts and fibrinogen] (Grade 1A) and/or a viscoelastic method. (Grade 1C)



Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems)

There is currently insufficient evidence to recommend the routine adoption of viscoelastometric point-of-care testing to help detect, manage and monitor hemostasis in the emergency control of bleeding after **trauma and during postpartum hemorrhage**.

Research is recommended into the clinical benefits and cost effectiveness of using viscoelastometric point-of-care testing to help in the emergency control of bleeding **after trauma or during postpartum hemorrhage**.



Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma-induced coagulopathy in adult trauma patients with bleeding (Review)



Three studies were included in the final analysis. All three studies used ROTEM as the test of global hemostatic function, and none of the studies used TEG.

Authors' conclusions

We found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM. The value of accuracy estimates are considerably undermined by the small number of included studies, and concerns about risk of bias relating to the index test and the reference standard. We recognise that the reference standards of PT and INR are imperfect, but in the absence of embedded clinical consensus these are judged to be the best reflection of current clinical practice. We are unable to offer advice on the use of global measures of haemostatic function for trauma based on the evidence on test accuracy identified in this systematic review. This evidence strongly suggests that at present these tests should only be used for research. We consider more thoroughly what this research could be in the Discussion section.



POCT in trauma - CONCLUSIONS



The current best strategy recommended for the management of bleeding and coagulopathy in trauma is the early and repeated monitoring of coagulation, using either a traditional laboratory determination and/or a viscoelastic method.

Moreover, resuscitation should be continued using a goal-directed strategy guided by standard laboratory coagulation values and/or viscoelastic tests. The POCTs benefit in trauma is currently unclear. Their use significantly reduces transfusion requirement and costs but impact on reducing bleeding, morbidity and mortality is still controversial.

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



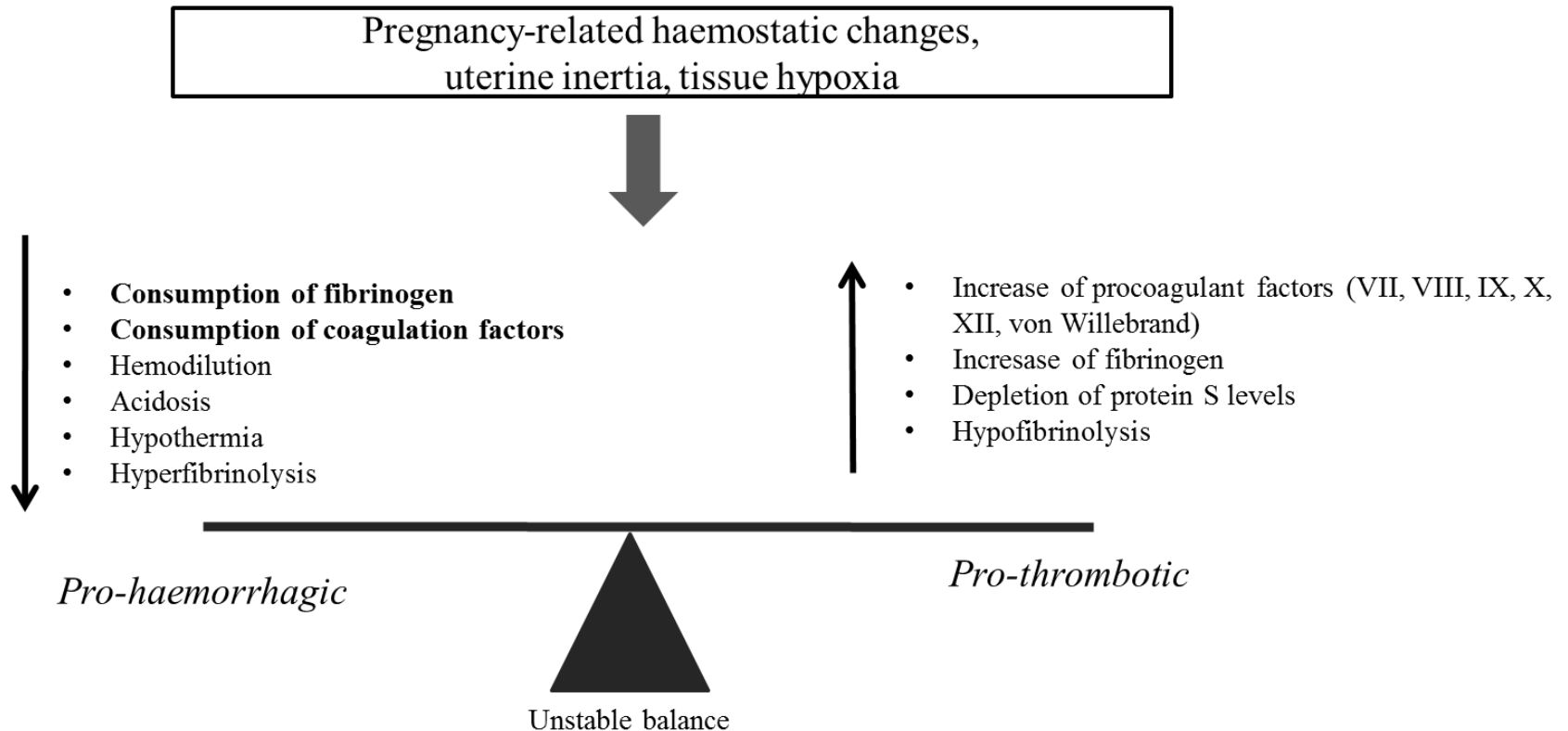
Rossaint et al. *Critical Care* (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Recommendation 23 We recommend that monitoring and measures to support coagulation be initiated immediately upon hospital admission. (Grade 1B)

Recommendation 12 We recommend that routine practice include the early and repeated monitoring of coagulation, using either a traditional laboratory determination [prothrombin time (PT), activated partial thromboplastin time (APTT) platelet counts and fibrinogen] (Grade 1A) and/or a viscoelastic method. (Grade 1C)

Recommendation 26 We recommend that resuscitation measures be continued using a goal-directed strategy guided by standard laboratory coagulation values and/or viscoelastic tests. (Grade 1C)

Coagulopathy in post-partum hemorrhage



Thromboelastometry allows for close monitoring of fibrinogen levels in plasma over the course of a major obstetric hemorrhage.

However, although viscoelastic assays appropriately depict coagulation changes and may allow early goal-directed decisions, there have been very few studies assessing the benefit of using TEG/ROTEM to guide hemostatic resuscitation during PPH, rendering an evidence-based recommendation about their use in this setting premature.

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Thromboelastometry can identify obstetric coagulopathy and hyperfibrinolysis and guide haemostatic therapy. **C**

In life-threatening PPH, we suggest a transfusion protocol with a fixed product ratio or individualised procoagulant intervention and factor substitution. **2C**

Considering physiologically elevated fibrinogen concentrations in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenaemia may be required. **C**

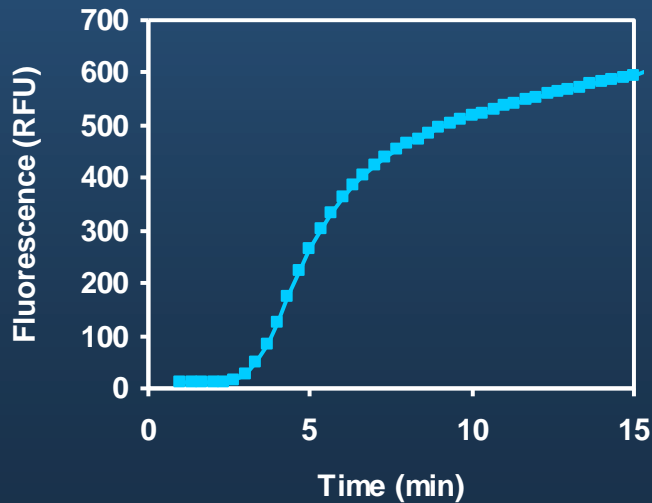
Thrombin generation test



Plasma
TF / phospholipids
CaCl₂ / fluorogenic (chromogenic) substrate



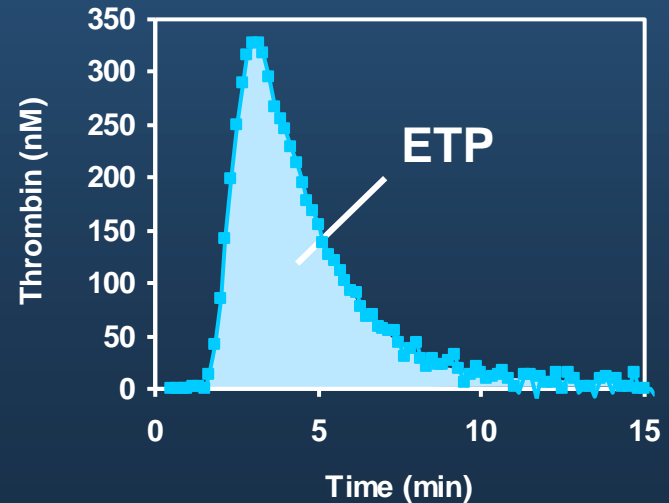
Detector



Raw data



Corrections
First derivative



Thrombin generation curve

Next-Generation Innovation In The Measurement Of Thrombin Generation

NOV 19, 2015



POCs IN THE MANAGEMENT OF SEVERE BLEEDING

	WHOLE BLOOD ROTEM –TEG	WHOLE BLOOD AGGREGOMETRY	WHOLE BLOOD THROMBIN GENERATION
EQUIPMENTS	AVAILABLE	AVAILABLE	NOT AVAILABLE
STANDARDIZATION	NO	NO	NO
LEVEL OF EVIDENCE FROM THE LITERATURE	STILL LOW (case series, retrospective studies, no RCT)	VERY LOW (case series)	NO
RATIONALE FOR USE	YES	YES	YES
DIFFUSION IN ICU, ER, OT (EUROPE)	INCREASING	LIMITED	NO
MAIN USERS	ANESTHESIOLOGISTS , SURGEONS, HEMATOLOGISTS	ANESTHESIOLOGISTS HEMATOLOGISTS	COAGULOLOGISTS HEMATOLOGISTS



CONCLUSIONS -PROS



- ✓ Our understanding of the pathophysiology of the complex world of coagulopathy in different clinical settings as well as the bleeding-related coagulopathy has improved greatly in recent years.
- ✓ Currently, a POCTs-based bleeding management strategy using ROTEM or TEG devices has proven more effective in reducing red blood cells, platelet and fresh frozen plasma transfusions than traditional coagulation tests-based.
- ✓ Moreover, cost-effectiveness analyses indicated that POCTs are cost-saving compared with classical coagulation tests or blinded management.
- ✓ The importance of POCTs for **coagulation monitoring** in bleeding is evident and recommended by current guidelines.



CONCLUSIONS -CONS



- ✓ Conversely, the currently available data do not show an improvement of clinical outcomes such as actual blood loss containment, re-operation, length of hospital or intensive care unit stay and overall mortality related to POCT use.
- ✓ Evidence needs to be corroborated through large clinical trials to find a consensus on the appropriate tests, the optimal moment to perform them and the cut-off considered for corrective measures.
- ✓ Finally, reference ranges need to be validated and internal and external quality controls implemented.

Save the Date



2nd INTERNATIONAL PADUA MEETING ON SEVERE BLEEDING MANAGEMENT

PADUA

16th-17th November 2016

Aula Morgagni
Policlinico Universitario

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Graziella Saggiorato

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