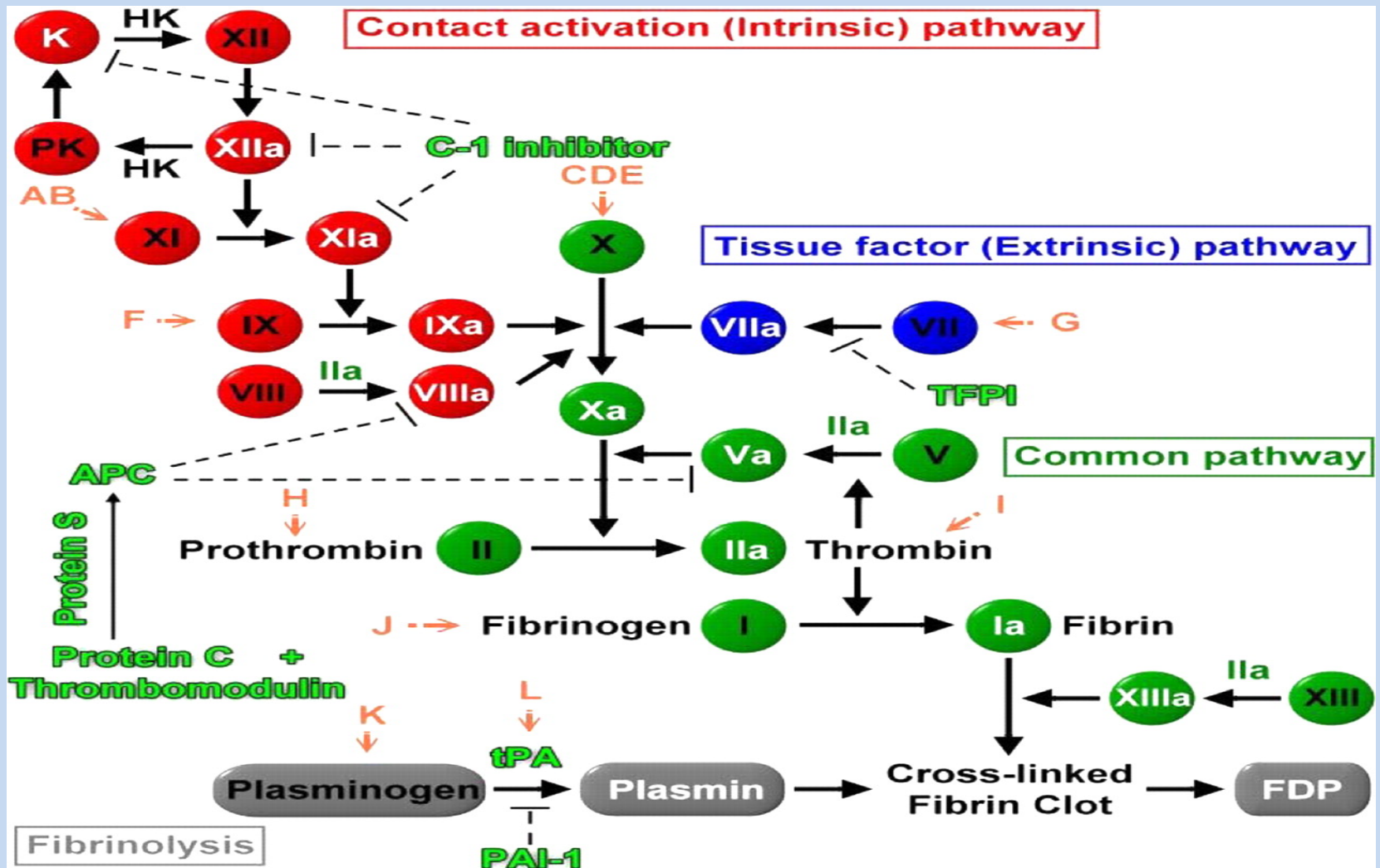


Concepts
in
Coagulation
with
Practical Applications

Lance Williams, MD
Assistant Professor
University of Alabama at Birmingham

I have no relevant financial disclosures associated with this presentation

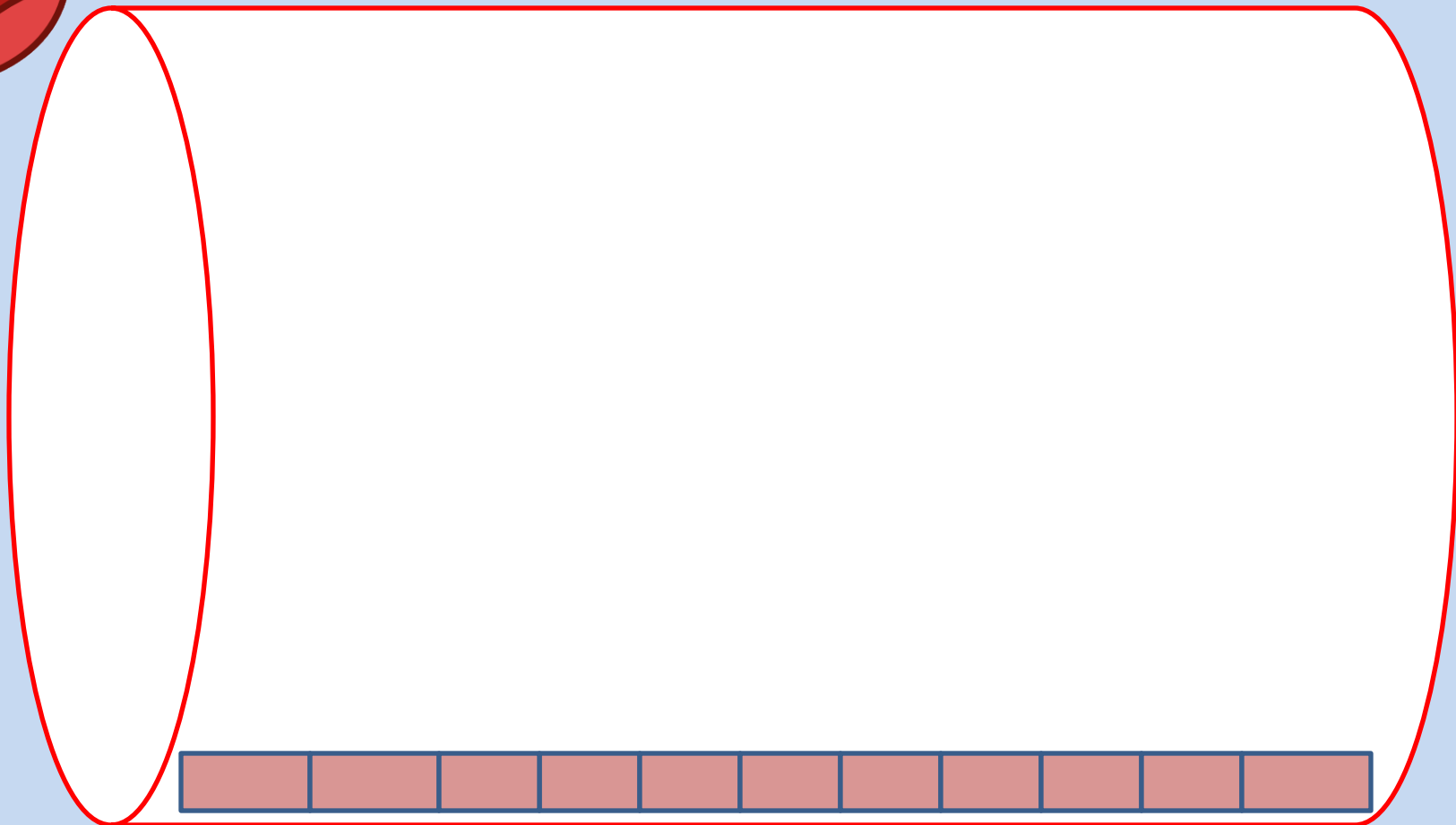
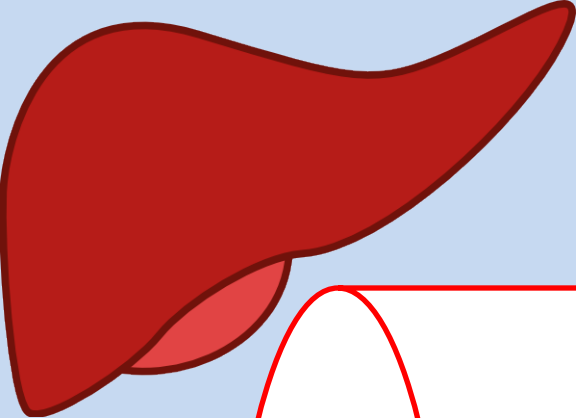
Simplified Coagulation Cascade???

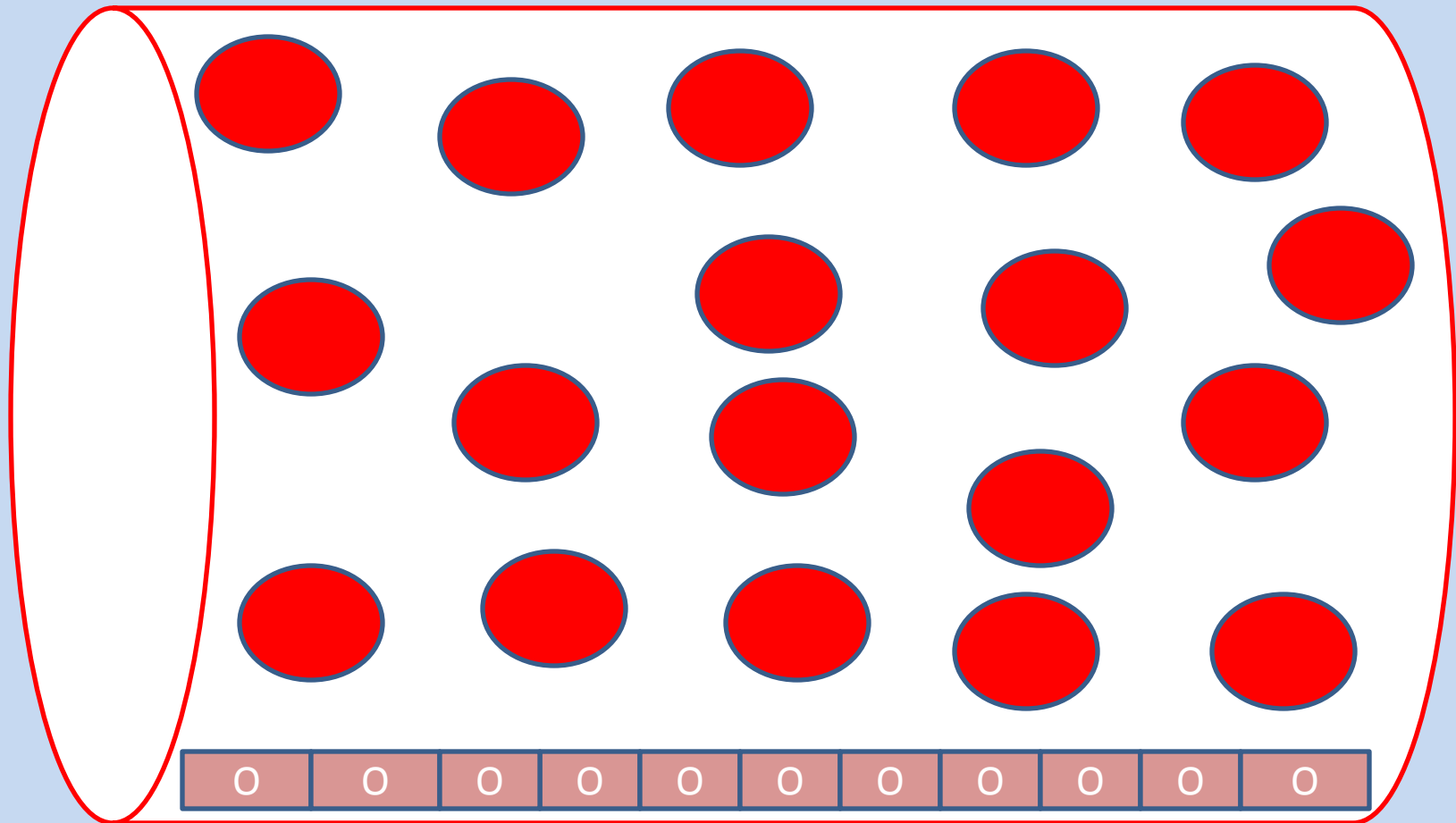


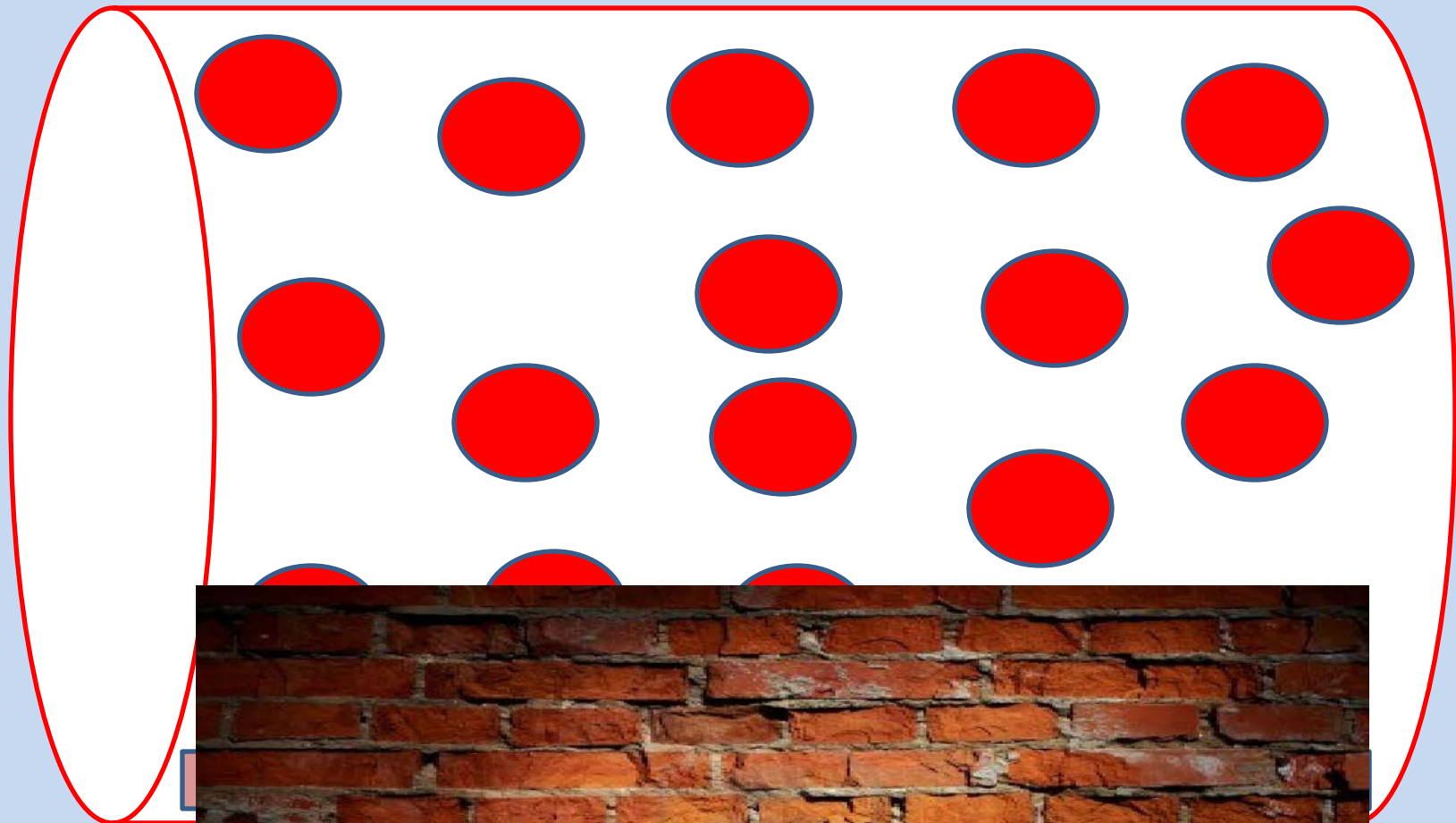
What will you learn today?

1. The normal state of blood is flowing and the endothelium normally functions to keep it that way (anticoagulant properties)
2. Vascular damage stops the anticoagulant properties of the endothelium and releases or activates pro-coagulant chemicals / enzymes
3. Many drugs can affect coagulation by different mechanism on platelets or coagulation factors
4. Blood products and /or factor concentrates can be used to assist in the coagulation process.
5. The current and future state of anticoagulant reversal.





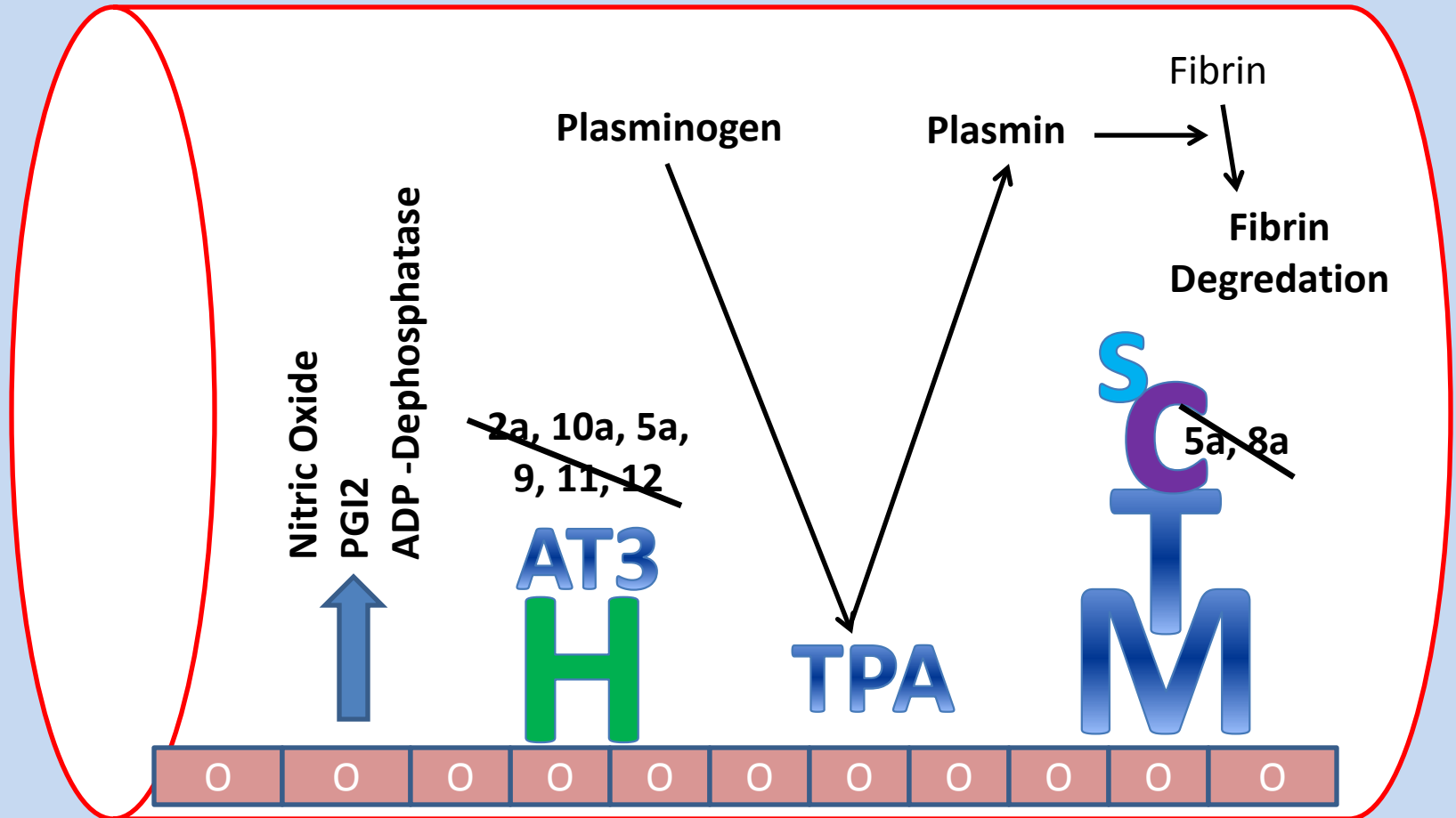




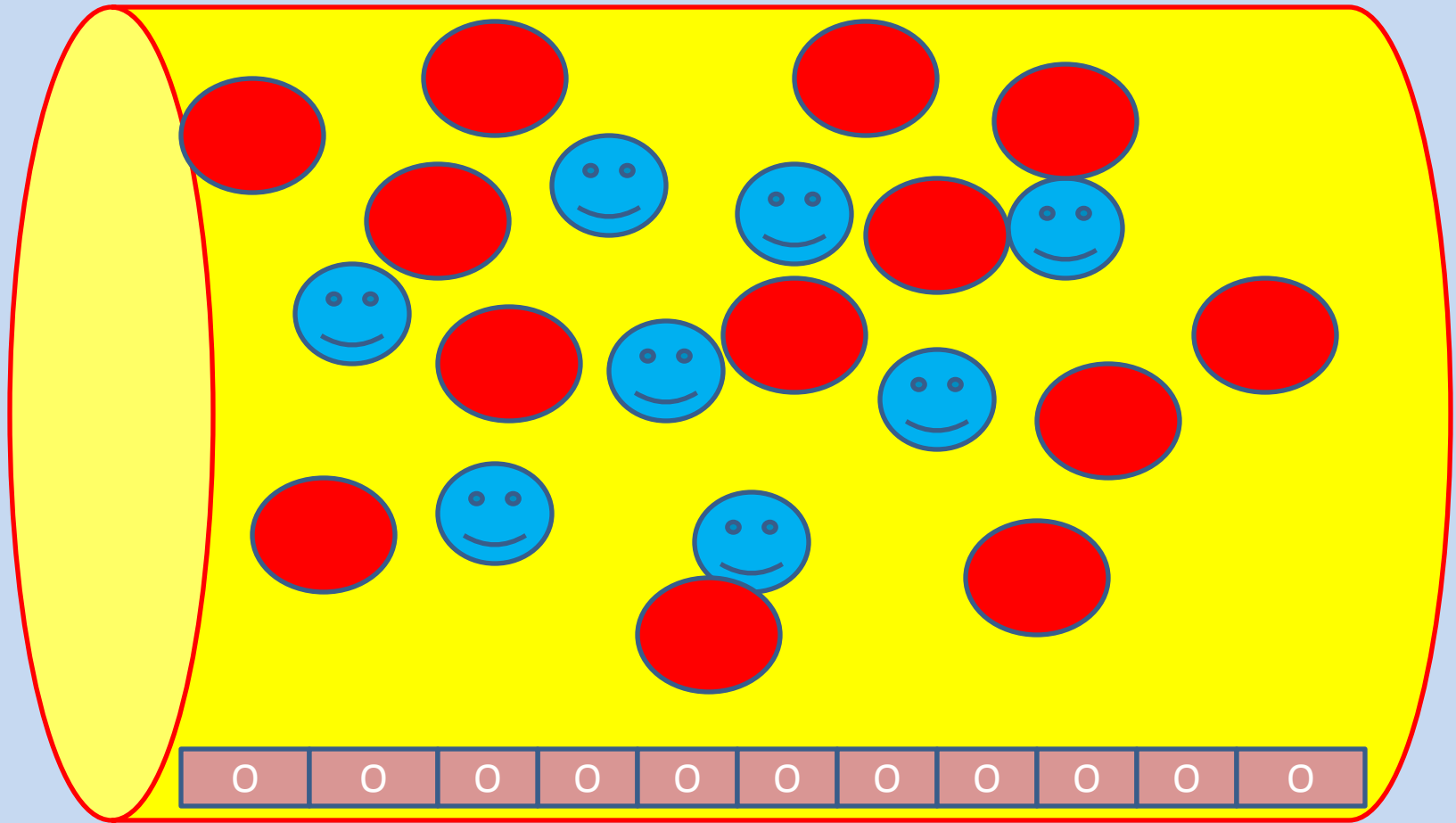
CONCEPT #1

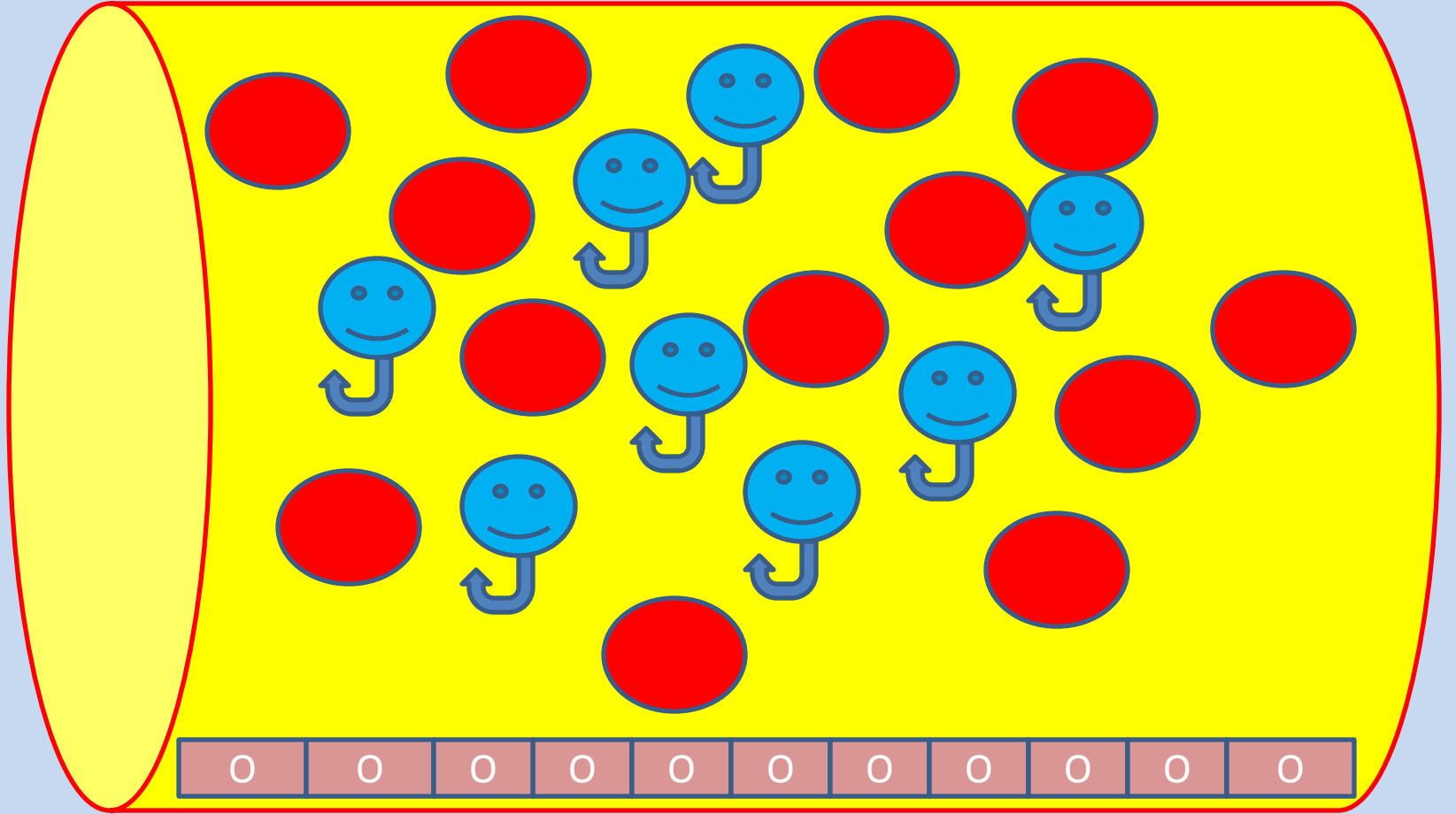
Healthy endothelium has
anti-thrombotic
and
anti-coagulant functions

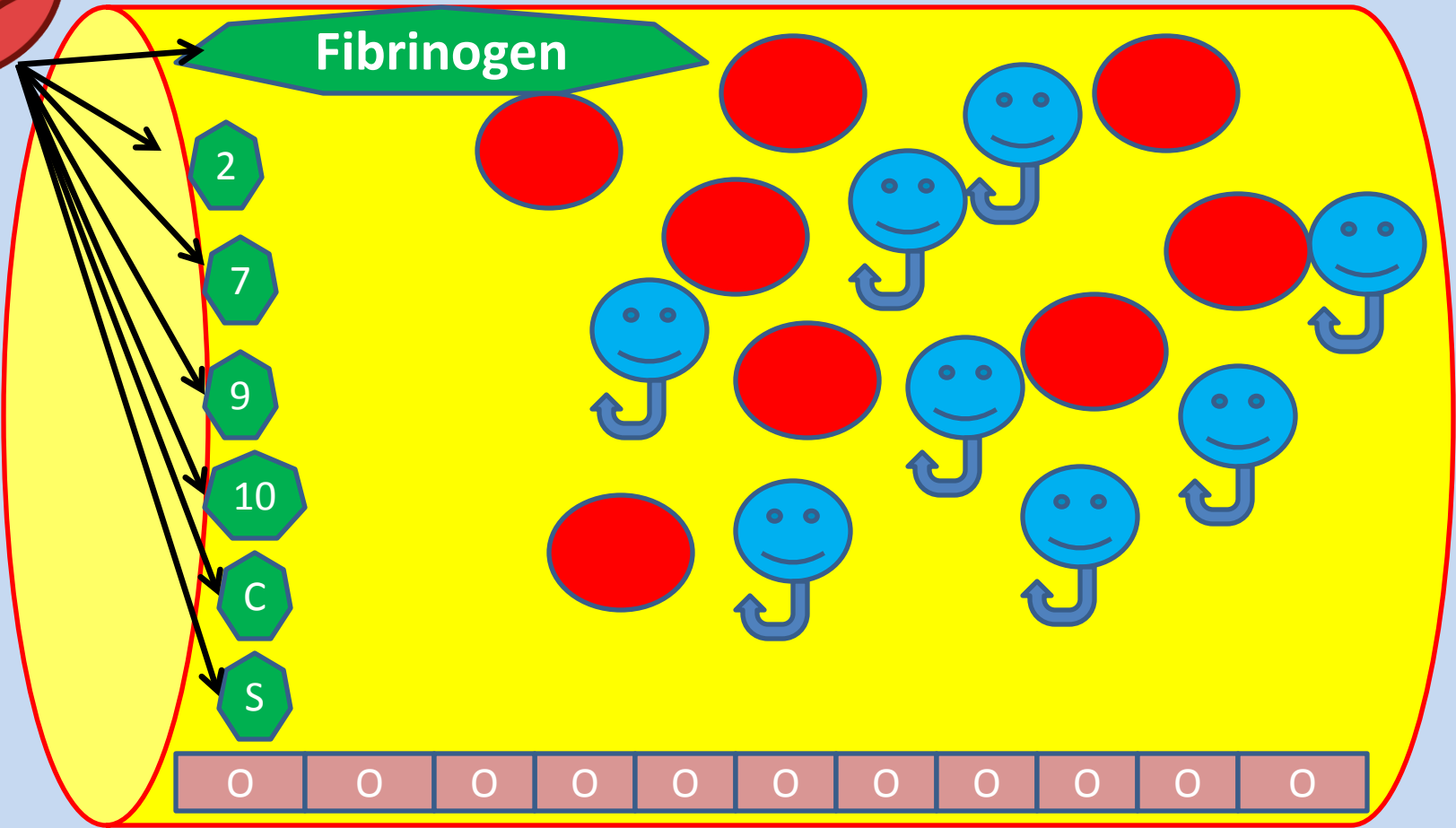
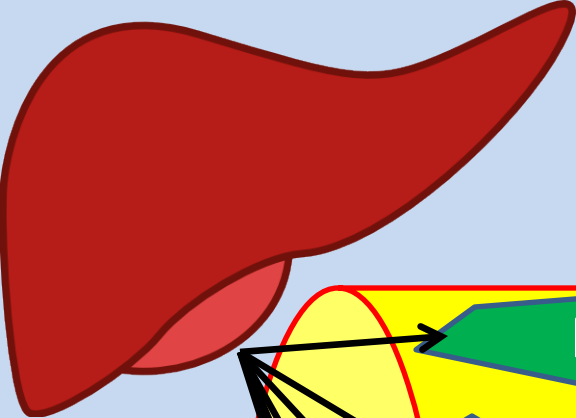
ANTI-COAGULANT FUNCTIONS OF ENDOTHELIUM



What is 'in' blood to help with coagulation?







Fibrinogen

2

7

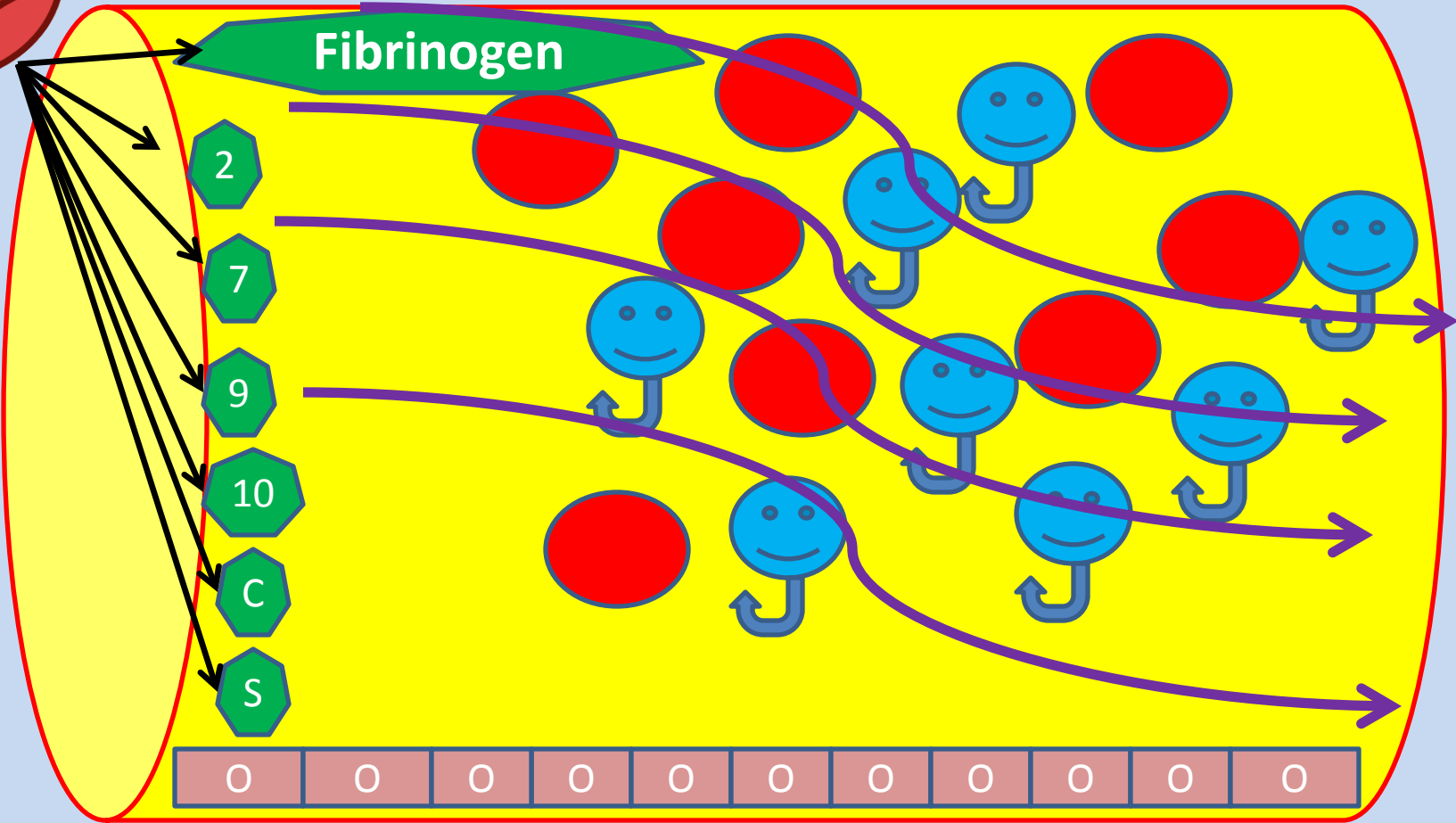
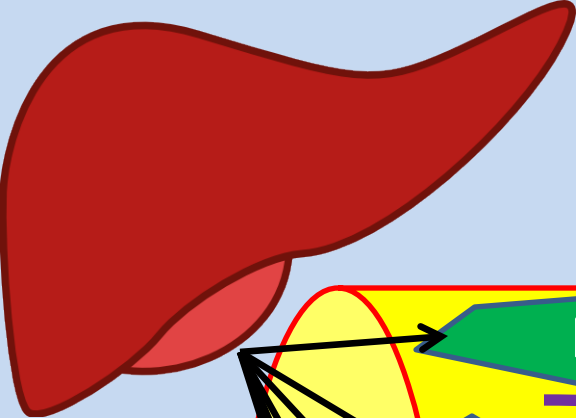
9

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Fibrinogen

2

7

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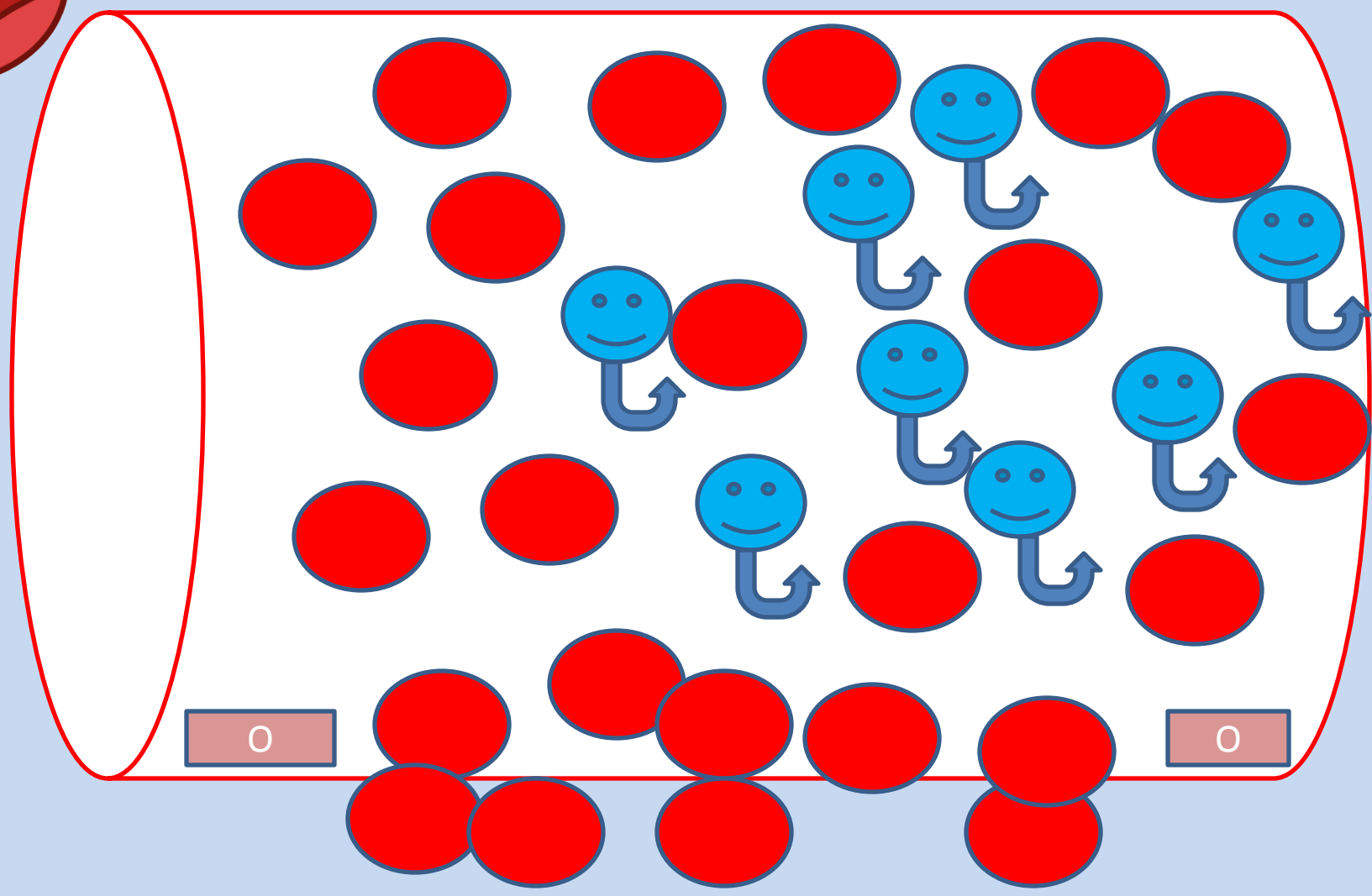
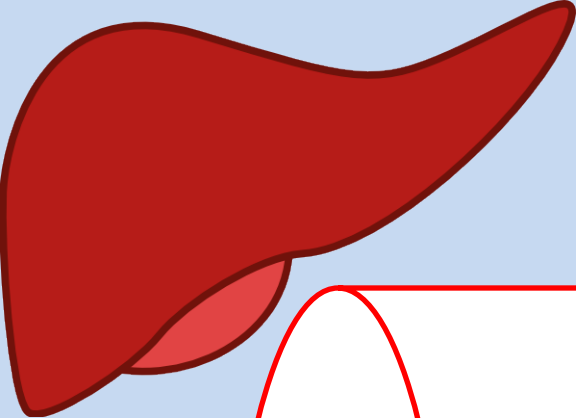
CONCEPT #2

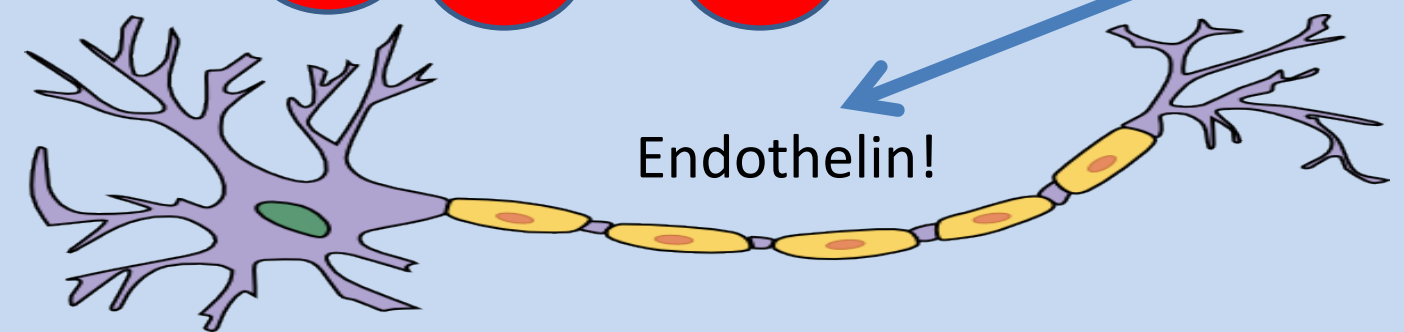
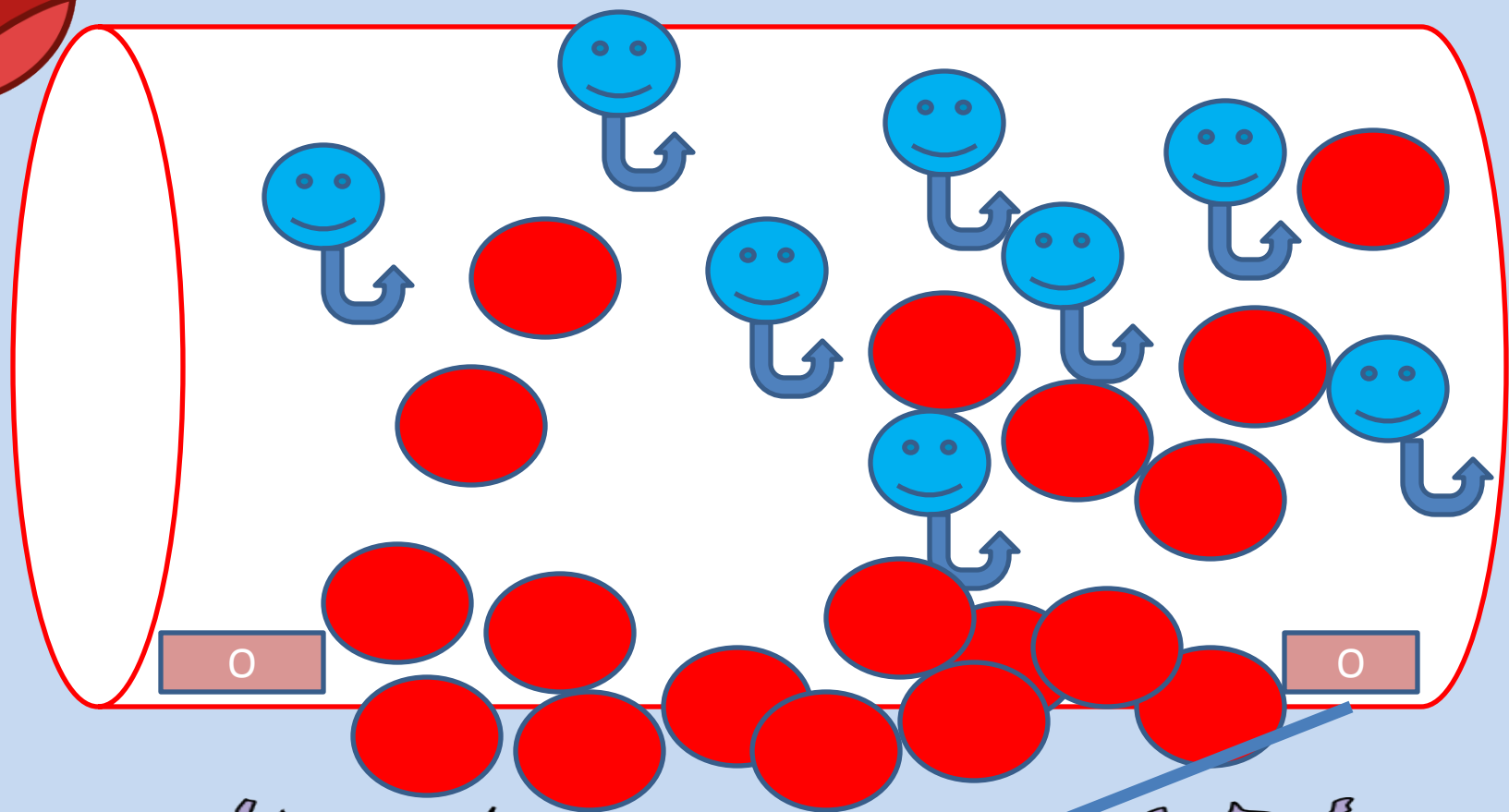
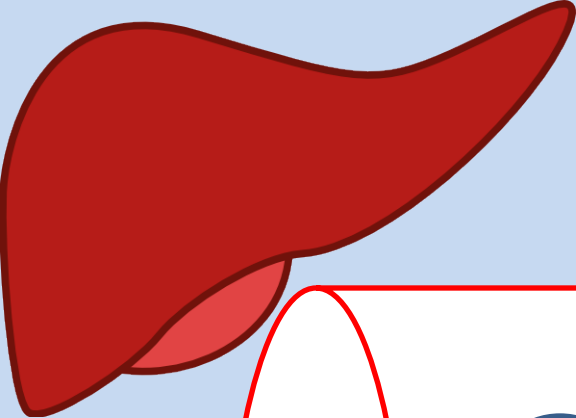
Injured endothelium has

PRO-thrombotic

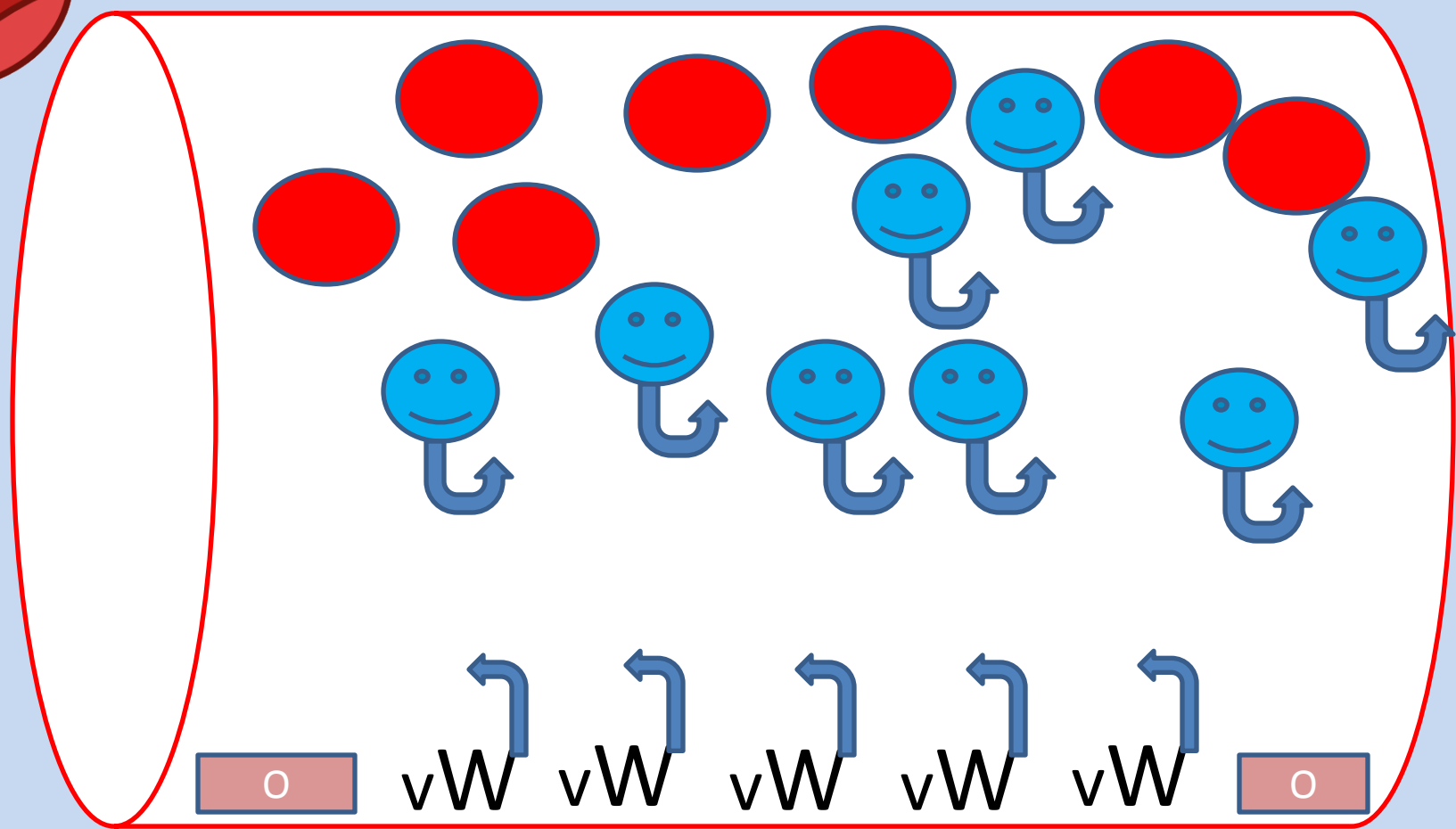
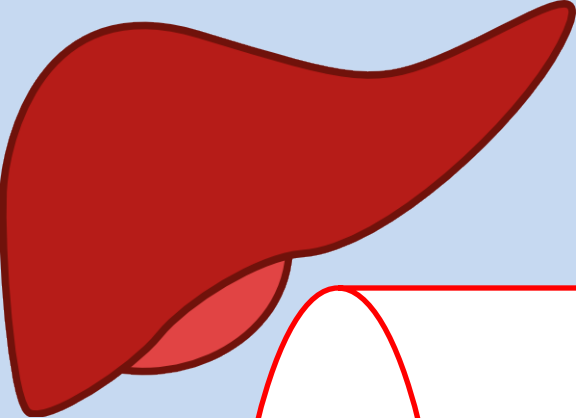
and

PRO-coagulant functions





Endothelin!



↑
DDAVP

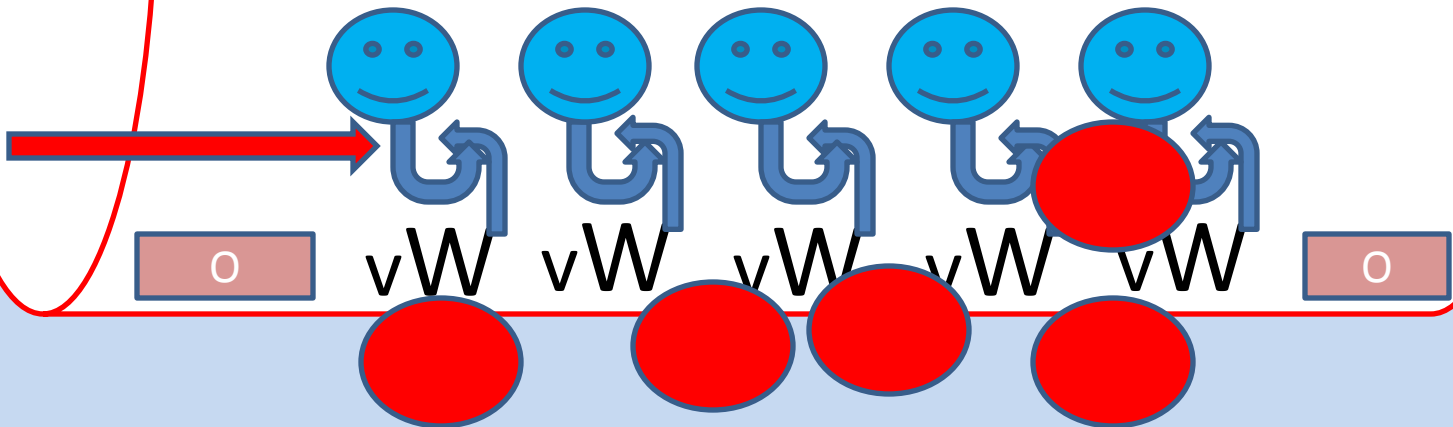
↑
Humate P

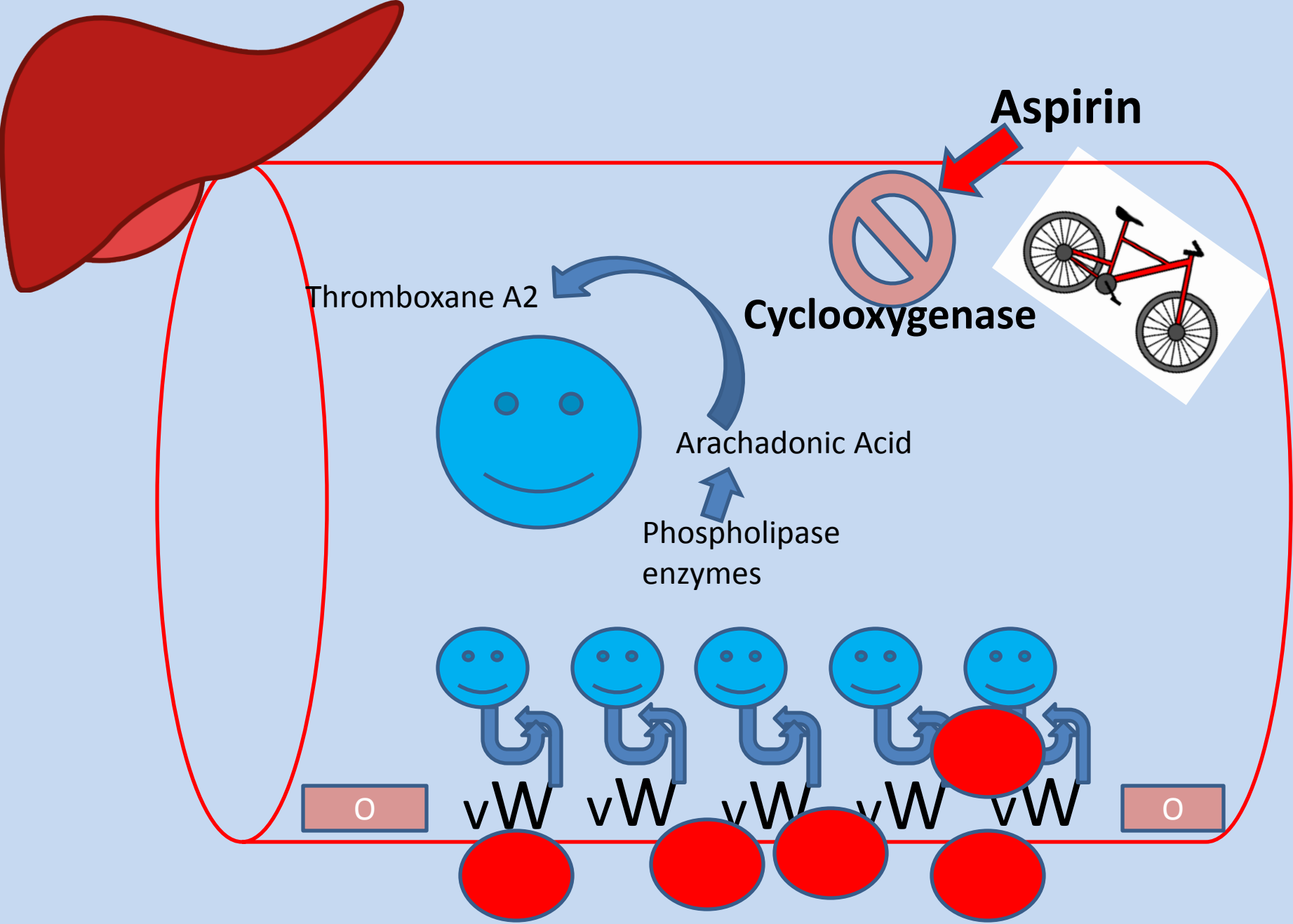
Note: VWF also carries Factor 8!

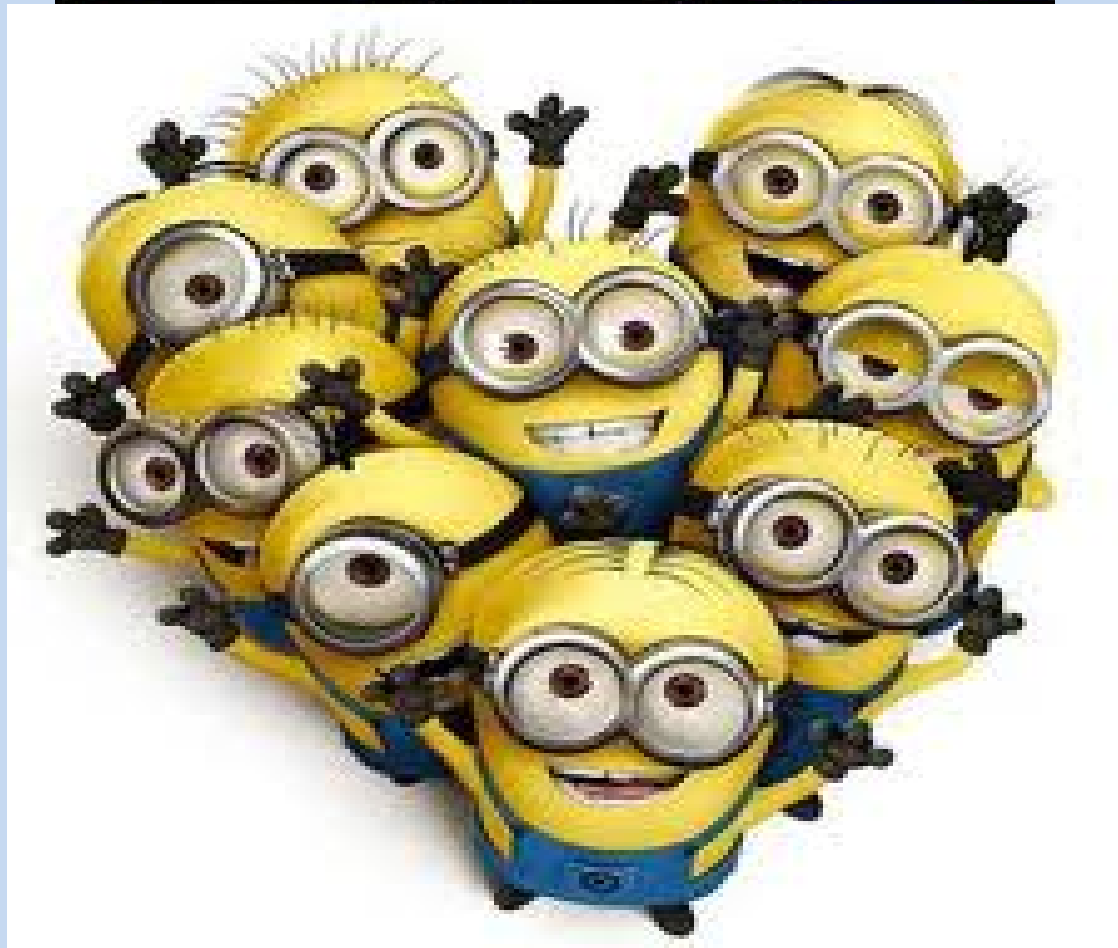
PLATELET ADHESION!



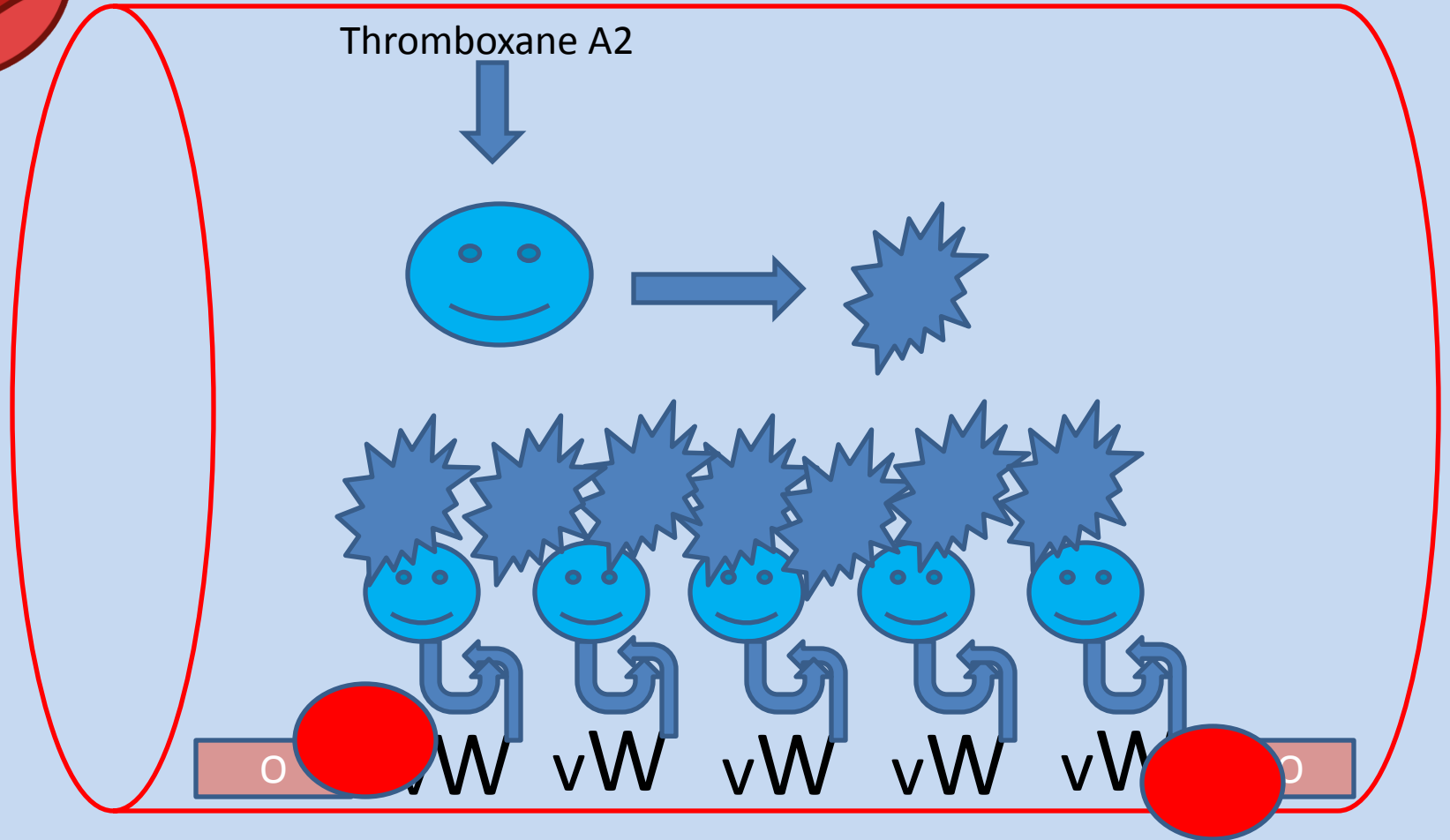
Abciximab

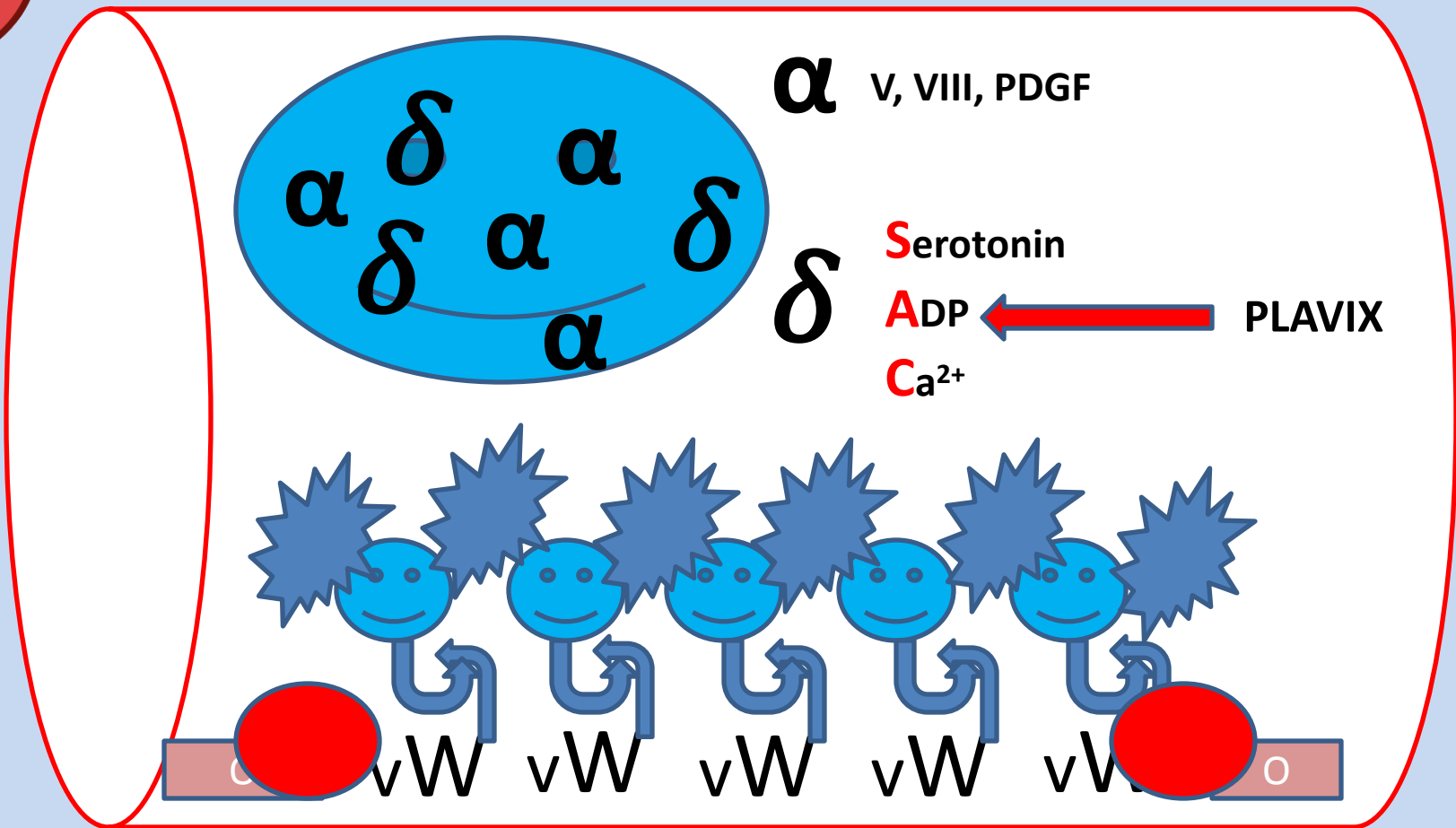
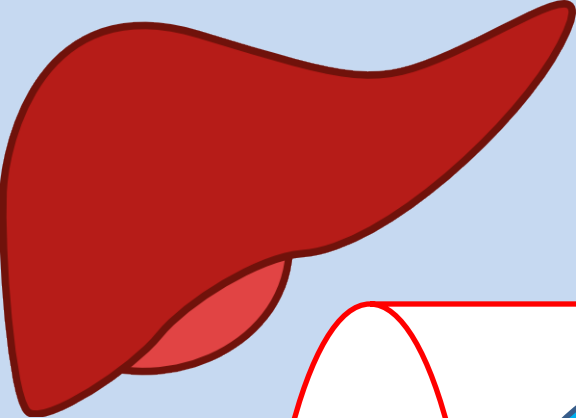




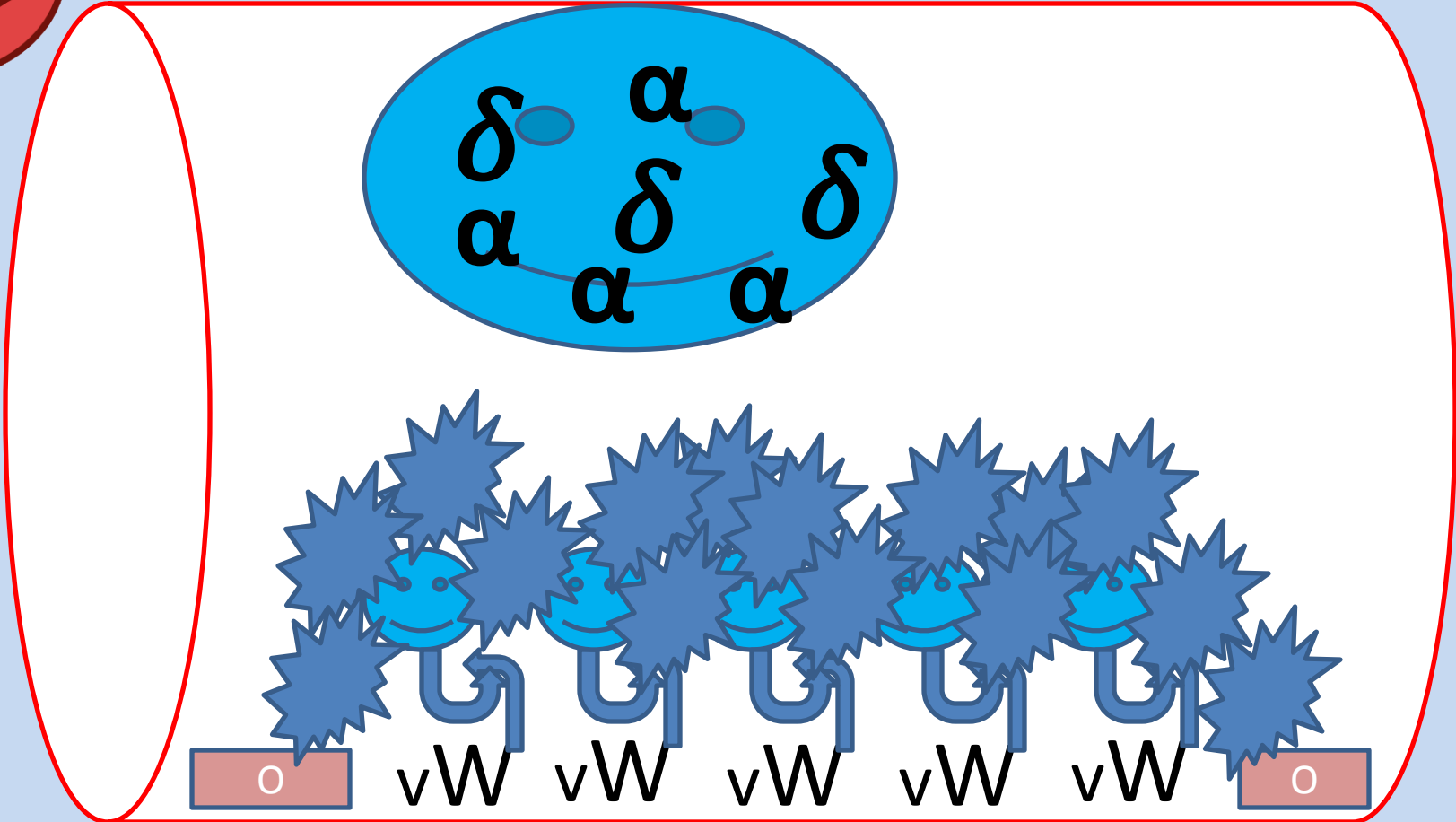


PLATELET AGGREGATION!!!

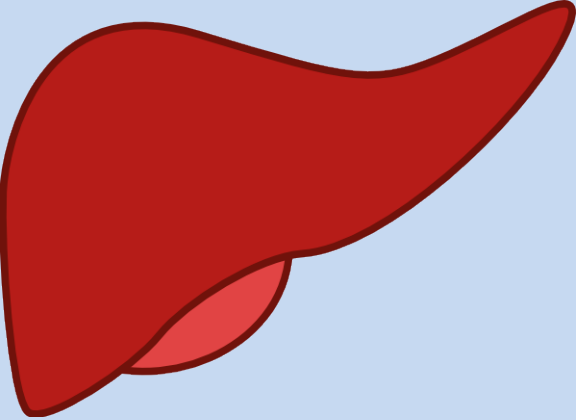




PRIMARY PLATELET PLUG!!!



Platelet Transfusion

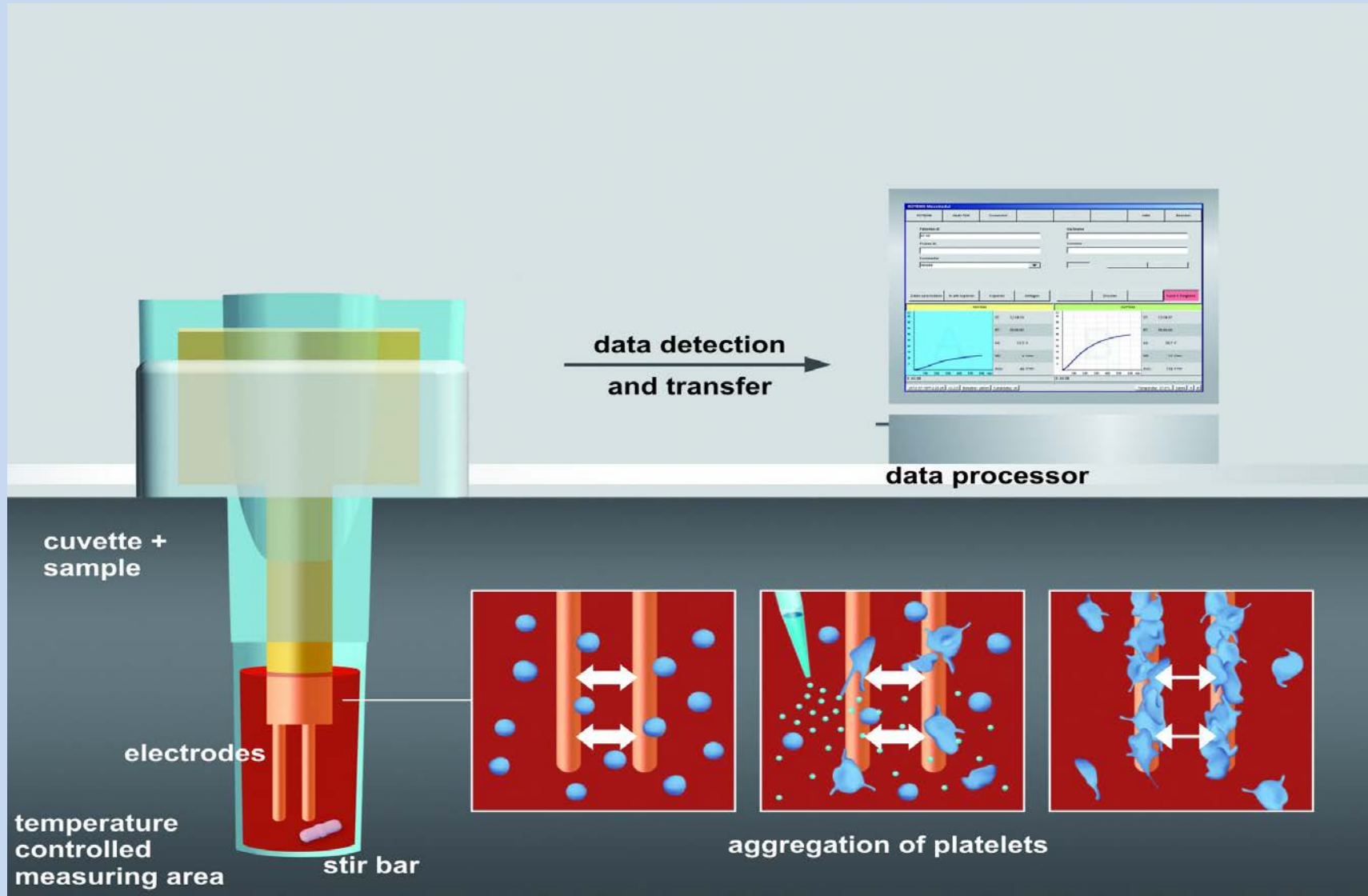


PLATELET FUNCTION TESTING

WHOLE BLOOD PLATELET AGGREGOMETRY

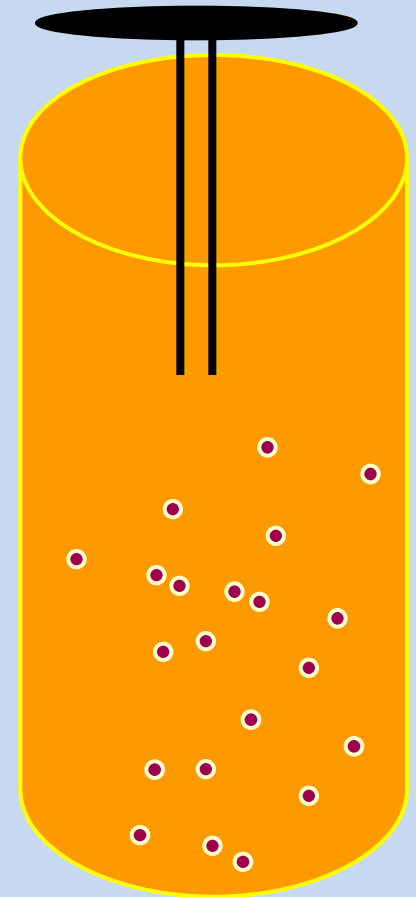


Whole Blood Aggregometry



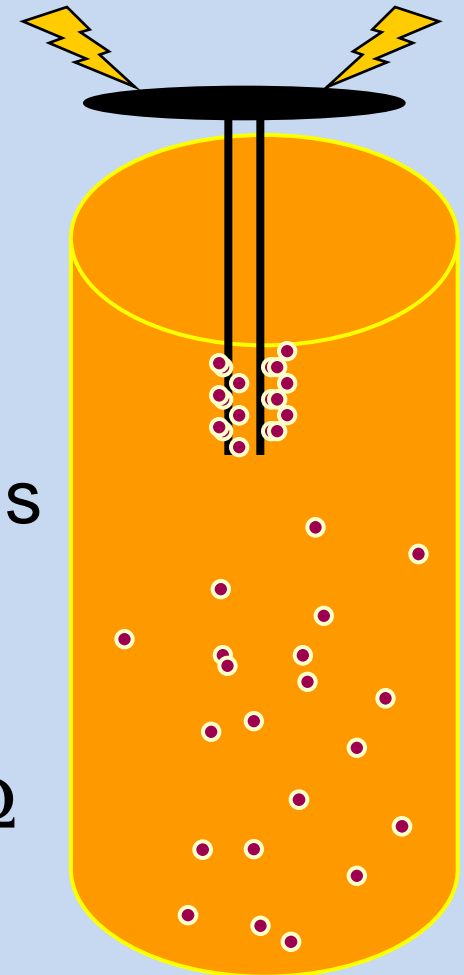
Whole Blood Aggregometry

- Collect 9 mL blood
 - 3 tubes each 2.7 mL + 0.3 citrate
- Dilute 1:1 with saline in cuvette
- Pipette agonist, timer starts
- Lower the electrodes into suspension

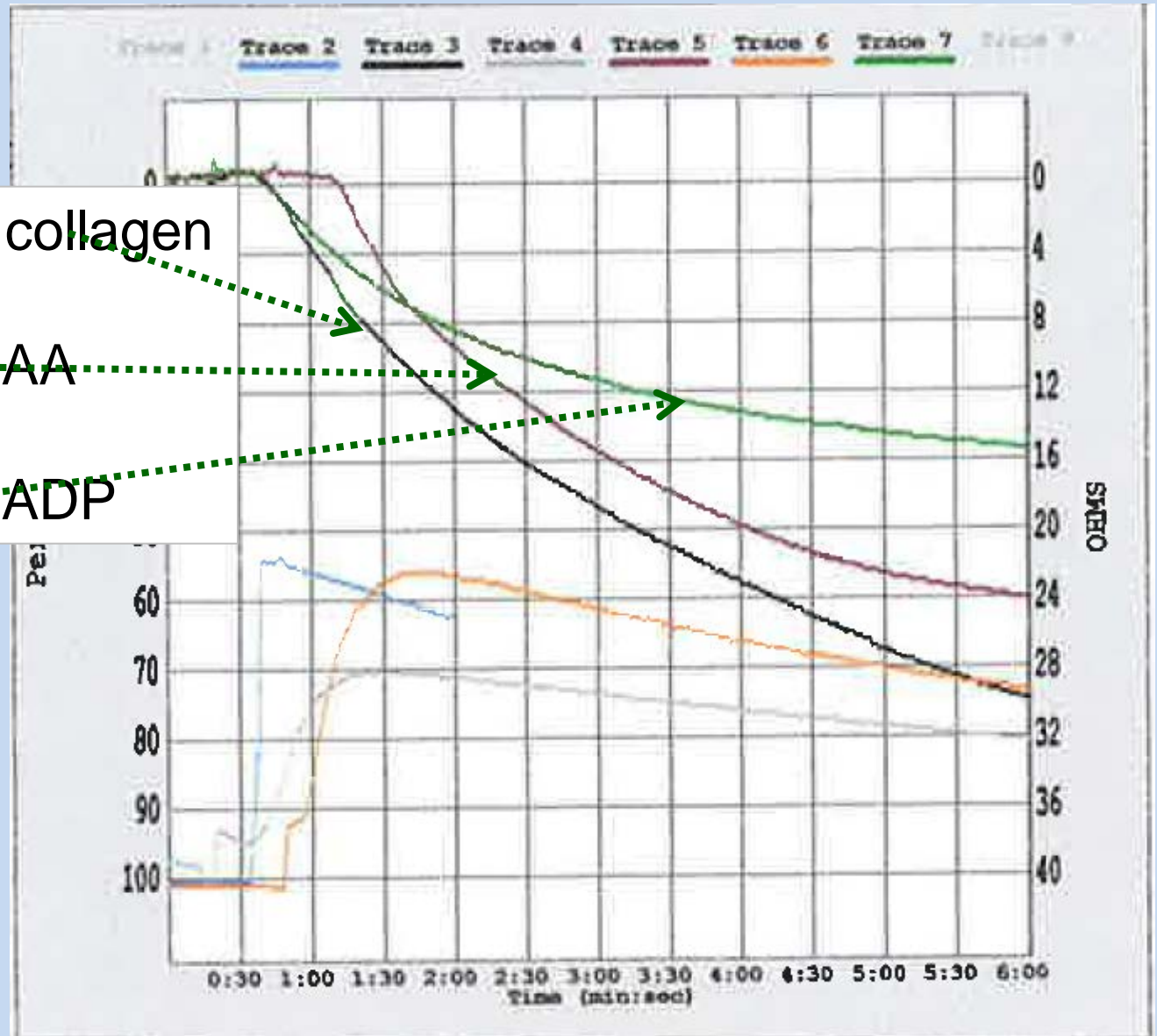


Whole Blood Aggregometry

- Aggregating platelets coat electrodes
- Current impeded by platelet layer
 - Impedance measured in ohms (Ω)
 - 0 (zero) Ω = no aggregation
 - Aggregation proportional to Ω



Normal Control



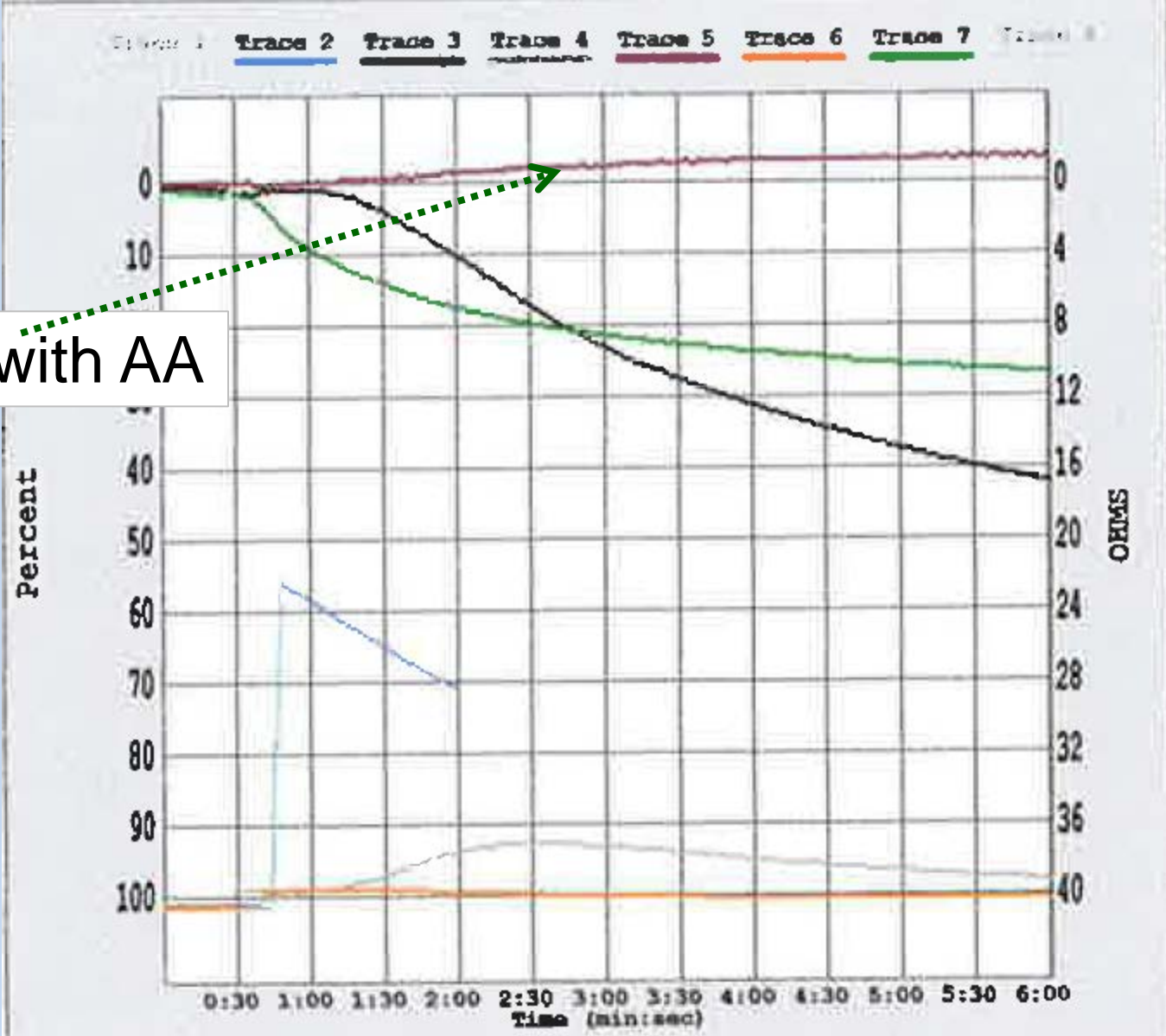
Aggregation with collagen

Aggregation with AA

Aggregation with ADP

AA=Arachidonic Acid
ADP= Adenosine Diphosphate

Aspirin Effect



No aggregation with AA

EPOXY GLUE



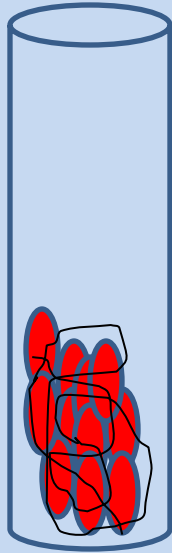
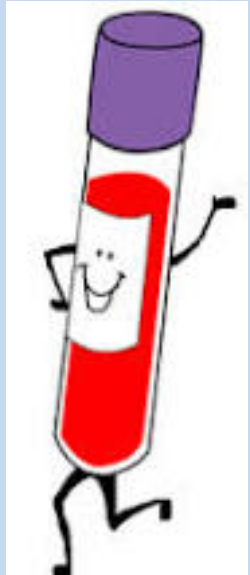
CONCEPT #3

Intrinsic

VS.

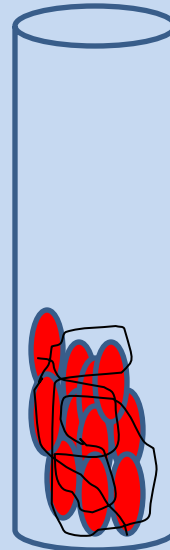
Extrinsic

SODIUM CITRATE



Calcium

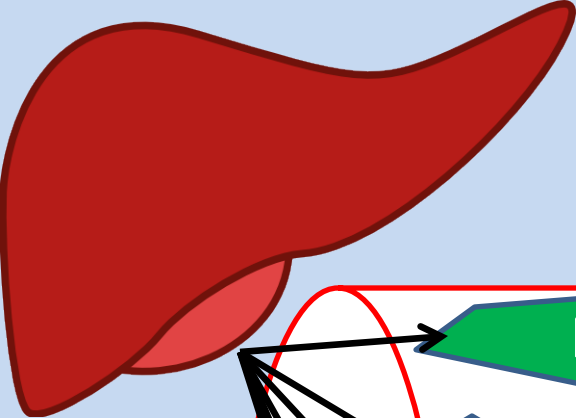
INTRINSIC



EXTRINSIC

CONCEPT #4

Coagulation factors
activate one another



Fibrinogen

2

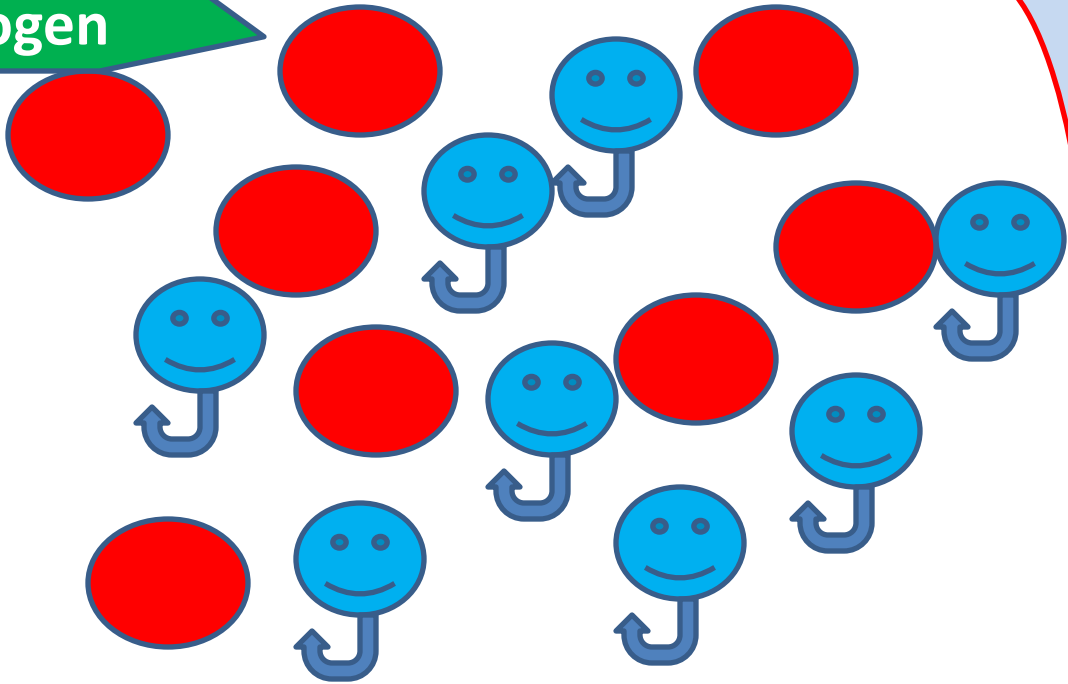
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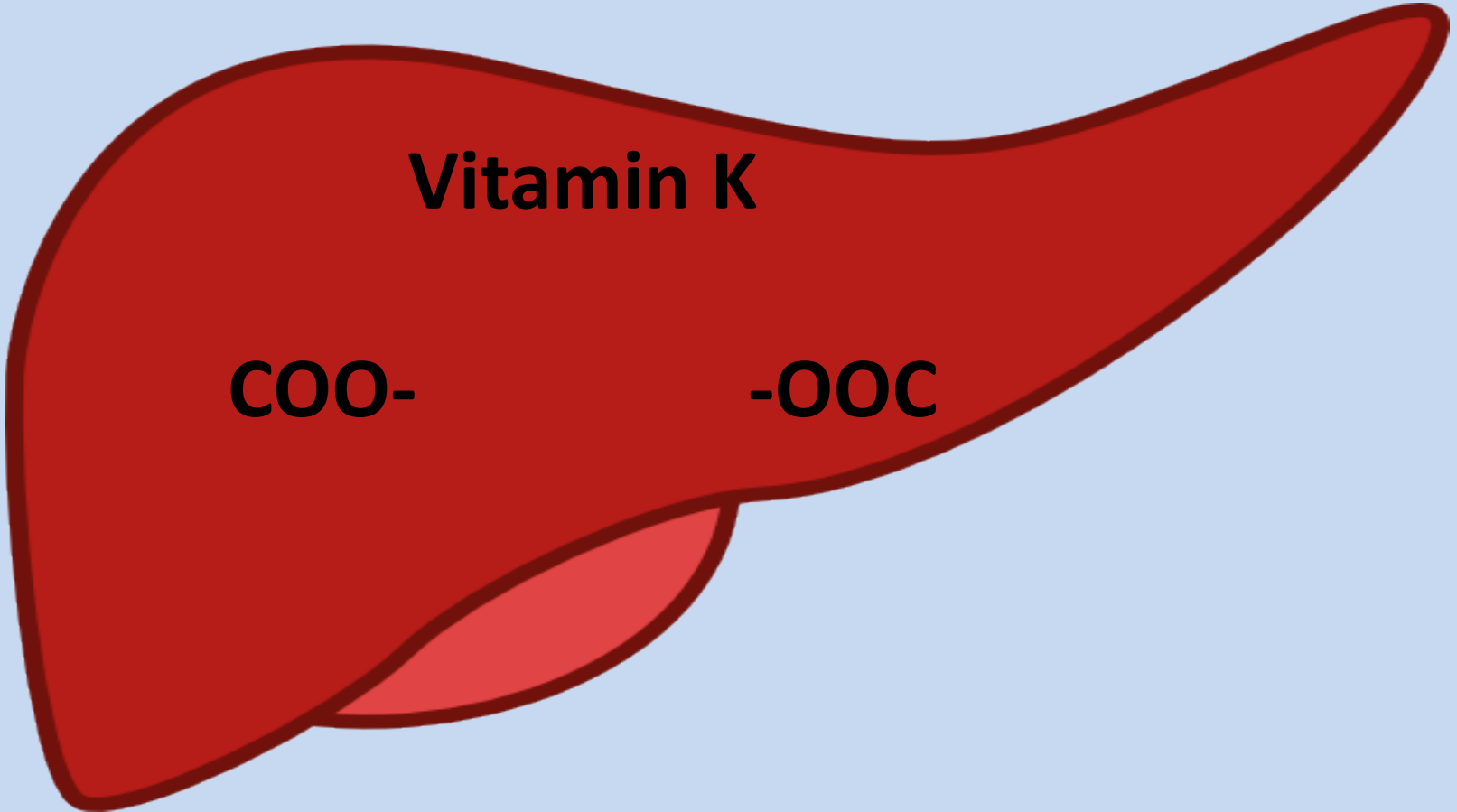


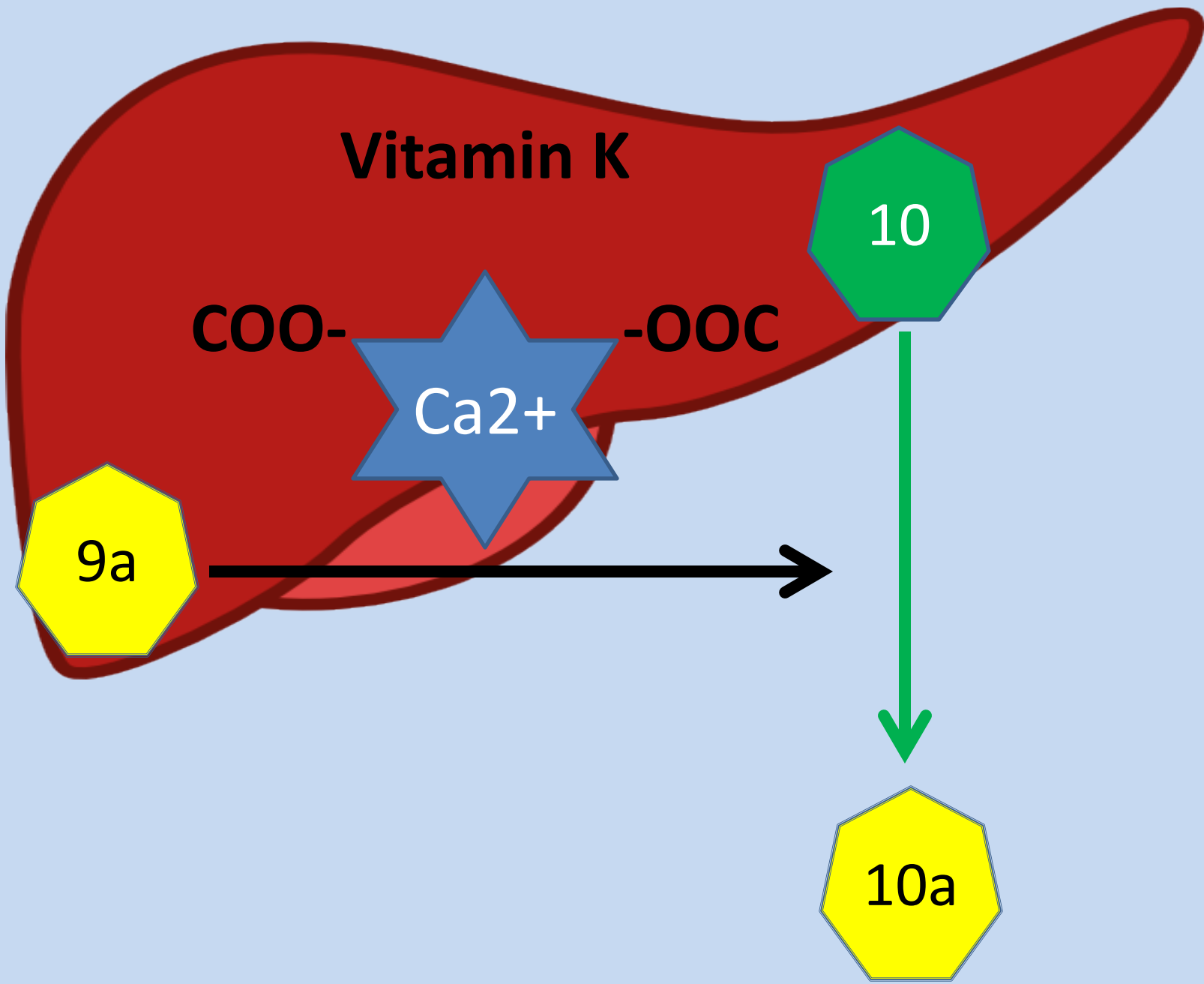
GAMMA CARBOXYLATION

Vitamin K

COO-

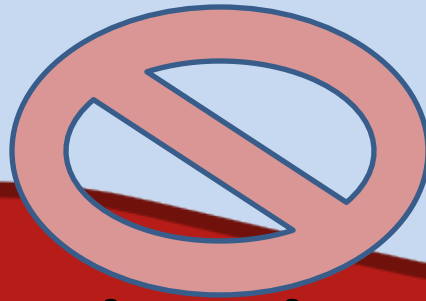
-OOC





WARFARIN/COUMADIN

Vitamin K blocked = no
carboxylation and no production
of Factors 2,7,9,10 and protein C,S



Vitamin K

COO-

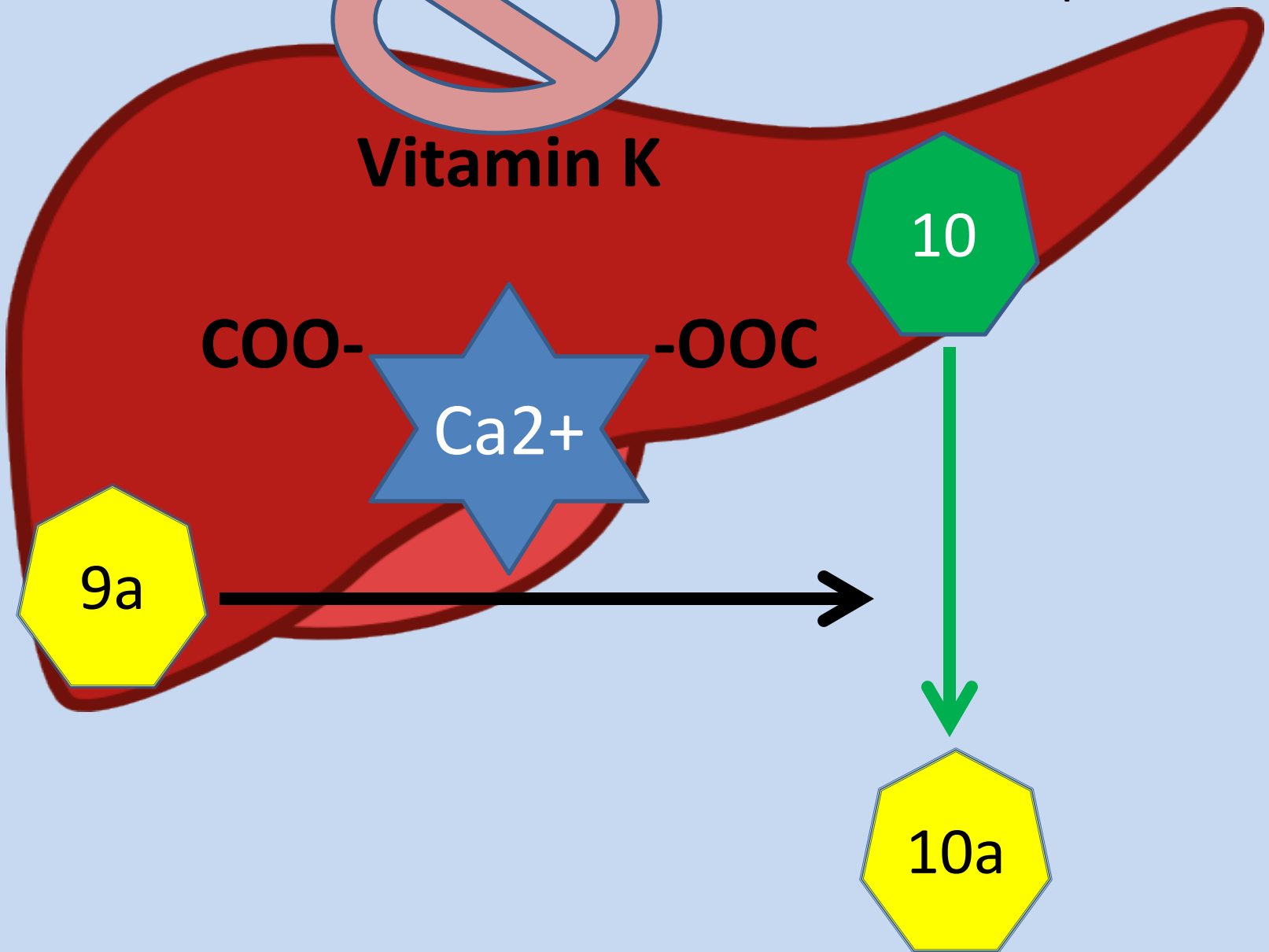
-OOC

Ca²⁺

10

9a

10a

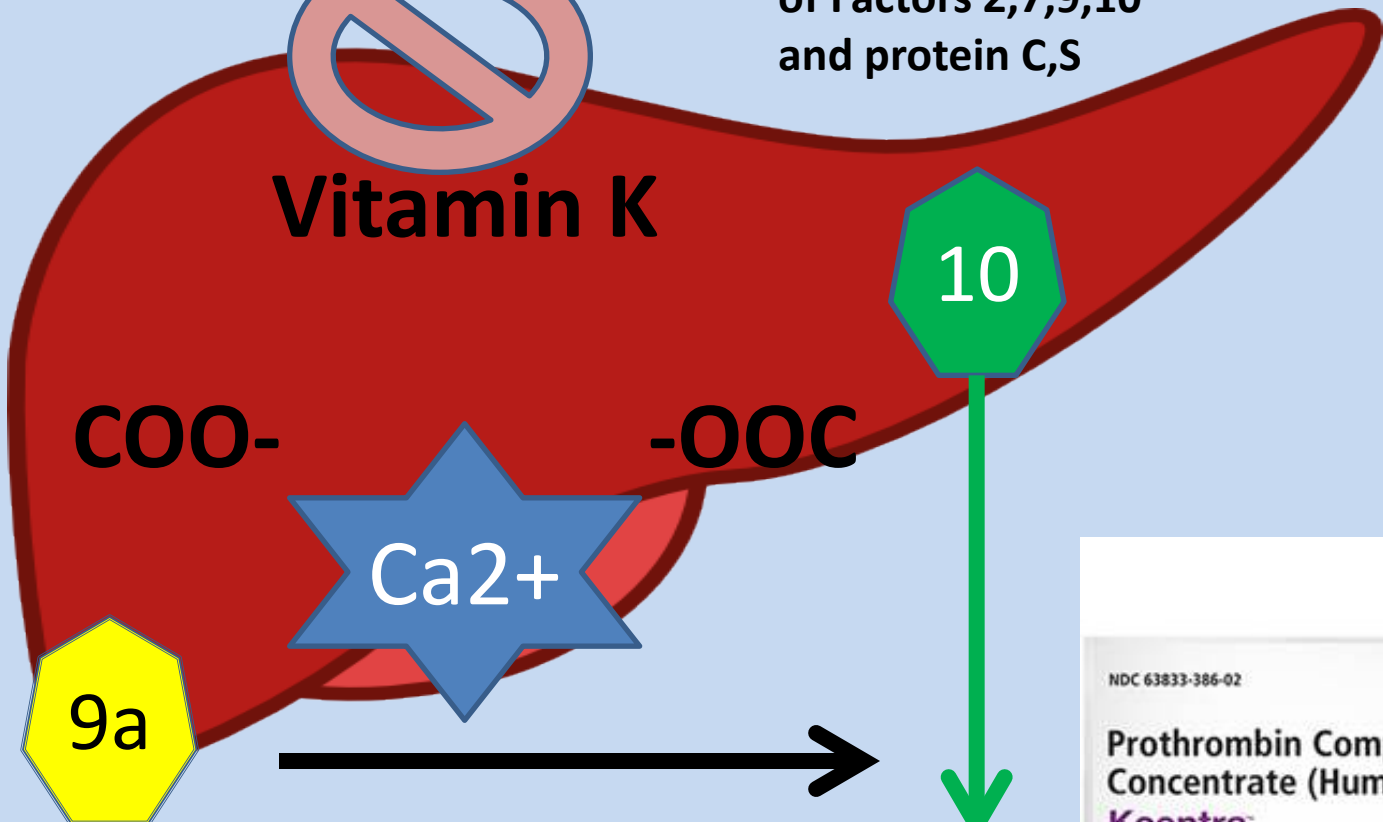


WARFARIN/COUMADIN

Vitamin K blocked =
no carboxylation
and no production
of Factors 2,7,9,10
and protein C,S

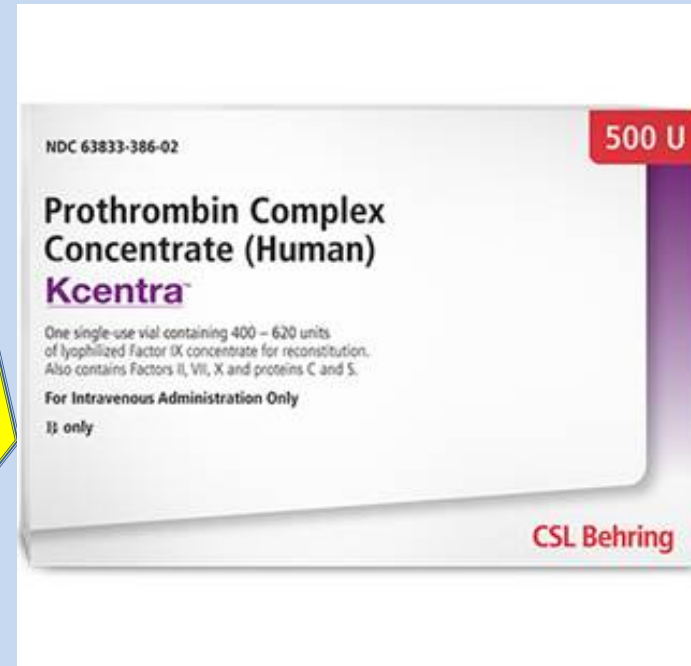


Vitamin K



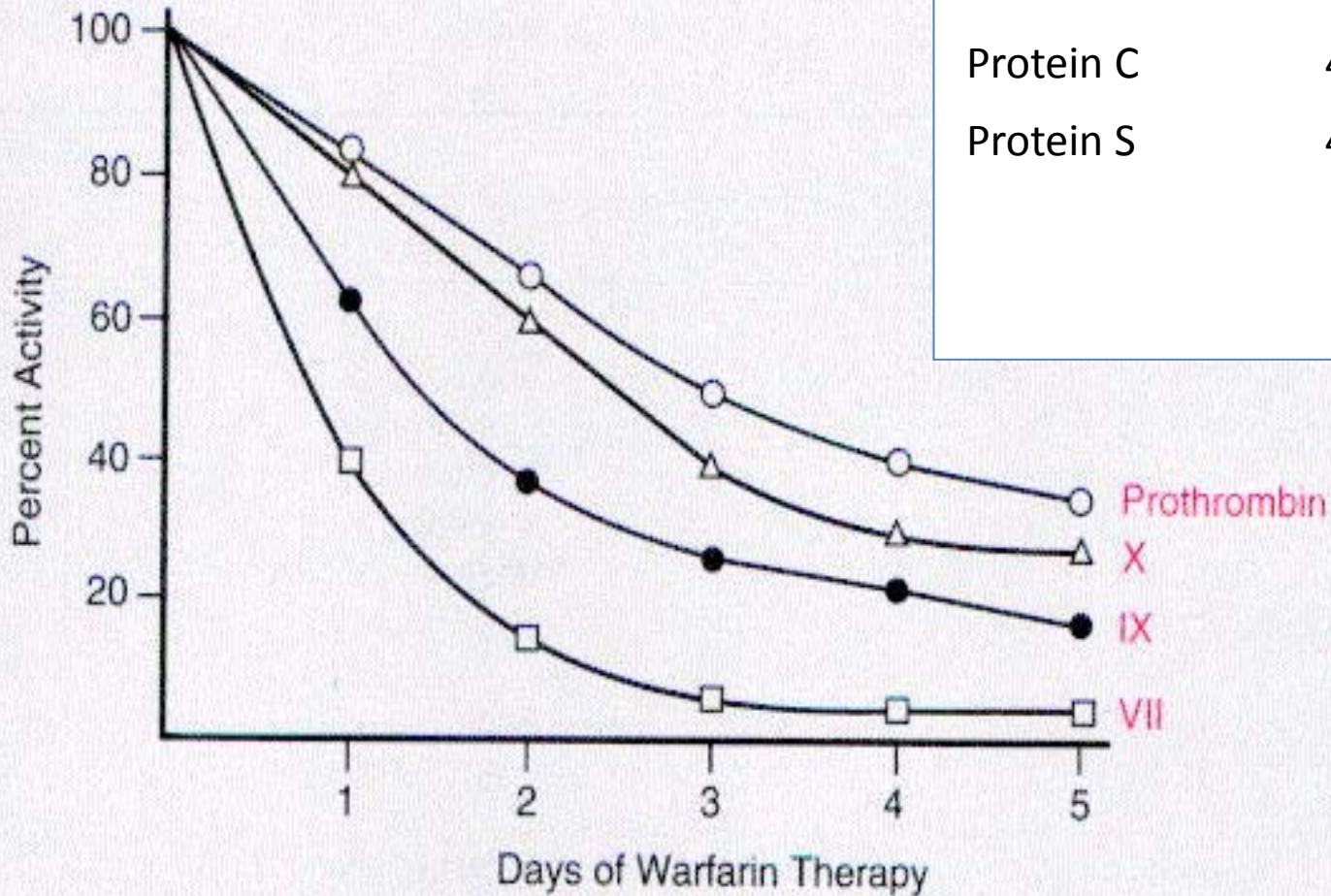
REVERSAL???

Kcentra (Factors 2,7,9,10, plus Protein C and S)
AND
Vitamin K



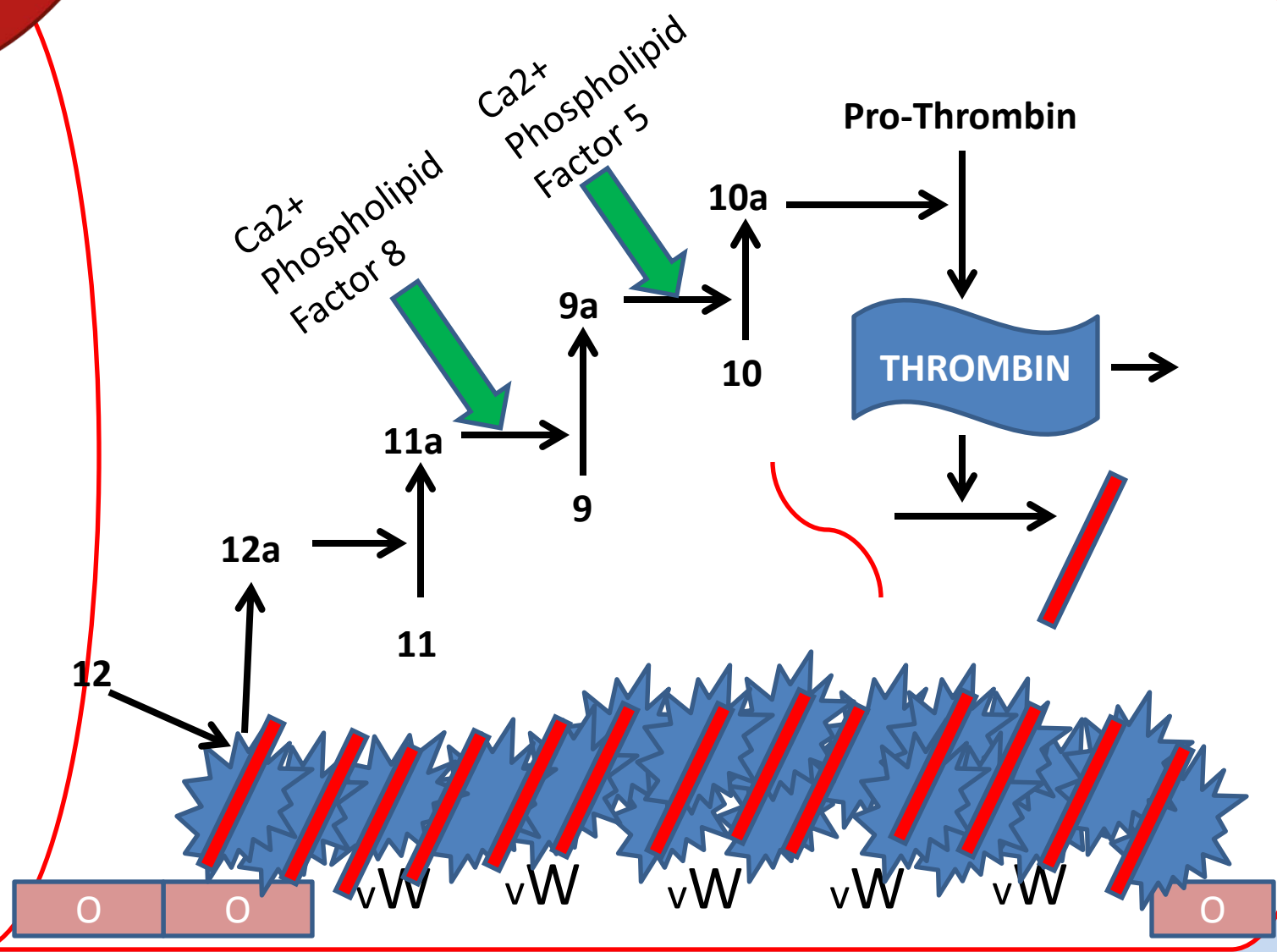
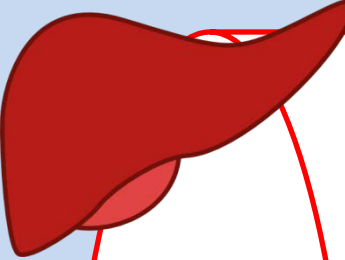
It takes about 4-5 days to reach warfarin therapeutic effect!

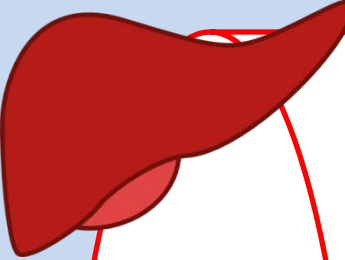
<u>Factor</u>	<u>Half-life (h)</u>
II	60
VII	4-7
IX	24
X	48-72
Protein C	4-6
Protein S	42-60



CONCEPT #5

The coagulation cascade is a process that ends with soluble fibrinogen being converted into insoluble fibrin strands!

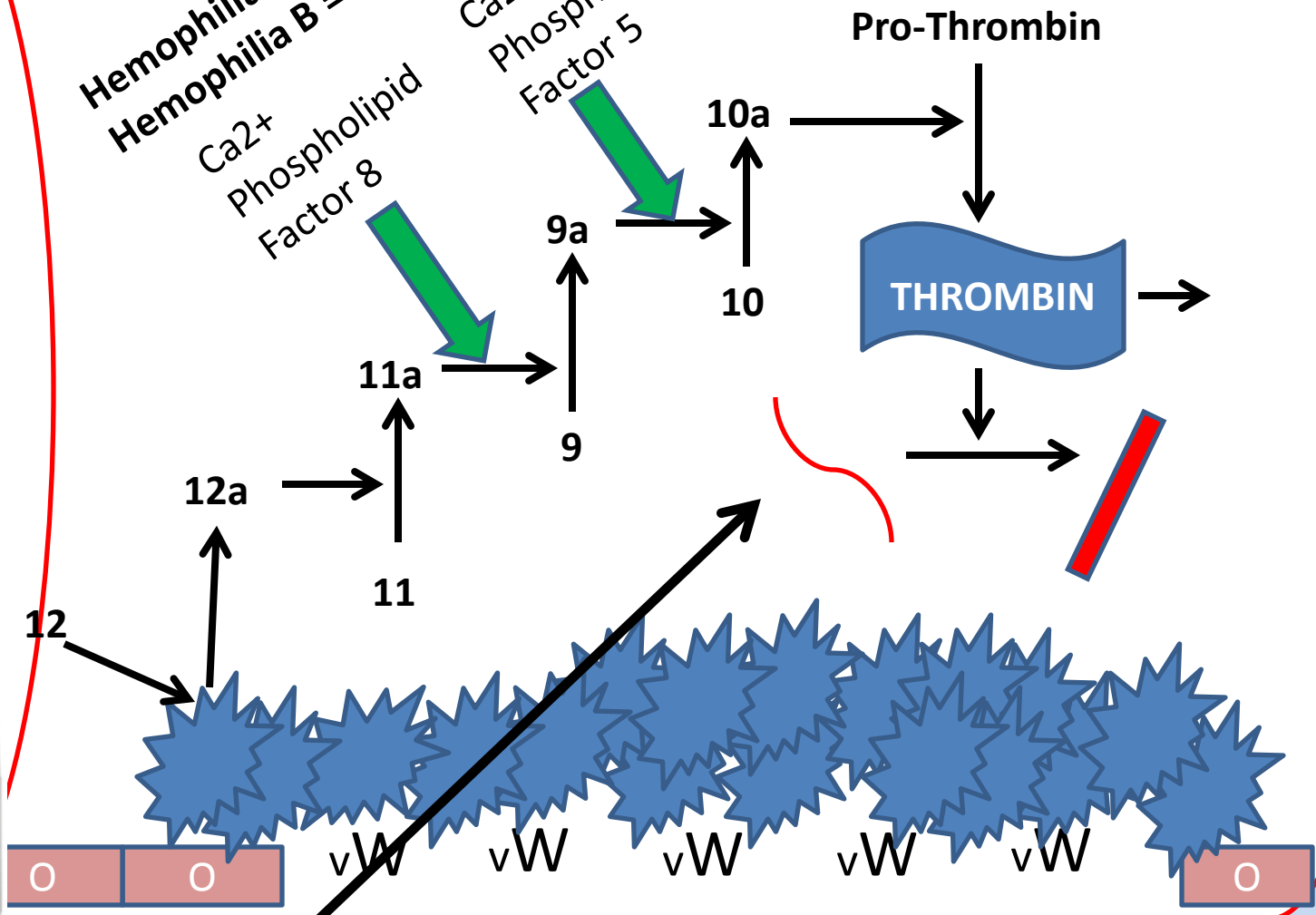




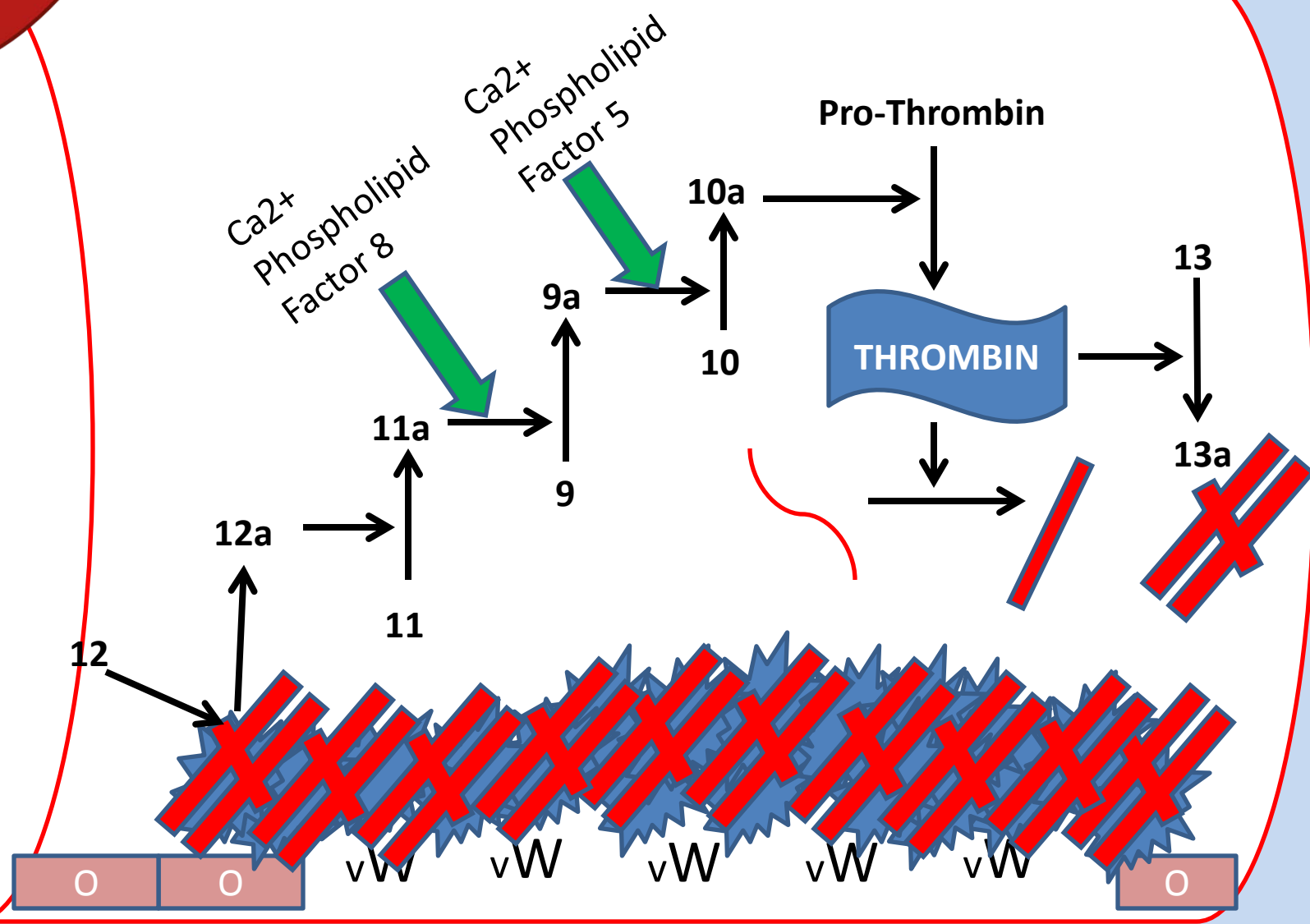
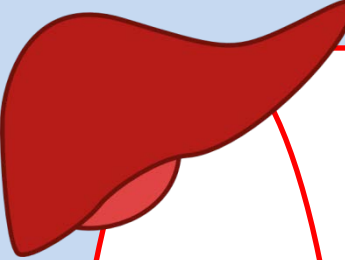
Hemophilia A = F8 def
Hemophilia B = F9 def

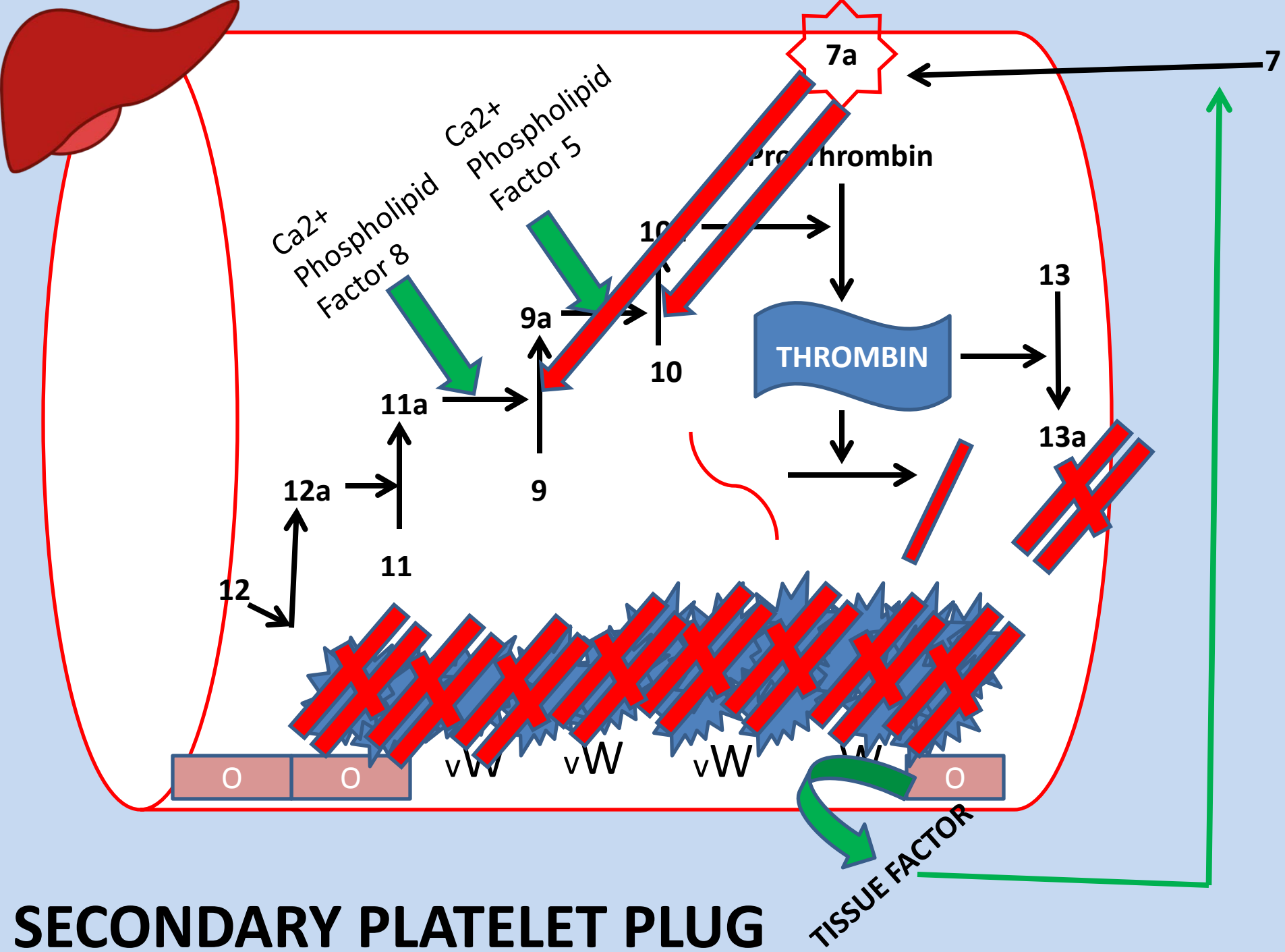
Ca²⁺
Phospholipid
Factor 8

Ca²⁺
Phospholipid
Factor 5

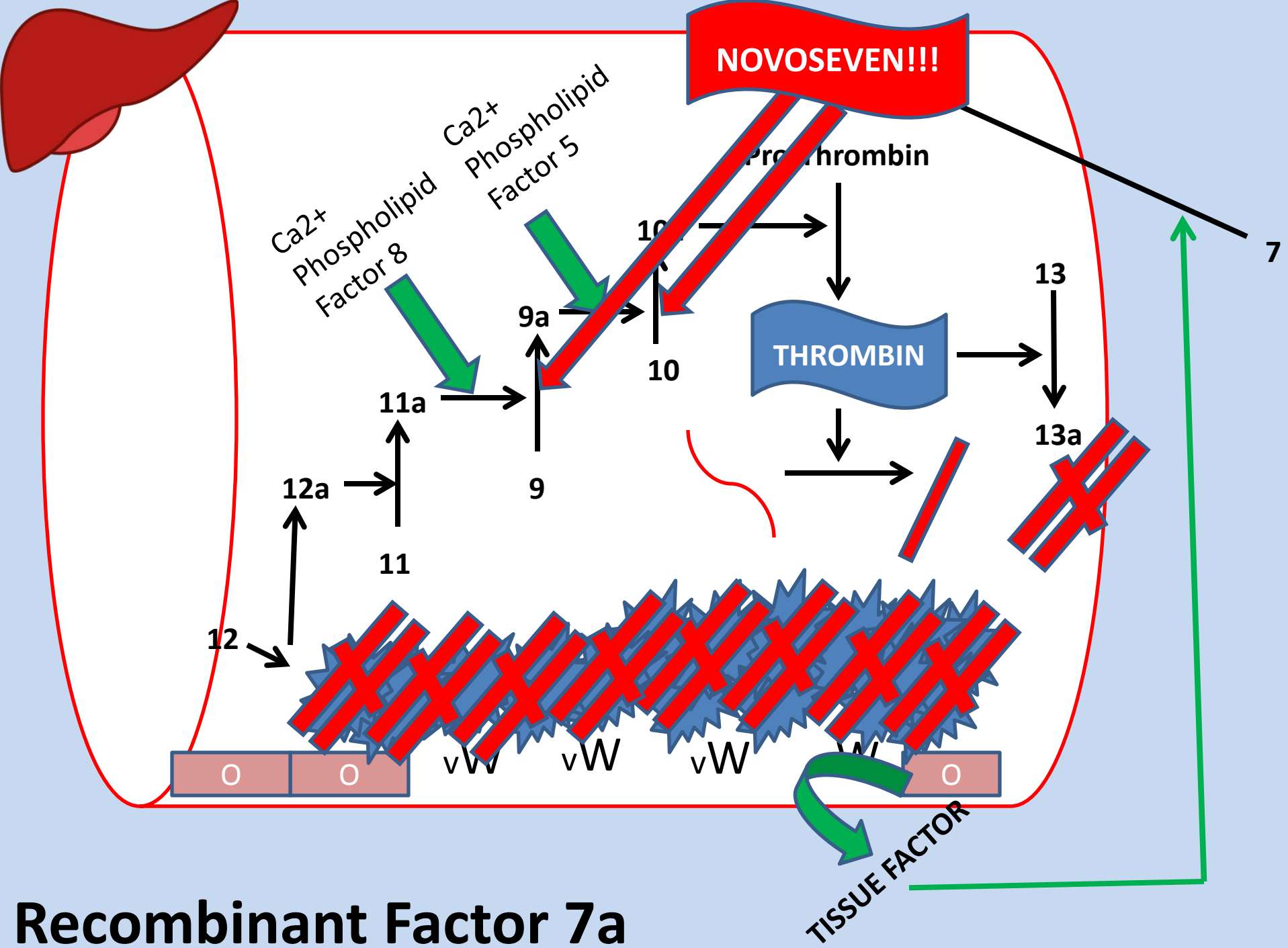


Cryoprecipitate



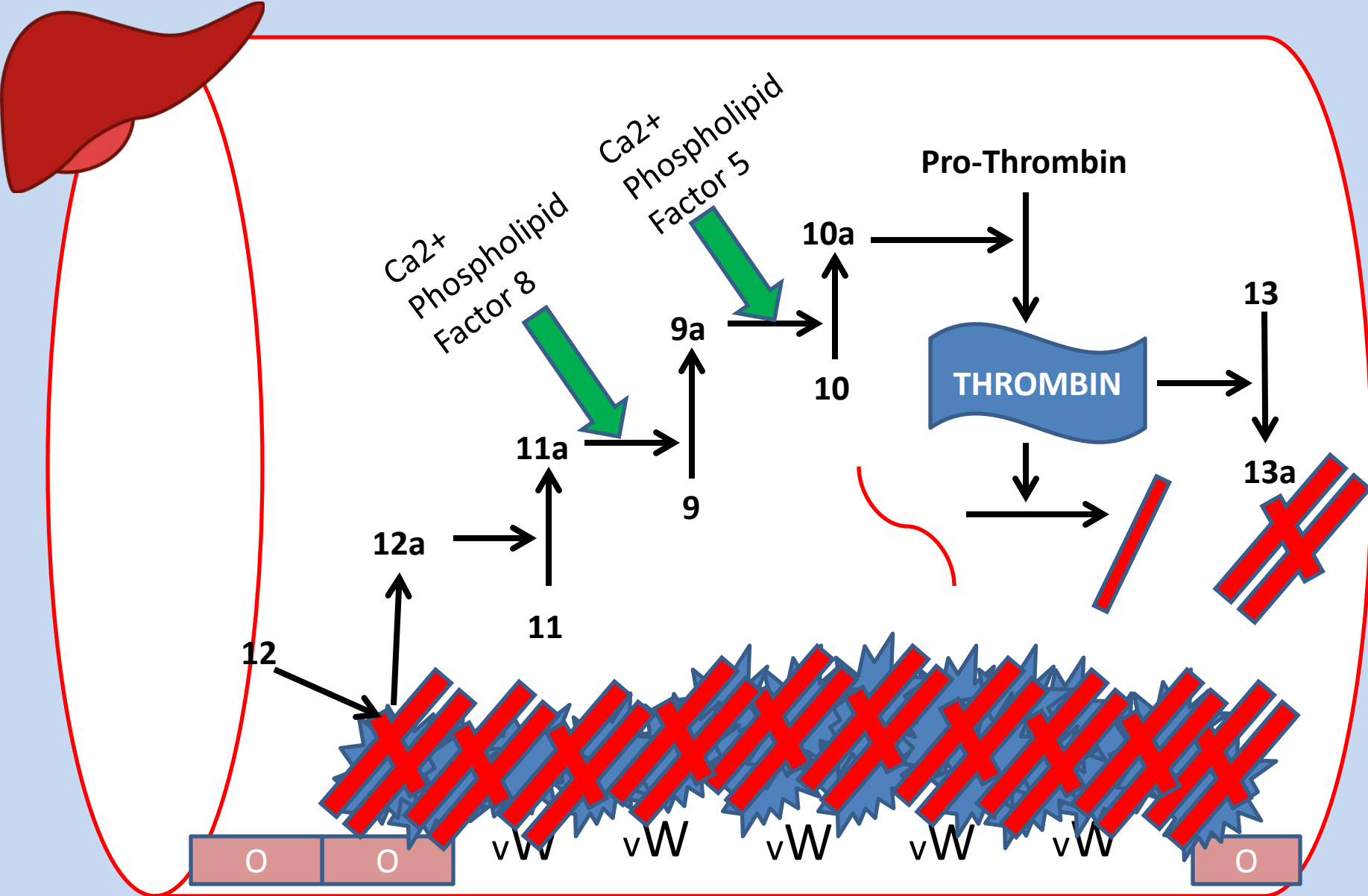


SECONDARY PLATELET PLUG



Recombinant Factor 7a

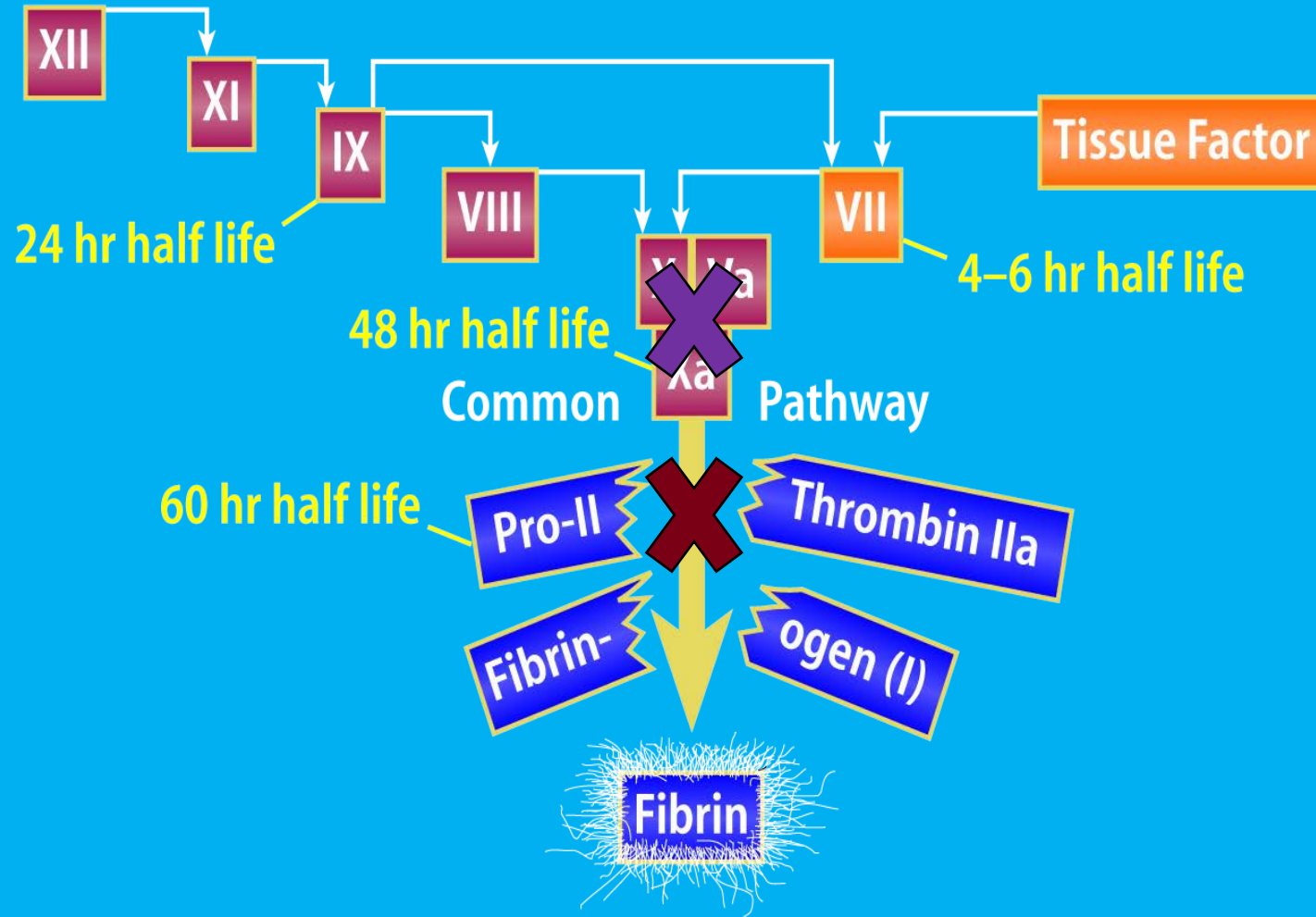
IF YOU WERE TO DESIGN AN ANTICOAGULANT???



Dabigatran, Rivaroxaban, & Apixaban

Intrinsic Pathway

Extrinsic Pathway



REVERSAL OF NEW ORAL ANTICOAGULANTS

IS IT REALLY POSSIBLE?

Measurement of effect

- Is the medication still in the body?
 - History
 - Half-life and renal/hepatic function
 - Laboratory test
 - Thrombin time
 - Anti-Xa assay

Do they affect the PT / INR and PTT?

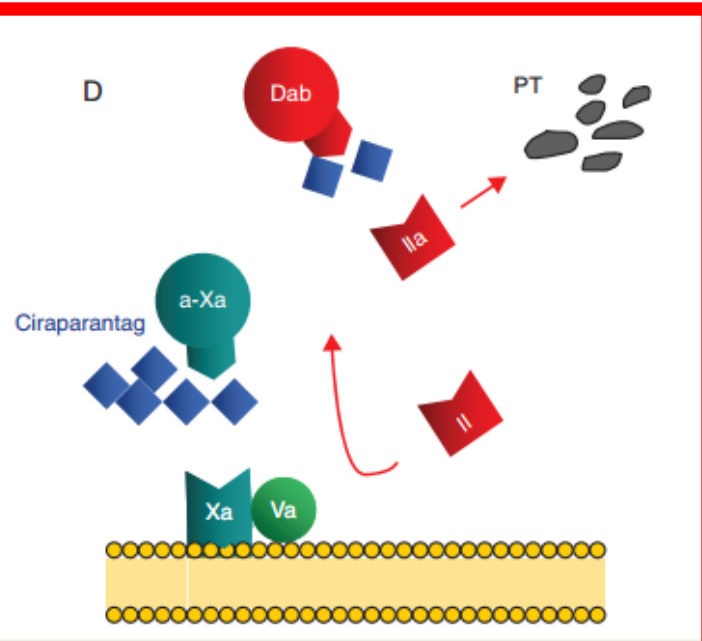
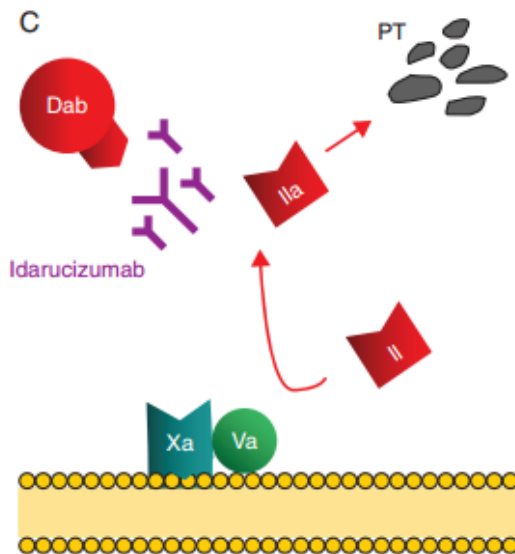
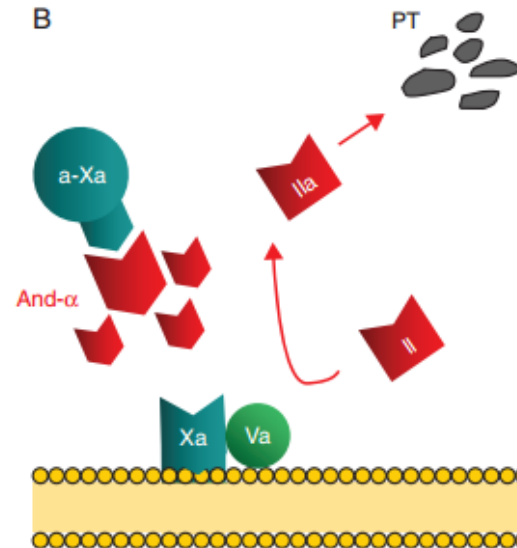
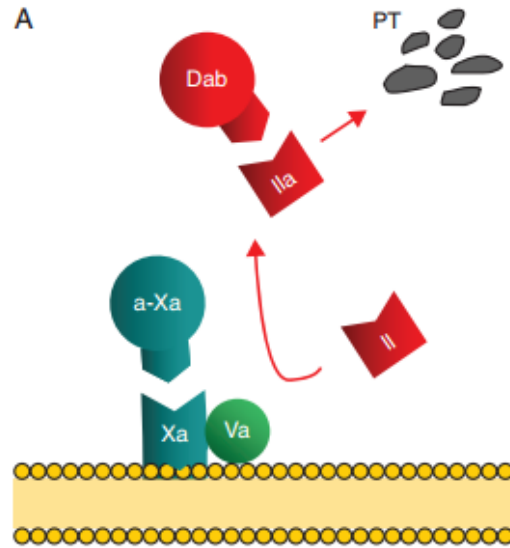
- **Yes, to varying degrees**
- **Effect not linear**
 - ◆ **Cannot be used clinically**
- **Source of great confusion and risk**
 - ◆ **Physicians may not realize the reason and/or implication**
 - ◆ **Clinical history MUCH more important than INR or PTT value!**

Emergent reversal

- No specific antidote at this time
- Guidelines are institution-specific
 - Stop medication
 - Activated charcoal
 - Coagulation factor concentrates

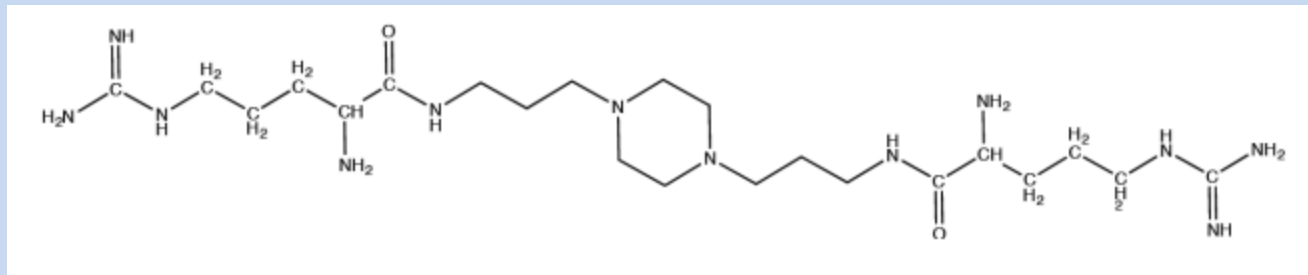


Universal Antidote



Universal Antidote (cont.)

- Ciraparantag
 - Small synthetic molecule that binds to unfractionated heparin, LMWH, fondaparinux, dabigatran, and direct Xa inhibitor through hydrogen binding and charge-charge interaction
 - Animal study
 - Complete reversal of heparin, fondaparinux, dabigatran, rivaroxaban, apixaban, and edoxaban



Ciraparantag

- Phase 1

- IV ciraparantag (100 and 300 mg) restored whole-blood clotting time to baseline in 10 minutes and the effect was sustained for 24 hrs

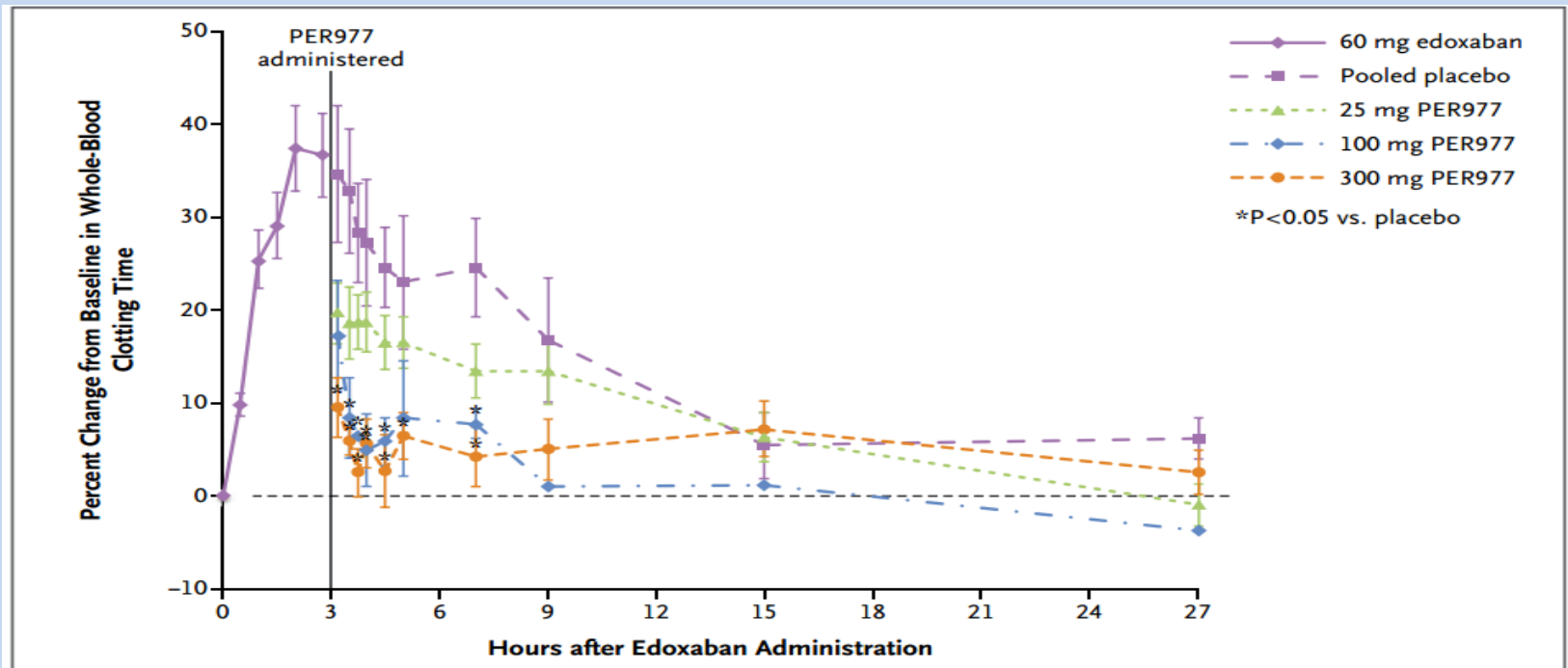
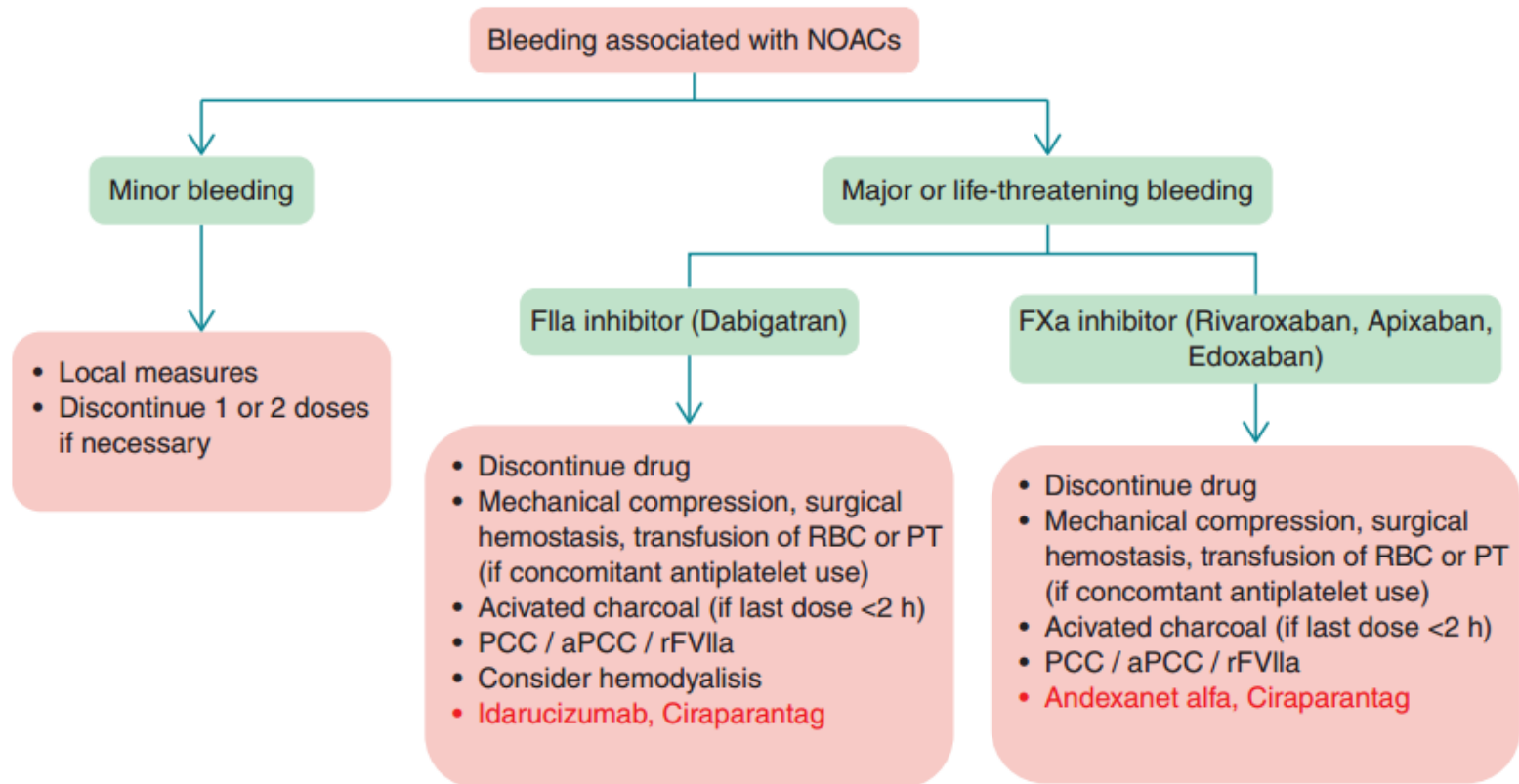


Figure 1. Effect of PER977 on Whole-Blood Clotting Time.

Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

Emergency Reversal – Algorithm



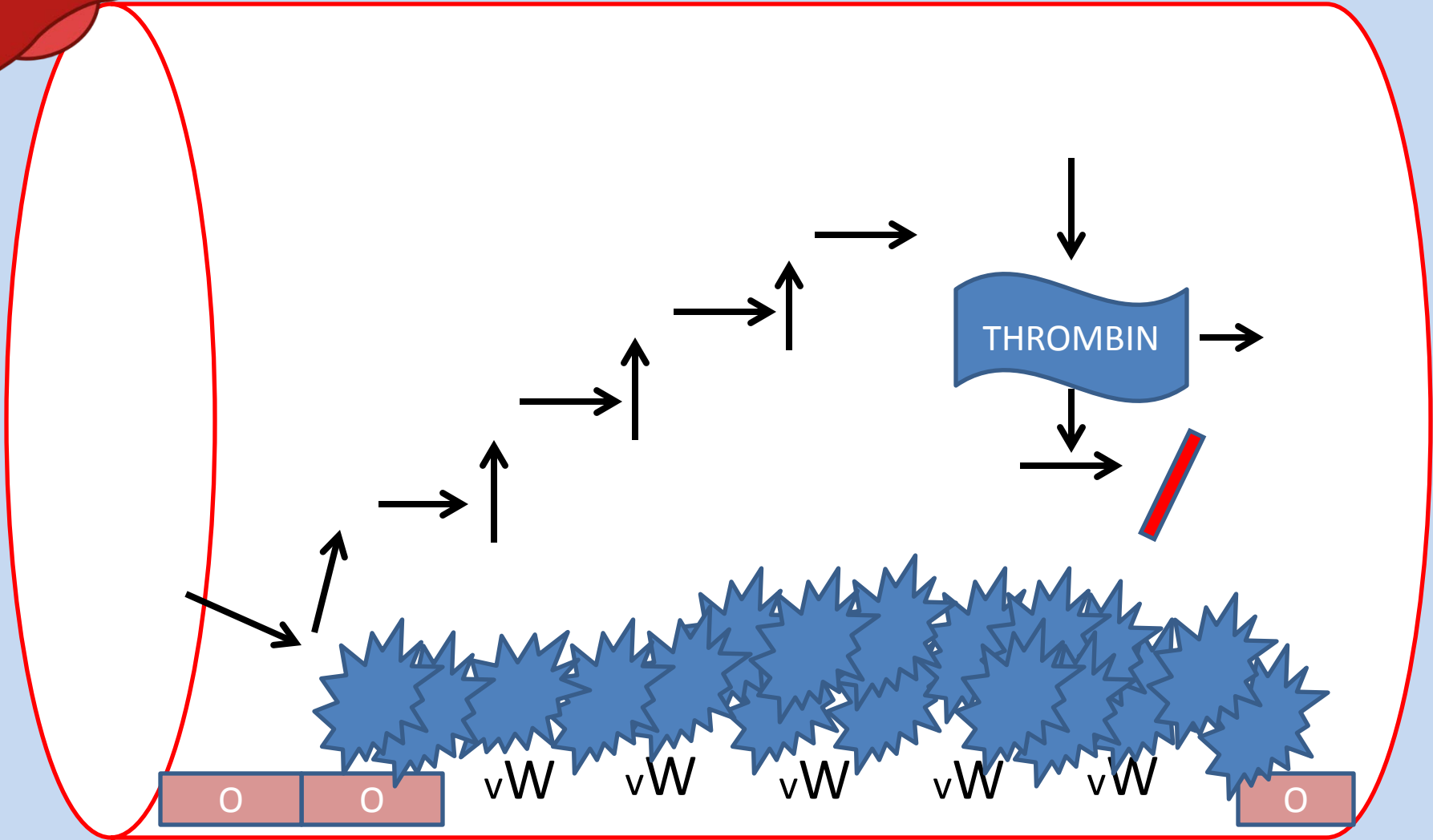
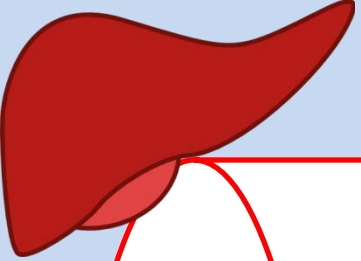
What have you learned today?

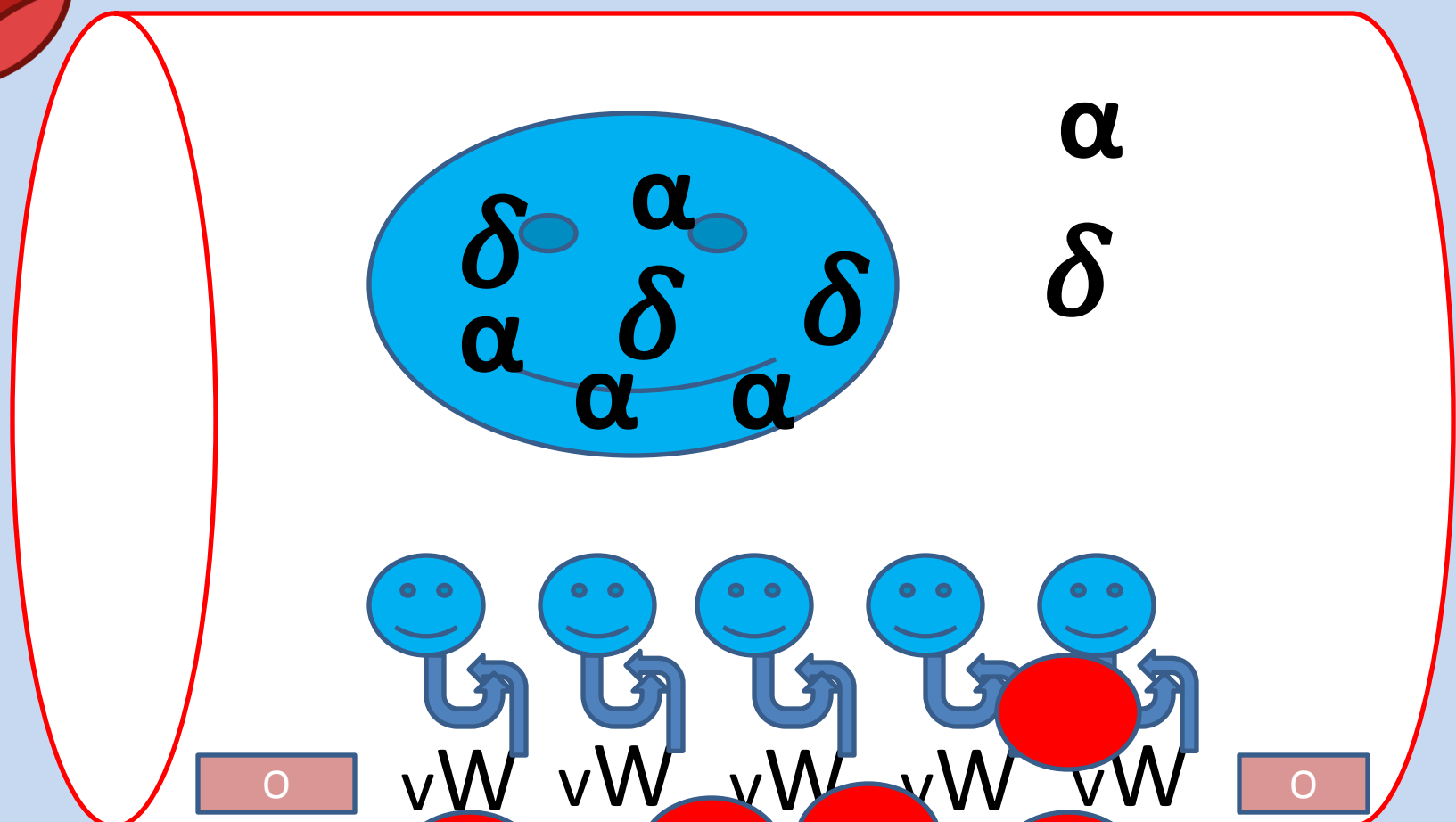
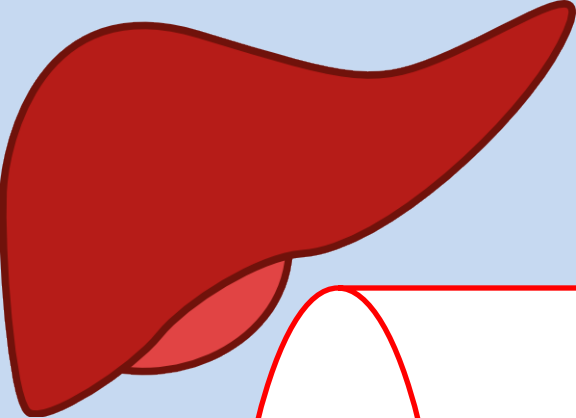
1. The normal state of blood is flowing and the endothelium normally functions to keep it that way (anticoagulant properties)
2. Vascular damage stops the anticoagulant properties of the endothelium and releases or activates pro-coagulant chemicals / enzymes
3. Many drugs can affect coagulation by different mechanism on platelets or coagulation factors
4. Blood products and /or factor concentrates can be used to assist in the coagulant process.
5. The current and future state of anticoagulant reversal.

The End



Botanical Gardens – Birmingham, AL





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 α δ δ
 α α

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vW

vW

vW

vW

vW

o

