COAGULATION DISORDERS AND ANAESTHESIA

PRESENTERS:

DR UNNIKRISHNAN P

DR SUNEESH THILAK

CO-ORDINATOR

DR C MADHUSOODHANAN PILLAI

MODERATORS:

DR GEETHA N K

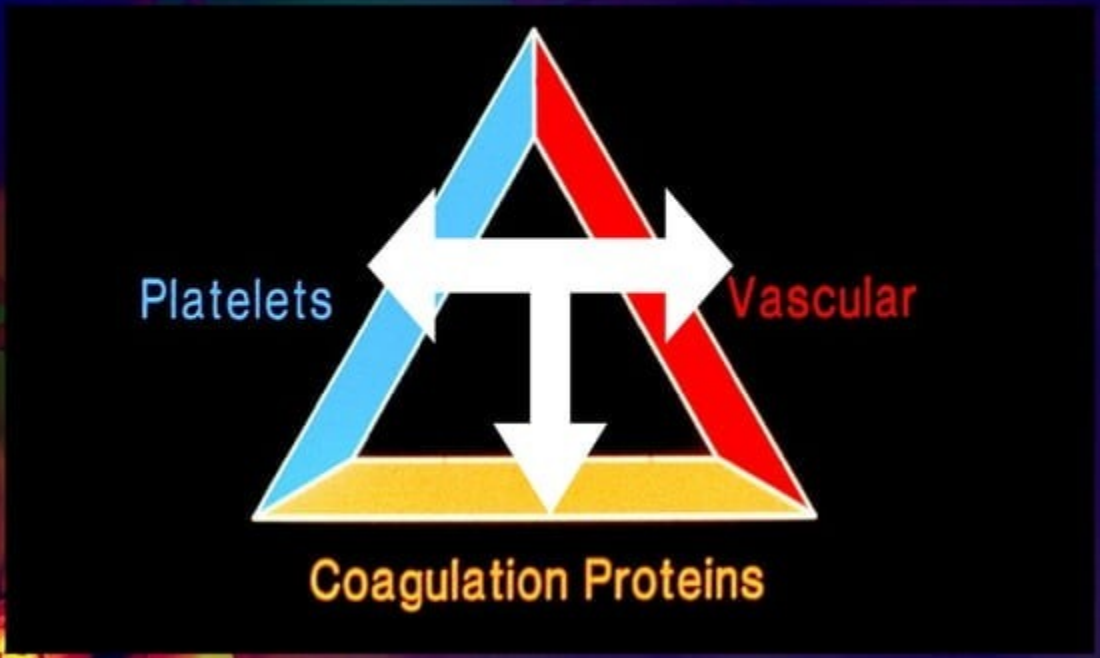
DR ASHA K S



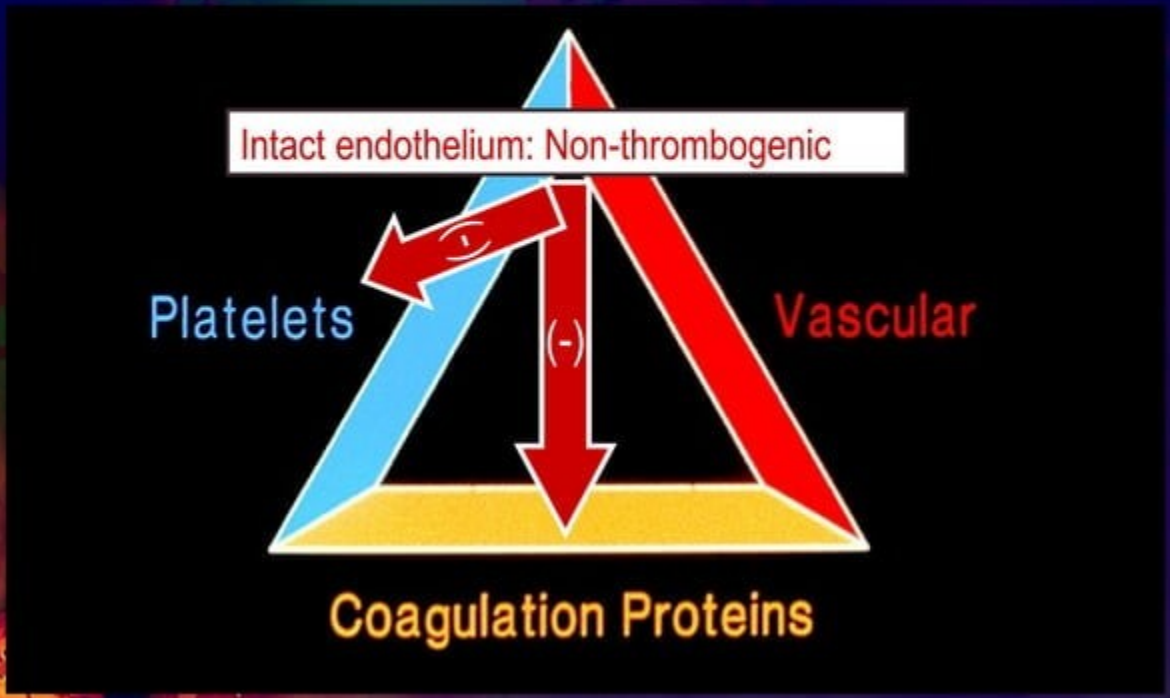
What is normal hemostasis?

- Clot at the spot….
- Not elsewhere…!

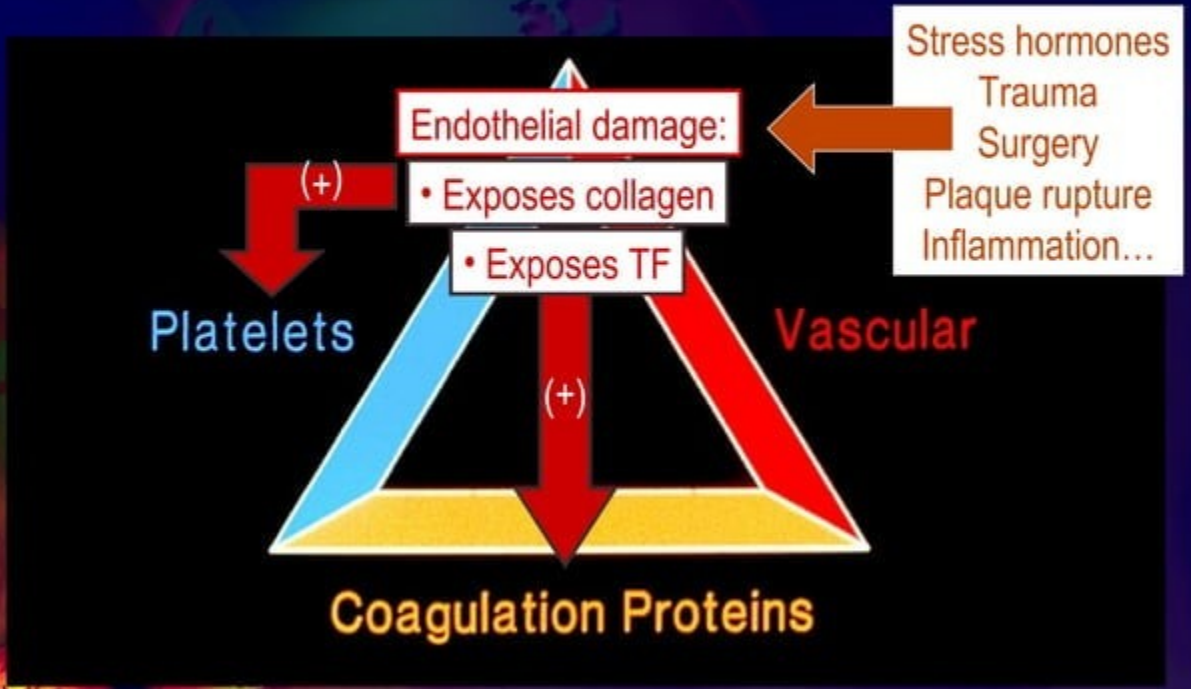
Components of hemostasis



Components: vascular



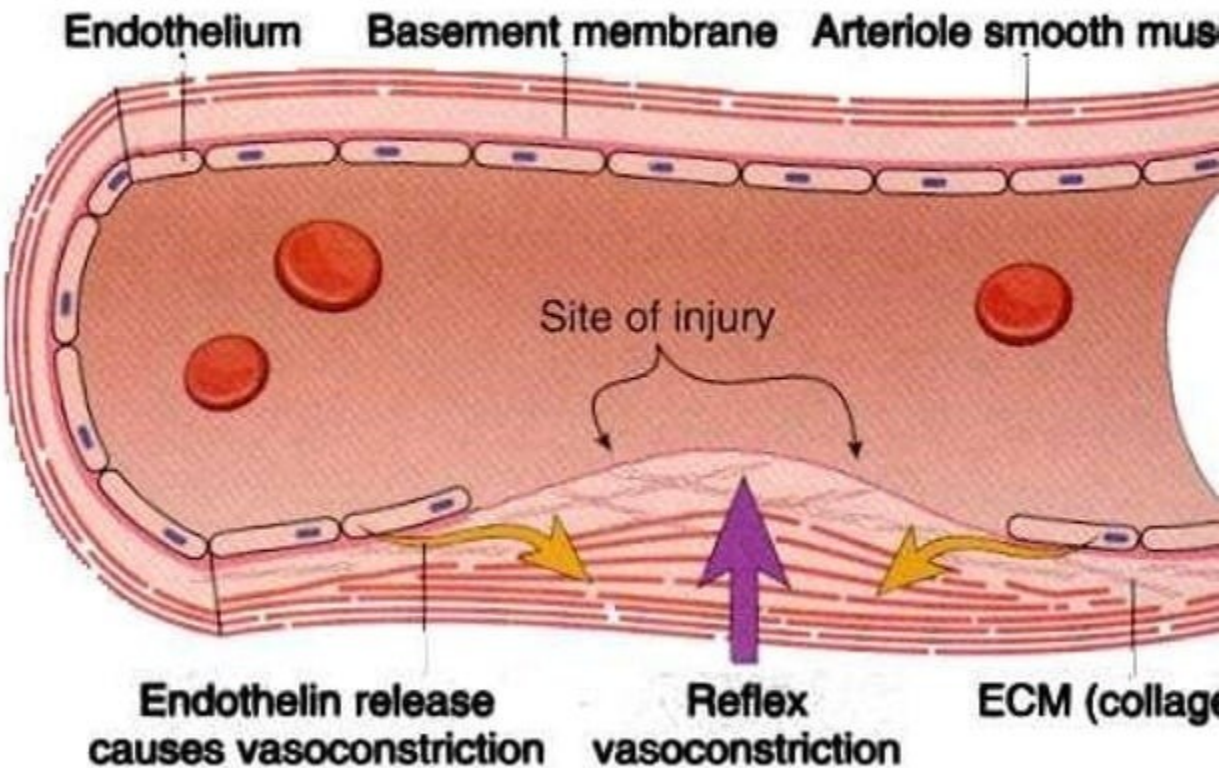
Components: vascular



The first event…..

- VASOSPASM
  - neurogenic
  - humoral
  - ……but can’t rely on it fully.

A. VASOCONSTRICTION



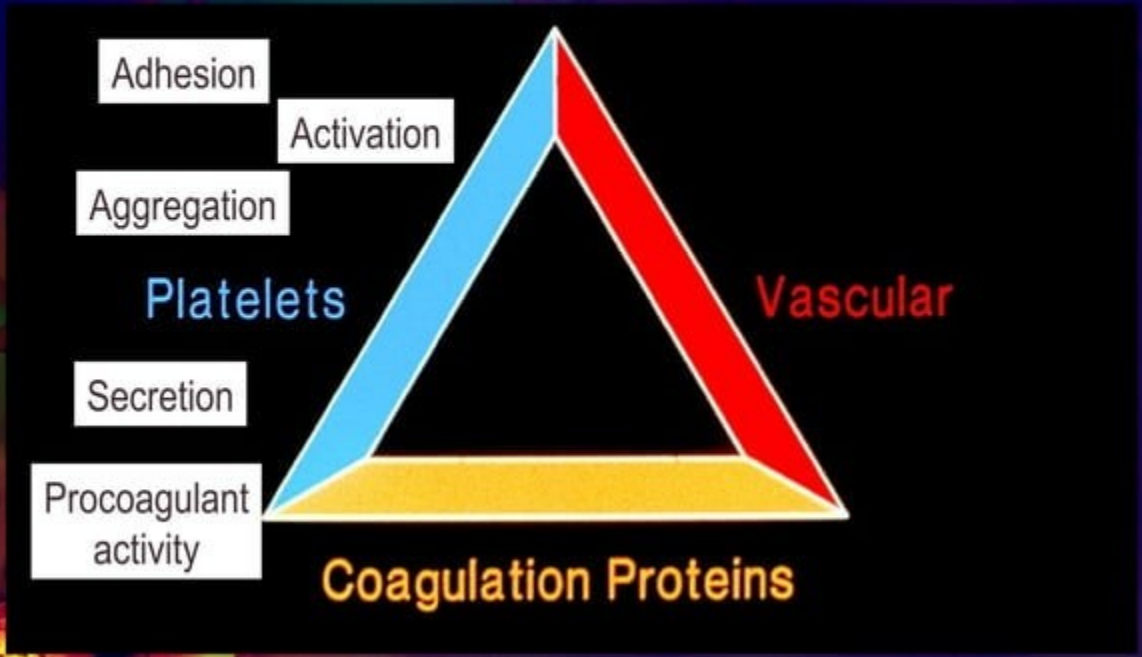
So the well equipped guy comes

PLATELETS

- They have receptors
- They provide a phospholipid surface…
- They contain granules

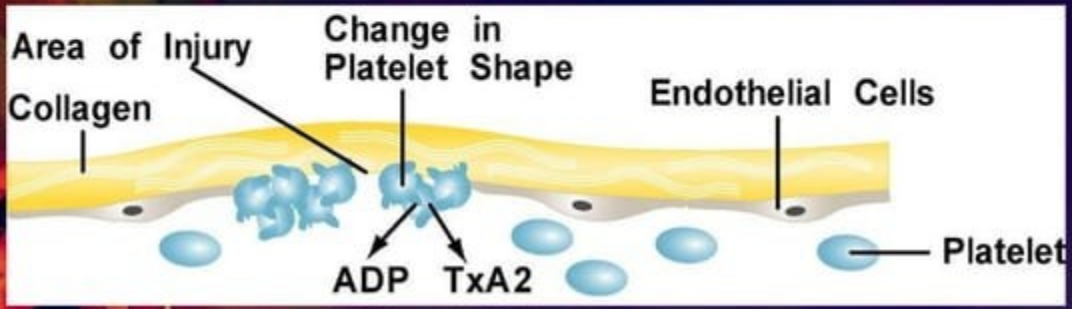
- **Dense** - serotonin , ADP , Ca++
- **Alpha** - coagulation factors , vWF , PDGF

Components: platelets



Endothelial damage:
Platelet plug formation

- Endothelial damage → exposure to collagen:
  - Promotes platelet adherence and activation
  - Activated platelets secrete ADP and TxA_2
    - ADP → promotes platelet recruitment
    - TxA_2 → promotes platelet aggregation
  - **Result**: formation of platelet plug (white clot)

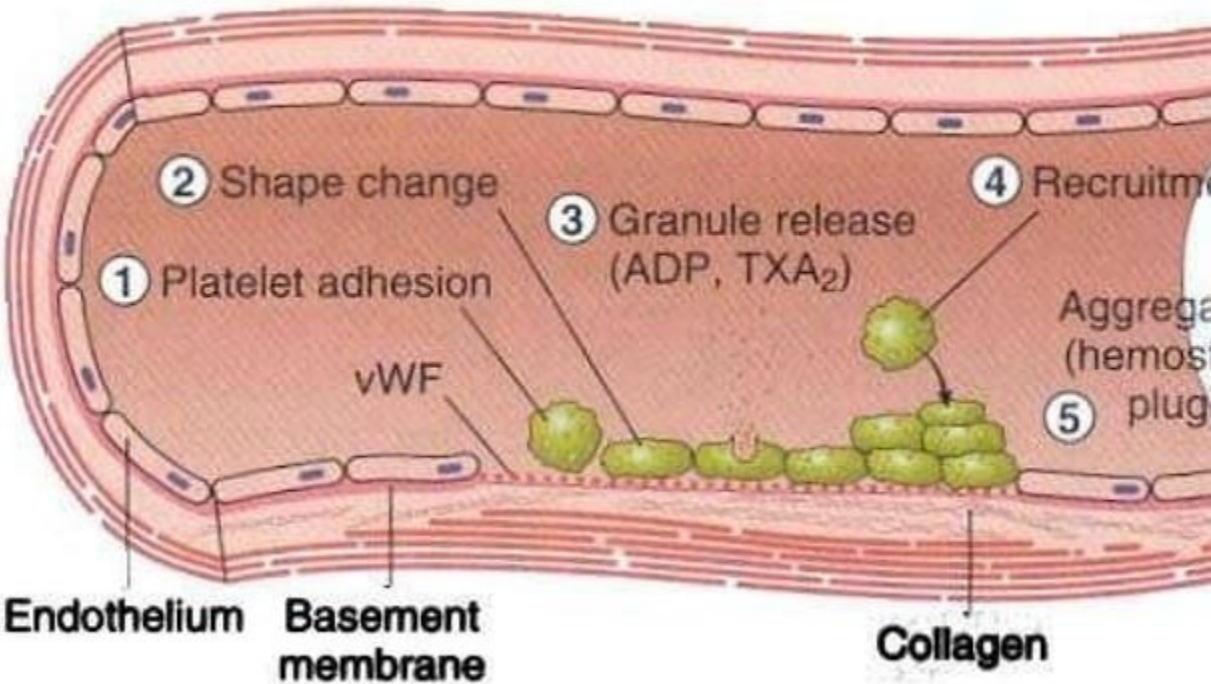


No one can hide the insults from them.....

- ADHESION – [vWF]
- SECRETION-[TxA2,ADP]
- AGGREGATION

Leads to ***PRIMARY HEMOSTASIS***

B. PRIMARY HEMOSTASIS



Leads to....

PRIMARY HEMOSTASIS

- Occurs within SECONDS

The *balancing act*

- PG E2
- PG I2
- NO .....

all these oppose TxA2 & ADP

In need of…. FIBRIN

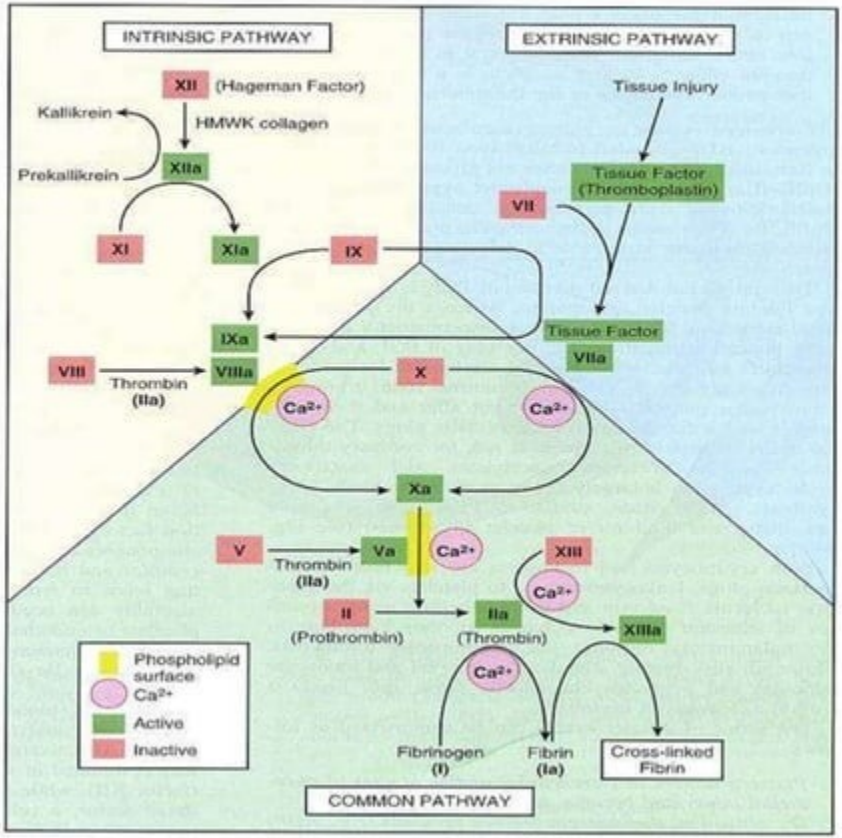
- The linking of platelets in the primary plug, by fibrin, converts it into a definitive clot. This requires the participation of the *Coagulation Cascade*. This process is known as ***SECONDARY HEMOSTASIS***

Prompt..... But finely controlled

- Precursor Zymogens → Active Enzyme
- Rapid response
- Finely regulated
  - Negative feedback loops
  - Decrease in substrate
  - Inhibitors
  - Quiescent endothelium

For example...

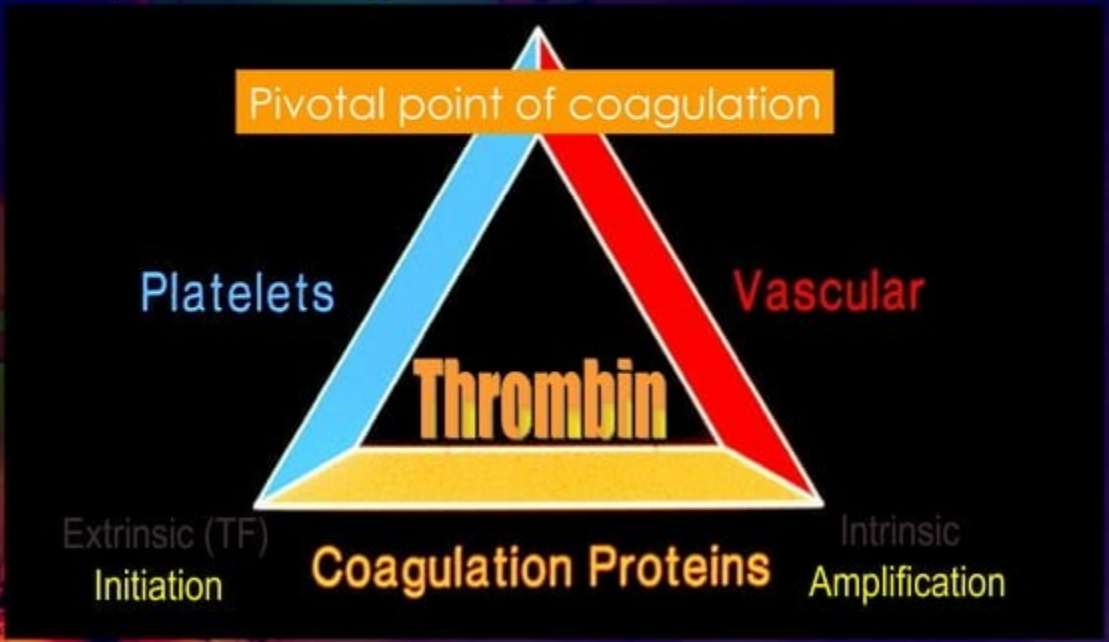




igure 5–8 ■

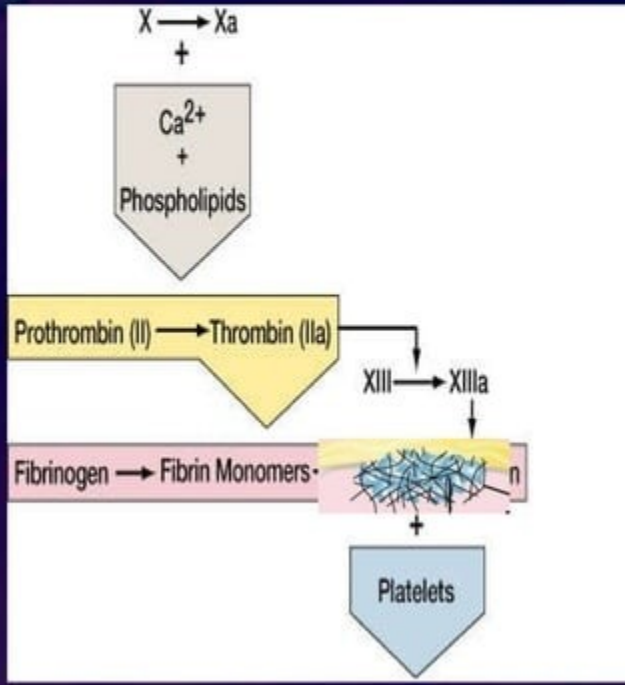
he coagulation cascade. Note the com-on link between the intrinsic and ex-insic pathways at the level of factor IX ctivation. Factors in red boxes represent active molecules; activated factors are dicated with a lower case "a" and a een box. PL, phospholipid surface; MWK, high-molecular-weight kinino-n. Not shown are the anticoagulant fibrinolytic pathways (see Figs. 5-6 and -11).

Components: coagulation pathways



Thrombin generation to fibrin-platelet clot formation

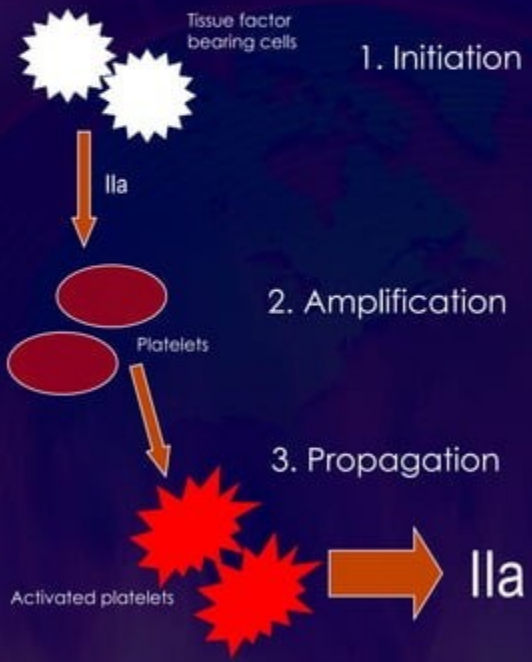
- Thrombin generation: the pivotal point of the coagulation process
- Thrombin actions:
  - Activates FXI, amplifying thrombin generation
  - Converts fibrinogen to fibrin
  - Activates FXIII
  - Activates platelets
- Result: RED CLOT



Cascade vs. cell-based model

Cell-based model

- Hemostasis represented as:
  - Occurring on two cell surfaces
    - Tissue factor bearing cells
    - Platelets
  - Three overlapping phases:
    - Initiation (TF bearing cells)
    - Amplification (platelets)
    - Propagation (platelets)
- The coagulation cascades are still important, but are cell-based
  - The extrinsic pathway works on the surface of the tissue factor bearing cells
  - The intrinsic pathway works on the surface of platelets
- Routine coagulation tests do not represent the cell-based model of hemostasis.



Cellular components

- *Platelets*
- *Endothelium*
- *Monocytes*
- *Erythrocytes*

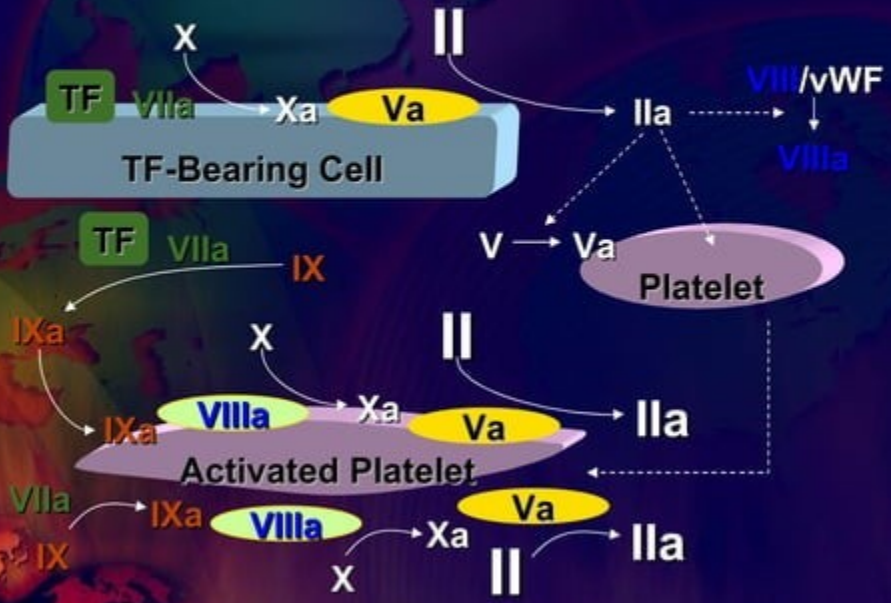
Molecular components

- *Coagulation factors* and *inhibitors*
- *Fibrinolytic factors* and *inhibitors*
- *Adhesive proteins*
- *Calcium*
- *Immunoglobulins*
- *PL PG Cytokines*

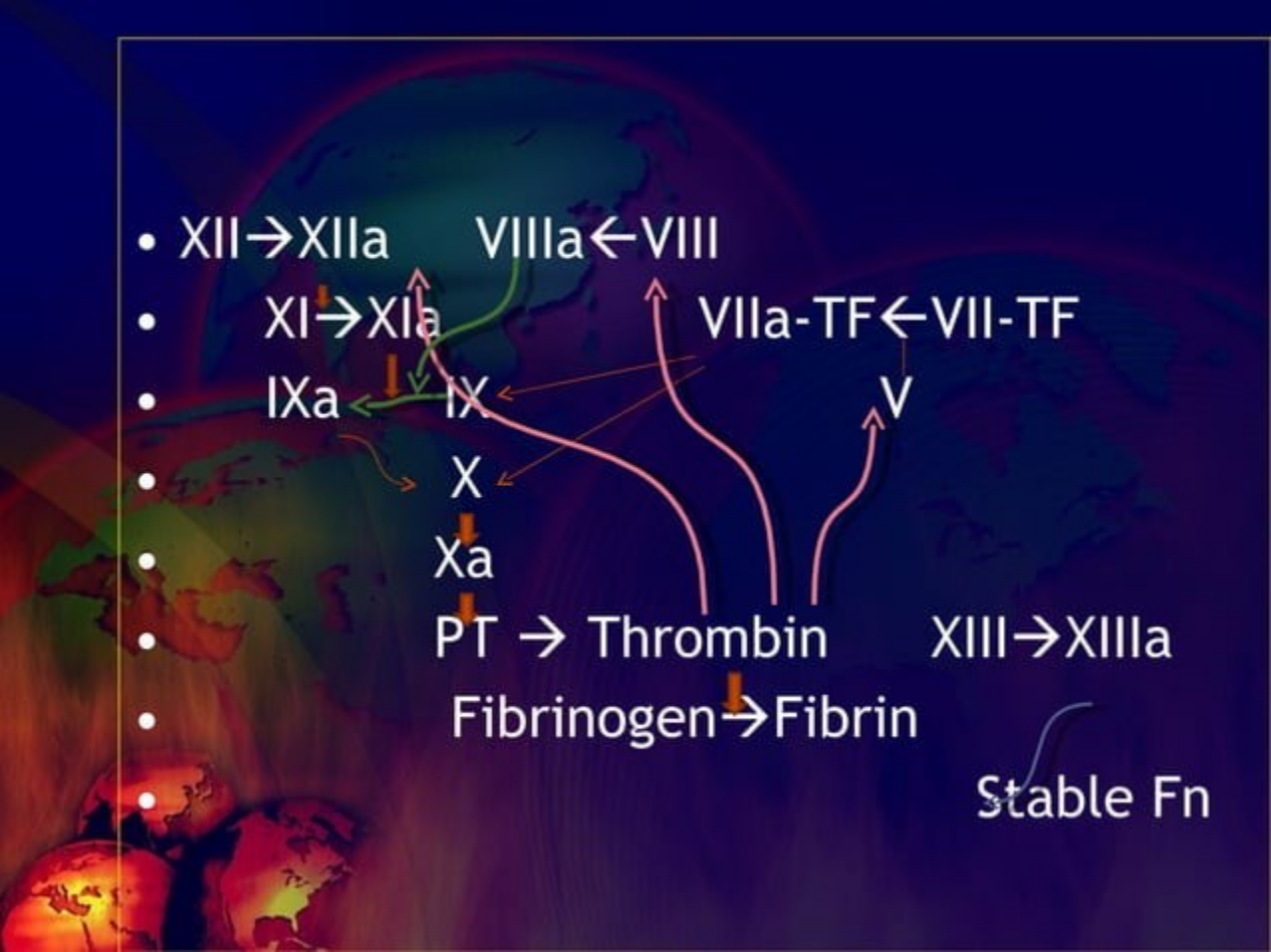
Current model of hemostasis

- initiation
- amplification
- propagation

Normal Hemostasis



Hoffman et al. *Blood Coagul Fibrinolysis* 1998;9(suppl 1):S61.


XII→XIIa
VIIIa←VIII
XI→XIa
VIIa-TF←VII-TF
IXa
IX
V
X
Xa
PT → Thrombin
XIII→XIIIa
Fibrinogen→Fibrin
Stable Fn

Endothelial damage:
Initiation of thrombin generation

Endothelial damage

↓

Exposure to tissue factor

↓

Initiation of extrinsic pathway

↓

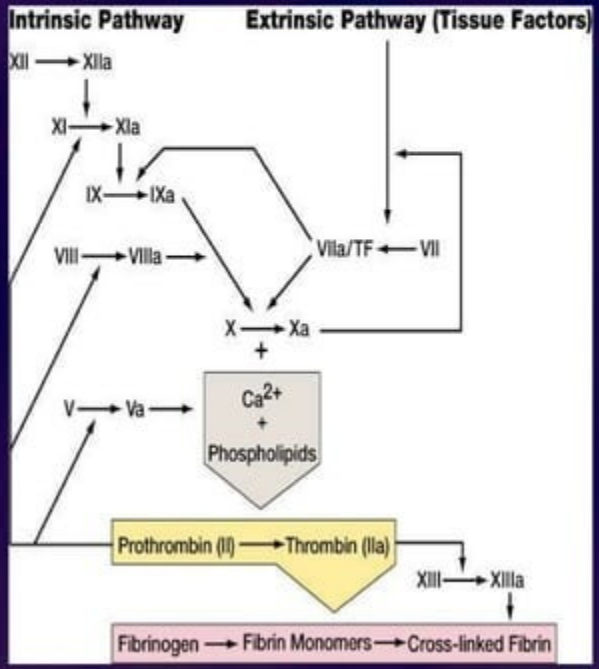
Initiate thrombin generation

↓

Activate FXI
(intrinsic pathway)

↓

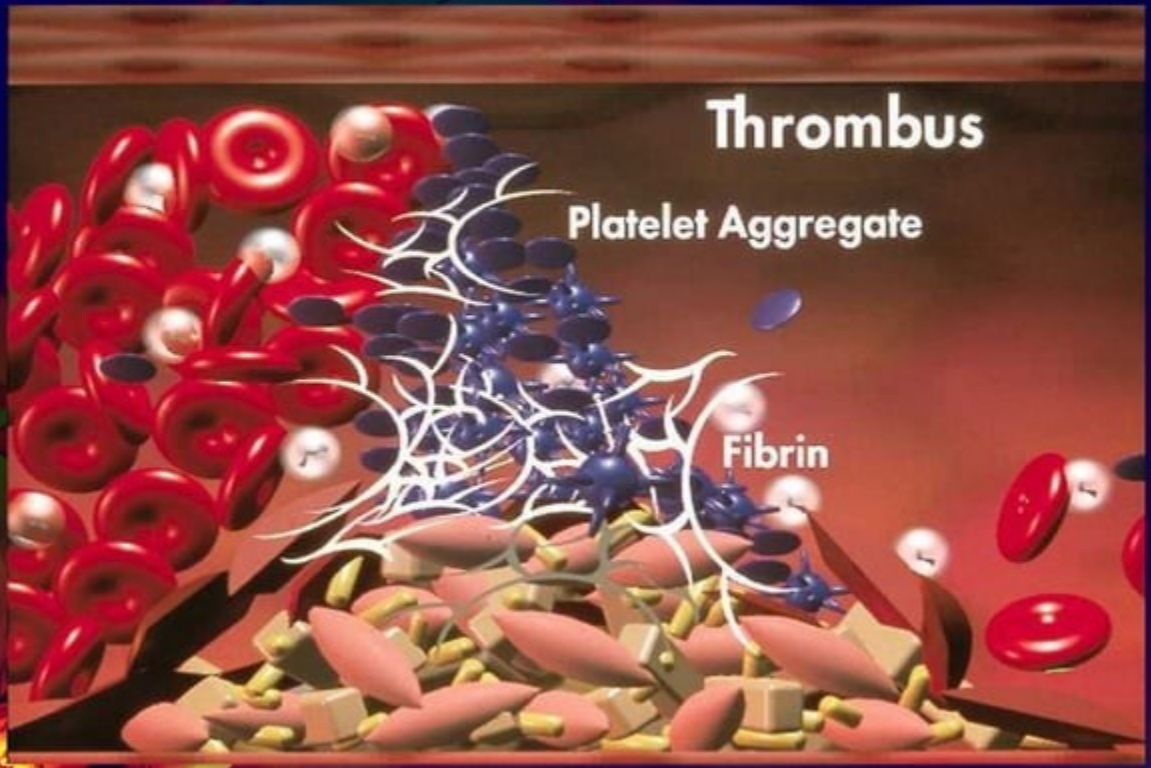
Amplify thrombin generation



Soldiers.....

I	FIBRINOGEN
II	PROTHROMBIN
III	THROMBOPLASTIN/TISSUE FACTOR
IV	CALCIUM
V	PROACCELERIN/LABILE FACTOR
VII	PROCONVERTIN/STABLE FACTOR
VIII	ANTIHAEMOPHILIC FACTOR A
IX	ANTIHAEMOPHILIC FACTOR B
X	STUARTPROWER FACTOR
XI	ANTIHAEMOPHILIC FACTOR C / PTA
XII	HAEGEMAN FACTOR / GLASS FACTOR
XIII	FIBRIN STABILIZING FACTOR
	PREKALLIKREIN / FLETCHER FACTOR
	KALLIEKREIN
	PLATELET PHOSPHOLIPID

...They work in concert to form a beautiful definitive clot!


Thrombus
Platelet Aggregate
Fibrin

Clot:
The end product of hemostasis



The rebels....

- ANTICLOTTING MECHANISMS

1 LIMITING COAGULATION CASCADE
2 FIBRINOLYTIC SYSTEM

Antithrombin iii

- II
- VII
- IX
- X
- XI
- XII

Protein C & Protein S

- VIIIa
- Va

TFPW-inhibitor

- Inhibits F VII-TF complex

Two more…

Protein C & Protein S

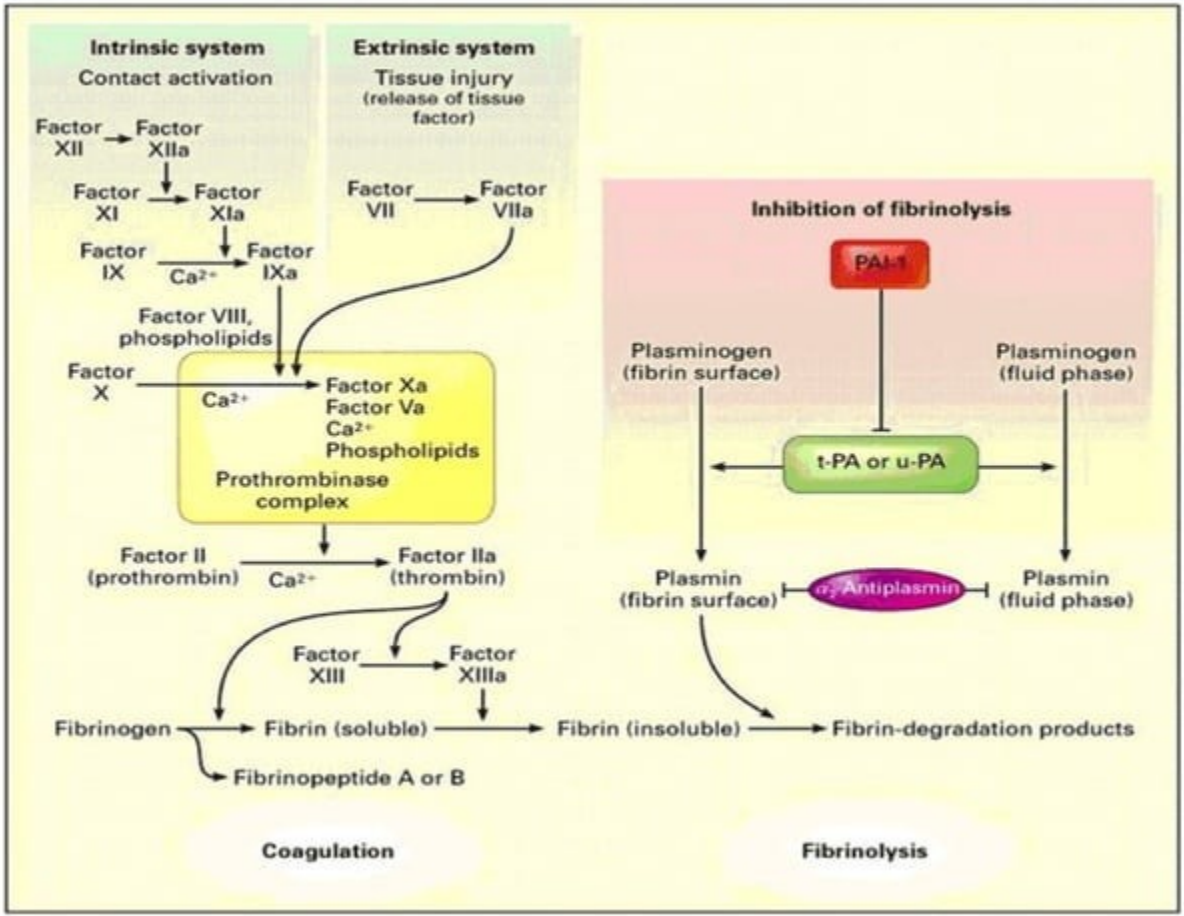
- VIIIa
- Va

TFPW- inhibitor

- Inhibits F VII-TF complex

Fibrinolysis

- Plasmin is the key component


Intrinsic system
Contact activation
Extrinsic system
Tissue injury
(release of tissue factor)
Factor XII → Factor XIIa
Factor XI → Factor XIa
Factor IX → Factor IXa
Ca2+
Factor VII → Factor VIIa
Factor VIII, phospholipids
Factor X → Factor Xa
Ca2+
Factor Va
Ca2+
Phospholipids
Prothrombinase complex
Factor II (prothrombin) → Factor IIa (thrombin)
Ca2+
Factor XIII → Factor XIIIa
Fibrinogen → Fibrin (soluble) → Fibrin (insoluble) → Fibrin-degradation products
Fibrinopeptide A or B
Coagulation
Inhibition of fibrinolysis
PAI-1
Plasminogen (fibrin surface)
Plasminogen (fluid phase)
t-PA or u-PA
Plasmin (fibrin surface)
α2-Antiplasmin
Plasmin (fluid phase)
Fibrinolysis

Serine Proteases

- XII
- XI
- X
- II
- VII

Cofactors

- VIII
- V
- III

Transglutaminase

XIII

VITAMIN-K dependent Factors



- Gamma carboxylation of these factors, after translation require Vit -k

Question hour in AAC

INFANCY
SURGERIES
FAMILY HISTORY
DRUGS
HORMONAL REPLACEMENT / OCP
HISTORY OF BLEEDING IN THE PAST

What to look for…?

PLATELET DISORDERS

- Superficial
- Comes immediately
- Local measures effective
- Petechiae, ecchymosis

COAGULATION DEFECTS

- Deep
  - s/c
  - Muscle
  - Joints
  - Retroperitoneal
- Delayed
- Unaffected by local measures
- haematomas

Surgery induces an increase in..

- *TISSUE FACTOR*
- *PLASMINOGEN ACTIVATOR INHIBITOR*
- *vWF*

..hyper coagulable

hypofibrinolytic state

These factors arise concern about the hemostasis

- Surgery
- Immobility
- Infection
- Ca
- Hypothermia
- Acidosis
- Volume expanders
- Extracorporeal circulation



MONITORING HEMOSTASIS

Lab tests

Feel.. There is no plan to stop

- Ohhh ..



Monitoring hemostasis
Cascade vs. cell-based model

Cascade model

- Common coagulation tests (PT, aPTT, platelet counts) do not reflect the roles of cells or contributions of local vascular and tissue conditions
  - Plasma-based assays *miss* the impact of platelets and platelet activation on thrombin generation.
  - Plasma-based assays use static endpoints (e.g. fibrin formation) - *miss* impact of altered thrombin generation on platelet function and clot structure.

Cell-based model

- Whole blood tests that measure the interaction of platelets, coagulation factors, and other cellular or plasma factors present during clot formation are required to examine hemostasis in the cell-based model.
- The TEG is one such test.

BLEEDING TIME

- Platelet function
- 2-9.5 minutes
- Limitations
- Technique very important
- Interferances
- Skin Vs other sites



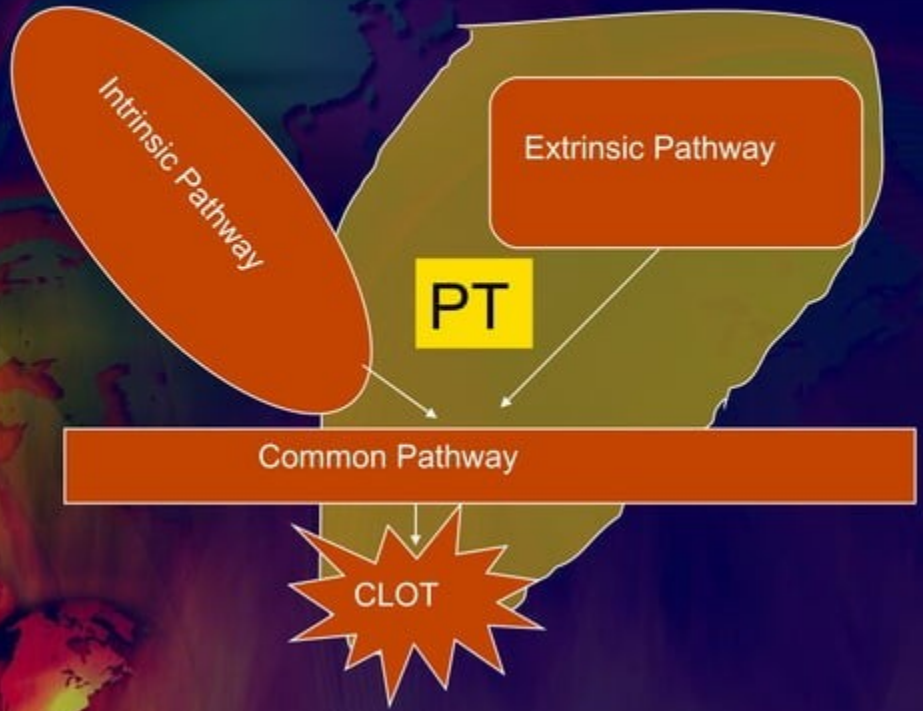
Platelet count

- 1.5 – 4.5 Lakhs/uL
- The grading of risk
- Idiot EDTA
- Coulter principle

Prothrombin Time

- 11.1-13.1 sec
- Extrinsic
- Recipe: plasma , Calcium and ThromboPlastin reagent

Prothrombin Time



What is INR?

- The aim is standardization of PT values
- ISI expresses the *sensitivity* of the PT reagent of a particular lab to that of WHO reagent.
- ***Patient PT / mean normal PT***
- ***[PT ratio]^ISI***



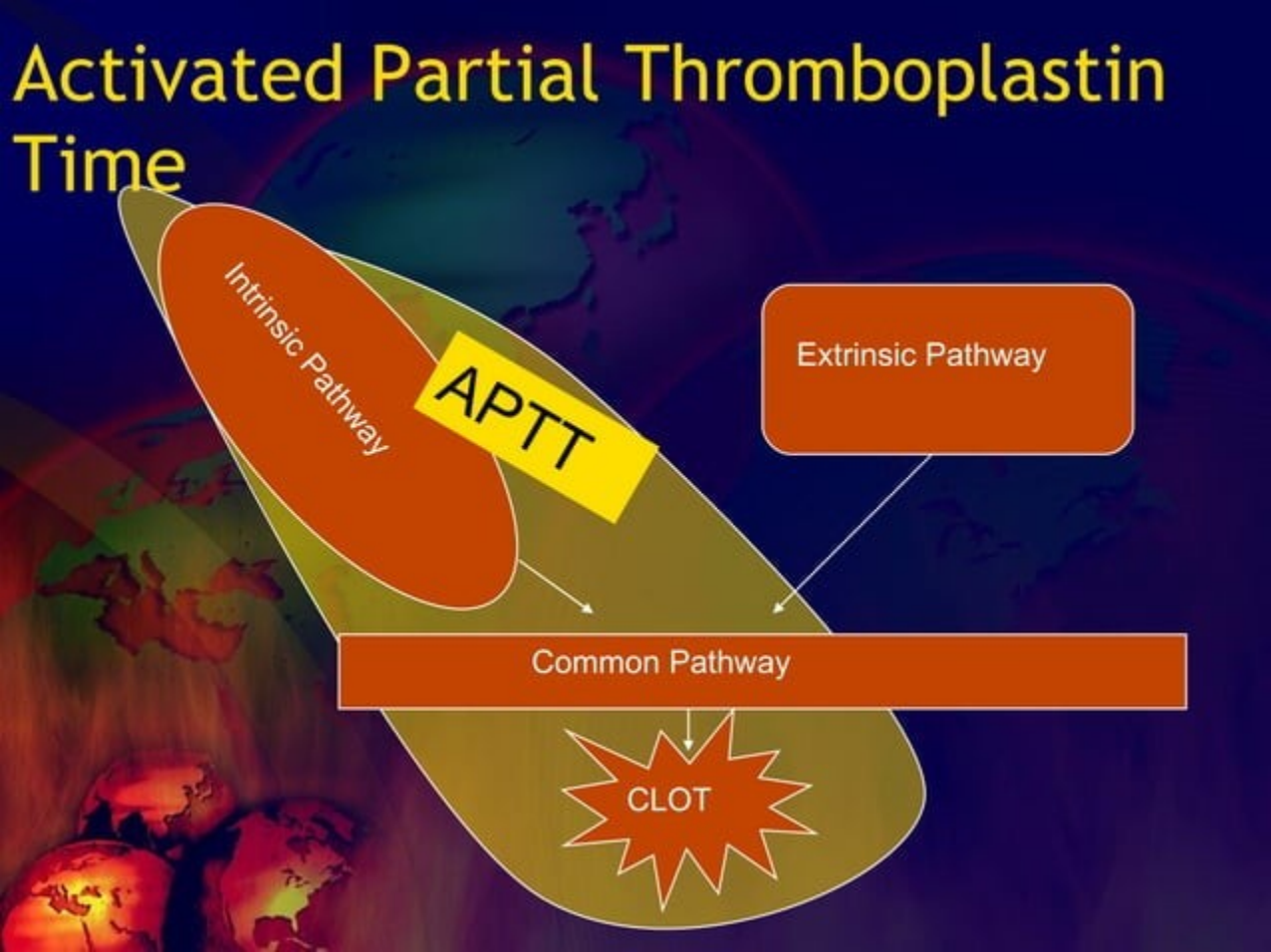
Prolonged??? Think of….

- V VII X deficiency
- Coumarin
- Vit k def
- Liver
- DIC
- Heparin?
- II/PT def
- hypofibrinogenemia

aPTT

- 22.1 – 35.1 sec
- Intrinsic
- V,VIII,IX,X,XI and XII
- ?- Heparin
  - Warfarin also
  - Liver disease
  - DIC

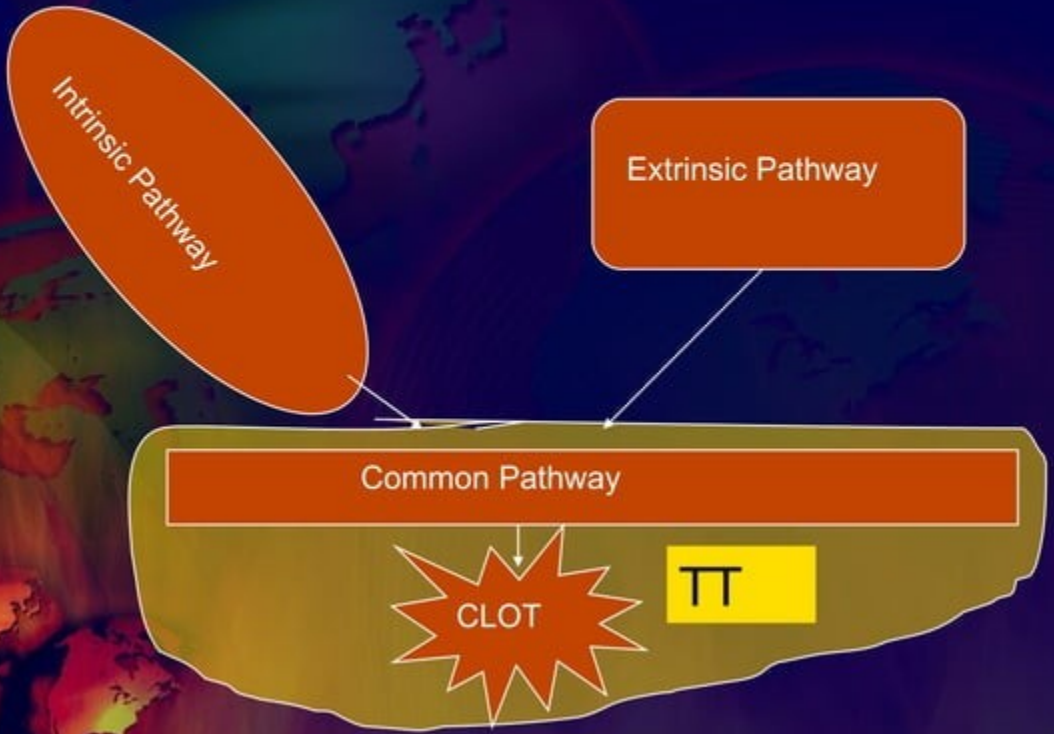
Activated Partial Thromboplastin Time



Thrombin Time

- Late…
- Circulating heparin levels
  - Hypofibrinogenemia
  - Increased FDP
  - 16 – 24 sec

Thrombin Time



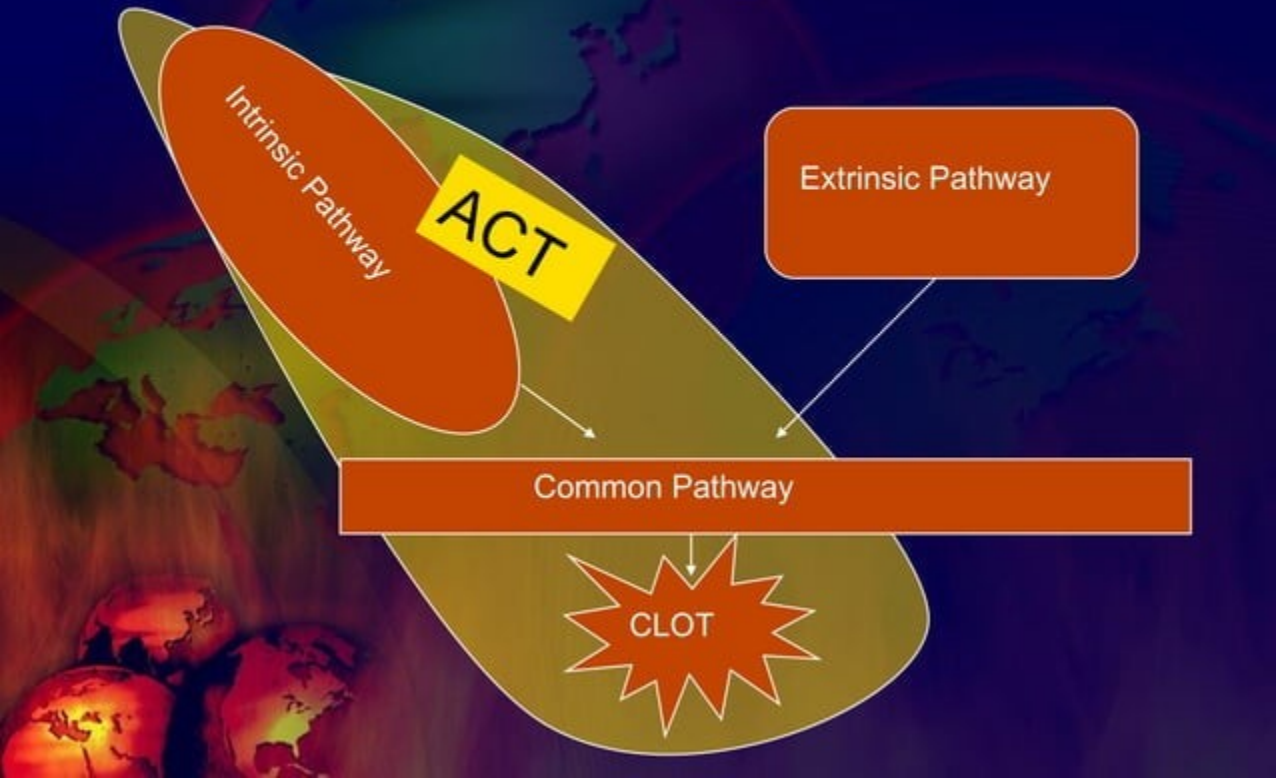
CLOTTABLE FIBRINOGEN CONCENTRATION

- 150-400MG/dL
- Modification of TT

Activated clotting time

- 70 – 180 secs
- Vascular surgeries
- C-P bypass
- HD
- Cardiac catheterisation
- Prolonged??

Activated Clotting Time



Thromboelastography

- Viscoelastic properties
- Blood product transfusion according to need.

The TEG® System

- CELITE activated 0.36ml blood
- Cuvette
- Piston
- 4.5*
- Cuvette oscillates , piston free
- Cuvette ⟷ Clot ⟷ Piston
- Plot of piston
- Stronger clot → THICK TEG
- Weaker clot → NARROW TEG

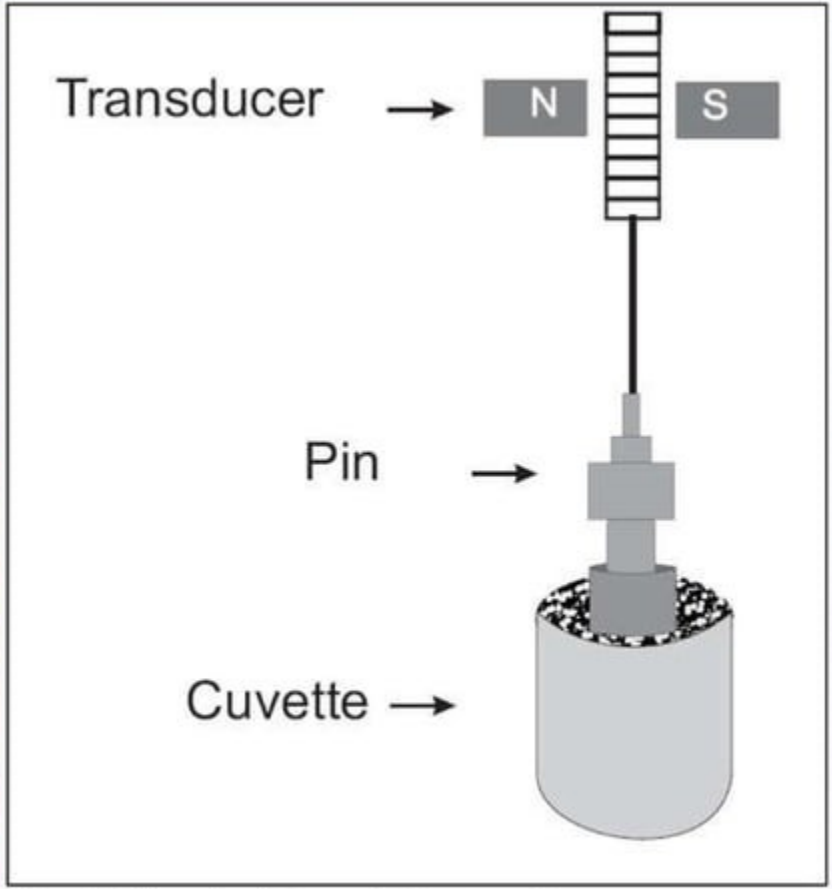
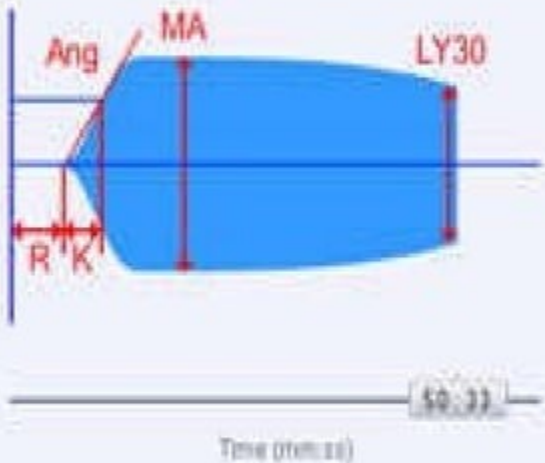


Figure 2 - Thromboelastograph Components

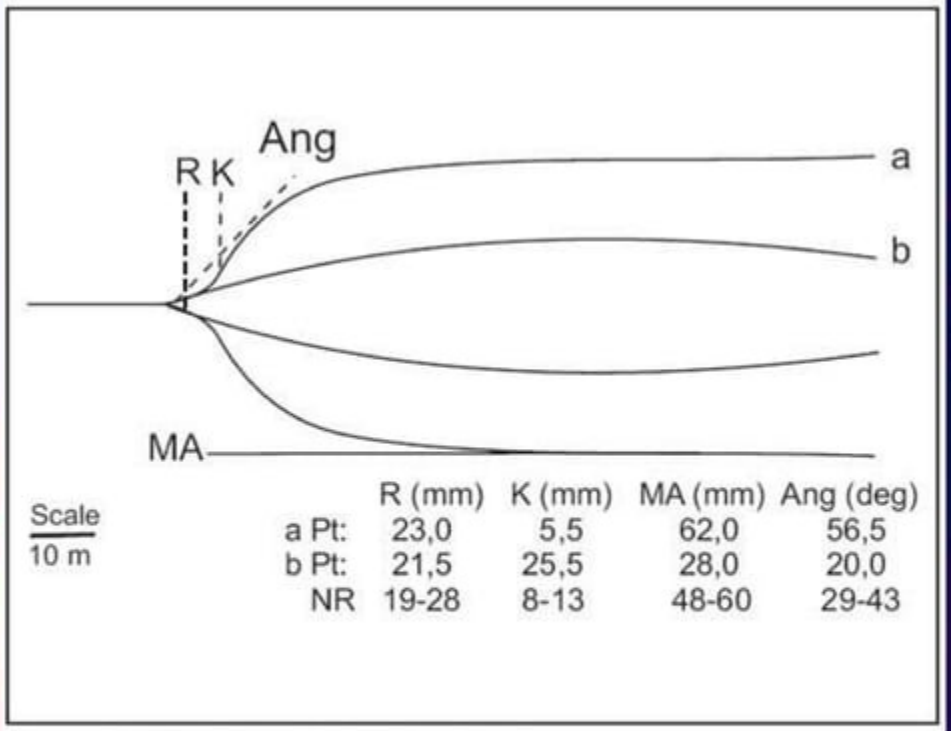
Thromboelastograph



Thromboelastogram



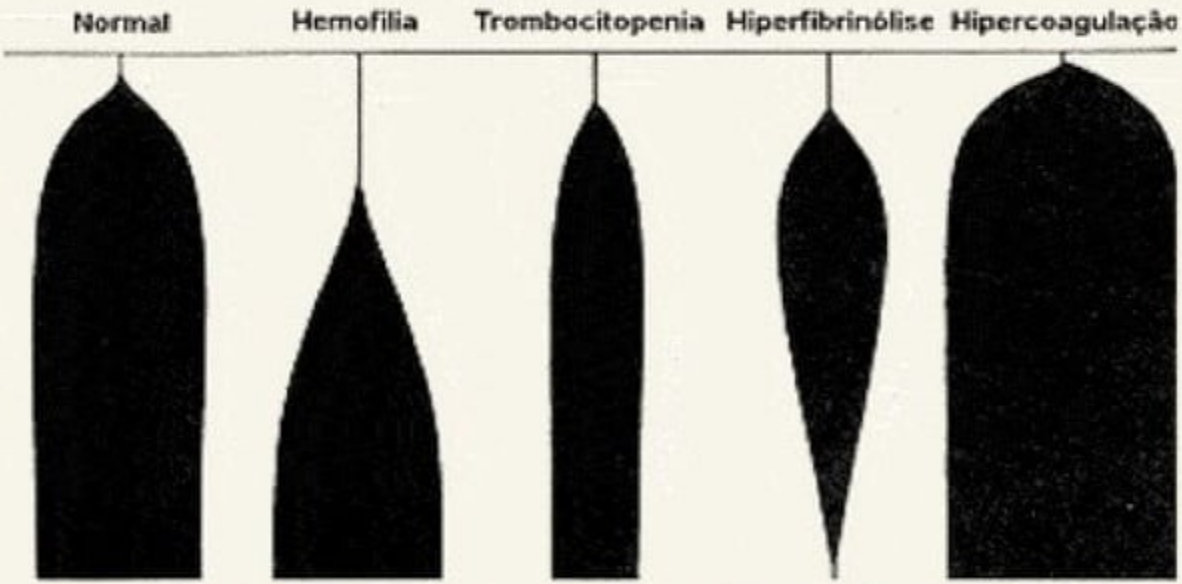
R(min)	K(min)	Ang(deg)	MA(mm)	LY30(%)
14	10	55	51	28



	R (mm)	K (mm)	MA (mm)	Ang (deg)
a Pt:	23,0	5,5	62,0	56,5
b Pt:	21,5	25,5	28,0	20,0
NR	19-28	8-13	48-60	29-43

Figure 3 - Two Combined Trhomboelastograms
Parameters values are shown below. Plot a: contains parameter marks with mild hypercoagulation state; plot b: shows severe fibrinolysis.
MA: maximum amplitude; Pt: patient; NR: normal range

Figura 1 - Padrões da TEG

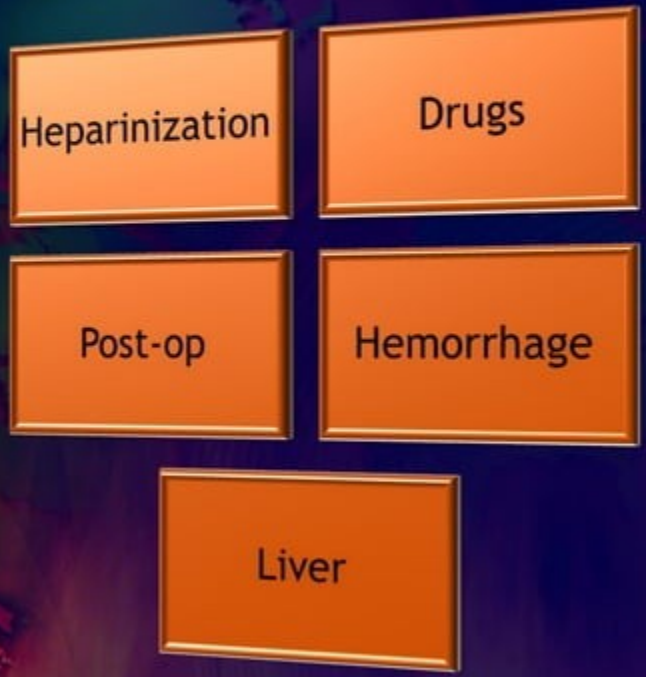


PLOT

- R = 6-8 mins
- K =10-12 mins
- Alpha angle = >50*
- MA = 50-70 mm
- A_{60}
- F = >300 mins



Application of TEG analysis



TEG analysis and clinical outcomes

- Detects hemorrhagic and prothrombotic states
- Reduces blood product usage, re-operations, hospital stays
- Provides guidance for proper therapy
- Monitors level of platelet inhibition
- Provides guidance for personalized drug therapies



Improves clinical outcomes

Lowers costs

????

The TEG can distinguish between surgical
bleeding and bleeding due to a coagulopathy.
True or False?

Next

Platelet function analyzers

- PFA-100
- MEDTRONIC HEMOSTATUS

Still not over…?$#

- Hmmm…





DISORDERS OF COAGULATION

INHERITED DISORDERS



DISEASE OF KINGS

….

What is Hemophilia?

- Hemophilia is an inherited bleeding disorder in which there is a deficiency or lack of factor VIII (hemophilia A) or factor IX (hemophilia B)

Degrees of Severity of Hemophilia

- Normal factor VIII or IX level = 50-150%
- Mild hemophilia
  - factor VIII or IX level = 6-50%
- Moderate hemophilia
  - factor VIII or IX level = 1-5%
- Severe hemophilia
  - factor VIII or IX level = <1%

CLINICAL FEATURES

- AURA... Believe them
- Pain F/B swelling
- Others

Types of Bleeds

- Joint bleeding - hemarthrosis
- Muscle hemorrhage
- Soft tissue
- Life threatening-bleeding
- Other

Life-Threatening Bleeding

- Head / Intracranial
  - Nausea, vomiting, headache, drowsiness, confusion, visual changes, loss of consciousness
- Neck and Throat
  - Pain, swelling, difficulty breathing/swallowing
- Abdominal / GI
  - Pain, tenderness, swelling, blood in the stools
- Iliopsoas Muscle
  - Back pain, abdominal pain, thigh tingling/numbness, decreased hip range of motion

Characteristics

Bleeding is...

- Delayed
- Unstoppable if untreated

Pressure effects

- Muscle ,Nerves
- Veins , 'Cancers'

Others include

- Mouth , gums
- Hematuria

Age of presentation....

SEVERE	MODERATE	MILD
• Cephal-hematoma • Circumcision	• Walk • Crawl	• Delayed • Young adults

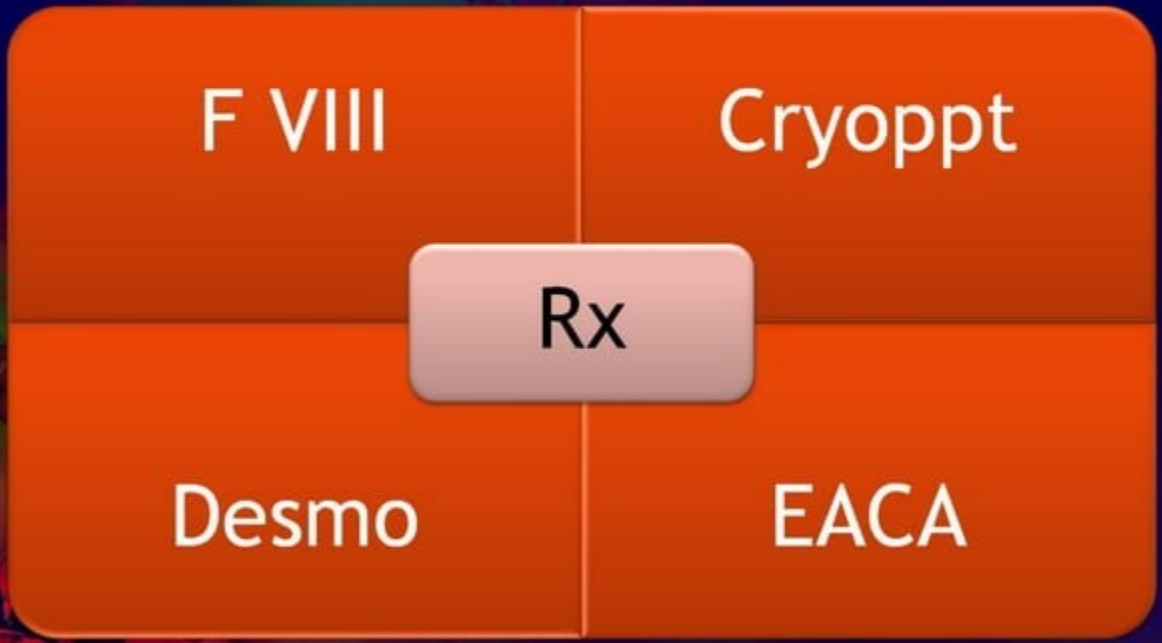
Do we bother about carriers?



Investigations…

- *Prolonged PTT with normal Platelet count, BT and PT supports the diagnosis*
- *F VIII assay confirms the diagnosis and allows differentiation from…..?*

Our weapons....



8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8

- T ½ : 8-12h
- VIALS: 250-2000 units
- Each unit of FVIII/Kg infused:2% increase
- “levels should be restored to 40% of normal before surgery.. So initial dose..
- Wt in Kg X desired level X 0.5
- E.g. 50 kg x 40% x 0.5 = 1000 U
- 3 ml/min adults, 100 u/min child

Infusion rate



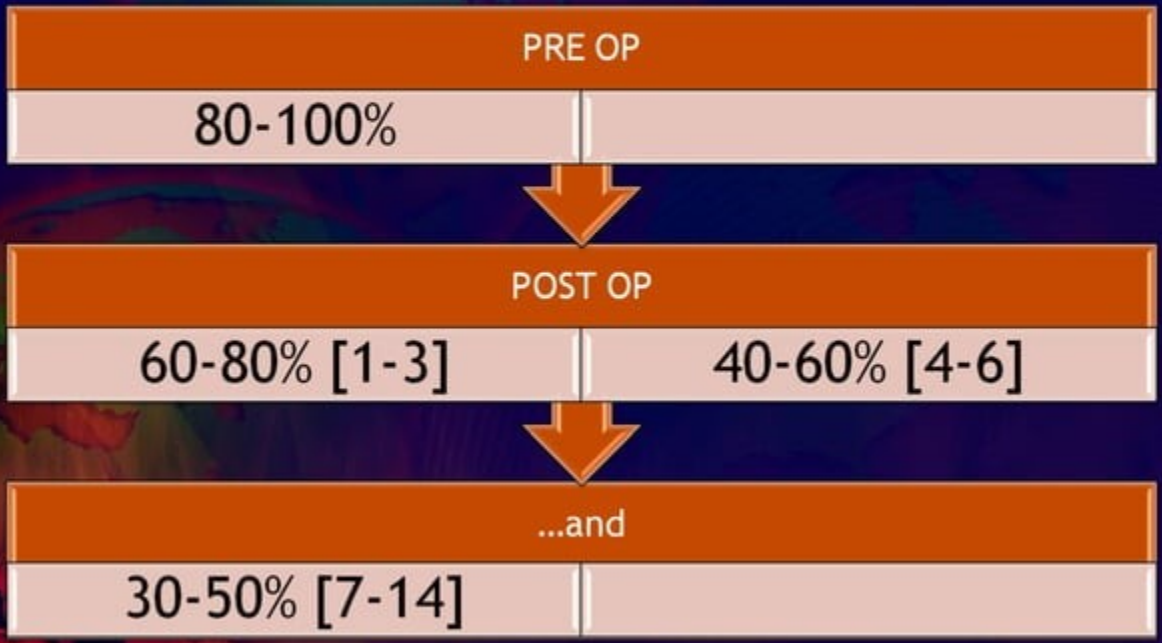
In another way…

1 U / Kg→0.02U/mL

Minor:0.3 U/mL

Major:0.5 U/mL

Perioperative needs..



Recommendations

SOFT TISUE BLEED- 15 TO 20 %

HEMARTHROSIS/RETROPERITONEAL-25-50% x72h

MAJOR Sx/ LIFE THREATENING BLEED- 50% x2 wk

B4 Sx .....

- Do a FVIII assay 48 hrs b4
- Screening for FVII inhibitors

INHIBITORS

TYPE 1

- FVIII → ABs ↑
- Porcine FVIII
  PT Complex Conc

TYPE 2

- FVIII dont ↑ ABs
- Rx :higher dose

Prophylaxis

Concept: <1%

25-40 U/Kg 3 times a week [2 for H-B]

B4 high risk activity

Expensive

Prevent jt bleed

Preserve function

Specialty posting!

- ORTHO(major): 3wks
- DENTAL(major): 2-3 days
- DENTAL(minor): FVIII SD+EACA 4-6g QID x3-4days

These should be kept in mind..



Iron deficiency anemia ????

- The money drains in to the hands of bank officials itself…!
- ….and what about prophylaxis?

Precautions

- Avoid Aspirin and others...
- Bleeding is delayed
- Stick to early Rx

Cryoprecipitate / FFP

SPECIFICATIONS-Cryoprecipitate	
60-100u in a vol of 30-40 ml	Miller:20U/ml

From virus neg donors	
easy	Risk of bleeding

FFP	
1U/mL	Viral reduction

Desmopressin

About DDAVP

- 0.3ug/kg
- Dil in saline
- 20-30 mins
- Not in severe & H-B and
- ?PREG
- <2YRS
- ??elderly

ADVANTAGES

- Low cost
- No dis..

COMPLICATIONS

- Flushing
- Tachy
- Tremor
- Na
- Thrombosis

TA & EACA

TA

- Plasminogen→Plasmin
- 3-4 g in divided dose
- C/I Tx Sx, Hematuria ,PT complex

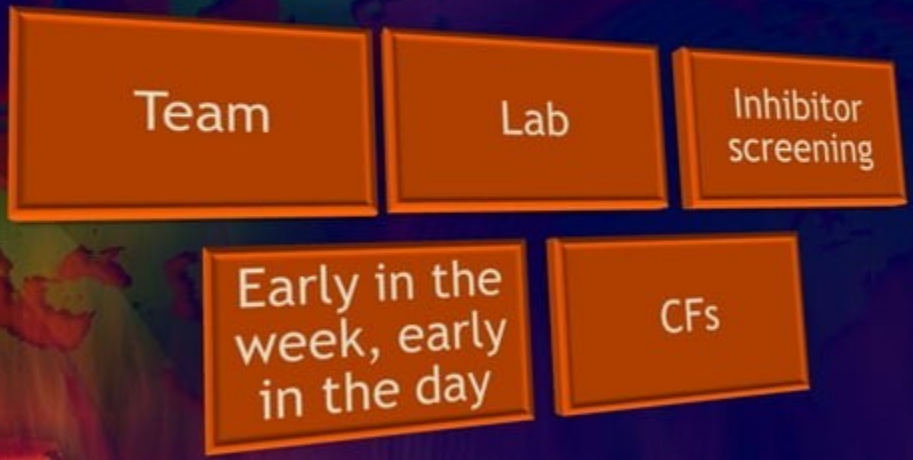
EACA

- 5g stat 1g every hr x 8hrs
- DIC, Myopathy

Anesthetic Implications

- Oral premedication, no im
- Vascular access… does not
- Extremities, pressure points ,joints
- Bleeding -oropharynx-ETT manipulation
- No nasal intubation
- Anticipate liver dysfunction
- Neuraxial if….
- Topical pressure
- AIDS

SURGERY/ MINOR PROCEDURE



Good news....



1. Heating
2. Absorbing & eluting techniques
3. Recomb FVIII

Hemophilia B

- ✓FACTOR IX DEFICIENCY
- ✓MIMICS HEMOPHILIA-A CLINICALLY
- ✓HENCE LAB DIAGNOSIS IS CRITICAL
  - ✓FFP
  - ✓ PLASMA FRACTION^*PROTHROMBIN COMPLEX*
- ✓Thrombosis and embolism



Prolonged aPTT ⬇F IX + normal F VIII

=....**HEMOPHILIA B**

Rx



F IX/FFP/others



FIX

- Each→1%
- 18-24hrs



FIX

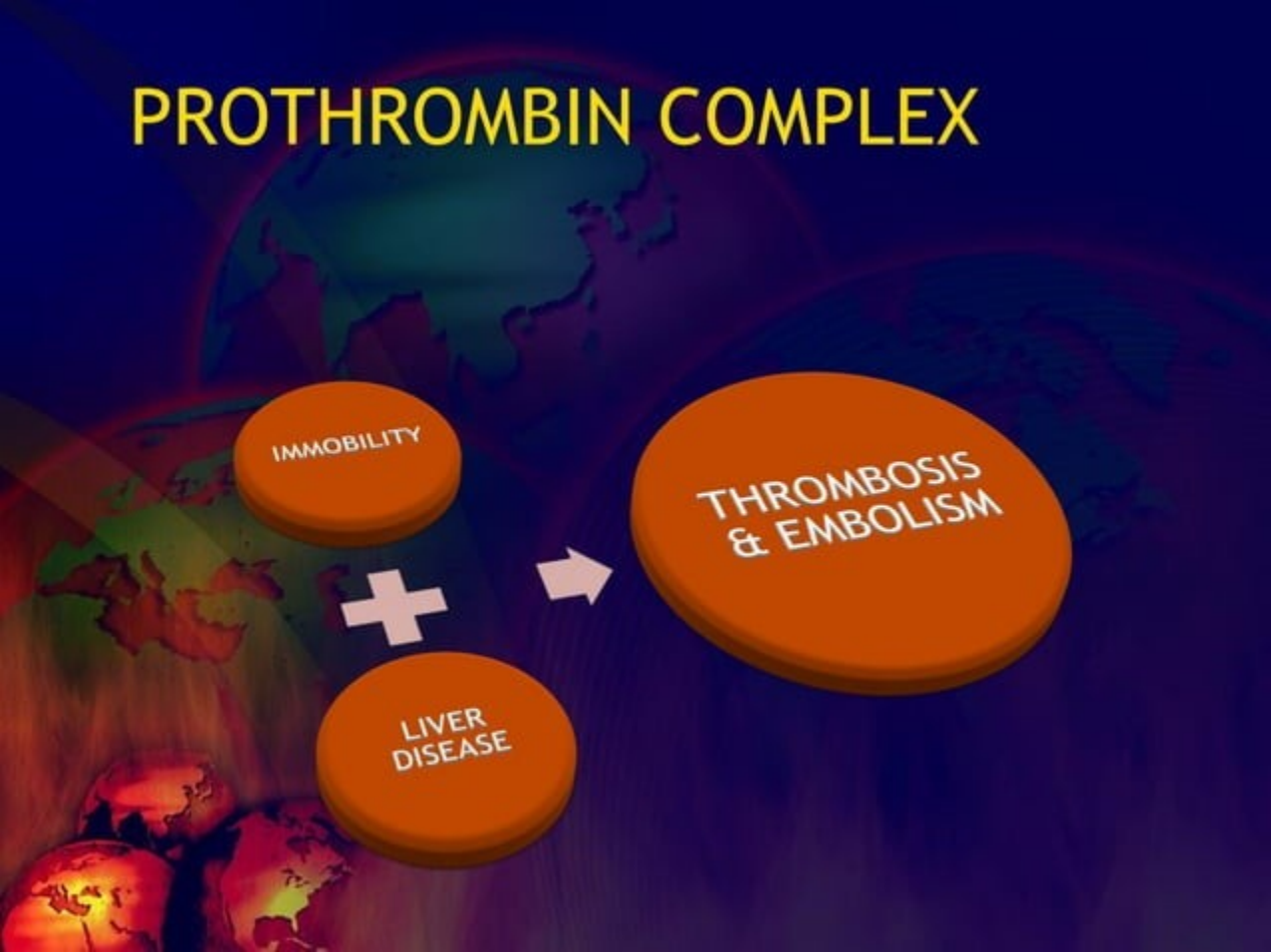
- Body weight in Kg x desired level [x 0.8 if ReFIX]
- .



others

- FFP 15-20ml/kg starting....
- Antifibrinolytic

PROTHROMBIN COMPLEX



Any factor concentrate for exhausted audience..???



Who am I ?



- Which is the most common inherited bleeding disorder?
- Bleeding only after surgery and minor trauma only….
- BT prolonged + reduced plasma F VIII activity

vWD

1/100-500
10mg/L
AUTOSOMAL DOMINANT
Affect PLATELET adhesion

I mild-moderate decrease

IIa Quantity N, Quality Abn
IIb inappropriate PLT binding

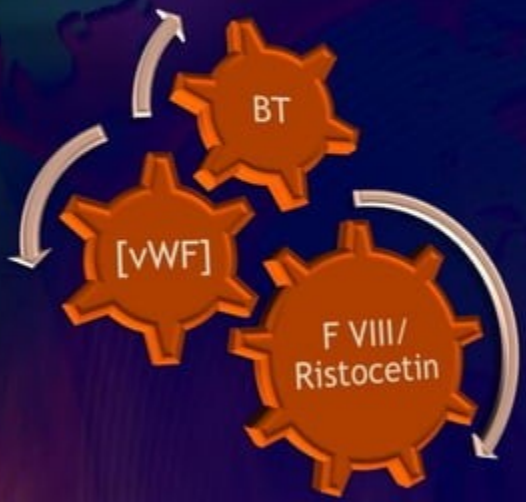
III vWF _ severe FVIII=H mild

Missing you... vWF

- Platelet adhesion
- Carrier of F VII



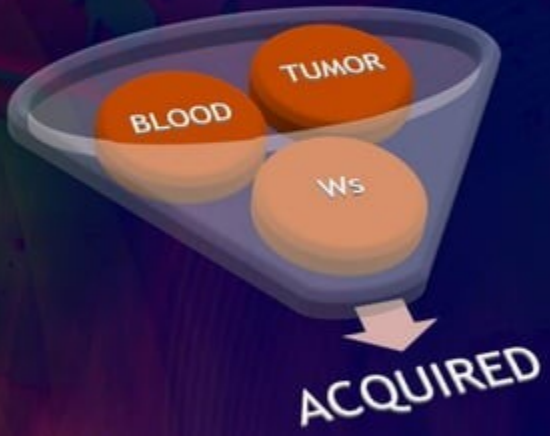
Lab report..



Treatment

- F VIII CONCENTRATE / CRYO PPT
  - BD x 2-3 days
- OCP for….
- DESMOPRESSIN
  - Especially type I
  - Test for response
  - Tachyphylaxis if>48 hrs→ so monitor
  - Worsen type IIa

And....



A FEW STRANGERS

AFIBRINOGENEMIA

- Umb stump
- Minor → severe
- All tests..
- Rx : Fibn / cryoppt

F V def

- mm bleed
- FFP V: 5-20%

F XII def

- Bypassed!
- PTT>100!
- Terribly unfit?
- Thrombo


F XIII
• Frail fibrin!
• All WNL
• Umb stump
• CNS
• FFP/CPPT
GREY PLT
• Alpha granules
• Severe bleed
Pre K def
• aPTT ,CT
• Associations

Hereditary Haemorrhagic Telengiectasia

- Telengiectasia + A-V-F + Aneurysm-CVS
- Paradoxical air embolism
- Arterial hypoxemia
- Epistaxis
- ANAESTHESIA Rx
  - Bleed oropharynx, trachea, oesophagus
  - ? Epidural ?

Hereditary thrombocytopenia

May Hegglin Anomaly

- No platelet dysfunction

Fechtner Syndrome

- Bruising +Renal +Hearing loss

Can our routine tests detect a fibrinolytic defect?

- Bleeding tendency+++
- But all tests normal
- E.g. Alpha 2 antiplasmin deficiency
- Rx - EACA

HYPERCOAGULABLE STATES

- PRO-PROCOAGULANT state!!
- Focal
- Don’t predispose to arterial thrombus

What's it?

- Useless Heparin!!! Govt supply??
- Very energetic F II & F V!
- DIC ,Liver disease, heparin Rx
- OCPs ? Hmm.. No.
- Rx :AT III [A/C] Oral Anti coagulants [C/C]

Protein C Deficiency

- F V , F VIII
- Acquired def seen in…
- Life threatening complications
- Be suspicious..
- Regional Vs GA , oral anticoagulants

Antiphospholipid antibody syndrome

Ven/Art thrombosis

Thrombocytopenia

Fetal loss

IHD

Mitral VD

Stroke-Visual..

Strategy ??

- Anesthesia ?
- Thrombosis- prophylaxis
- Cardiac Sx


THANK YOU



No thanks

.....?%#



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