Advances in Haemostasis Diagnostics

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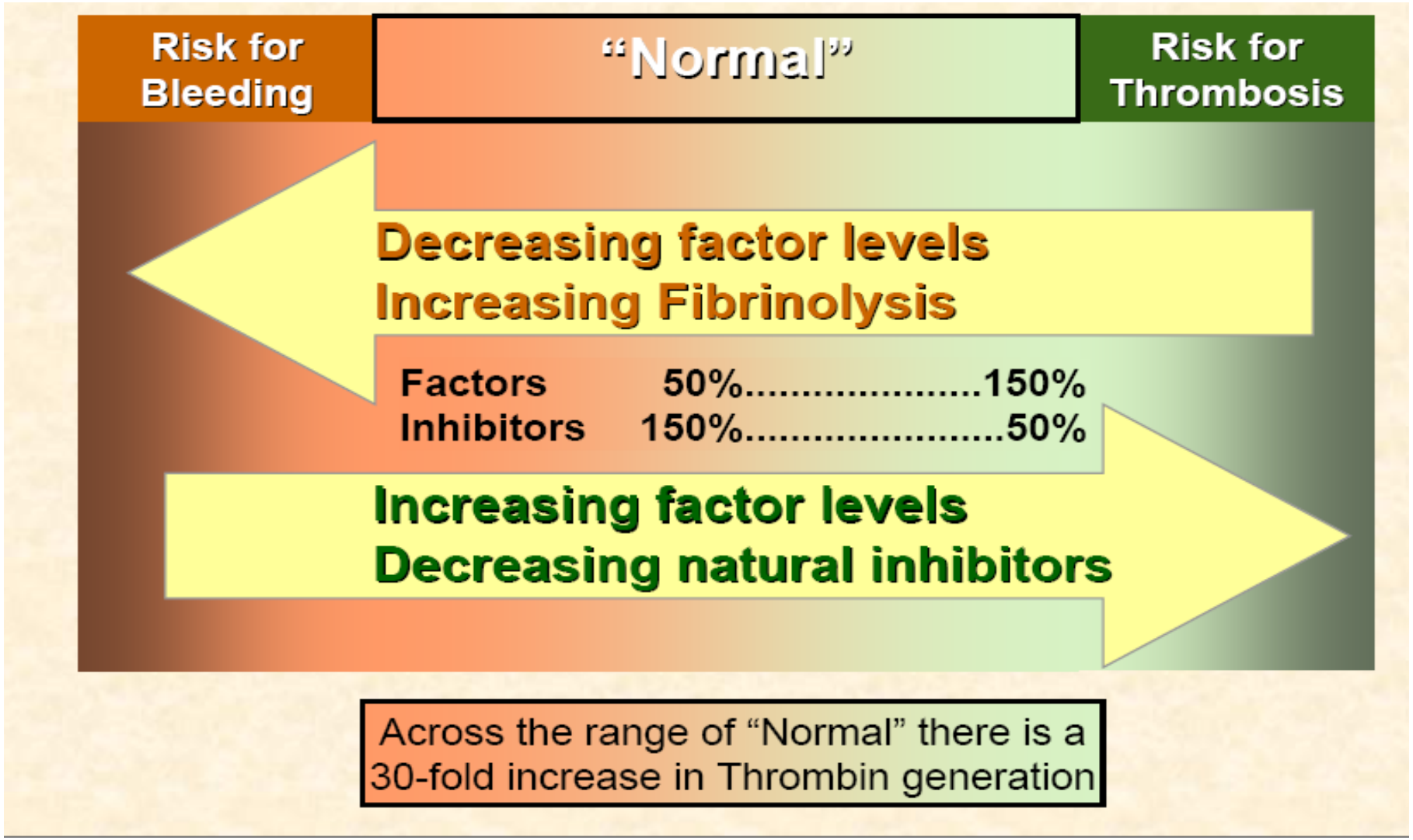
Hemostatic Risk –A Continuum



Why need for advances ?

- Traditional coagulation tests, such as PT and APTT do not assess the whole coagulation system.
- Since platelet poor plasma is used for testing, the role of platelets in hemostasis is not monitored.
- Clot formation - end point,
- when only 5% of all physiologically relevant thrombin is formed.
- Hence, traditional tests inform on the initiation of clotting but not the hemostatic capacity in terms of clot formation and maximal thrombin generation.

Limitations of plasma clotting time (PT/APTT)

- Need different tests for different purposes
- Do not detect a thrombotic tendency
- Do not detect mild bleeding tendency
- Are not proportional to clinical risks
- Do not detect platelet problems
- Detects only the initial part of clot formation
- Cannot be used to monitor patients on newer anticoagulants
- Cannot be used to monitor patients of severe Hemophilia on treatment (VIIa/FEIBA) and now for Emicizumab prophylaxis

Why APTT for heparin and PT for VKAs ?

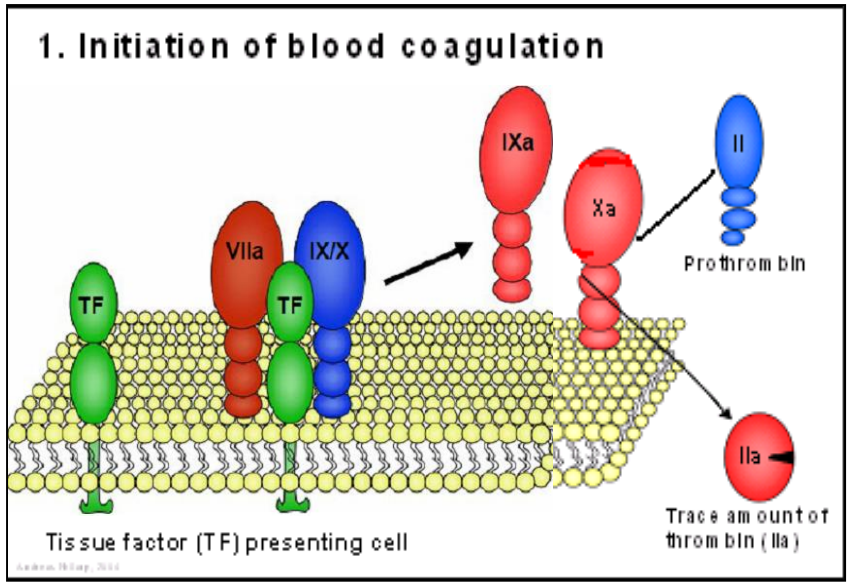
Why does a normal APTT not exclude perioperative bleeding risk?

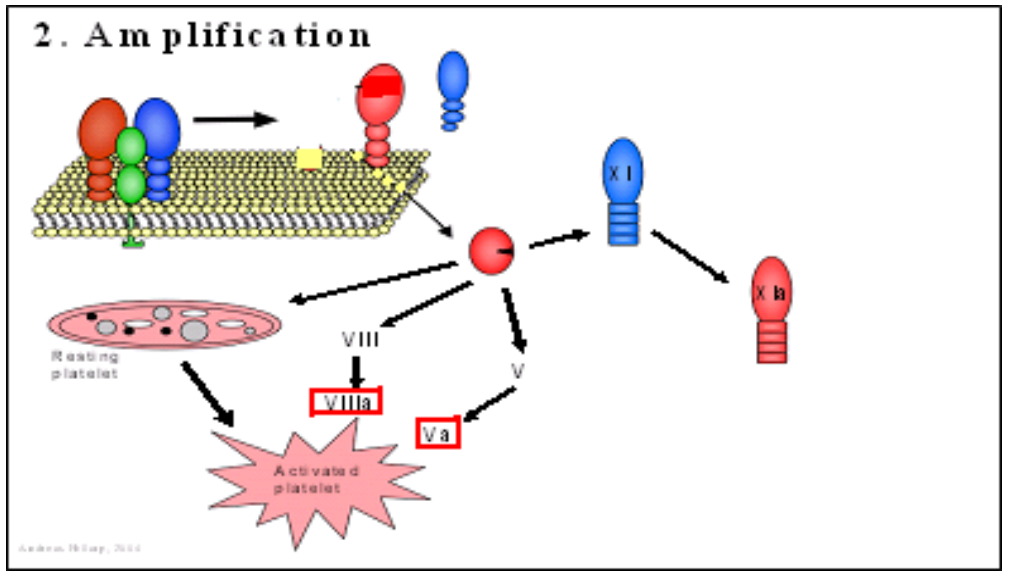
Patients with cirrhosis has a long PT but does not bleed

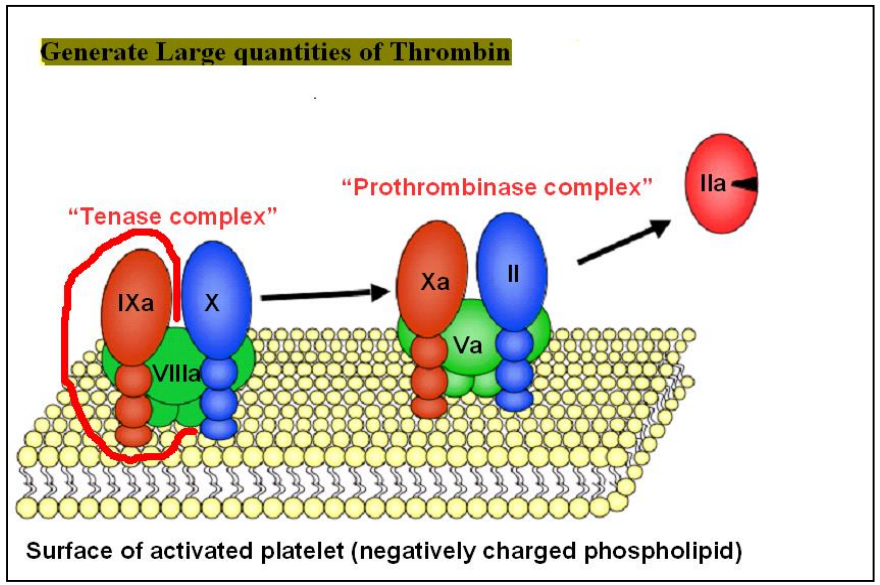
Why is the APTT normal in my patient with thrombosis ?

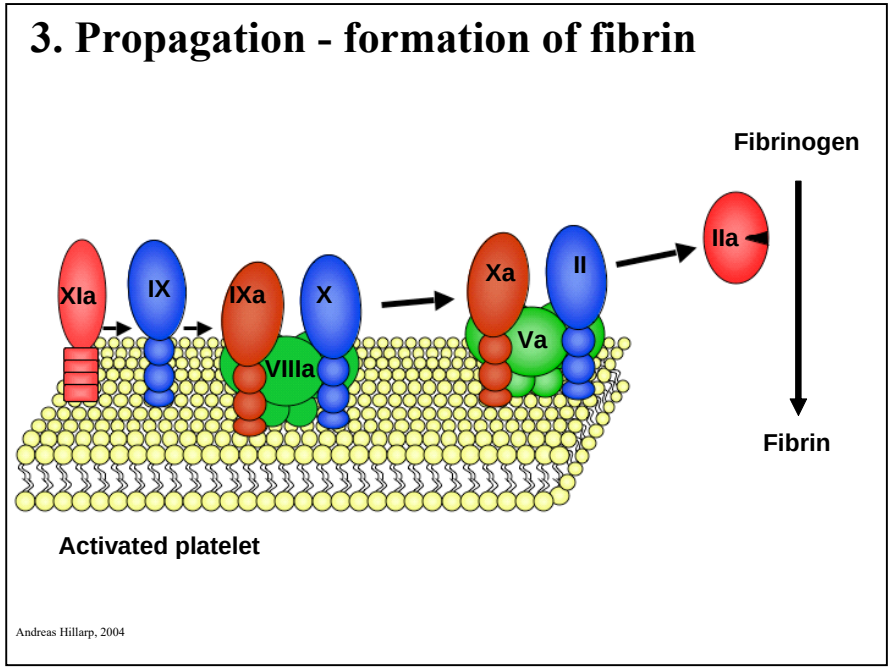
Why is the “oral contraceptive pill” a risk for thrombosis without influence on clotting times ?

Any many more unanswered questions


1. Initiation of blood coagulation
IXa
II
Xa
VIIa
IX/X
Prothrombin
TF
TF
IIa
Trace amount of thrombin (IIa)
Tissue factor (TF) presenting cell

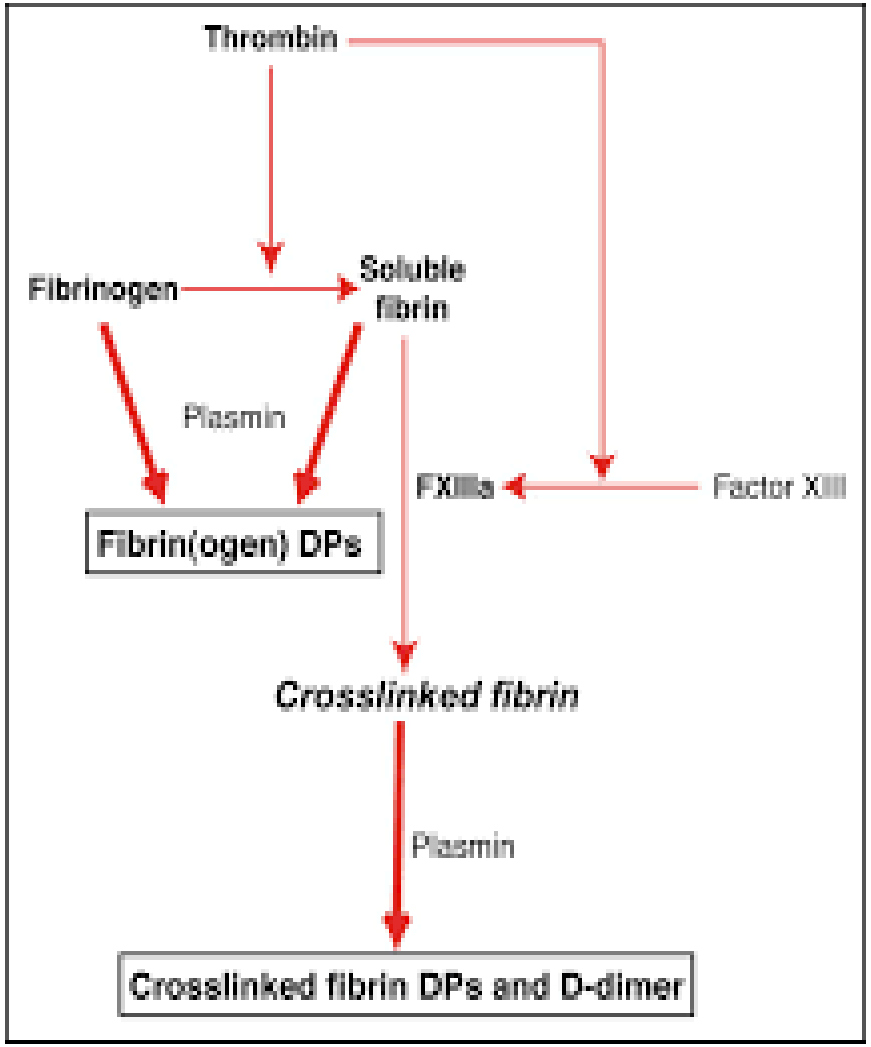

2. Amplification
XI
XIa
Resting platelet
VIII
V
VIIIa
Va
Activated platelet


Generate Large quantities of Thrombin
"Tenase complex"
"Prothrombinase complex"
IIa
IXa
X
Xa
II
VIIIa
Va
Surface of activated platelet (negatively charged phospholipid)


3. Propagation - formation of fibrin
Fibrinogen
XIa
IX
IXa
X
Xa
II
IIa
VIIIa
Va
Fibrin
Activated platelet
Andreas Hillarp, 2004

Hemostasis

- Primary hemostasis (Platelets & vWF
- Secondary hemostasis
- Tertiary hemostasis
  - Fibrinogen
  - Factor XIII
  - Fibrinolysis

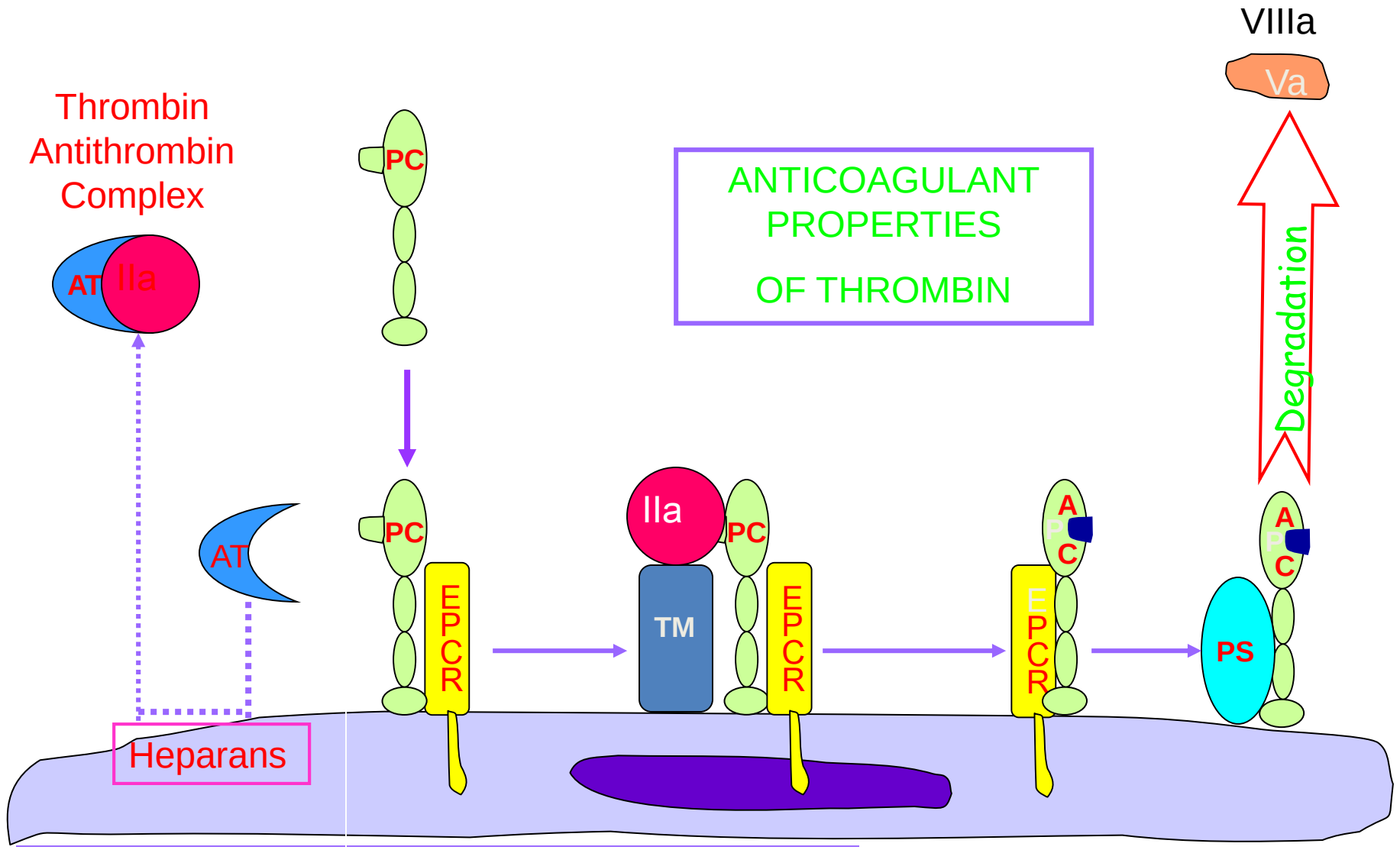


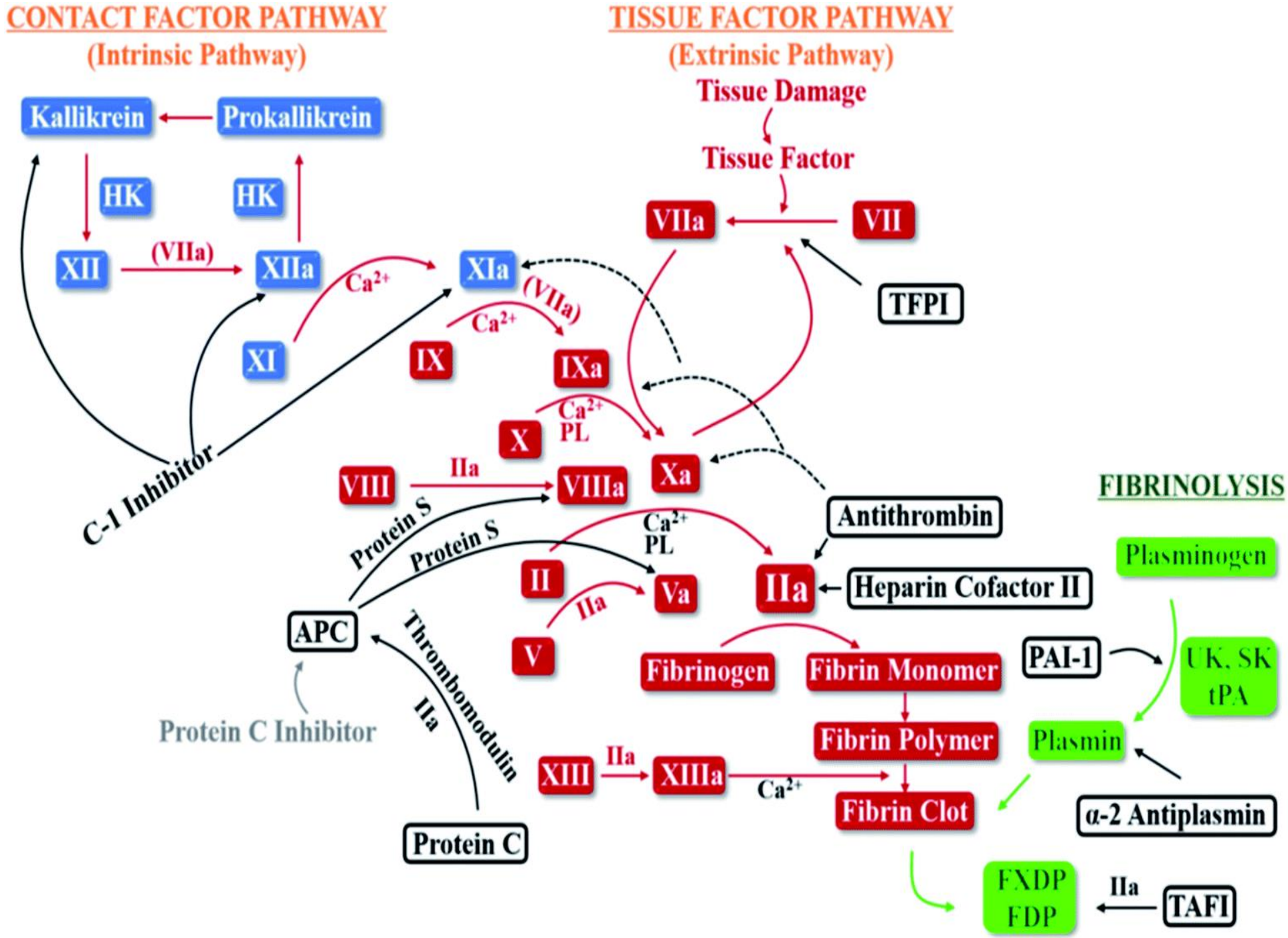
Anticoagulant system – regulate clot formation

- PC – Vit K dependent protein, enzyme
- PS – Vit K dependent protein, cofactor
- AT – serine protease inhibitor
  - Inhibits – XIIa, XIa, IXa, Xa, IIa, plasmin and Kallikrein
  - FVIIa – only serine protease that AT does not significantly inhibit
  - Exerts anticoagulation effects by primarily inhibiting factors – IIa & Xa
  - Gives heparin its anticoagulant properties

INACTIVATION

OF THROMBIN




CONTACT FACTOR PATHWAY
(Intrinsic Pathway)
TISSUE FACTOR PATHWAY
(Extrinsic Pathway)
Tissue Damage
Tissue Factor
Kallikrein
Prokallikrein
HK
HK
XII
(VIIa)
XIIa
XI
Ca2+
XIa
(VIIa)
Ca2+
IX
IXa
VIIa
VII
TFPI
X
Ca2+
PL
Xa
C-1 Inhibitor
VIII
IIa
VIIIa
Protein S
Protein S
Ca2+
PL
Antithrombin
FIBRINOLYSIS
Plasminogen
II
Va
IIa
Heparin Cofactor II
APC
V
IIa
Fibrinogen
Fibrin Monomer
PAI-1
UK, SK
tPA
Thrombomodulin
IIa
Protein C Inhibitor
Fibrin Polymer
Plasmin
XIII
IIa
XIIIa
Ca2+
Fibrin Clot
α-2 Antiplasmin
Protein C
FXDP
FDP
IIa
TAFI

Ideal coagulation test

- Easy to perform and quick to obtain high reliable and robust results.
- Accurate estimation of the thrombotic and bleeding risk.
- Employ flow condition, endothelial interaction and platelet contribution.
- Physiological conditions such as pH and temperature.

CURRENTLY DOES NOT EXIST !!!

- However, there are attempts to develop assays, which fulfill these requests, at least partially.
- Global coagulation tests
  - Viscoelastic tests – TEG/ROTEM
  - Thrombin generation tests
  - Clot waveform analysis
  - Thrombodynamics

Questions one can discuss in advances

1. Can new technologies help predict likelihood of thrombosis recurrence? Role of mutation analysis in predicting Thrombosis

Role of automated D dimer

2. Has an understanding of the role of a disintegrin-like and metalloprotease with thrombospondin type 1 motifs (ADAMTS13) in microangiopathy resulted in improved diagnostic methods for this disorder?

3. Does thrombelastography / Thromboelastometry allow better definition of bleeding risk than conventional hemostasis assays, especially in settings of acute hemostatic pathology?

4. Role of clot wave form analysis ?

5. Role of chromogenic assays for anti xa and factor VIII assay ?

5. advances in diagnostics for HIT , autoimmune HIT and VITT?

6. effect of DOACS on haemastatic tests

Post partum hemorrhage

- Obstetric emergency
- *cumulative blood loss of greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process*

One of the top 5 causes of maternal mortality

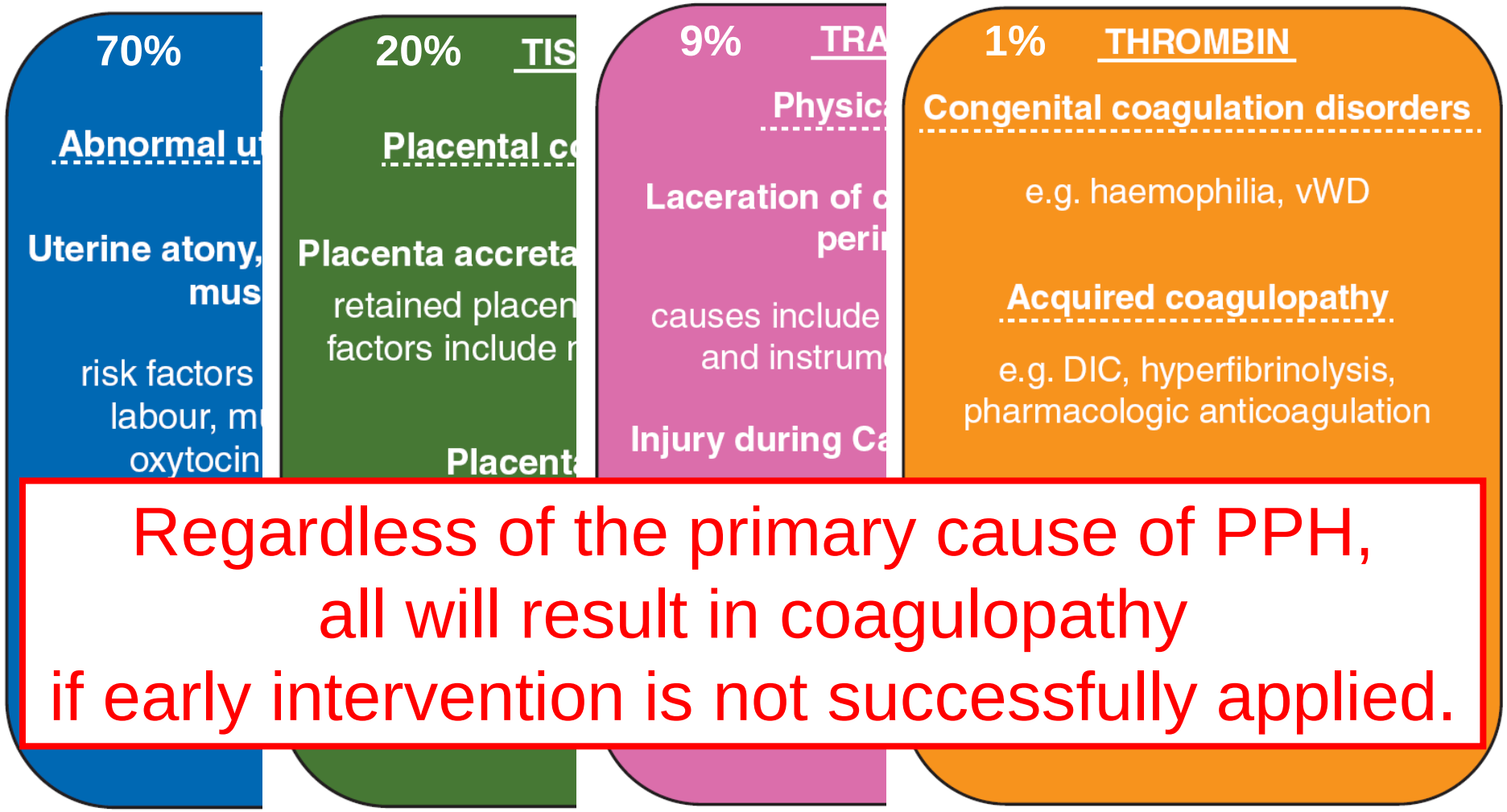
- Primary PPH(early PPH)
  - occurring in the first 24 hours after delivery
- Secondary PPH(late, or delayed PPH)
  - occurring from 24 hours to as late as upto 12 weeks after delivery

Br J Anaesth. 2013 Jun;110(6):1054-5.

BJA

Haemostatic monitoring during postpartum haemorrhage and implications for management

C. Solomon[1*], R. E. Collis[2] and P. W. Collins[3]



Regardless of the primary cause of PPH,
all will result in coagulopathy
if early intervention is not successfully applied.

Physiological changes to coagulation during pregnancy

- **Platelet-** Decrease (not < 70000/uL)
- **Coagulation** factors- FVIII, vWf, RCoA , FX and FXIIincrease during pregnancy. FVII till 100 times Inc .
- **Fibrinogen- 4.4-7.2 g/dL (median 4.9) (normal 1.5- 4g/dL)**
- **PT & APTT shortened**
  - Examined levels of D-dimers in **1131 pregnancies 1.1 ±1.0 µg/ml (1100 FEU) in 1st trimest**er (normal < 500 FEU)
  - **2.2 ±1.1 µg/ml in 3rd trimester**

ISTH Scoring system for overt DIC

Parameter	Value	Score
PT prolongation	≥ 3 sec ≥ 6 sec	1 2
D-Dimer	Moderate increase Strong increase	2 3
Platelet count	≤ 100,000/cu mm ≤ 50,000/cu mm	1 2
Fibrinogen	≤ 100mg/dl	1

Calculate Score

If ≥ 5: compatible with Overt DIC

If < 5: Suggestive of non-overt DIC

Fibrinogen in Obstetrical PPH

- Analyzed serial coagulation tests
  - Fibrinogen was the only marker associated with the occurrence of severe PPH
  - NPV of FG > 4g/L = 79%
  - PPV of FG < 2g/L = 100%
  - Normal value of one hr post delivery fibrinogen in 161 ladies median 4.7 (4.1-5.4) Ref range 3.6- 6.8 ***deLange et al BJA (2014) doi10.1093/bja/aet480***

British Journal of Anaesthesia 108 (6): 984–9 (2012)
Advance Access publication 6 April 2012 · doi:10.1093/bja/aes096

BJA

OBSTETRICS

Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial

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[9] Hospices civils de Lyon, Service de Gynécologie-Obstétrique de l'Hôpital de La Croix-Rousse, F-69000 Lyon, France
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Editor's key points

- The aim of the study was to observe whether the fibrinogen level at diagnosis of postpartum haemorrhage (PPH) is associated with the severity of bleeding.
- This study suggests that a low fibrinogen level at PPH diagnosis is associated with a higher risk of severe PPH, independently of the other laboratory indicators.

Background. The aim of the study was to determine whether the fibrinogen level at diagnosis of postpartum haemorrhage (PPH) is associated with the severity of bleeding.

Methods. This is a secondary analysis of a population-based study in 106 French maternity units identifying cases of PPH prospectively. PPH was defined by a blood loss exceeding 500 ml during the 24 h after delivery or a peripartum haemoglobin decrease of more than 20 g litre^{-1}. This analysis includes 738 women with PPH after vaginal delivery. Fibrinogen levels were compared in patients whose PPH worsened and became severe and those whose PPH remained non-severe. Severe PPH was defined as haemorrhage by occurrence of one of the following events: peripartum haemoglobin decrease $\geq$40 g litre^{-1}, transfusion of concentrated red cells, arterial embolization or emergency surgery, admission to intensive care, or death.

Results. The mean fibrinogen concentration at diagnosis was 4.2 g litre^{-1} [standard deviation (SD)=1.2 g litre^{-1}] among the patients without worsening and 3.4 g litre^{-1} (SD=0.9 g litre^{-1}) ($P<0.001$) in the group whose PPH became severe. The fibrinogen level was associated with PPH severity independently of other factors [adjusted odds ratio=1.90 (1.16–3.09) for fibrinogen between 2 and 3 g litre^{-1} and 11.99 (2.56–56.06) for fibrinogen <2 g litre^{-1}].

Conclusions. The fibrinogen level at PPH diagnosis is a marker of the risk of aggravation and should serve as an alert to clinicians.

Keywords: blood coagulation; fibrinogen; postpartum haemorrhage

Accepted for publication: 26 January 2012

New approaches to obstetric hemorrhage: the postpartum hemorrhage consensus algorithm

Thierry Girard[a], *Manfred Mörtl*[b], *and Dietmar Schlembach*[c]

Curr Opin Anesthesiol 2014, 27:267–274

Traditional laboratory analyses of coagulation, such as activated partial thromboplastin time (aPTT) and international normalized ratio (INR), are frequently only **available after 45–60 min.** With point-of-care monitoring of coagulation, such as thromboelastography (TEG) and **rotational thromboelastometry (ROTEM), whole-blood coagulation as well as fibrinolysis can be monitored within minutes .**

Fibrin polymerization, as monitored in the **FIBTEM**, had a good correlation with fibrinogen concentration (R^2 = 0.75) and was **detectable after 5 min .**

History

- 21 year old female patient Primigravida,

  underwent LSCS on 20/11/2018 at a pvt hospital in Bhagalpur, Bihar, discharged after 3 days post LSCS.

  Antenatal period was uneventful

4 days post surgery →decreased urine output associated with pedal edema and facial puffiness Very low Hb

There is no history of fever

AKI

Underwent 2 sessions of Hemodialysis and transfusions

USG abdomen showed presence of retained products of conception(RPOC)

Underwent D&C on 30/11/2018

Persistent AKI→ referred to SGRH

Admitted in SGRH on 5/12/2018

Complete Blood Picture	05/12/2018
Hb	10.4g%
TLC	9,200/ul
Platelets	256000/ul
DLC	N-69%,L-15%,M-15%,E-1,B-0
Peripheral smear examination	RBC-Mild anisopoikilocytosis , NC/NC WBC-Mild monocytosis Platelets adequate

Hospital course

- Underwent Hemodialysis ~alternate day, persistent anuria
- Developed bleeding PV from 07/12/2018 (**Secondary PPH**)
- USG abdomen →
  - Bulky uterus
  - Hematoma in endometrial cavity
  - Hetero echoic collection 6x5x4cm~59ml in lower uterine segment along scar (Scar hematoma)

D&C for RPOC on 7/12/2018 ~2.1L blood/clots along with RPOC removed under USG guidance

Hb 10.8→6.8g%

Complete Blood Picture	07/12/2018
Hb	6.8g%
TLC	10,670/ul
Platelets	97,000/ul
DLC	N-72%,L-15%,M-11%,E-0,B-0
Peripheral smear examination	RBC-Mild anisopoikilocytosis , NC/NC WBC-Mild neutrophilia Platelets mildly reduced
PT	***14.7 (Mn-11.7)***
APTT	***32.2 (Mn-30.8)***

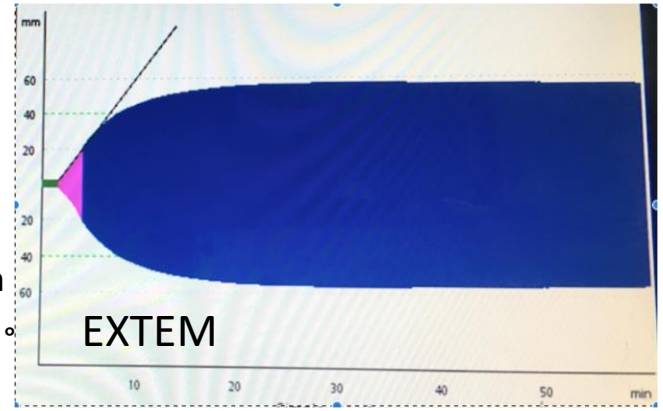
TEG 08/12/18

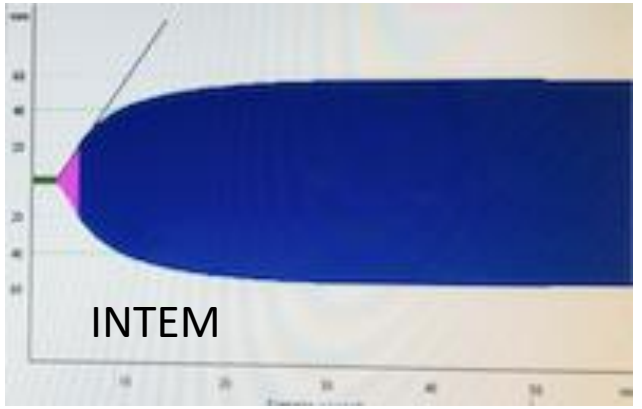
- *R:* 2.7min (4-8 min)
- *K:* 1.8min (1-4 min)
- *α-Angle:* 65.5° (47-74°)
- *MA:* 64mm (55-73mm)
- *LY 30: 2.2%* (0-8%)

Rotational ThromboElastoMetry (ROTEM)

08/12/18

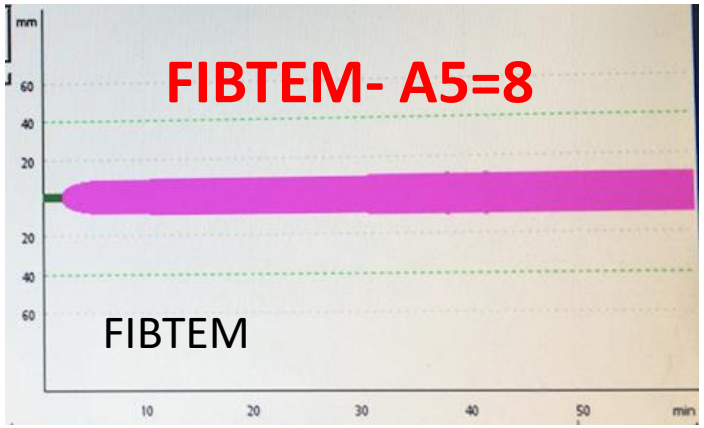
CT-109s
CFT-149 s
A5-35mm
A10-48mm
MCF-56mm
α-Angle-62 °
LI30-100



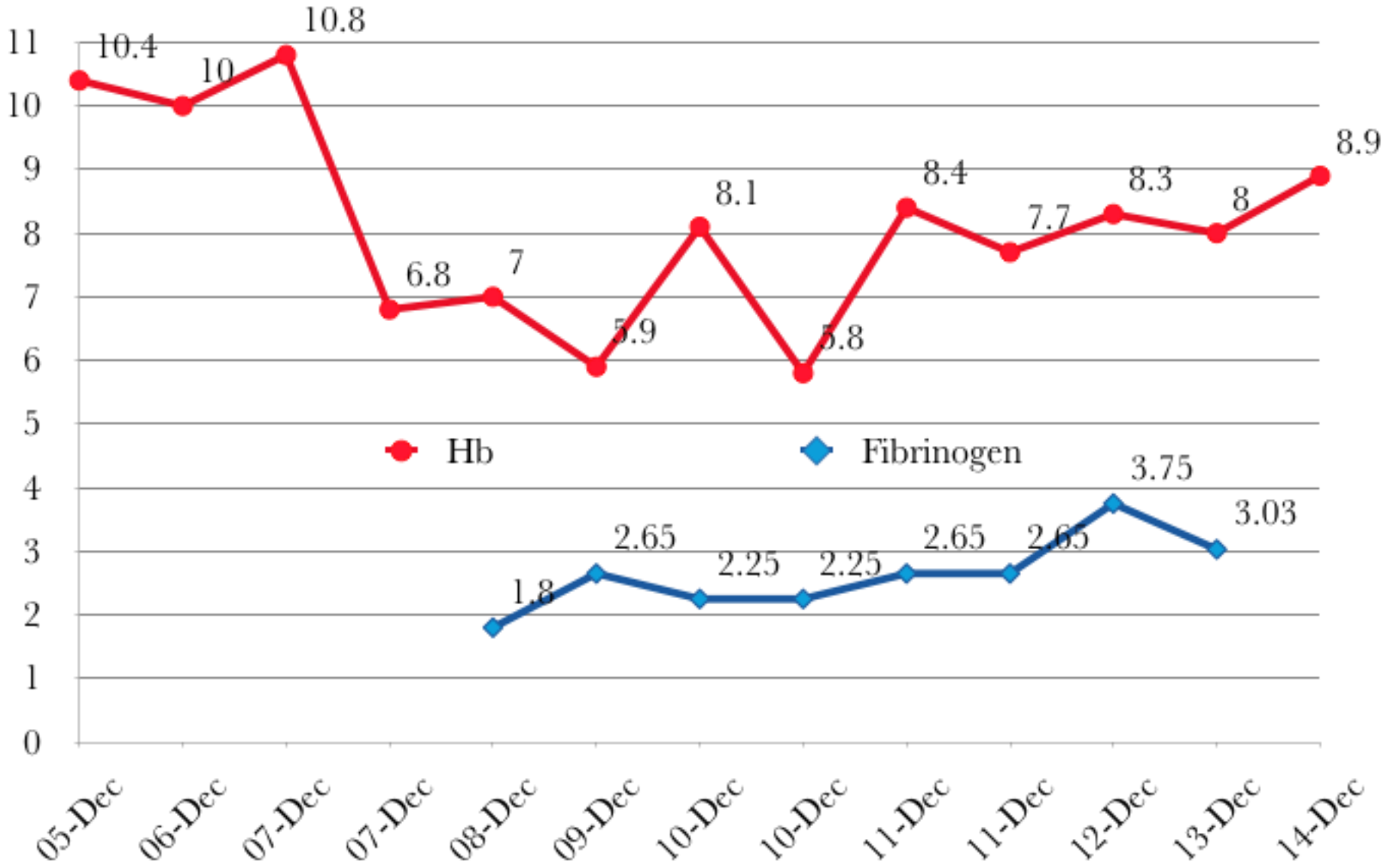


CT-166s
CFT-131s
A5-35mm
A10-47mm
MCF-56mm
α-Angle-64 °
LI30-100

CT-114 s
CFT– 170 s
A5-8mm
A10-9mm
MCF-9mm
α-Angle-64 °
LI30-100



Plasma Fibrinogen	***1.8mg/L***
D-Dimer	***3720ug/ml***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9
8
7
6
5
4
3
2
1
0
10.4
10
10.8
6.8
7
5.9
8.1
5.8
8.4
7.7
8.3
8
8.9
Hb
Fibrinogen
1.8
2.65
2.25
2.25
2.65
2.65
3.75
3.03
05-Dec
06-Dec
07-Dec
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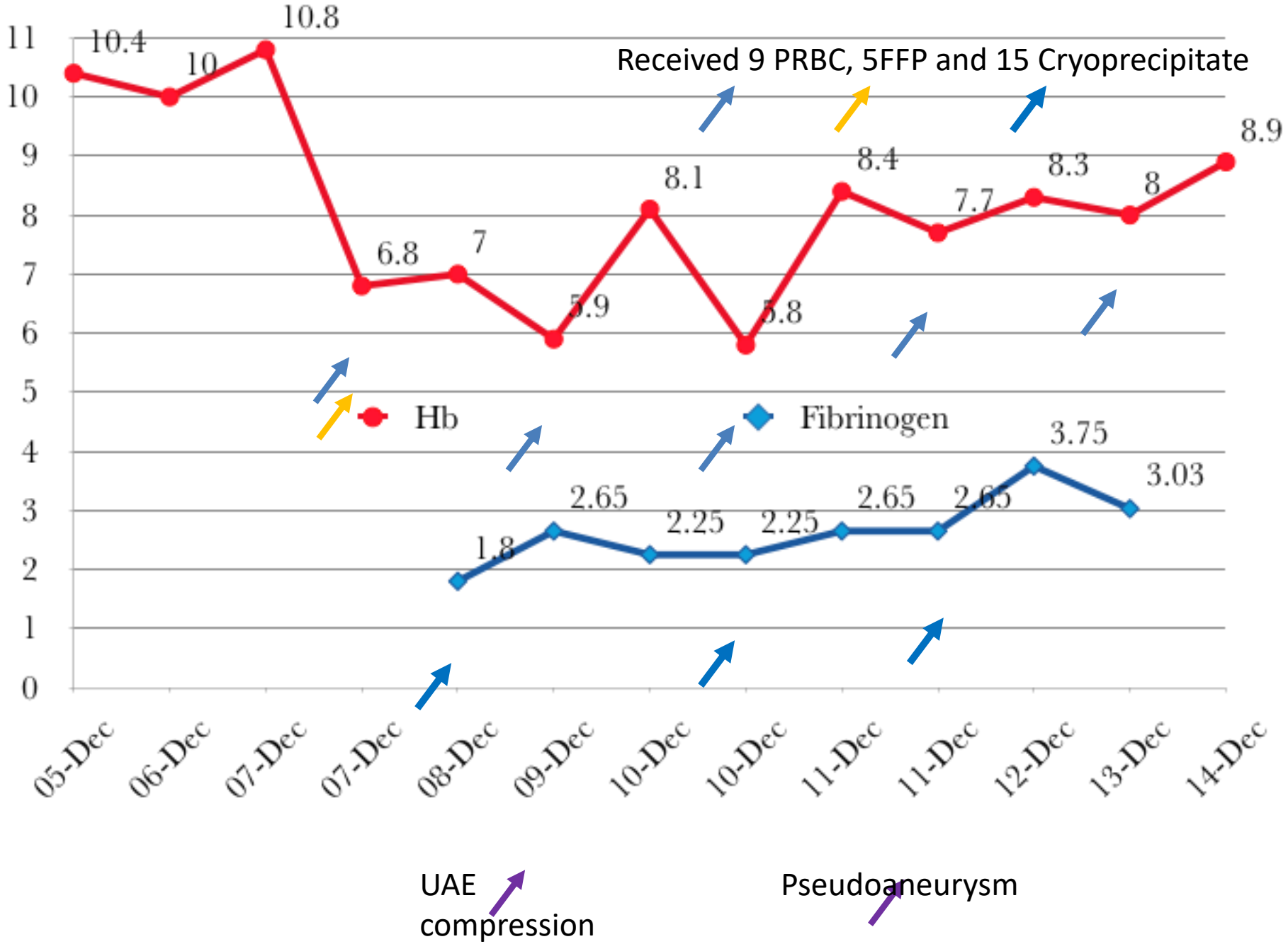
10-Dec
11-Dec
11-Dec
12-Dec
13-Dec
14-Dec


Received 9 PRBC, 5FFP and 15 Cryoprecipitate
Hb
Fibrinogen
10.4
10
10.8
6.8
7
5.9
8.1
5.8
8.4
7.7
8.3
8
8.9
1.8
2.65
2.25
2.25
2.65
2.65
3.75
3.03
05-Dec
06-Dec
07-Dec
07-Dec
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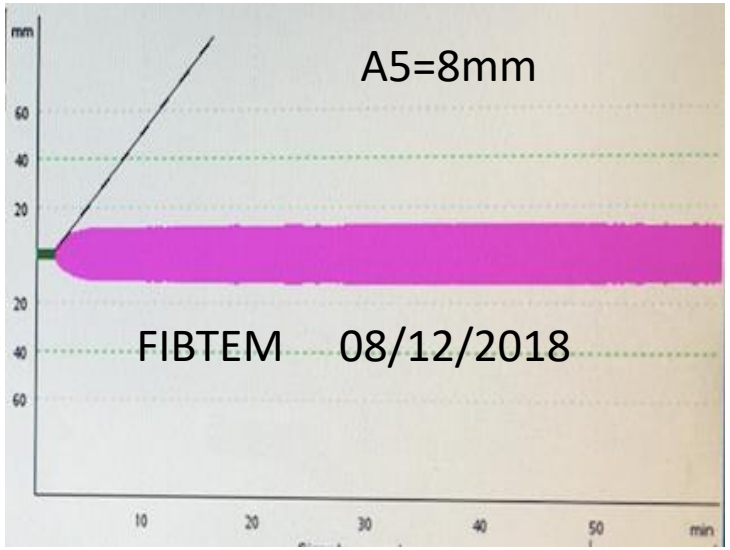
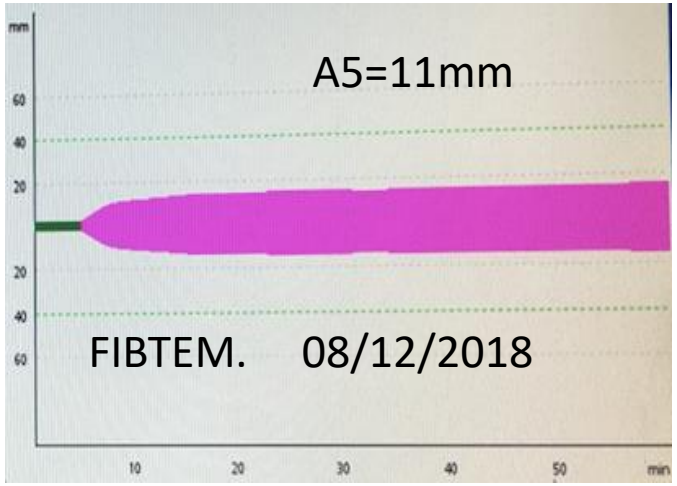
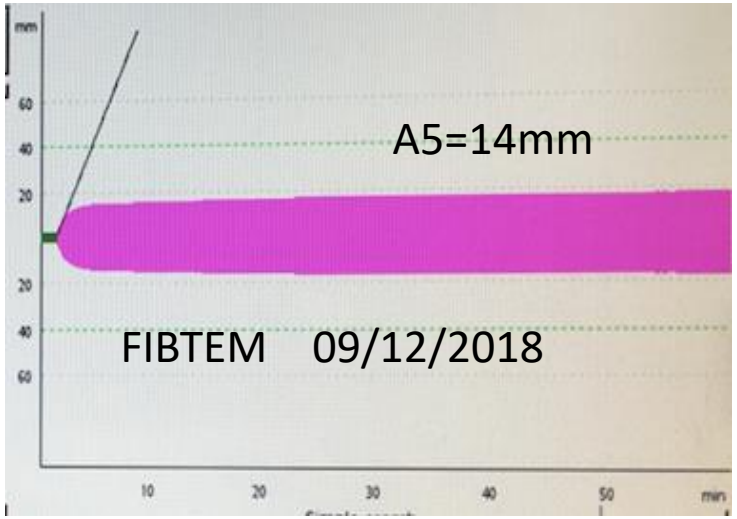
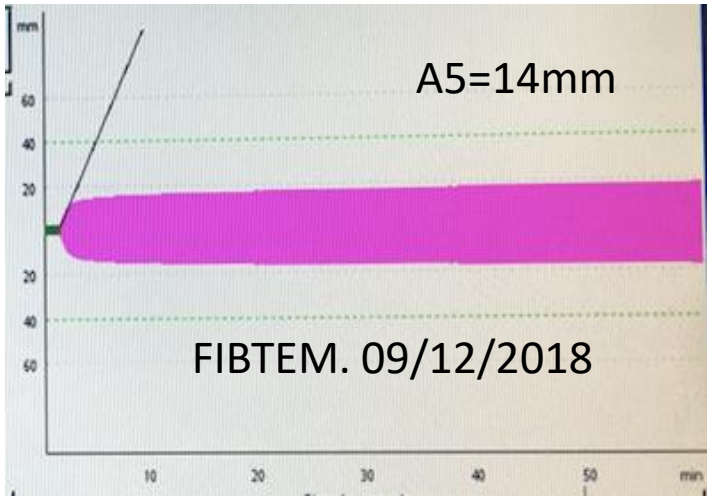
UAE
compression
Pseudoaneurysm


A5=8mm
FIBTEM 08/12/2018


A5=11mm
FIBTEM. 08/12/2018


A5=14mm
FIBTEM 09/12/2018


A5=14mm
FIBTEM. 09/12/2018

TEG & ROTEM

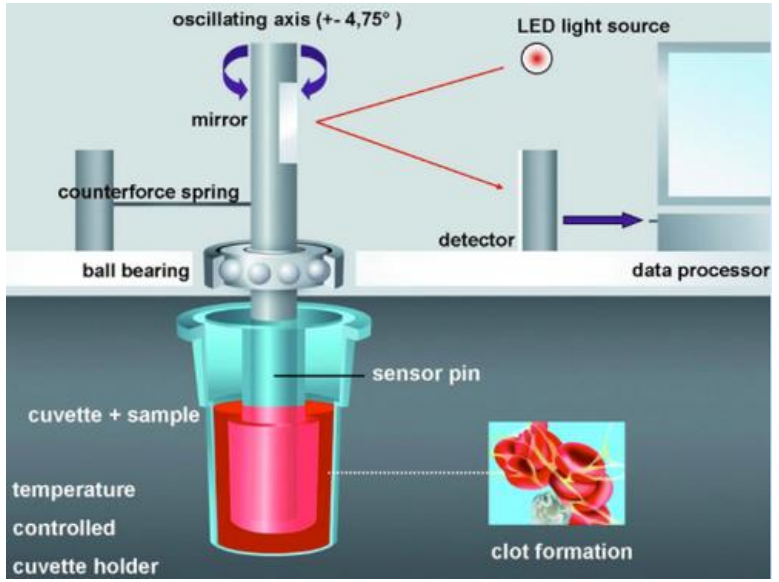
- **TEG** is **T**hrombo**E**lasto**G**raphy
- **ROTEM** is **RO**tational **T**hrombo**E**lasto**M**etry
  - Point of care tools of assessing whole blood clotting (real time)
  - provide global information on the dynamics of clot development, stabilisation and dissolution that reflect

    in vivo haemostasis

  - Sample required
    - Whole blood
    - Citrate vial

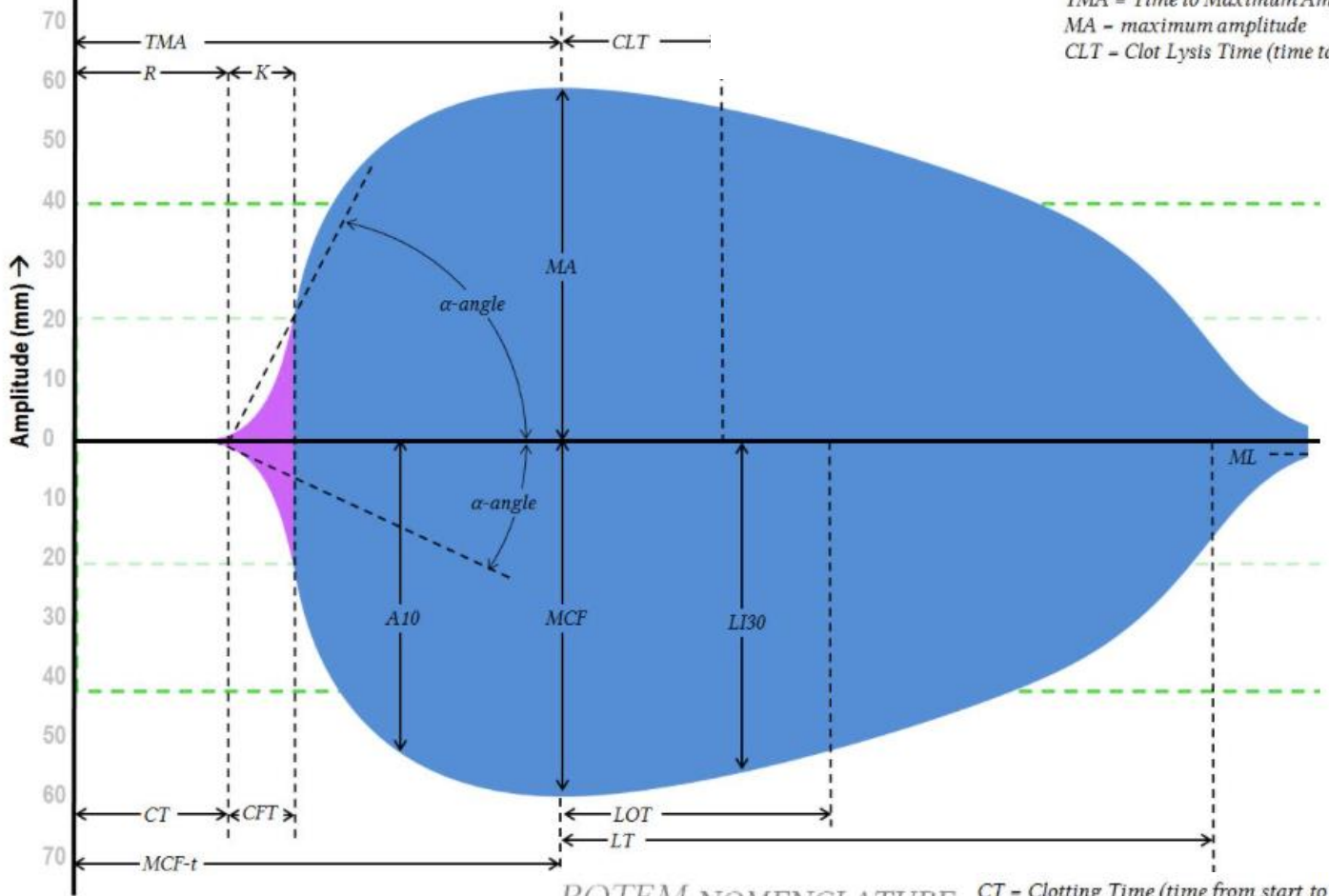
PRINCIPLE

- Whole blood at body temperature (37º) is added to a heated cuvette. A pin is suspended into the cup, and rotation takes place.
- The degree of impediment is recorded as "amplitude", and displayed on the time vs. amplitude graph



TEG NOMENCLATURE

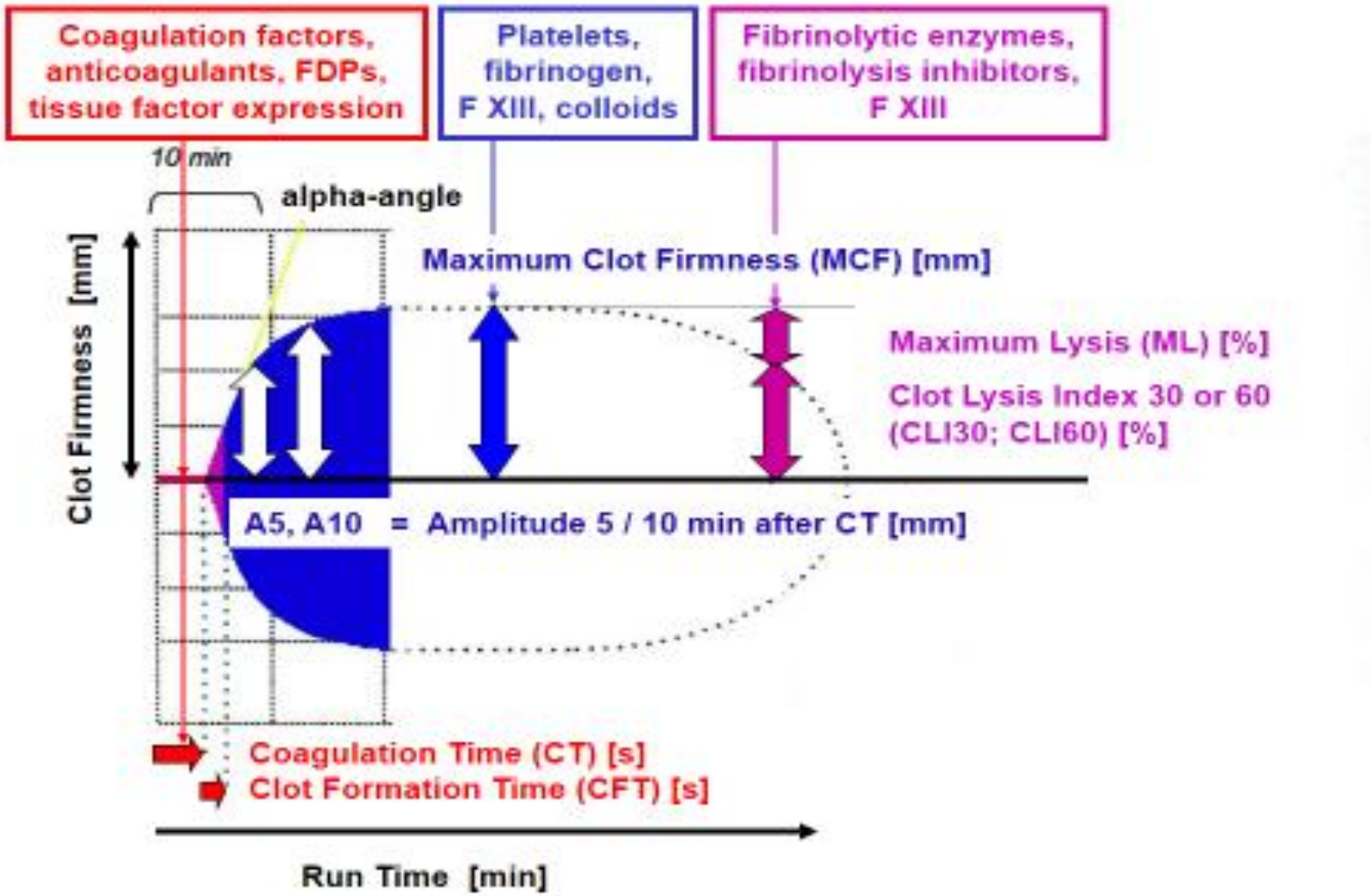
R = Reaction time (time from start to amplitude = 2mm)
K = Kinetics (time from amplitude = 2mm until amplitude = 20mm)
α-angle = slope from 2mm to 20mm amplitude
TMA = Time to Maximum Amplitude
MA = maximum amplitude
CLT = Clot Lysis Time (time taken for amplitude to decrease by 2mm from MA

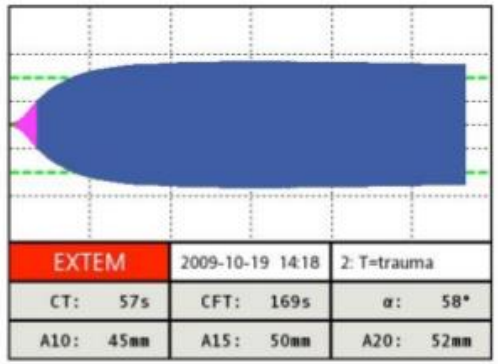


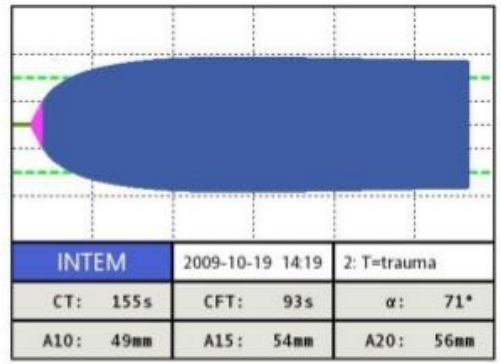
ROTEM NOMENCLATURE

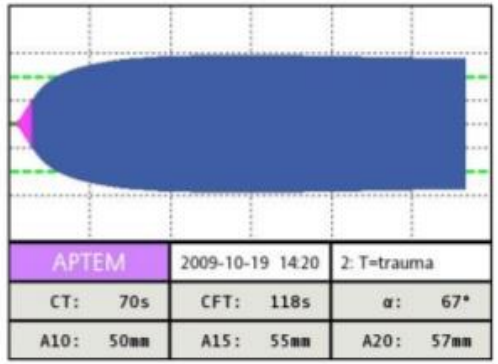
CT = Clotting Time (time from start to amplitude = 2mm)
CFT = Clot Formation Time (time from amplitude = 2mm until amplitude = 20mm)
α-angle = slope of the line at 2mm amplitude
A10 = amplitude at 10 minutes; ...there can be any number of A(x) variables
MCF-t = Time to Maximum Clot Firmness
MCF = Maximum Clot Firmness
LOT = Lysis Onset Time (time taken for amplitude to decrease by 15% of MCF)
LT = Lysis Time (time taken for amplitude to drop to 10% of MCF)
LI30 = Lysis Index at 30 minutes (% drop in amplitude from MCF)
ML = Maximum Lysis (minimum amplitude achieved at the end of test run time)

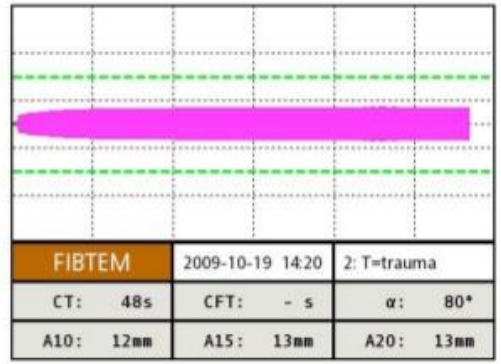
DECODING THE “TEMOGRAM”





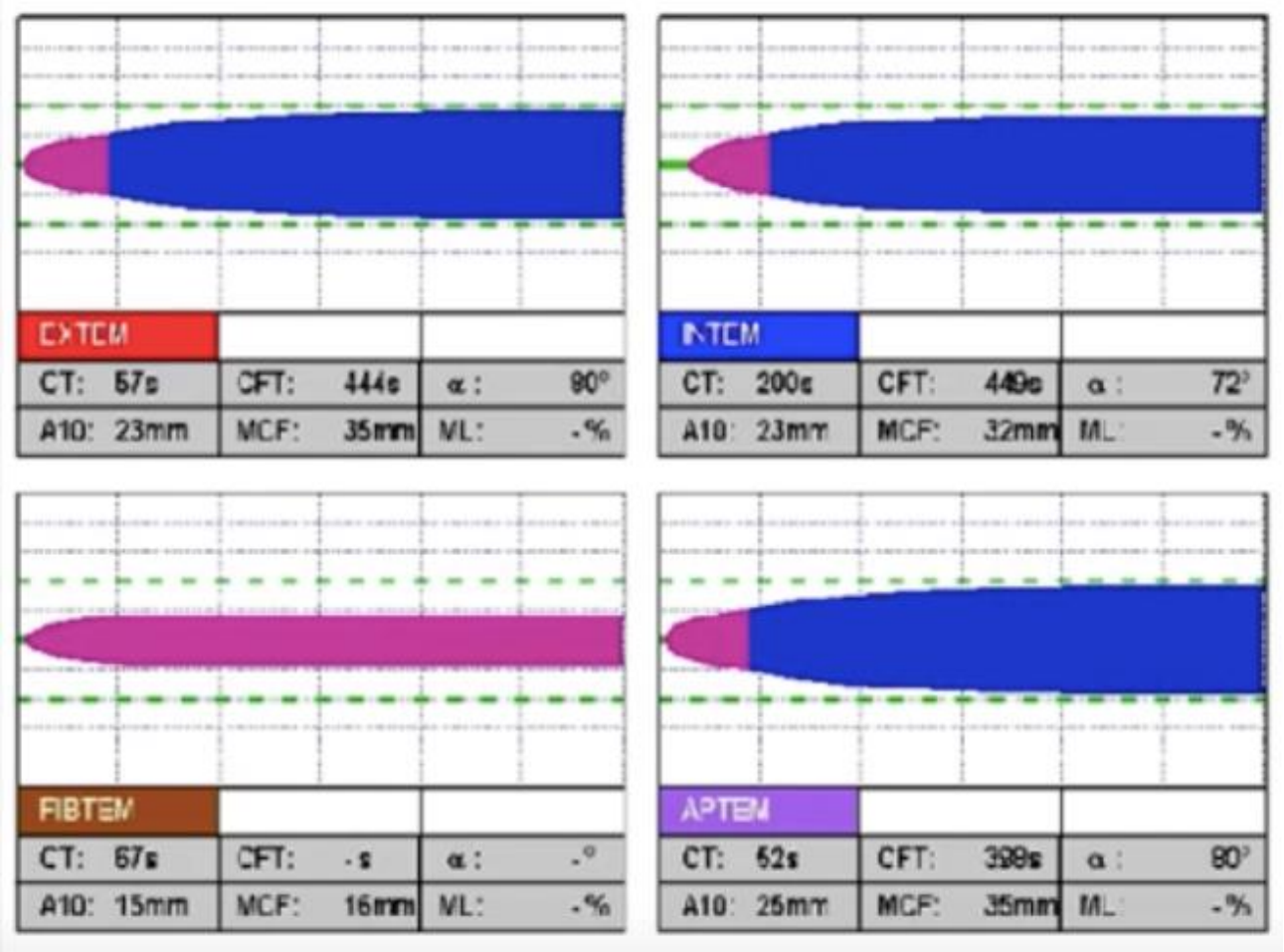




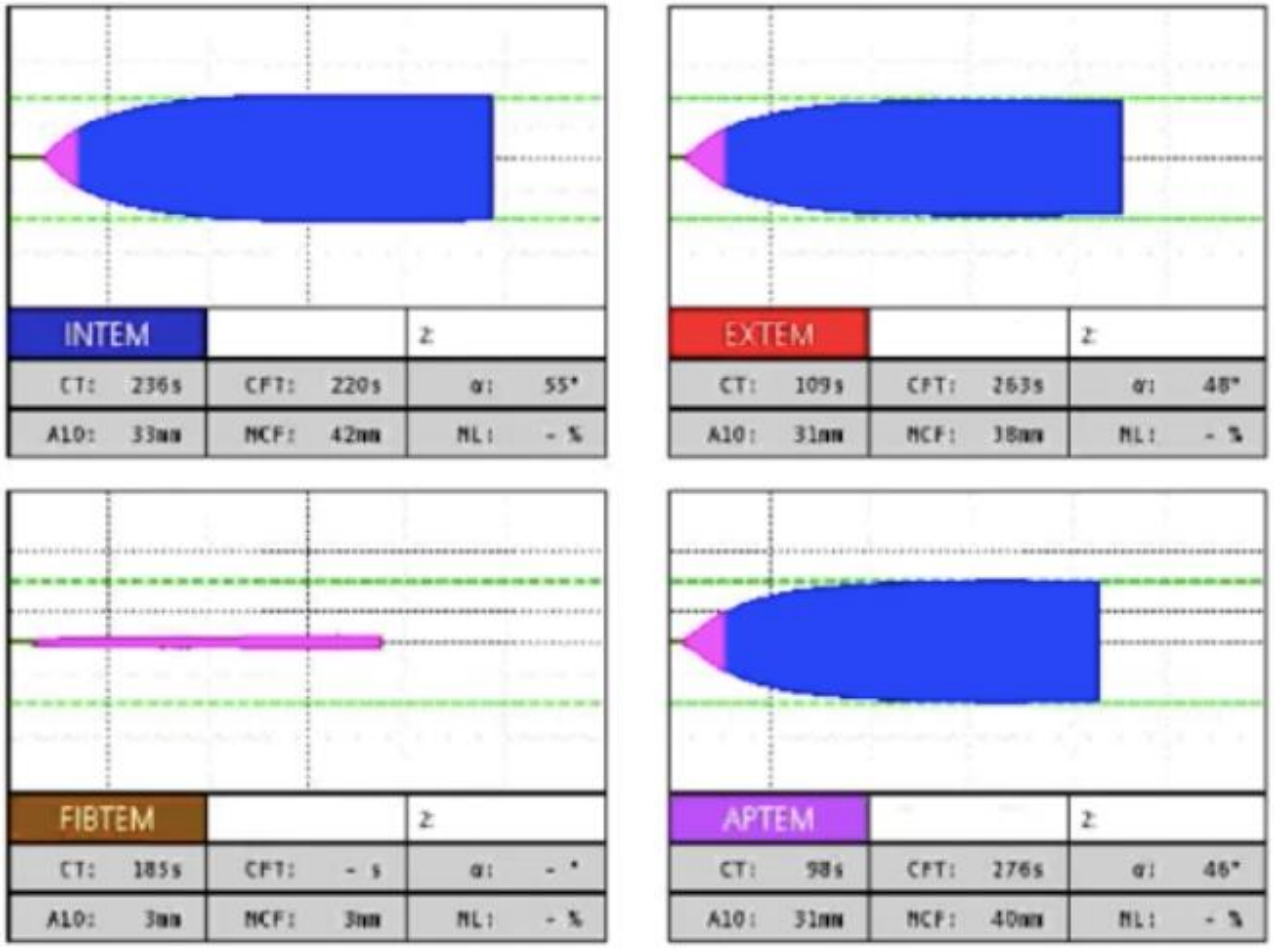


Test name	Reagent	Use
INTEM	Ellagic acid	Intrinsic pathway defects of coagulation activation
EXTEM	Recombinant tissue factor	Extrinsic pathway defects of coagulation activation
FIBTEM	Recombinant tissue factor and Cytochalasin D (platelet inhibitor)	Assesses for fibrinogen deficiency by blocking platelet contribution to clot formation
APTEM	Recombinant tissue factor and Aprotinin (fibrinolysis inhibitor)	Assesses for hyperfibrinolysis

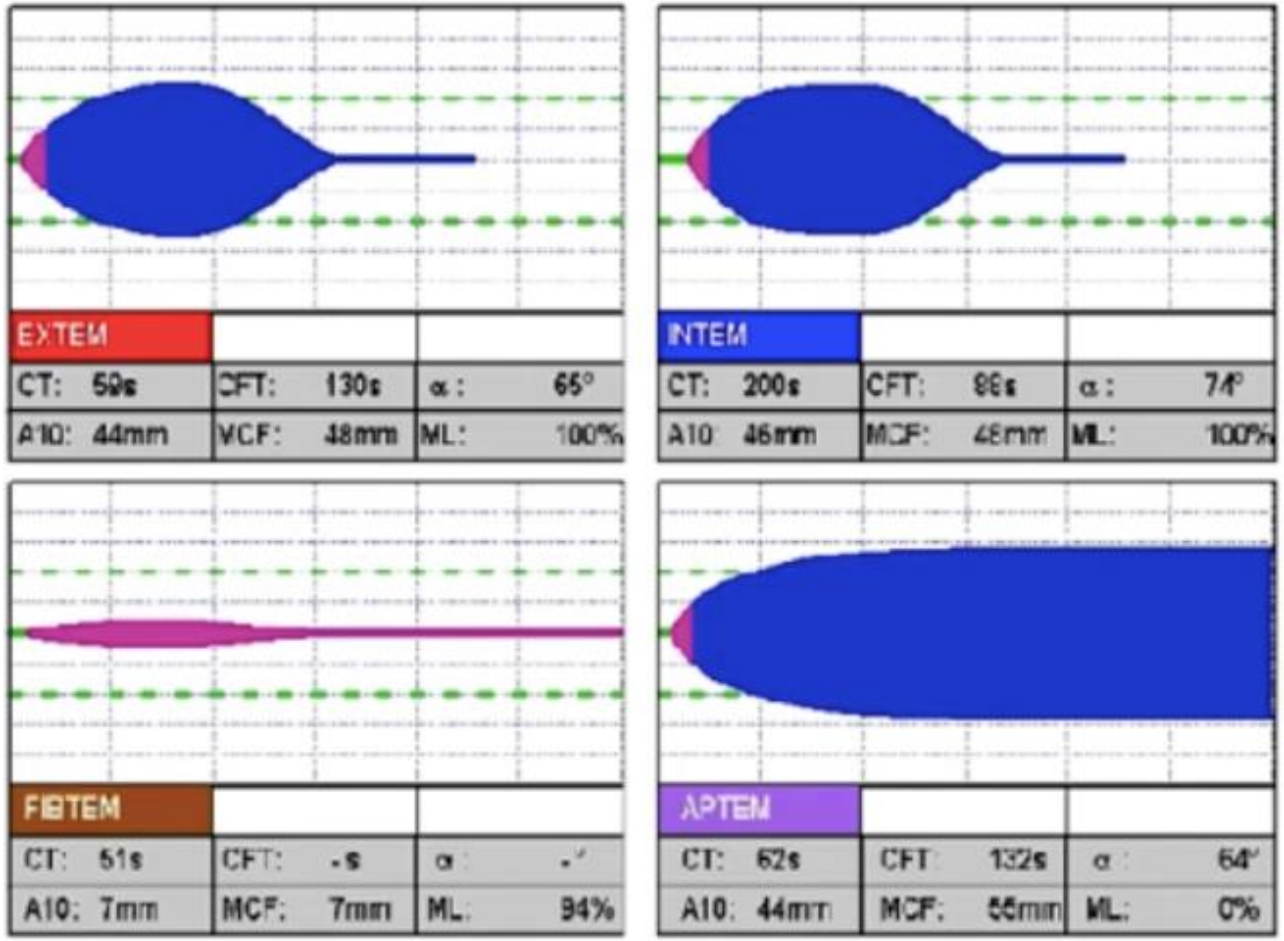
Thrombocytopenia/platelet dysfunction



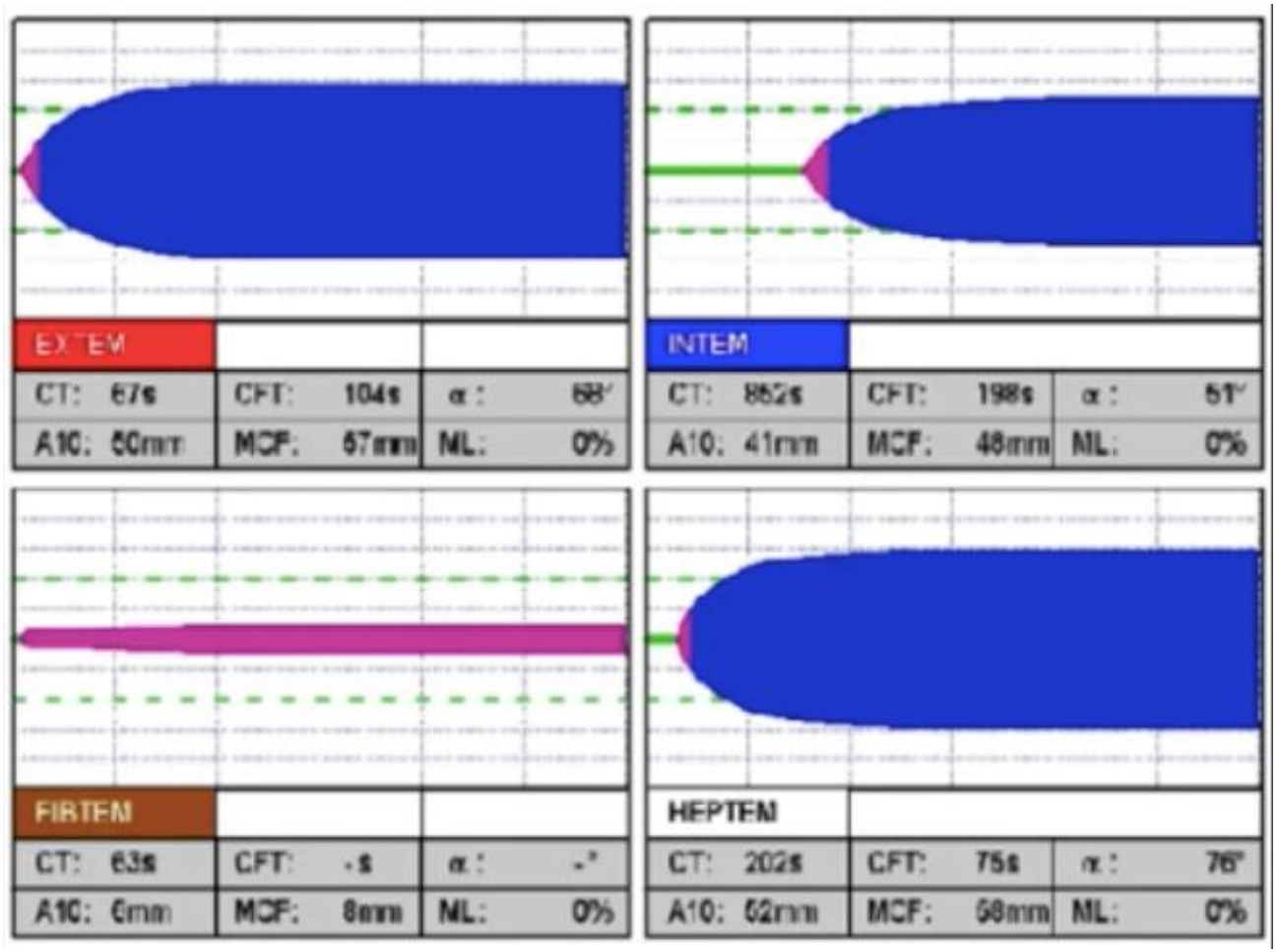
Fibrinogen deficiency



Hyperfibrinolysis

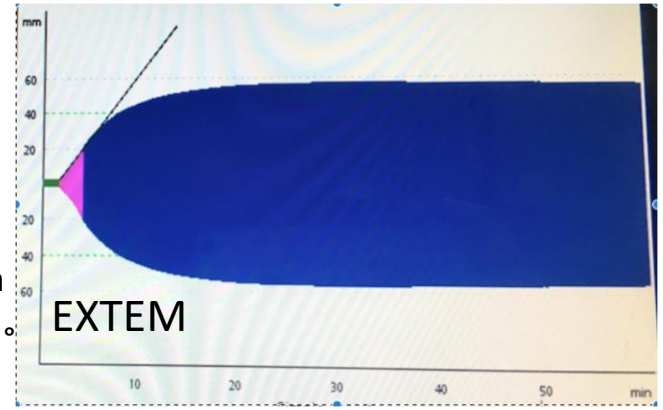


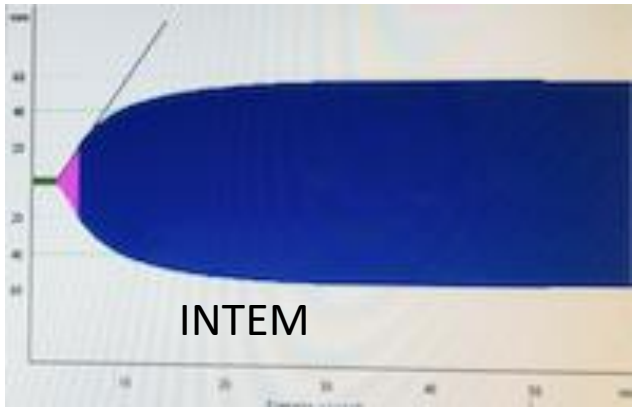
Heparin effect



ROTEM 08/12/18

CT-109 s
CFT-149 s
A5-35mm
A10-48mm
MCF-56mm
α-Angle-62 °
LI30-100

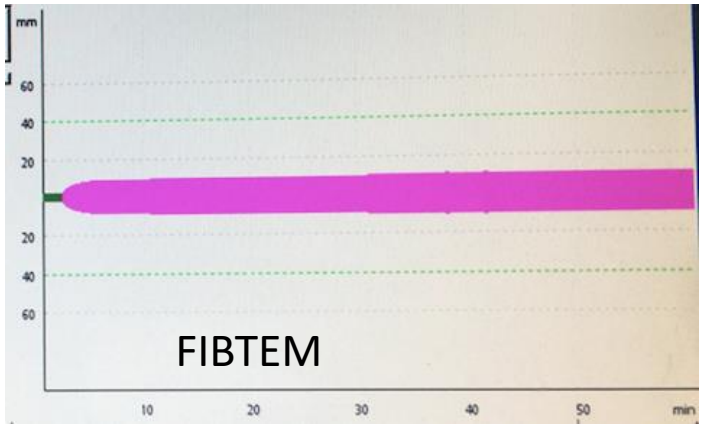




CT-166 s
CFT-131 s
A5-35mm
A10-47mm
MCF-56mm
α-Angle-64 °
LI30-100

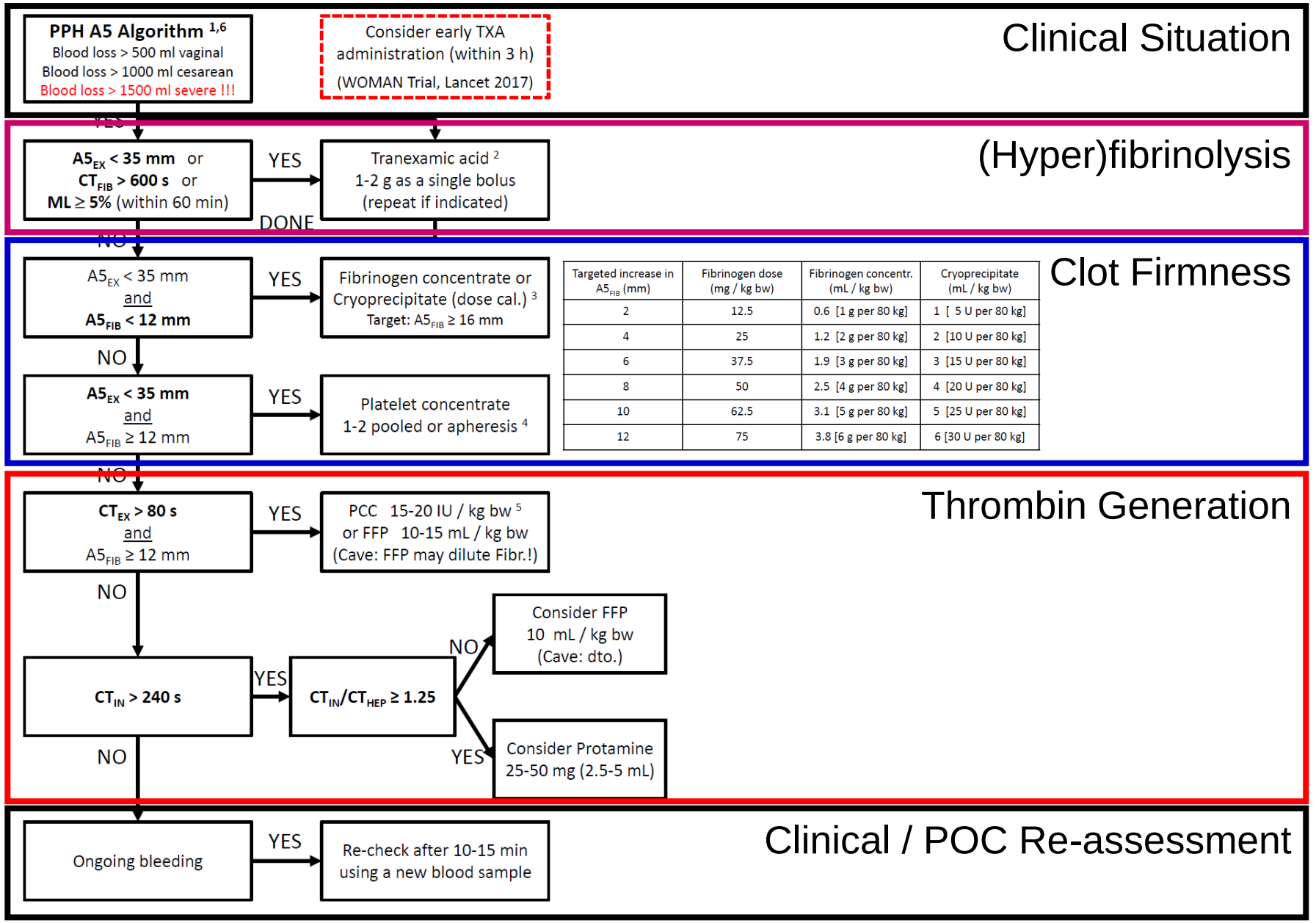
FIBTEM- A5=8

CT-114 s
CFT—160 s
A5-8mm
A10-9mm
MCF-9mm
α-Angle-64 °
LI30-100



08/12/2018

Evidence-based ROTEM A5 PPH Algorithm 2016



Targeted increase in $A5_{FIB}$ (mm)	Fibrinogen dose (mg / kg bw)	Fibrinogen concentr. (mL / kg bw)	Cryoprecipitate (mL / kg bw)
2	12.5	0.6 [1 g per 80 kg]	1 [5 U per 80 kg]
4	25	1.2 [2 g per 80 kg]	2 [10 U per 80 kg]
6	37.5	1.9 [3 g per 80 kg]	3 [15 U per 80 kg]
8	50	2.5 [4 g per 80 kg]	4 [20 U per 80 kg]
10	62.5	3.1 [5 g per 80 kg]	5 [25 U per 80 kg]
12	75	3.8 [6 g per 80 kg]	6 [30 U per 80 kg]

 doi:10.1111/anae.12859

Original Article

Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage

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Patients were included in the study if they had a major obstetric haemorrhage (estimated blood loss > 1500 ml) associated with coagulopathy (FIBTEM A5 < 12 mm, indicative of a plasma fibrinogen level of 2 $g.l^{-1}$). Patients receiving anticoagulant therapy were excluded.

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Point-of-care viscoelastic testing improves the outcome of pregnancies complicated by severe postpartum hemorrhage

Table 2
Postoperative outcomes of the study population[a].

	PCVT ($n = 28$)	Non-PCVT ($n = 58$)	*P*-value
Hysterectomy, yes	7 (25.0%)	31 (53.5%)	0.013
Estimated blood loss (mL)	2000 (1600–2500)	3000 (2000–4000)	<0.001
Red blood cells (units)			<0.001
- 0	11 (39.3%)	3 (5.2%)	
- 1	7 (25.0%)	3 (5.2%)	
- ≥2	10 (35.7%)	52 (89.6%)	
Fresh frozen plasma (units)			<0.001
- 0	25 (89.3%)	16 (27.6%)	
- ≥1	3 (10.7%)	42 (72.4%)	
Platelets (units)			<0.001
- 0	28 (100%)	32 (55.2%)	
- ≥5	0 (0%)	26 (44.8%)	
Length of hospitalization after delivery (days)	4 (3–4)	5 (4–6)	<0.001
ICU admission	1 (3.6%)	25 (43.1%)	<0.001

Utility of Fibrinogen levels and Rotational thrombo Elastometry (ROTEM) in predicting Post Partum Hemorrhage

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INTRODUCTION

Post Partum Hemorrhage (PPH) is a common cause of maternal mortality.[1] Whatever the initial etiology of PPH, dilutional coagulopathy sets in all patients. Standard coagulation tests are time consuming and its values differ in pregnant women from the general population. ROTEM is emerging as a point of care device in PPH.[2]Thus the present study was planned to evaluate the correlation between ROTEM (A5, A10) as a point-of-care marker with plasma fibrinogen levels in obstetric patients.

AIM

To study correlation between fibrinogen levels and FIBTEM parameters on ROTEM in women delivering after 34 weeks of gestation. The second objective is to study the utility of FIBTEM and fibrinogen levels in predicting PPH. Study was approved by Institute Ethics Committee.

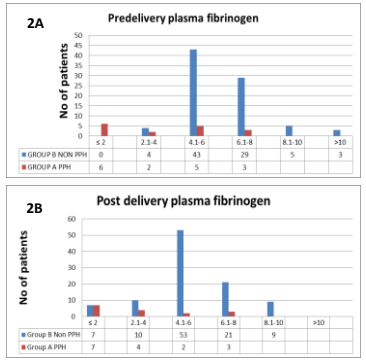
METHOD

- 100 pregnant women (34+ weeks) admitted for delivery were enrolled after excluding patients with hematological disorders and anticoagulant therapy.
- Samples drawn- Pre and post-delivery (1 hour or on onset of PPH)
- Tests performed -CBC, PT, APTT, fibrinogen, d-dimer and ROTEM.
- After delivery those who suffered from PPH were labeled as group A (study group) while rest were labeled as group B (control group).
- Sample size =100 with power (80%) to give valid estimates at 95% confidence level for detecting difference of 0.07 for the presumption value of correlation coefficient (r = 0.83) between FIBTEM A5 and fibrinogen as reported by Huissoud et al.[3]

RESULTS

- 16 out of 100 women suffered from PPH. (Group A= 16)
- The reference ranges of Hb, platelets, D-dimer, ROTEM parameters in pregnant women pre delivery and post delivery established (Fig 1)
- Group A had lower levels of plasma fibrinogen as compared to group B. Median (IQR) of plasma fibrinogen was 3.2 g/L (2.3 – 4.8)and 5.96 g/L (5.77 – 6.45) resp. (Fig 2)
- FIBTEM A5 reduced in Group A both before and after delivery as compared to group B. Median (IQR) of FIBTEM A5 in group A was 18 mm (12.46-21.67) before delivery and 17 mm (10-18.24) after delivery. In group B patients it was 25 mm (24-26.8) before delivery and 28 mm (22-25) after delivery.(fig 3)
- Clot amplitude of FIBTEM at 5 minutes -A5 had a positive correlation with fibrinogen levels with r^2 =0.713. (Fig 6)
- Pre and Post delivery fibrinogen <2 mg/L was 100% predictive of PPH. (Fig 2, 4)
- On the basis of ROC curves fibrinogen <2.79g/L was found to be the best cut off to predict PPH with 92% accuracy. Pre-delivery FIBTEM A5 values <16.5 mm had 81% predictive accuracy for PPH. (Fig 6)

Fig 2: Distribution of patients with (Group A) and without PPH (Group A) for plasma fibrinogen levels Predelivery Fig 1A and post delivery Fig 1B



FIBTEM	Group A (N=16)			Group B (N=84)		
	Pre-delivery	Post-delivery	P Value	Pre-delivery	Post-delivery	P value
CT (s)	79.37±28.89	94.06±51.60	0.3284	61.14±13.13	63.23±13.57	0.3109
CFT (s)	223±250.70	326±237.99	0.4083	125.82±119.19	136.77±96.07	0.5214
A5 (mm)	17.06±8.64	14.25±7.49	0.3333	25.51±6.26	24.03±5.58	0.1086

Fig 3: Comparison of Pre-delivery FIBTEM parameters with post-delivery FIBTEM parameters in group A and B.

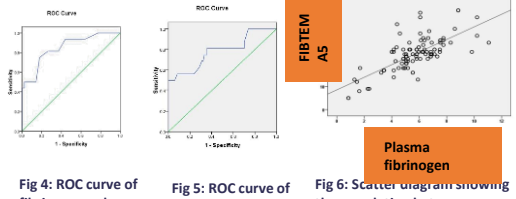


Fig 4: ROC curve of fibrinogen values after delivery for prediction of PPH

Fig 5: ROC curve of FIBTEM values after delivery for prediction of PPH

Fig 6: Scatter diagram showing the correlation between plasma fibrinogen and FIBTEM A5

Fig 1 Hb, Plts and D-dimer predelivery between group A , and group B

Characteristics	Group A (N=16) Mean±SD	Group B (N=84) Mean±SD	P Value
HB (gm%)	9.90±1.83	11.63±1.37	**P<0.0001**
PLT (10^3/µl)	118.437±94.806	199.969±79.082	**0.0004**
d-Dimer(µg/ml)	4.24±4.11	0.96±0.99	**P<0.0001**

Fig 1 Comparison of FIBTEM A5 (pre-delivery)between group A and groupB

FIBTEM	Group A		Group B	
	Pre-delivery	Post-delivery	Pre-delivery	Post delivery
CT(S)	74 (63.98-94.77)	79.5 (66-121)	59 (58-63)	60 (60.29-66)
CFT(S)	128 (43.66-402.34)	336 (105-546)	93.5 (99-152)	108 (115-158)
A5(mm)	18 (12.46-21.67)	17 (10-18.24)	25 (24-26.8)	28 (22-25)

CONCLUSIONS

- There is a fall in level of fibrinogen after delivery with the fall more pronounced in patients with PPH. Plasma fibrinogen ≤ 2 .79 g/L is 100 % predictive of PPH.
- FIBTEM parameters show a strong and significant correlation with Plasma fibrinogen levels with CT/CFT having a negative correlation and clot amplitudes having a positive correlation.
- Plasma fibrinogen level of ≤ 2.79 g/L has sensitivity of 50%; specificity of 100% ; positive predictive value (PPV) of 100%; negative predictive value (NPV) of 91% and accuracy of 92% for prediction of PPH. Women likely to have PPH had lower fibrinogen and high d-dimer levels. This suggests that pre-delivery ensuing endothelial activation and utilization of fibrinogen to form fibrin and breakdown of fibrin to give d-Dimer is more in women who develop PPH. This along with lower Hb and increased aPTT can be a predictor of likely PPH.
- FIBTEM A5 value of 16.5 mm has sensitivity of 75% ; specificity of 82% PPV of 44%; NPV of 94% and accuracy of 81% for prediction of PPH.
- Plasma fibrinogen level and FIBTEM A5 can be used for predicting PPH and guiding blood transfusion in an appropriate manner once PPH has occurred[4,5].

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CONTACT INFORMATION drjyotikotwal@gmail.com

Conclusions of our study

- 16 out of 100 women suffered from PPH.
- The reference ranges of fibrinogen, PT, APTT, d- dimer, and ROTEM parameters in pregnant women in predelivery and I hr post-delivery established.
- Pre as well as Post-delivery fibrinogen ≤2 mg/L was 100% predictive of PPH.
- Clot amplitude of FIBTEM at 5 minutes -A5 had a positive correlation with fibrinogen levels (r2 =0.713).
- Clot formation time (CFT) and Clotting time (CT) on FIBTEM had a negative correlation with fibrinogen.
- On the basis of ROC curves fibrinogen ≤2.79g/L was found to be the best cut off to predict PPH with 92% accuracy
- FIBTEM A5 values ≤16.5 mm had 81% predictive accuracy for PPH.
- Further studies are required to validate the application of ROTEM in the management of PPH.

ROTEM Assays

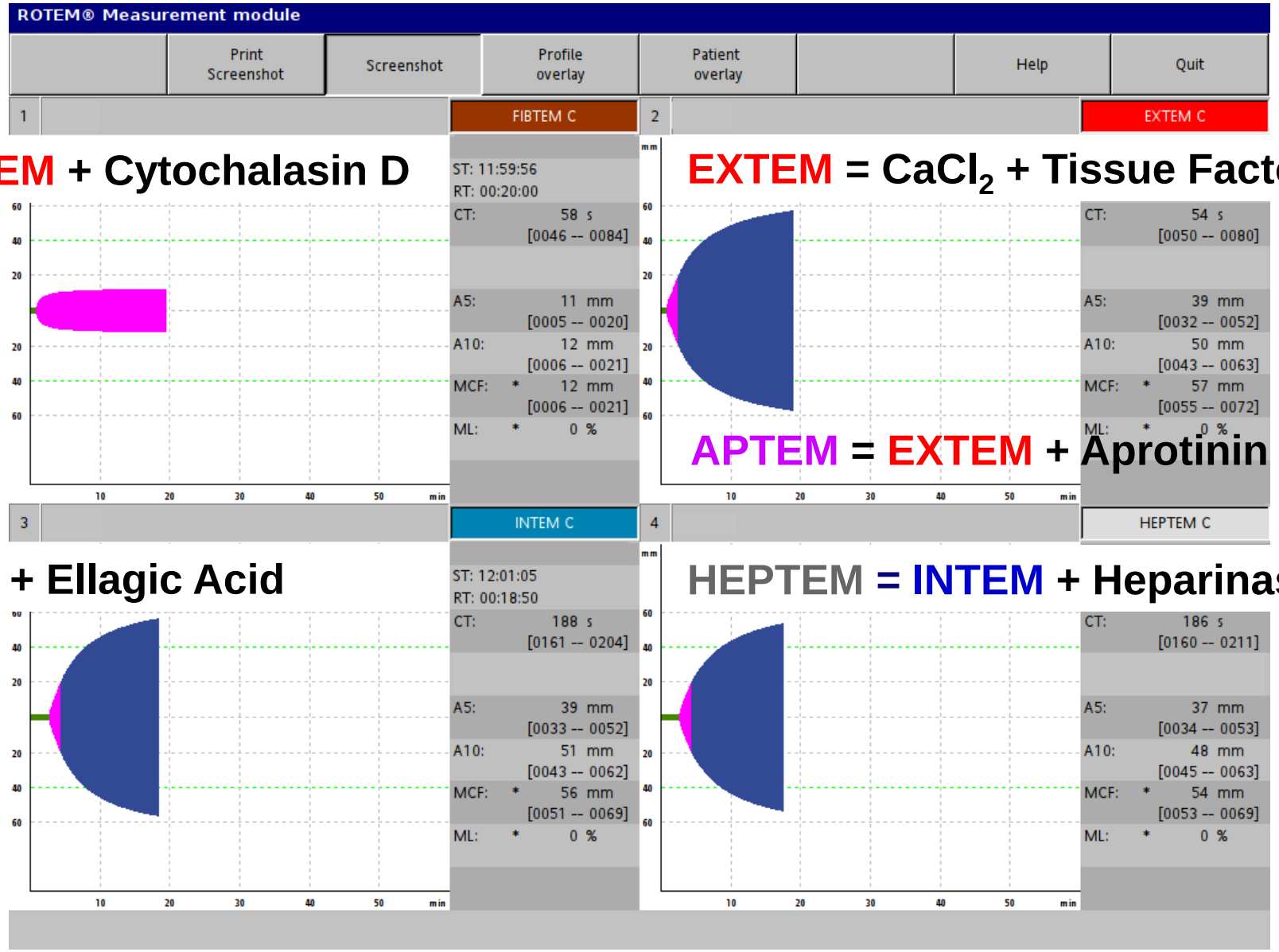
FIBTEM = EXTEM + Cytochalasin D

EXTEM = $CaCl_2$ + Tissue Factor + Polybrene

APTEM = EXTEM + Aprotinin / TXA

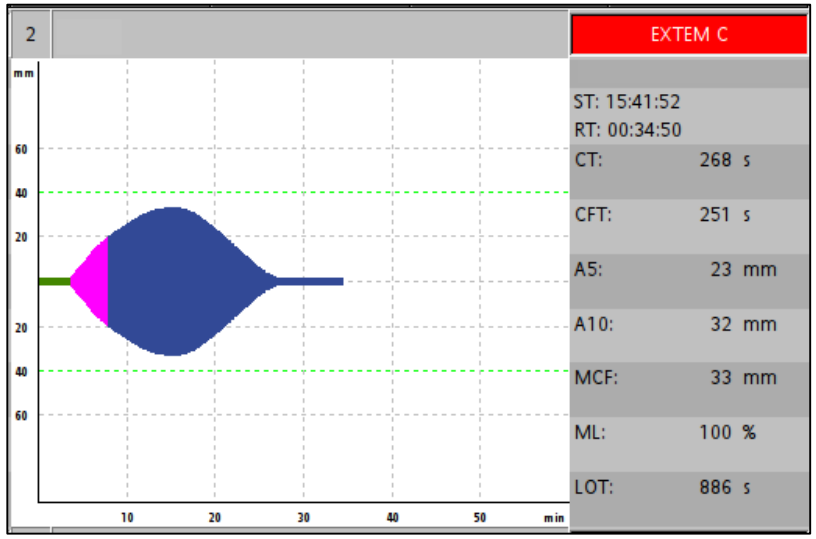
INTEM = $CaCl_2$ + Ellagic Acid

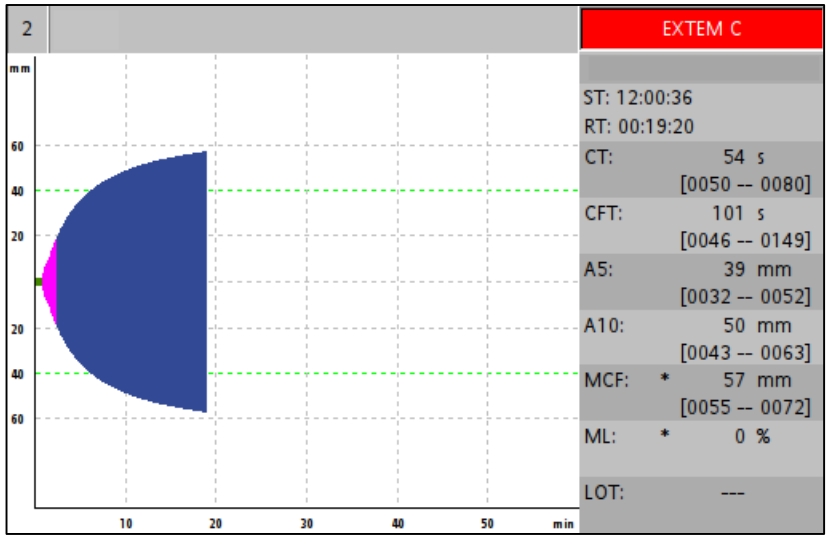
HEPTEM = INTEM + Heparinase

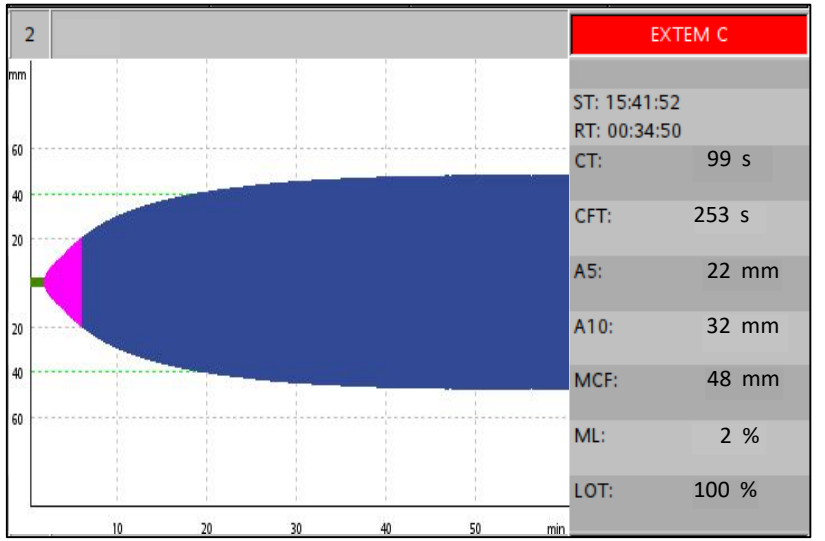


Time Management

Fibrinolysis Management



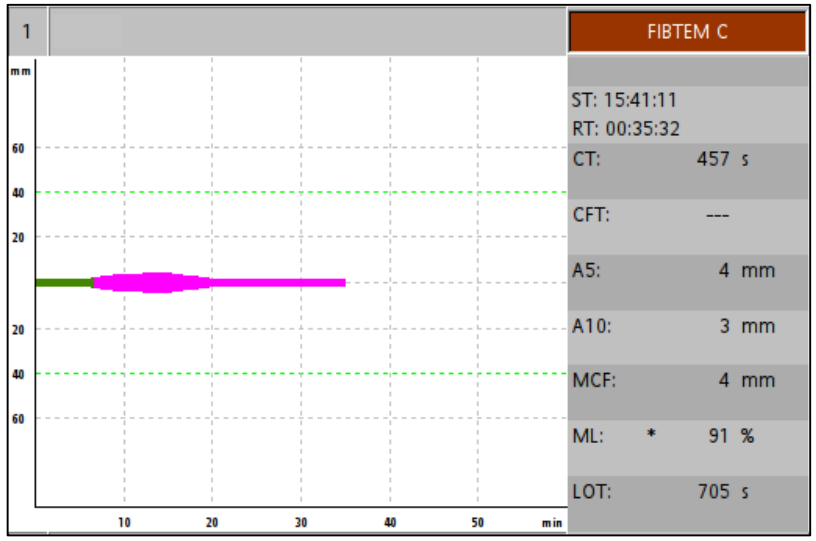


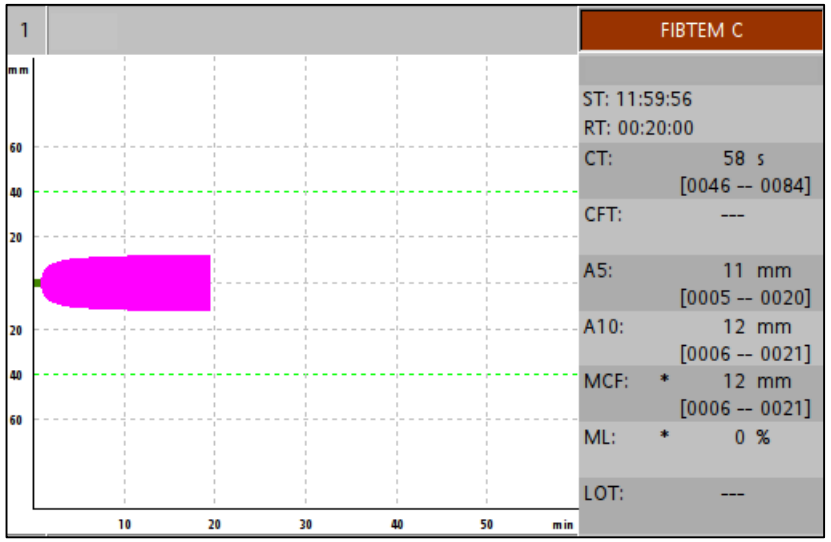


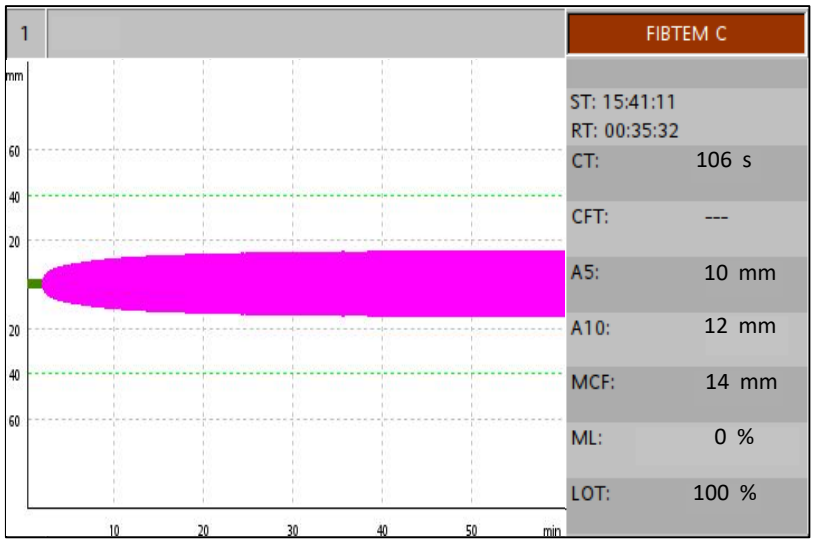
HYPERFIBRINOLYSIS

NORMAL

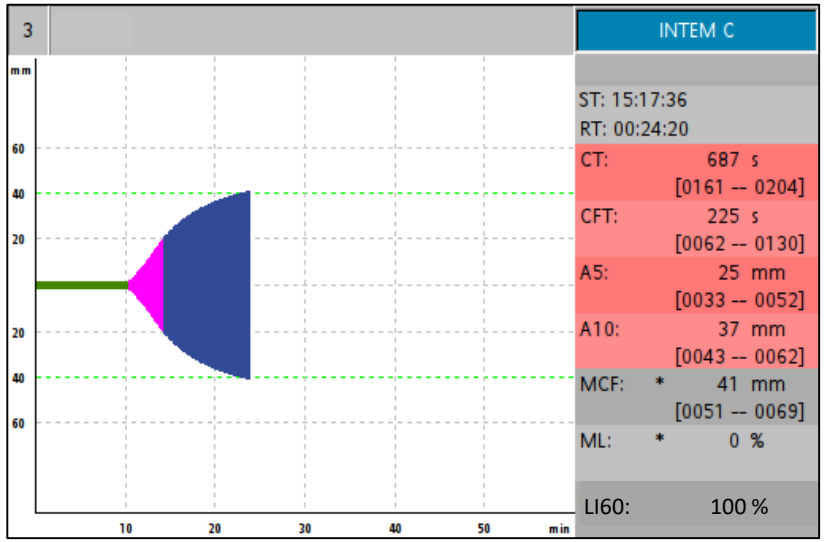
FIBRINOLYSIS SHUTDOWN

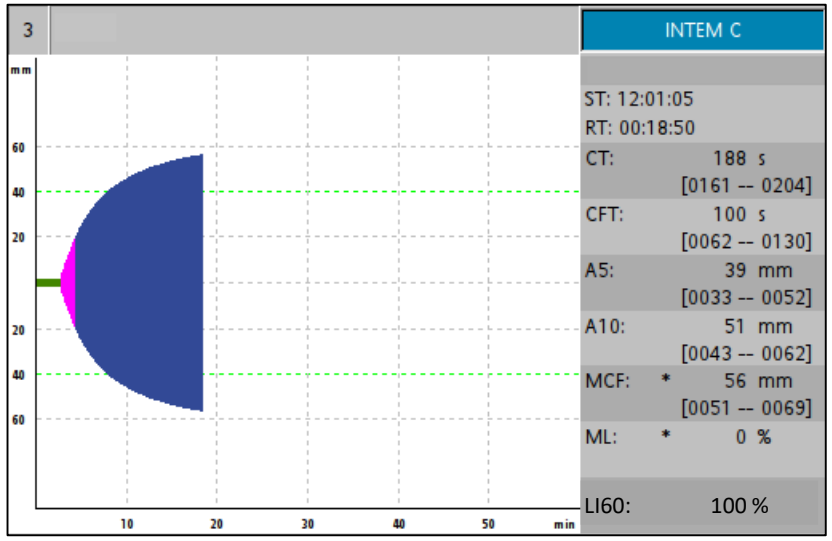


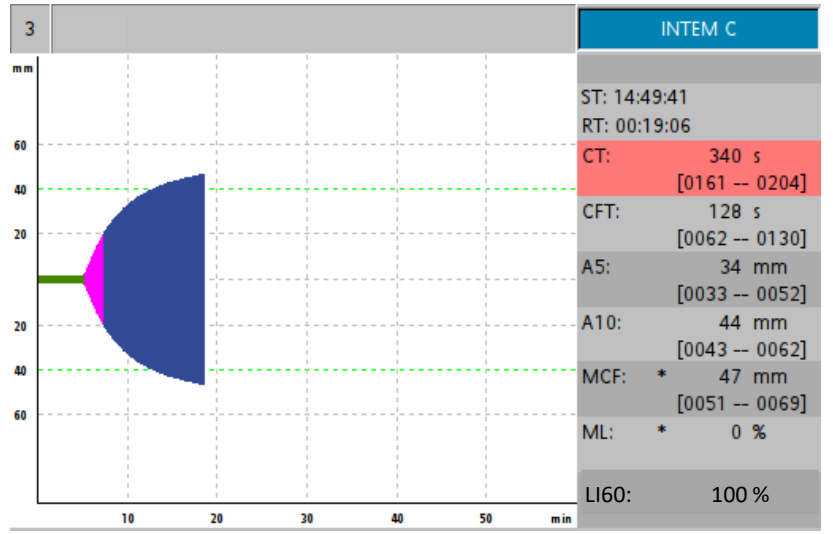




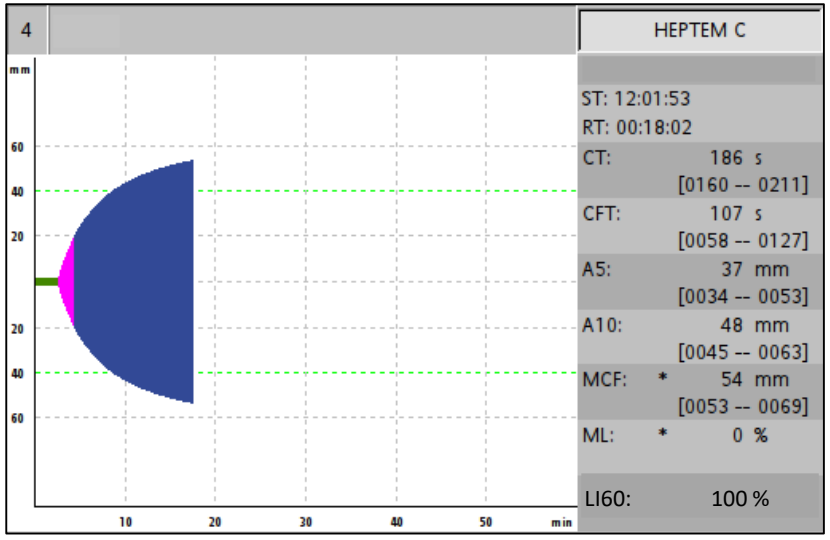
Heparin Protamine Management







RESIDUAL HEPARIN EFFECT



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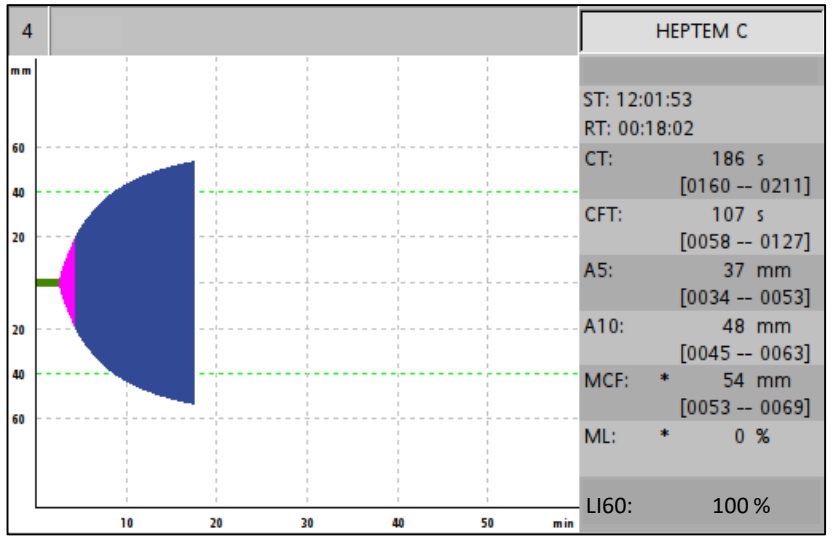
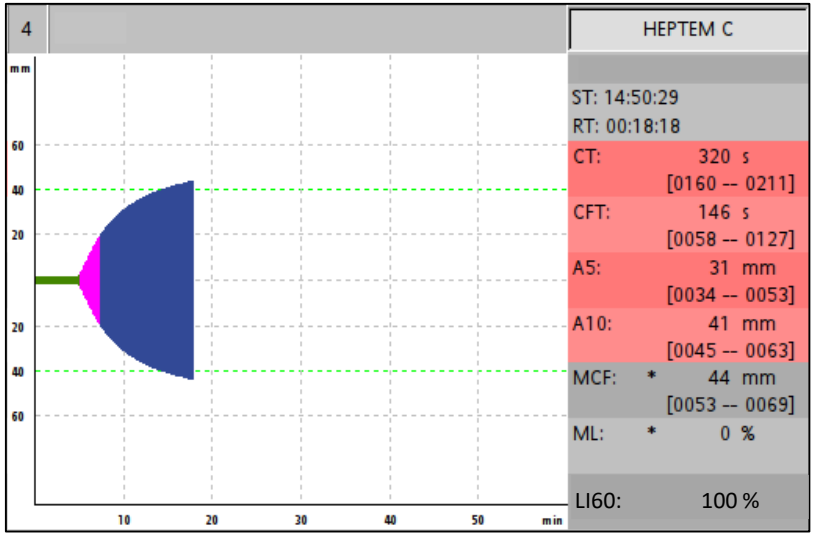
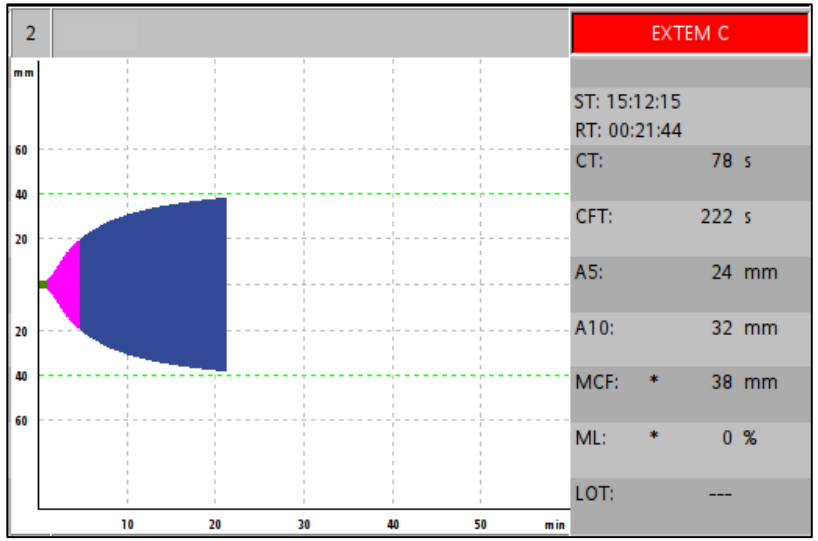


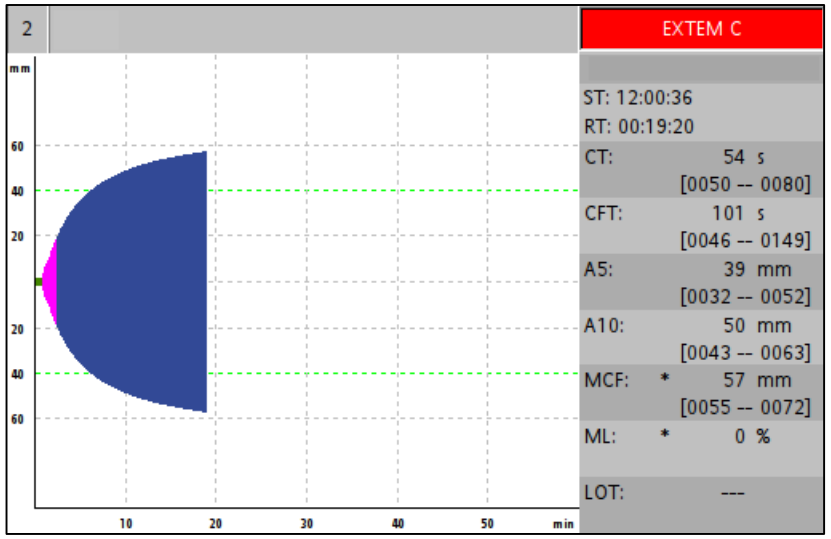
PROTAMINE OVERDOSE OR DEFICIENCY OF INTRINSIC FACTORS



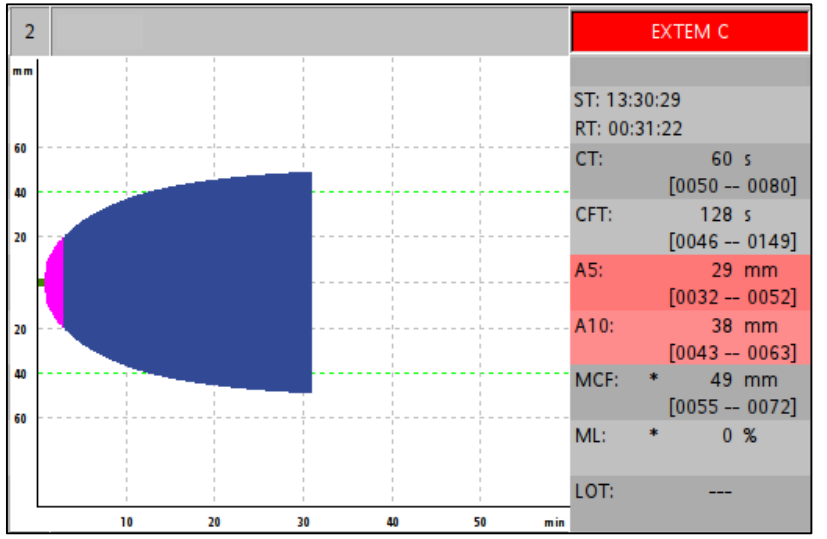
Clot Firmness Management



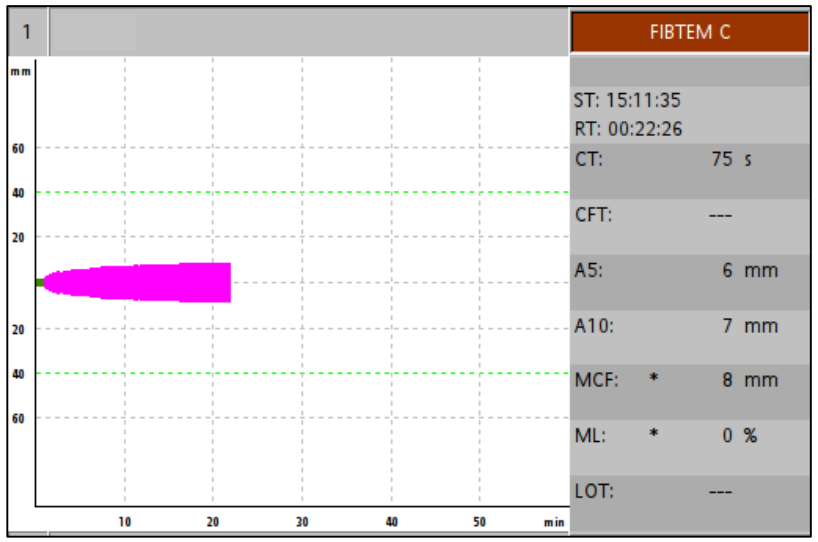
LOW FIBRIN CONTRIBUTION

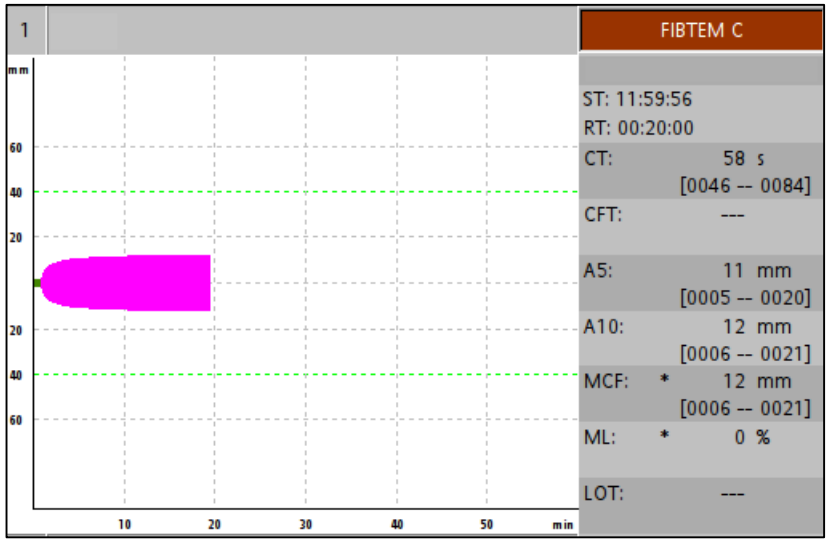


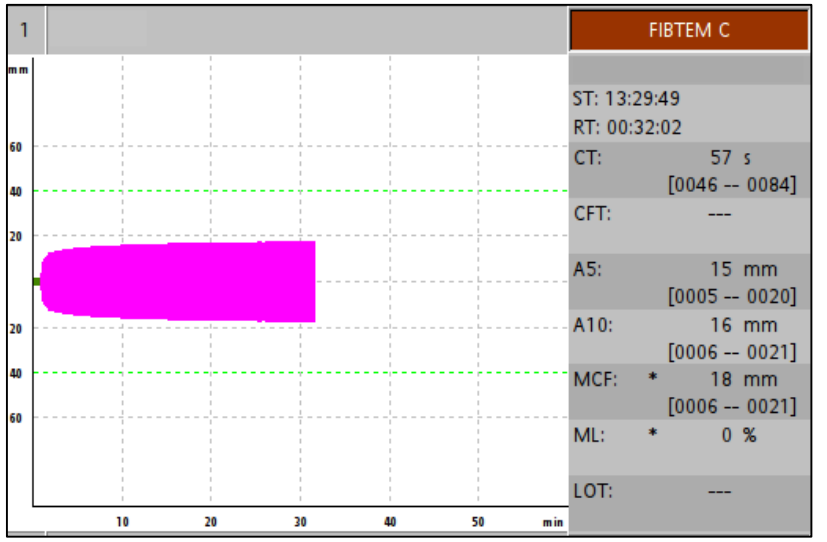
NORMAL



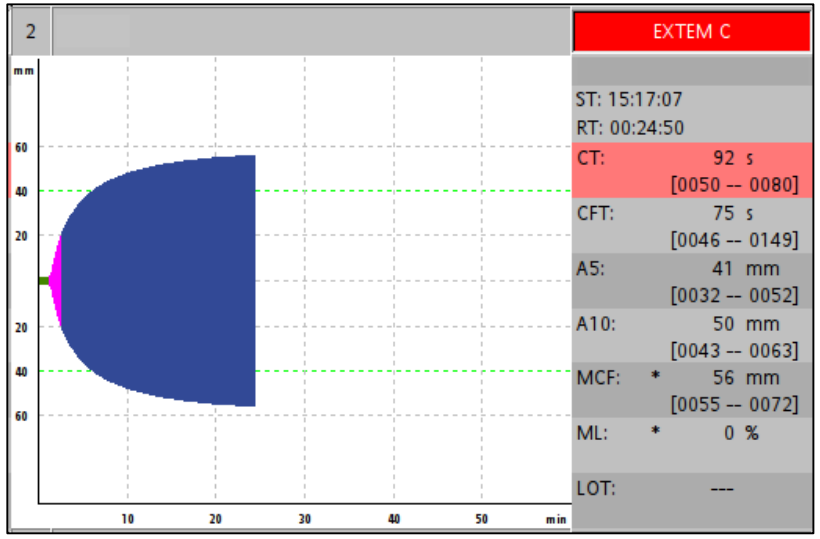
LOW PLATELET CONTRIBUTION



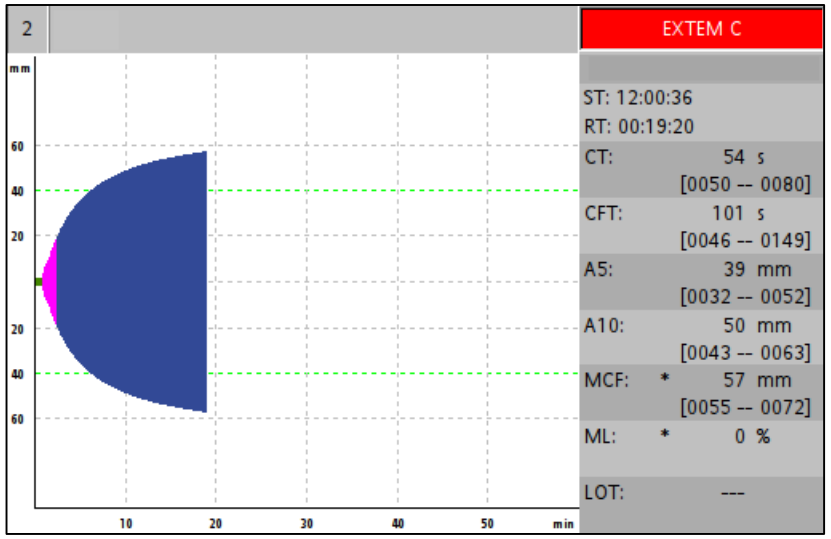




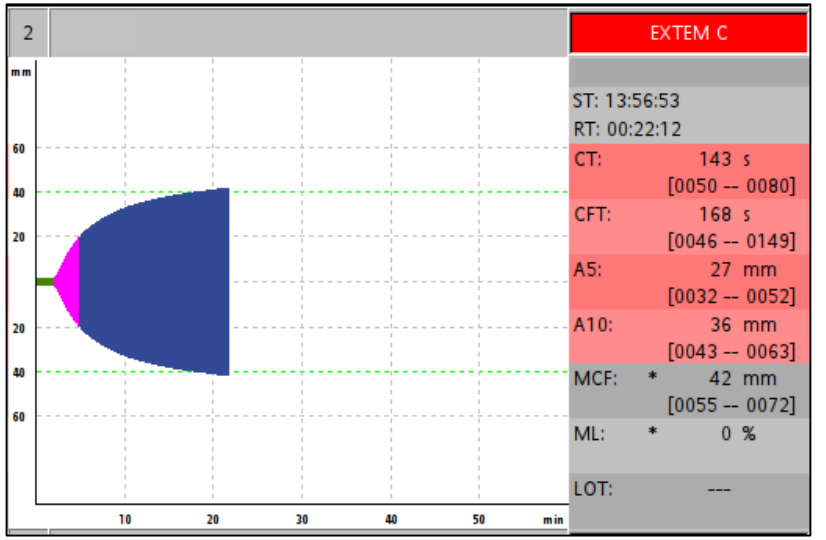
Thrombin Generation Management



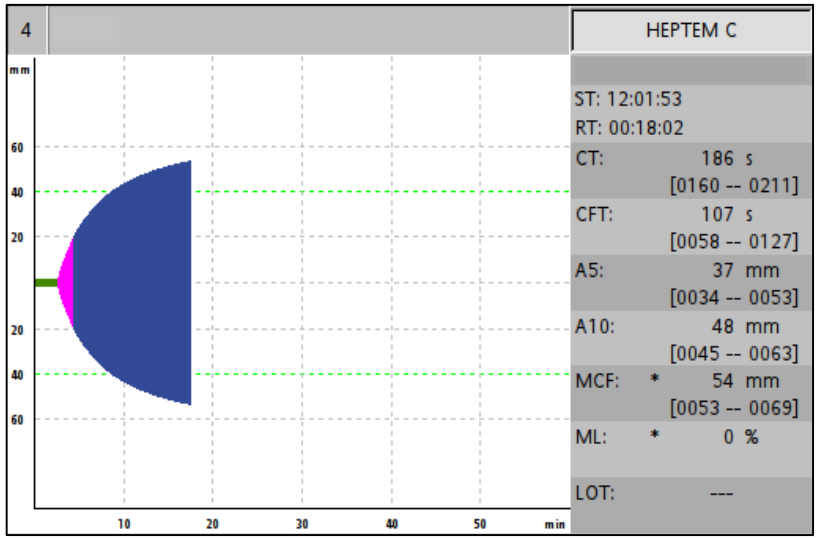
DEFICIENCY OF VITAMIN K-DEPENDENT FACTORS OR VKA (e.g., WARFARIN)

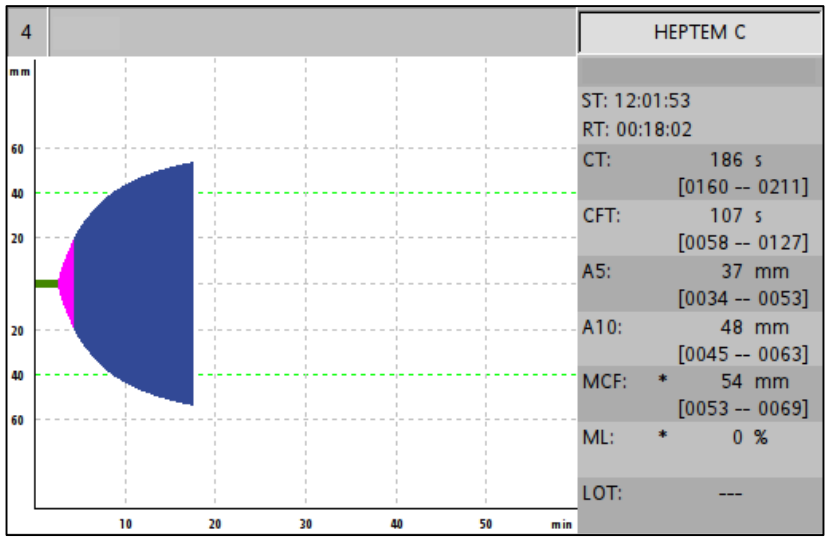


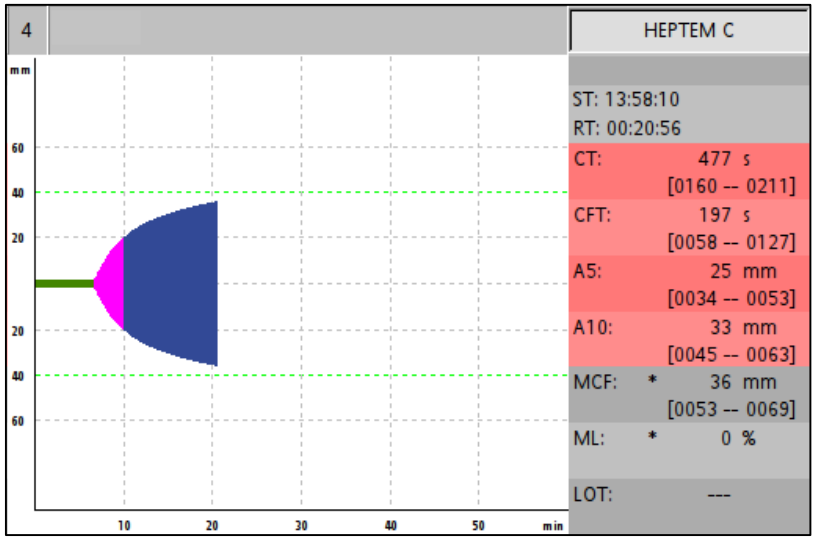
NORMAL



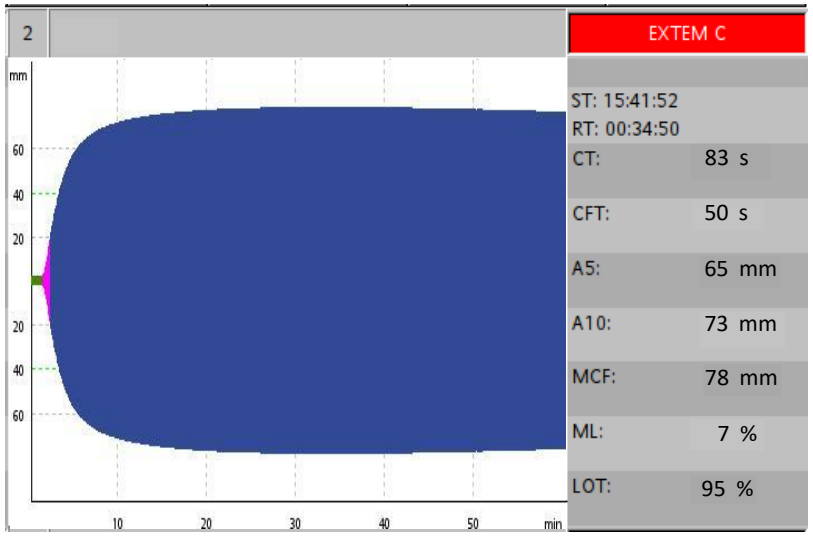
DEFICIENCY OF FACTORS OF THE COMMON PATHWAY OR DOACs (e.g., DABIGATRAN)



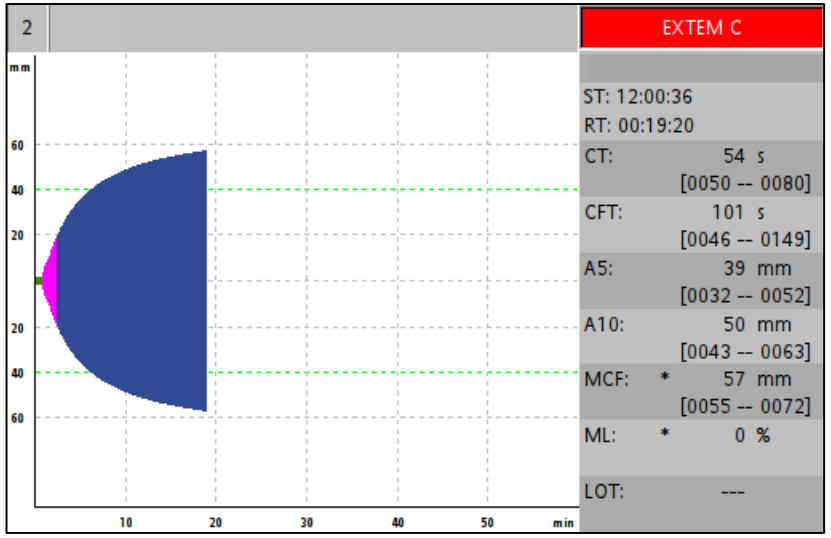




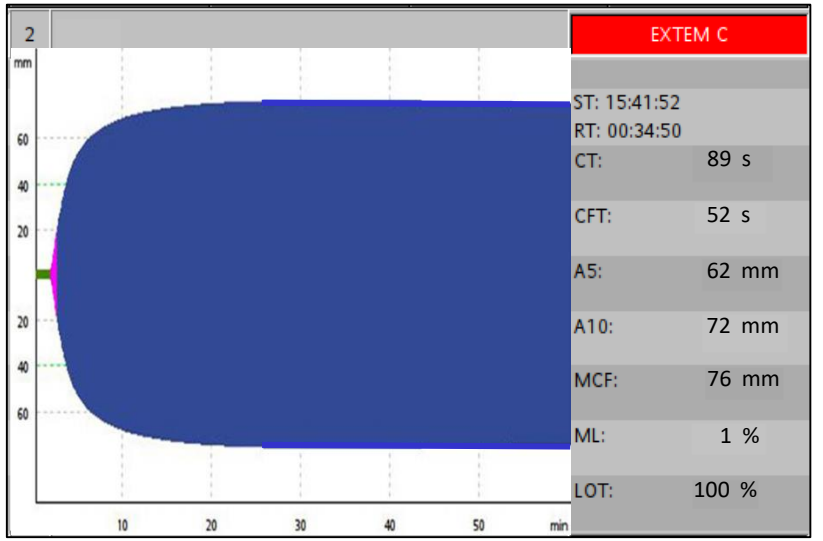
Hypercoagulability



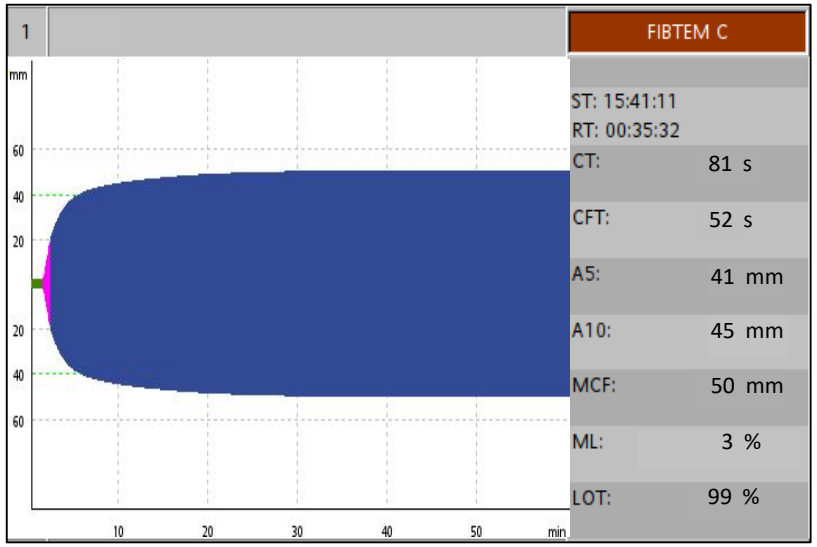
HYPERCOAGULABILITY WITH PHYSIOLOGIC FIBRINOLYSIS

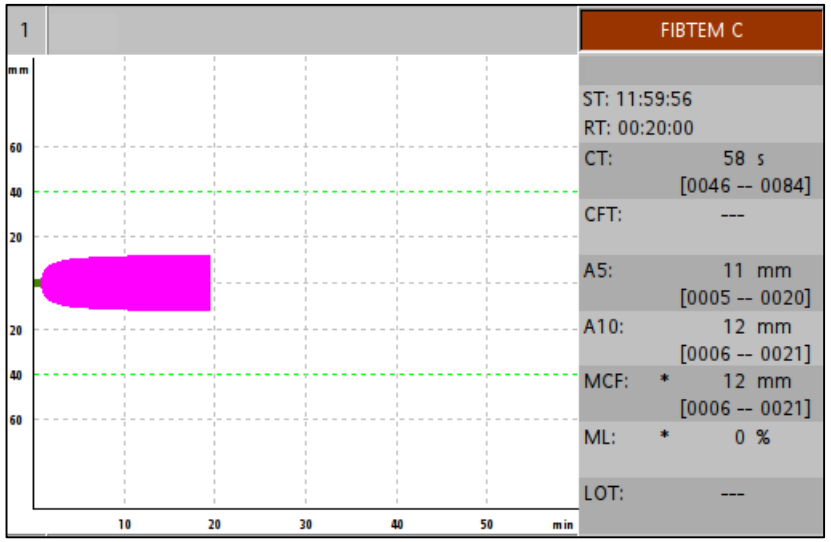


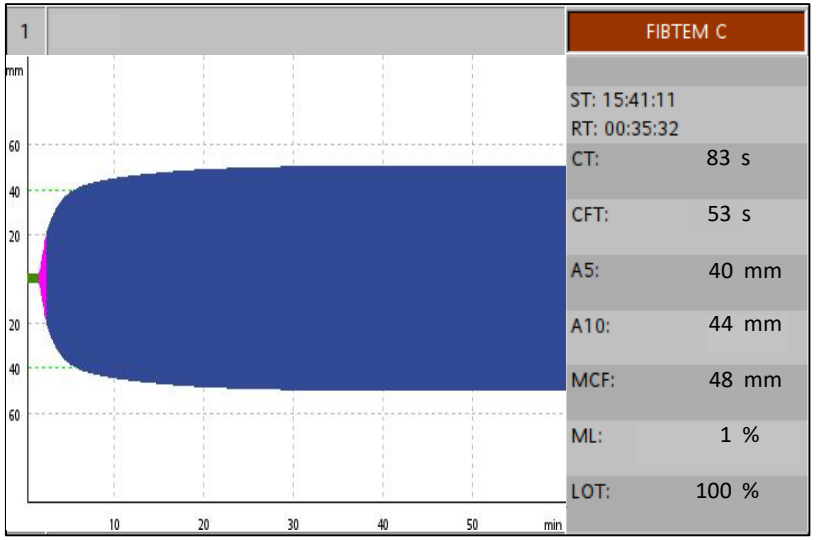
NORMAL



HYPERCOAGULABILITY WITH FIBRINOLYSIS SHUTDOWN







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KJA
Korean Journal of Anesthesiology

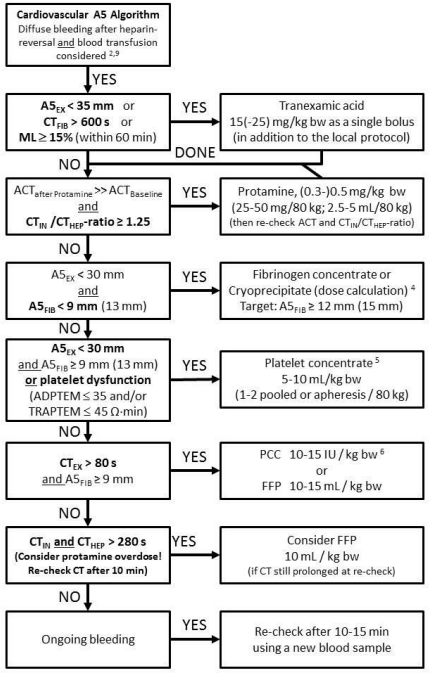
Review Article
pISSN 2005-6419 · eISSN 2005-7563

PRECISION MEDICINE

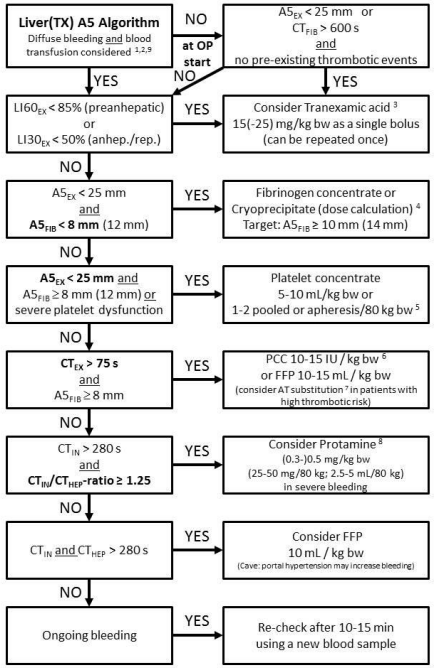
The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management

Klaus Görlinger[1,2], Antonio Pérez-Ferrer[3], Daniel Dirkmann[1], Fuat Saner[4], Marc Maegele[5,6], Ángel Augusto Pérez Calatayud[7], and Tae-Yop Kim[8]

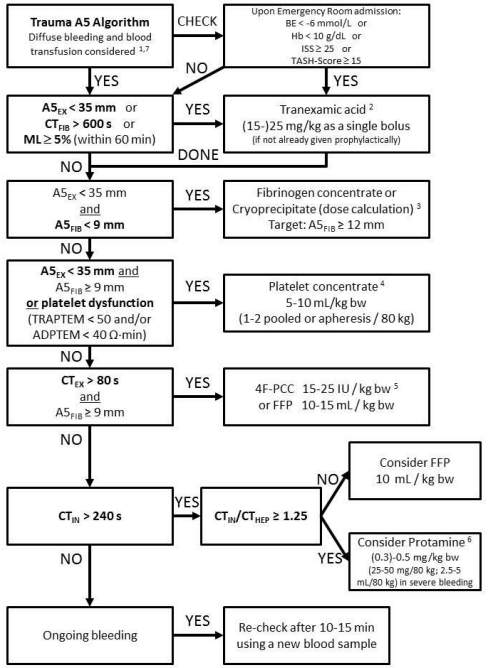
Cardiovascular



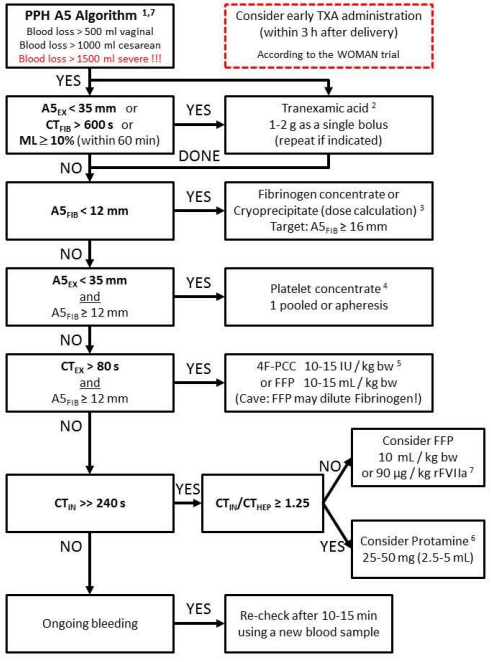
Liver/Abdominal



Trauma/Orthopedics



Obstetrics/PPH



Gupta *et al. Blood Research* (2024) 59:19
https://doi.org/10.1007/s44313-024-00018-6

Blood Research

RESEARCH Open Access

Assessment of the phenotypic severity of hemophilia A: using rotational thromboelastometry (ROTEM) and APTT-clot waveform analysis

Deepika Gupta[1], Vandana Arya[1], Jasmita Dass[2], Nitin Gupta[1], Manas Kalra[3], Anupam Sachdeva[3] and Jyoti Kotwal[1*]

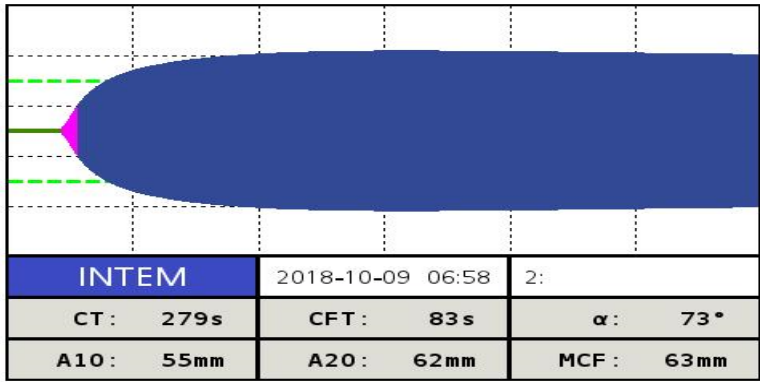
Results A total of 66 patients were recruited for this study. Statistically significant differences were observed between the four phenotypically categorized groups using ROTEM and APTT-CWA. On comparing patients with mild/moderate-to-severe phenotypes (Group II) with SHA without inhibitors (Group IV), no significant difference was found for all parameters of ROTEM or APTT-CWA. The MCF, MA30, MAXV, and Alpha angle values using ROTEM were found to be the lowest in patients with SHA with inhibitors, which helped differentiate them from those with SHA without inhibitors. However, these two groups could not be differentiated using the APTT-CWA parameters.

Conclusion ROTEM can be used to distinguish patients with SHA with inhibitors from those with SHA without inhibitors using a combination of parameters with high sensitivity and specificity. However, APTT-CWA cannot be used to differentiate these patient groups.

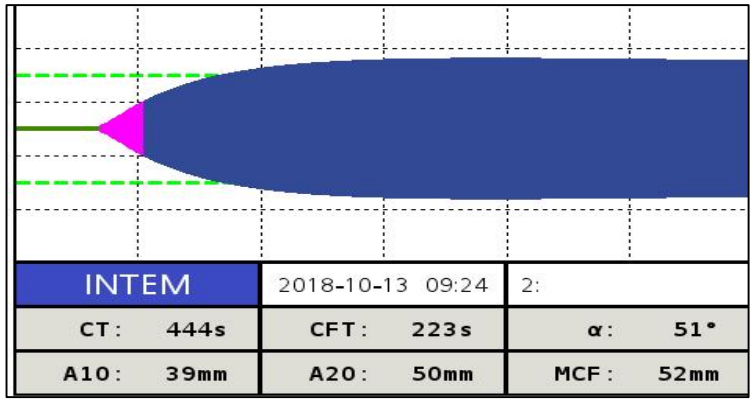
Keywords Hemophilia A, ROTEM, APTT-CWA, Phenotype severity, Bleeding disorder, Bethesda assay

TEMOGRAMS OF ALL THE FOUR GROUPS

I



II



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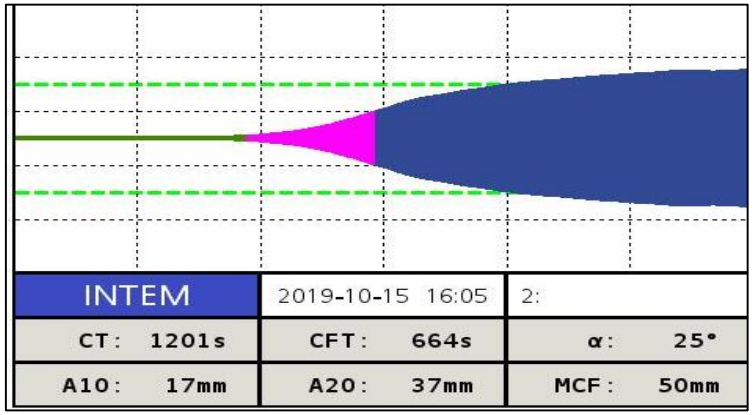
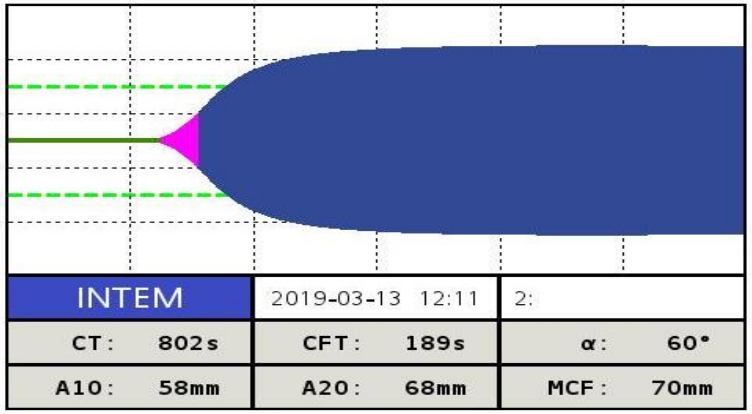


IV



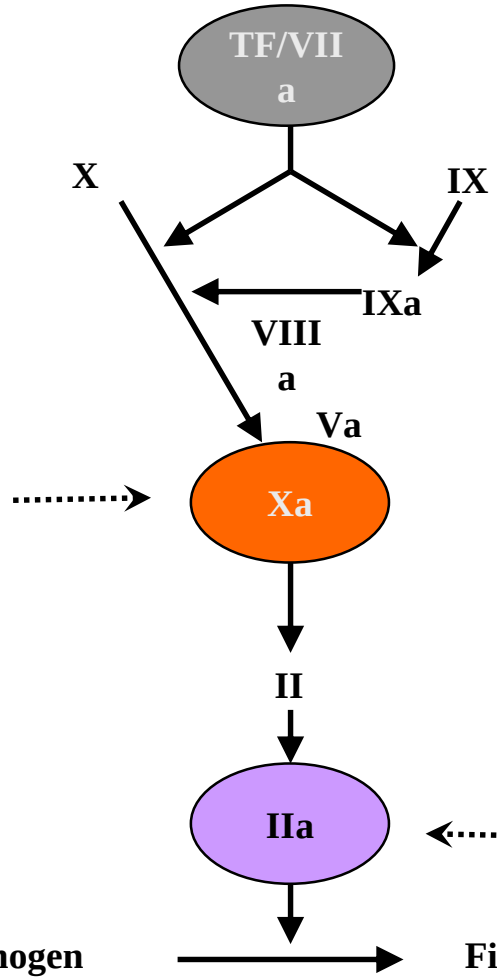
Direct specific factor inhibitors

rivaroxaban
(XARELTO®)

apixaban
(ELIQUIS®)

edoxaban
(LIXIANA®
SAVAYSA®)

betrixaban
(BEVYXXA®)



dabigatran
(PRADAXA®)

Advantages of DOAC over VKA / Heparin

- Orally active
- Rapid onset and offset of action
- Safe drug PK profile
  - Broad therapeutic window
  - Short half-life
  - Limited influence of genetic factors
  - Limited drug-drug interactions

Fixed-dose administration

- No routine laboratory monitoring
- No need for dose adjustment

An interesting case 6 yrs back

- 85 yrs lady (mother of doctor)- ICU History of not having orally for week or so. 36 hrs after admission PT INR (26s/2.5) and APTT prolonged (45sec). History of Anticoagulants denied. LMWH started that morning itself. BUN -70. In azotemia. Thrombin time(TT) was 90sec (14-19 sec)
- Because of INR wanted us to rule out factor VII inhibitors. Factor VII unrecordable . Normal on 1: 4 dilution. PT normalized on dilution
- On questioning AF. Checking old documents gave Answer

An interesting case

- AF on Pradaxa & Amidarone
- Stopped on admission
- Renal Dysfunction

Pharmacological properties

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Pro-drug	Yes	No	No	No
Half-life,h	12-17 h	5–9 h (young) 11–13 h (elderly	12h	9-11h
Time to maximum plasma concentration	0.5–2	2–4 h	1–4 h	1–2 h
Renal excretion	80%	35%	25%	50%
Liver metabolism	20%	Yes	Yes	50%

Pharmacological properties

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Gastrointestinal tolerability	Dyspepsia	No problem	No problem	No problem
Absorption with food	No effect	+39%more	No effect	6–22%more
Intake with food	No	Mandatory	No	Official recommendation
Dosing	Twice daily	Once daily	Twice daily	Once daily
Usual dose regimen	150 mg BID	20 mg QD In acute VTE 15mg BID for 21 days then 20mg OD	5 mg BID	60 mg QD

Drug Interactions

- Dabigatran: Substrate for p-glycoprotein
- Rivaroxaban: p-glyco (subs) + 51% CYP 3A4 metabolism
- Apixaban: p-glycoprotein +25% CYP 3A4 metabolism
- Edoxaban - p-glycoprotein Minimal CYP 3A4 metabolism

Drug Interaction Examples	
Strong CYP3A4 inhibitors+combined P-gp inhibitor	Itraconazole, ketoconazole, ritonavir
Moderate CYP3A4 inhibitors+combined P-gp inhibitor	Clarithromycin, diltiazem
Strong CYP3A4 inducer+combined P-gp inducer	Carbamazepine, rifampin, St. John's wort
Strong CYP3A4 inducers	Phenytoin
P-gp inhibitors	Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin ivacaftor, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil
P-gp inducers	Rifampin

Condition		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug-drug interactions P-gp/CYP3A4 inhibitors	**Quinidine**	**+53%**	-	-	**+76%**
	Amiodarone	**+60%**	-	-	**+40%**
	Diltiazem	-	-	**+31%**	-
	Dronedarone	**+136%**	-	-	**+84%**
	Verapamil	**+18 to +143%**	-	-	**+53%**
	Ketoconazole	**+138%**	**+82 to +158%**	**+99%**	**+87%**
	Naproxen	-	NS	**+55%**	NS
	Fluconazole	-	**+42%**	-	-
	Ritonavir	-	**+153%**	-	-
	Clarithromycine	**+19 to +50%**	**+34 to +54%**	-	**+85%**
	Erythromycine	NS or -24%	NS	-	-
	Proton pump inhibitors				
Drug-drug interactions P-gp/CYP3A4 inducers	Rifampicin Carbamazepin Phenytoin Phenobarbital	**-67%**	**-50%**	**-54%**	**-35%**
Drug-drug interactions P-gp/CYP3A4 substrates	Atorvastatin	NS	NS	-	NS
	Digoxin	NS	NS	-	NS
	Midazolam	-	NS	-	-

Patterns of DOAC interference in hemostasis/thrombosis assays

Expected change	Assays	Notes
Clotting time prolongation	• aPTT (dabigatran > direct Xa inhibitors) • PT (rivaroxaban > edoxaban > apixaban) • Thrombin time (dabigatran)	Effects on clotting times are reagent dependent. aPTT and PT mixing tests are expected to show incomplete correction in the presence of DOACs.
False increase	• Clot-based protein C activity • Clot-based protein S activity • Antithrombin activity (in factor IIa–based assays with dabigatran, in factor Xa–based assays with direct Xa inhibitors) • Activated protein C resistance ratio	False increase in protein C, protein S, and antithrombin activities may result in misdiagnosis of a patient with true deficiency as normal. Falsely elevated activated protein C resistance ratio may result in misdiagnosis of a patient with factor V Leiden mutation as normal.
False decrease	• aPTT-based factor assays (VIII, IX, XI, XII) • PT-based factor assays (II, V, VII, X)	Dilutions in factor assays may show nonspecific inhibitor effect.
False positive (or potentially false negative)	• LA assays	Includes aPTT- and DRVVT-based assays, among other clotting time-based LA assays; effects are drug and reagent dependent.
No change	• Clauss fibrinogen activity (for most reagents, rare methods show false decrease in presence of high concentrations of dabigatran) • D-dimer • Chromogenic protein C activity • Free and total protein S antigen • Anticardiolipin, anti-β2GP1 ELISAs • von Willebrand activity and antigen assays • DNA-based assays (eg, factor V Leiden mutation, prothrombin G20210A mutation)	

How to measure effect

Table 2 Effect of novel oral anticoagulants on commonly used coagulation tests

Novel anticoagulant	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)	Thrombin clotting time (TCT)	Ecarin clotting time	Haemoclot assay	Anti-factor Xa activity	
						Clot-based	Chromogenic
Dabigatran	↑ or no change (low sensitivity, varies with reagents)	↑ (varies with reagents)	↑	↑	↑[a]	↑	ND
Rivaroxaban	↑ or no change (not sensitive at low concentrations, varies with reagents)	↑ or no change (less sensitive than PT)	—	—	—	↑	↑[a] (sensitive and specific when calibration curve used)
Apixaban	↑ or no change (other tests more sensitive, may vary with reagents)	↑ or no change (other tests more sensitive, may vary with reagents)	—	—	—	↑[a]	↑[a]

ND, no data.

[a]Preferred test. Adapted from previously published review articles.[41,59]

Assessment of the degree of anticoagulation

Guidance from the British Committee for Standards in Haematology

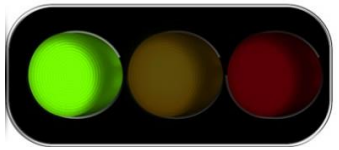
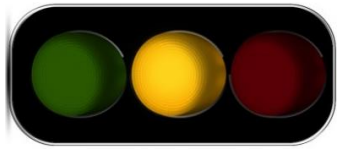
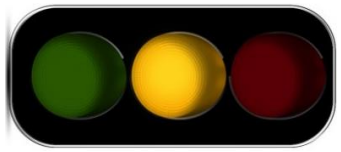
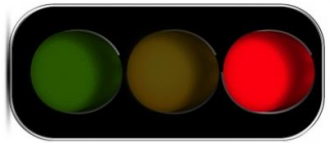
- Peak plasma concentrations: 100 - 400 ng/mL
- Trough concentrations: 20 - 150 ng/mL

- Urgent assessment of the degree of anticoagulation may be required:
  - before surgery or invasive procedure when a patient has taken a drug in the previous 24 h (or longer if CrCl < 50 mL/min)
  - when a patient is bleeding
  - when a patient has taken an overdose
  - when a patient has developed renal failure
  - when a patient has thrombosis on treatment (to assess whether there is a failure of therapy or lack of adherence)

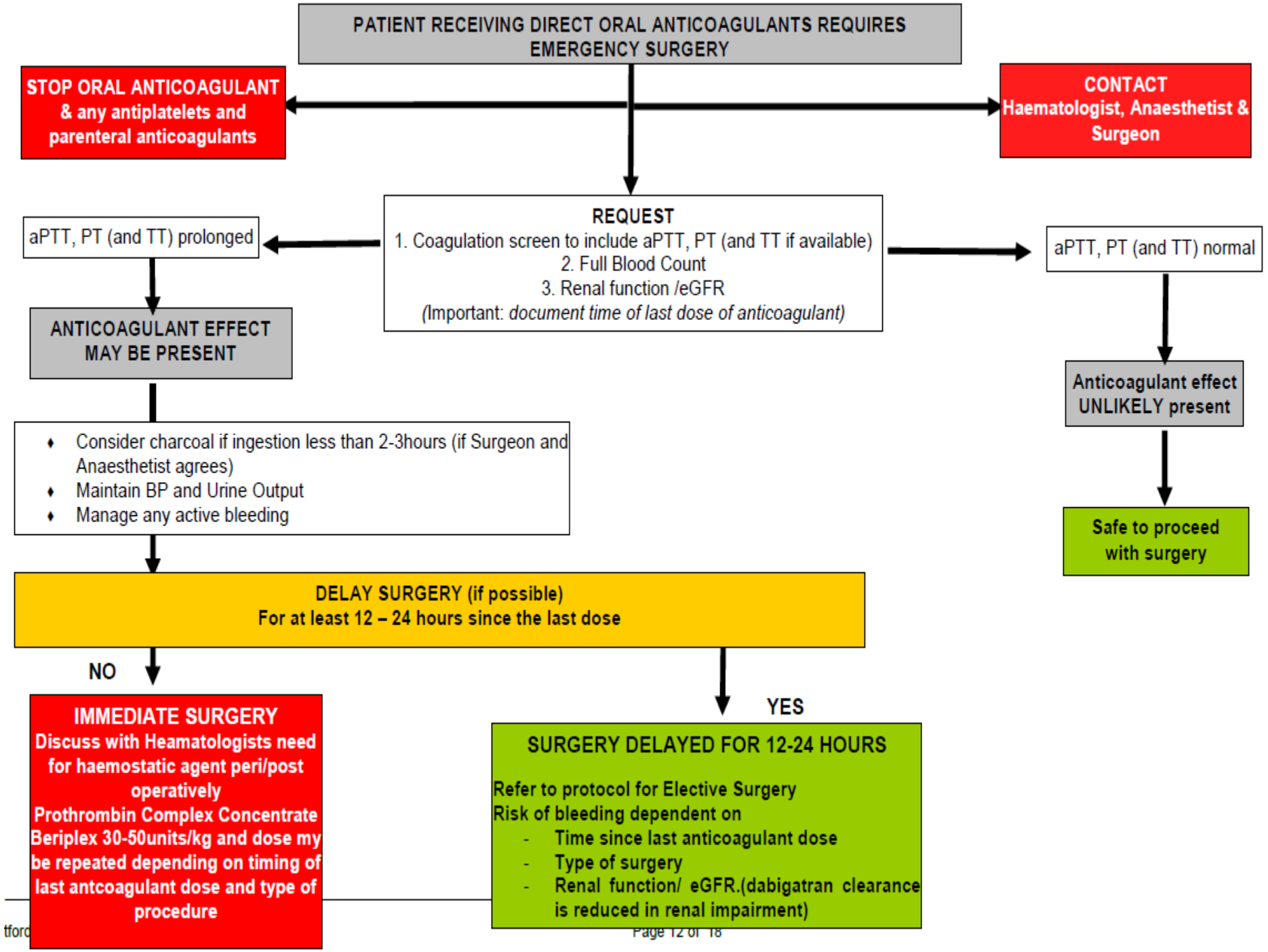
Baglin T et al. Br J Haematol 2012; 159: 427-9

French GIHP recommendation

Perioperative situation (dabigatran, rivaroxaban)

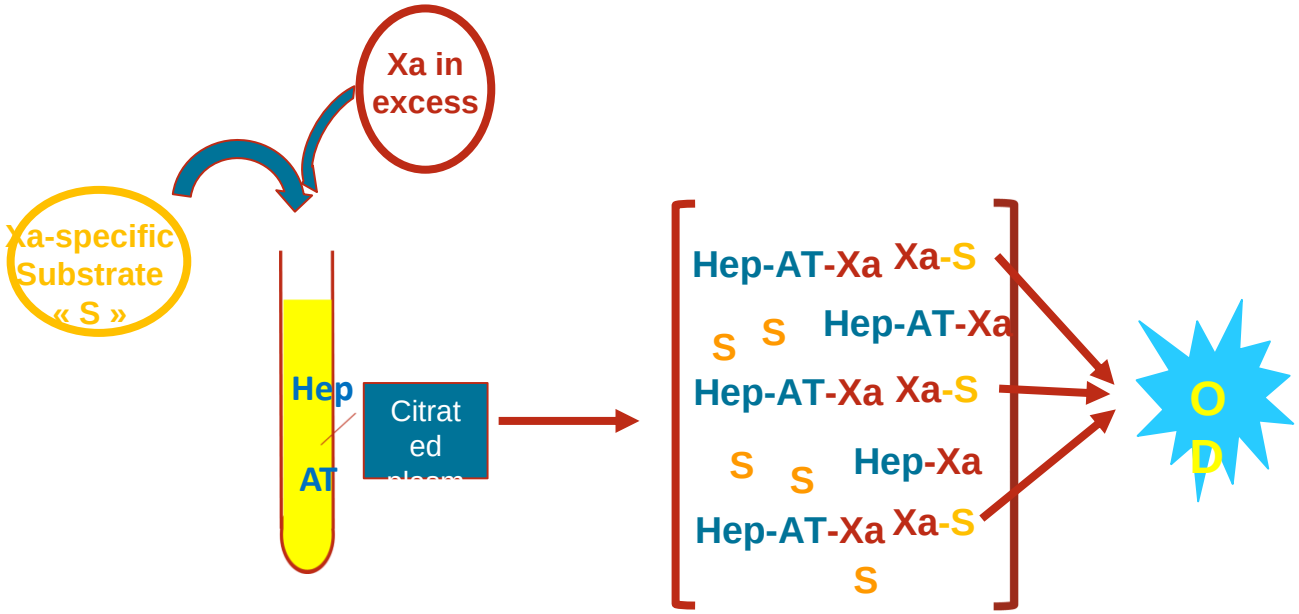
	**< 30 ng/mL**	➢ Perform surgery
	**30 – 200 ng/mL**	➢ wait 12 hours, and repeat drug measurement ➢ if surgery cannot wait for 12 hours, perform surgery • in case of abnormal bleeding, consider antidote (PCC, Feiba)
	**200 – 400 ng/mL**	➢ wait 12 - 24 hours, and repeat drug measurement ➢ if surgery cannot wait for 12 - 24 hours, delay surgery as much as possible • consider antidote in case of abnormal bleeding
	**> 400 ng/mL**	➢ overdose ➢ risk of major bleeding

Pernot G, Abaladejo P. GIHP recommendation, February 2013, available at eurekapro.fr


PATIENT RECEIVING DIRECT ORAL ANTICOAGULANTS REQUIRES EMERGENCY SURGERY
STOP ORAL ANTICOAGULANT & any antiplatelets and parenteral anticoagulants
CONTACT Haematologist, Anaesthetist & Surgeon
REQUEST
1. Coagulation screen to include aPTT, PT (and TT if available)
2. Full Blood Count
3. Renal function /eGFR
(Important: document time of last dose of anticoagulant)
aPTT, PT (and TT) prolonged
aPTT, PT (and TT) normal
ANTICOAGULANT EFFECT MAY BE PRESENT
Anticoagulant effect UNLIKELY present
Consider charcoal if ingestion less than 2-3hours (if Surgeon and Anaesthetist agrees)
Maintain BP and Urine Output
Manage any active bleeding
Safe to proceed with surgery
DELAY SURGERY (if possible)
For at least 12 – 24 hours since the last dose
NO
YES
IMMEDIATE SURGERY
Discuss with Heamatologists need for haemostatic agent peri/post operatively
Prothrombin Complex Concentrate Beriplex 30-50units/kg and dose my be repeated depending on timing of last antcoagulant dose and type of procedure
SURGERY DELAYED FOR 12-24 HOURS
Refer to protocol for Elective Surgery
Risk of bleeding dependent on
- Time since last anticoagulant dose
- Type of surgery
- Renal function/ eGFR.(dabigatran clearance is reduced in renal impairment)

Anti-Xa chromogenic assay: a universal tool for all anti-Xa drugs

Principle of the assay



Hybrid curve

- UFH international standard → UFH IU/mL
- LMWH international standard → LMWH IU/mL
- Danaparoid sodium → danaparoid U/mL
- Direct anti-Xa drug reference

Dedicated quality controls:

- UFH
- LMWH
- Danaparoid sodium
- Direct anti-Xa drug reference compound (rivaroxaban, apixaban, edoxaban)

Stago

Can heparin-calibrated anti-Xa assay be used for DOACs?

ISTH July 2022 – London, UK

OC 65. 1 **Prediction of apixaban or rivaroxaban concentrations based on low molecular weight heparin anti-Xa activity using nomograms: a useful tool in emergency clinical situations like thrombolysis in stroke**

Presenting author: Virginie Siguret – Hôpital Lariboisière AP-HP, Paris, France

STA®-Liquid-Anti-Xa (Stago®):

- LWMH-anti-Xa (IU/mL; Multi-HEP®-Stago® calibrator)
- DOAC-specific calibrator (ng/mL) with the DOAC

LMWH (IU/mL)	apixaban (ng/mL) [95% CI]	
< 0.1	20 [15;27]	
0.1	22 [17;29]	← Threshold of 30 ng/mL
0.2	25 [19;32]	
0.3	27 [21;36]	
0.4	30 [23;39]	
0.5	33 [25;43]	
0.6	36 [28;48]	← Threshold of 50 ng/mL
0.7	40 [31;53]	
0.8	44 [34;58]	
0.9	49 [37;64]	
1.0	54 [41;71]	
1.1	60 [45;78]	
1.2	66 [50;86]	
1.3	72 [55;95]	← Threshold of 100 ng/mL
1.4	80 [61;105]	
1.5	88 [67;116]	
1.6	97 [74;128]	
1.7	107 [82;141]	
1.8	118 [90;155]	
1.9	130 [99;171]	
2.0 and over	144. [109;189] and over	

Stago

Risk of recurrence after a first episode of unprovoked VTE

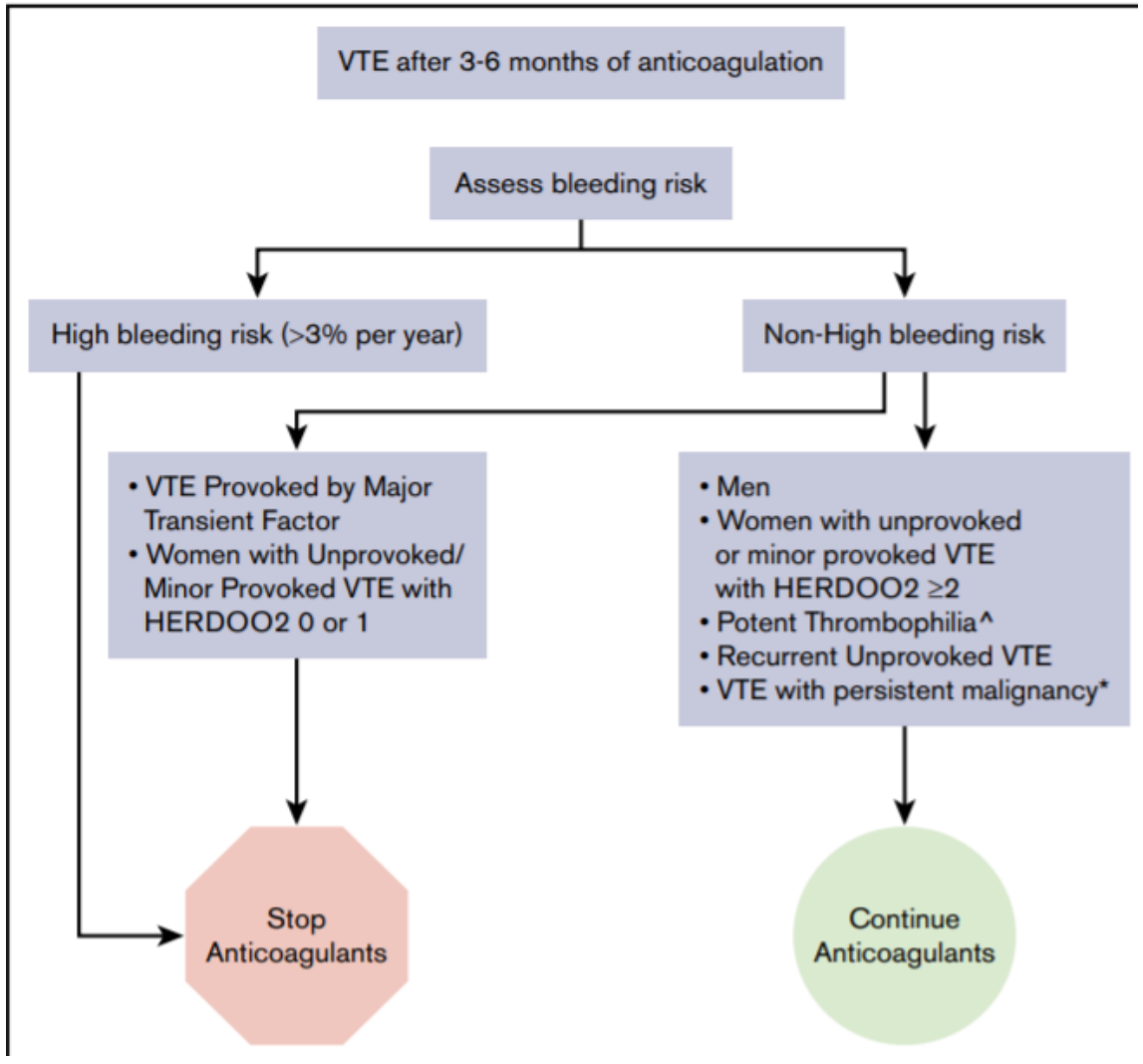
Risk factors for DVT recurrence

Proximal DVT location	Male sex	Persistence of residual vein thrombosis at ultrasound
Obesity	Non-zero blood group	High D-dimer values
Old age	Early PTS development	Role of inherited thrombophilia is controversial

Clinical prediction rules assessing risk of recurrent VTE after first episode of unprovoked VTE[71]

Score	Vienna prediction model	DASH score	HERDOO-2
Parameters	• D-dimer level at 3 weeks and 3, 9, 15, 24 months after stopping anticoagulation • Male sex • VTE location (Distal DVT, Proximal DVT, PE)	• Abnormal D-dimer 3–5 weeks after stopping anticoagulation • Male sex • Age<50 years • VTE not associated with oestrogen-progestatif therapy in women	• Abnormal D-dimer before stopping anticoagulation • Post thrombotic symptoms (hyperpigmentation, edema and redness) • Age ≥65 years • BMI ≥30
Validation study	Yes	Yes	Yes
Commentaries	Different nomograms are available to calculate risk of VTE recurrence at different time	Patients with low score (≤1) have an annual recurrence rate of 3.1%	It is applicable in women only. Women with low score (≤1) have an annual recurrence rate of 1.3%

Who should get long-term anticoagulant therapy for venous thromboembolism and with what?




THANK YOU