Anticoagulación en Cardiopatías

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CÁTEDRA DE FISIOLOGïA

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Primaria → secundaria

Cuatro mecanismos

1. Espasmo vascular (**vasoconstricción**)

2. Formación del tapón plaquetario (**Adherencia y agregación**)

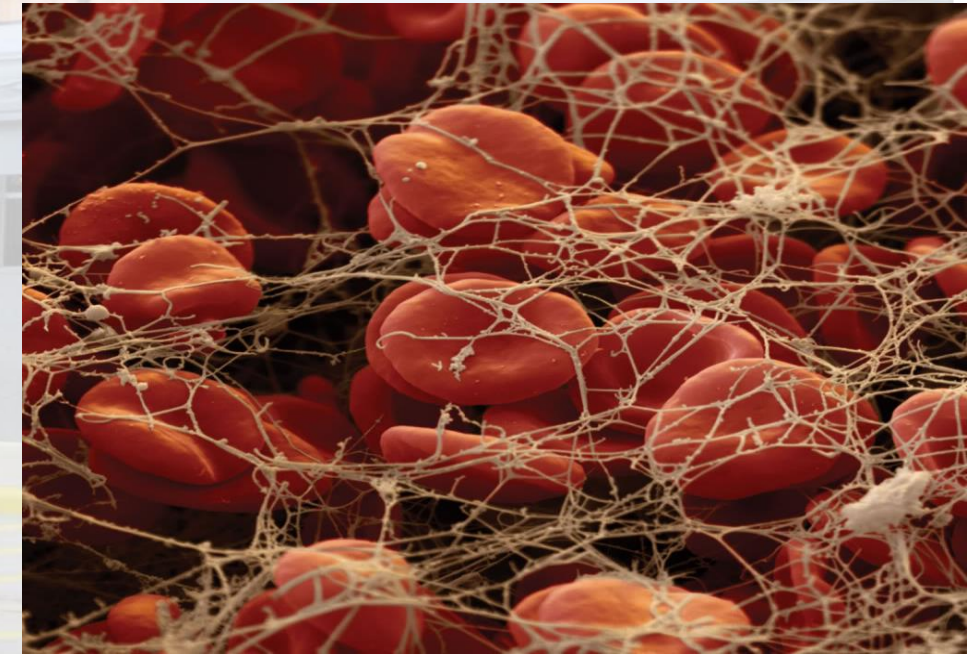
3. Coagulación

4. Organización y/o disolución del coagulo (Fibrinólisis)

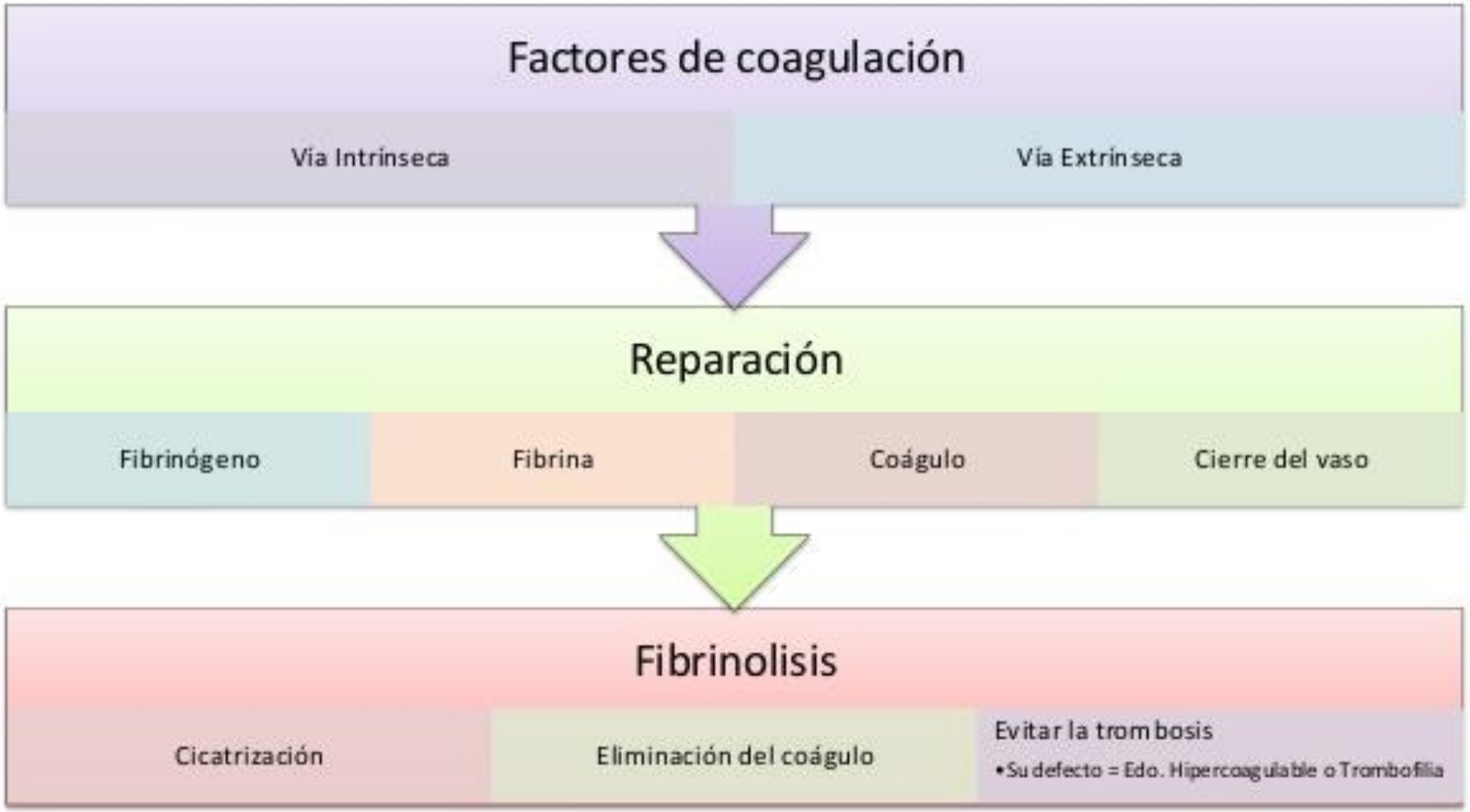
Coagulación

Fibrinógeno → **Fibrina**

plaquetario inestable
a
tapon hemostatico
estable



Fase Plasmática o Fluida

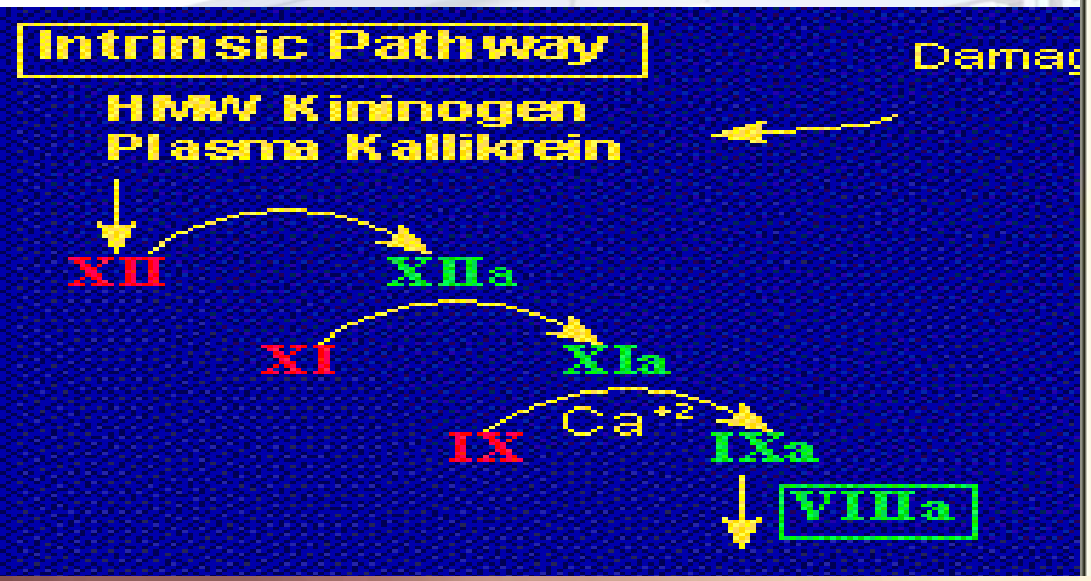


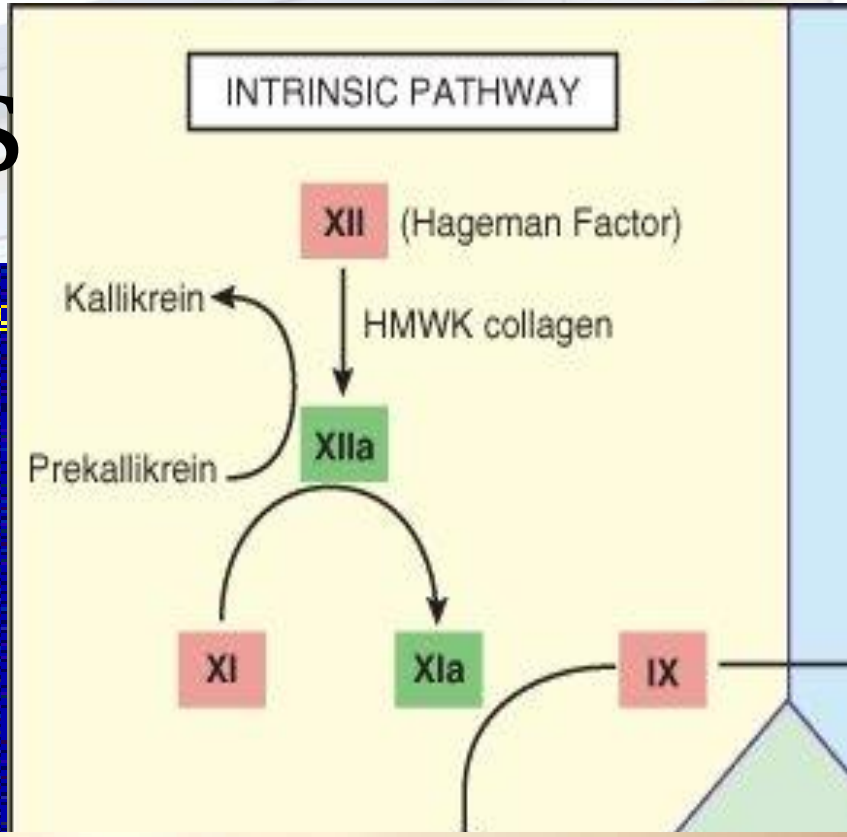
Factor	Nombre común	Función
I	Fibrinógeno	Se convierte en fibrina por acción de la trombina. La fibrina constituye la red de formación del coágulo.
II	Protrombina	Se convierte en trombina por la acción de Xa. La trombina catalisa la formación de fibrinógeno a partir de fibrina.
III	Tromboplastina o factor tisular	Se libera con el daño celular, activa al factor X por la vía extrínseca.
IV	Ión Calcio	Median la unión de los factores IX, X, VII y II a fosfolípidos de membrana.
V	Proacelerina	Potencia la acción de Xa sobre la protrombina.
VI	No existe	-
VII	Proconvertina	Participa en la vía extrínseca, forma un complejo con los factores III y IV para activar el factor X.
VIII C	Factor Antihemofílico	Indispensable para la acción del factor X. Su ausencia causa hemofilia A.
VIII R	Factor Von Willebrand	Media la unión del factor VIII C a plaquetas. Su ausencia causa la enfermedad de Von Willebrand.
IX	Factor Christmas	Su activación y unión con los complejos IX, VIII y IV activan al factor X. Su ausencia causa hemofilia B.
X	Factor Stuart-Power	Responsable de la hidrólisis de protrombina para formar trombina.
XI	Tromboplastina Plasmática	Convertido en la proteasa XIa por la acción del factor XII, activa al factor IX.
XII	Factor Hageman	Activa al factor XI, en contacto de una superficie extraña.
XIII	Factor Lali Lorand	Por la acción de trombina, forma enlaces cruzados entre lisina y glutamina contiguos de las fibrinas, estabilizándolos.
Precalicreína	Factor Fletcher	Estando activa, activa al factor XII.
Cinbinógeno	Factor Fitzgerald-Flaujeac-Williams	Ayuda también a la activación del factor XII.

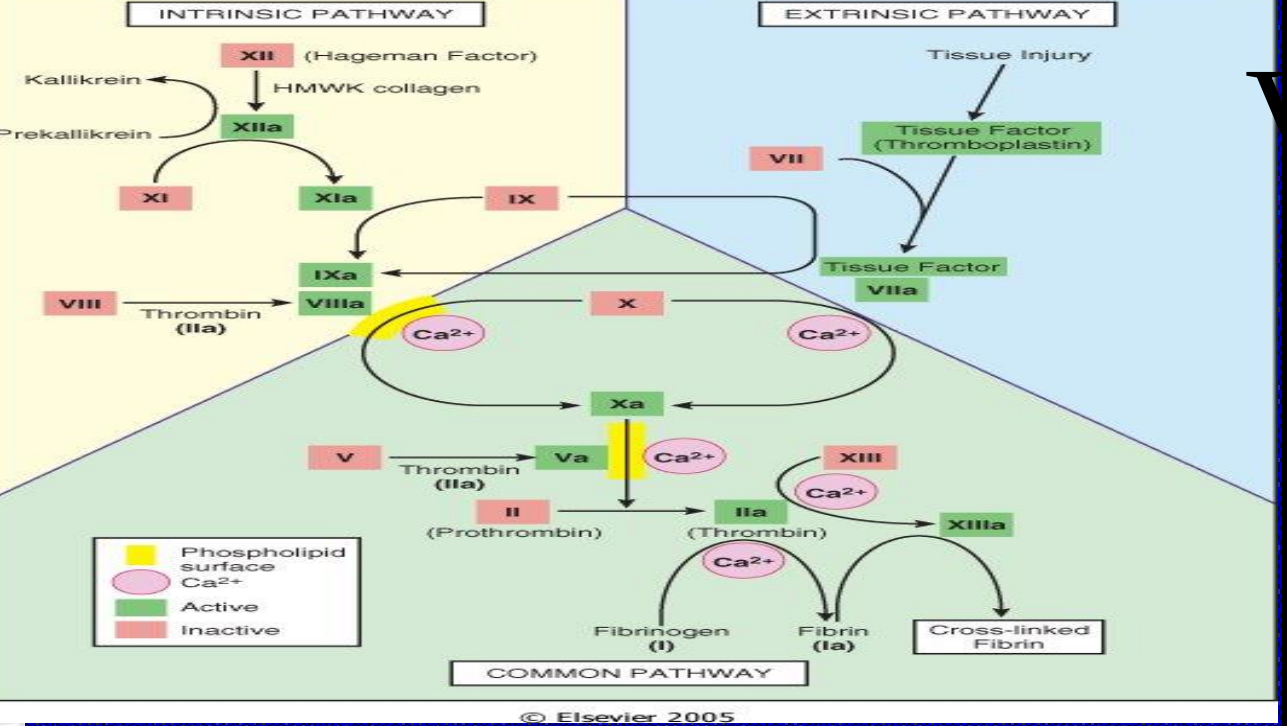
Clotting factor number	Clotting factor name	Function
I	Fibrinogen	Clot formation
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets
III	TF	Co factor of VIIa
IV	Calcium	Facilitates coagulation factor binding to phospholipids
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex
VI	Unassigned	
VII	Stable factor, proconvertin	Activates factors IX, X
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II
XI	Plasma thromboplastin antecedent	Activates factor IX
XII	Hageman factor	Activates factor XI, VII and prekallikrein
XIII	Fibrin-stabilising factor	Crosslinks fibrin
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen
XV	HMWK- (F Fitzgerald)	Co factor
XVI	vWf	Binds to VIII, mediates platelet adhesion
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases
XVIII	Heparin cofactor II	Inhibits IIa
XIX	Protein C	Inactivates Va and VIIIa
XX	Protein S	Cofactor for activated protein C

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor

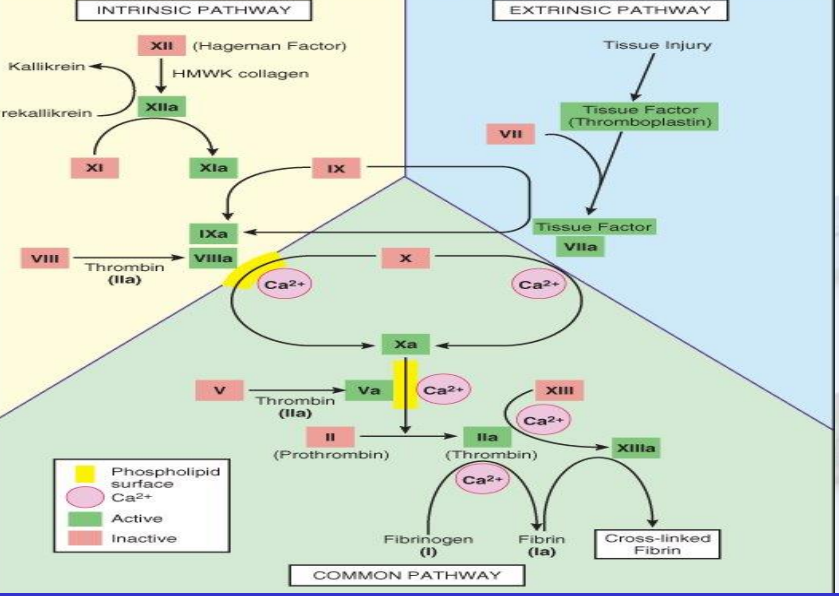
Vía Intrínsecas



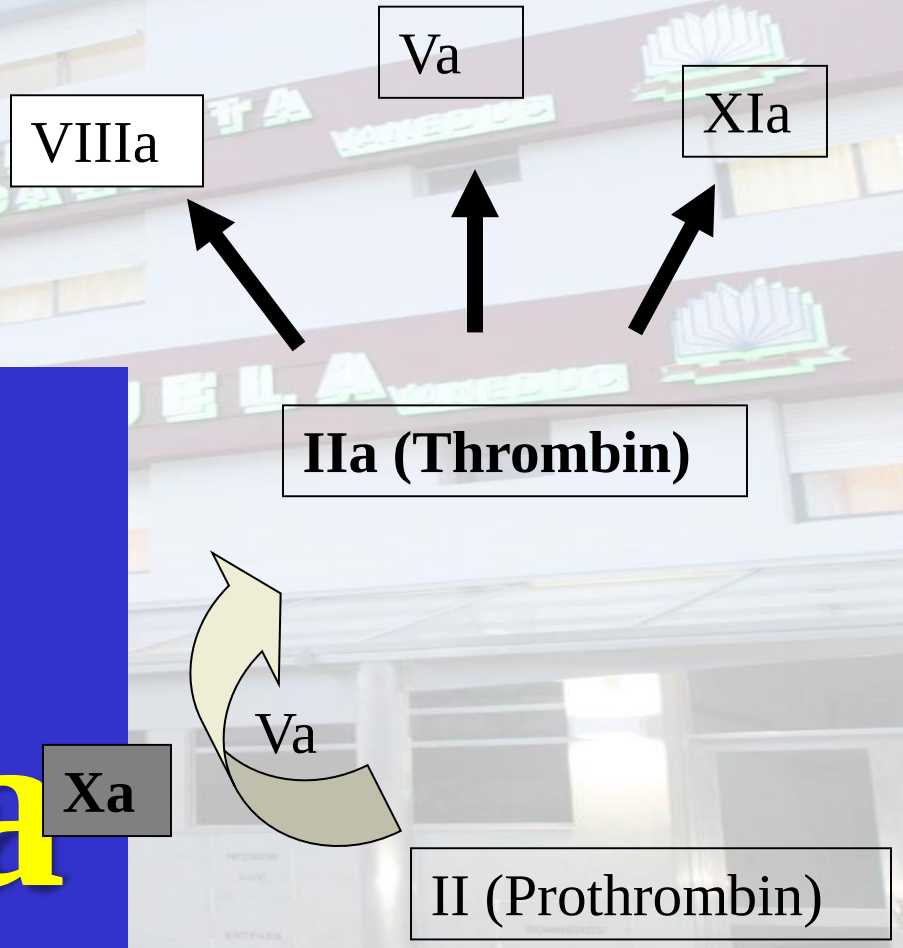



INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII
(Hageman Factor)
Kallikrein
HMWK collagen
Prekallikrein
XIIa
XI
XIa
IX
Tissue Injury
Tissue Factor
(Thromboplastin)
VII
IXa
Tissue Factor
VIIa
VIII
Thrombin
(IIa)
VIIIa
X
Ca2+
Ca2+
Xa
V
Thrombin
(IIa)
Va
Ca2+
XIII
Ca2+
II
(Prothrombin)
IIa
(Thrombin)
XIIIa
Ca2+
Phospholipid surface
Ca2+
Active
Inactive
Fibrinogen
(I)
Fibrin
(Ia)
Cross-linked Fibrin
COMMON PATHWAY
© Elsevier 2005

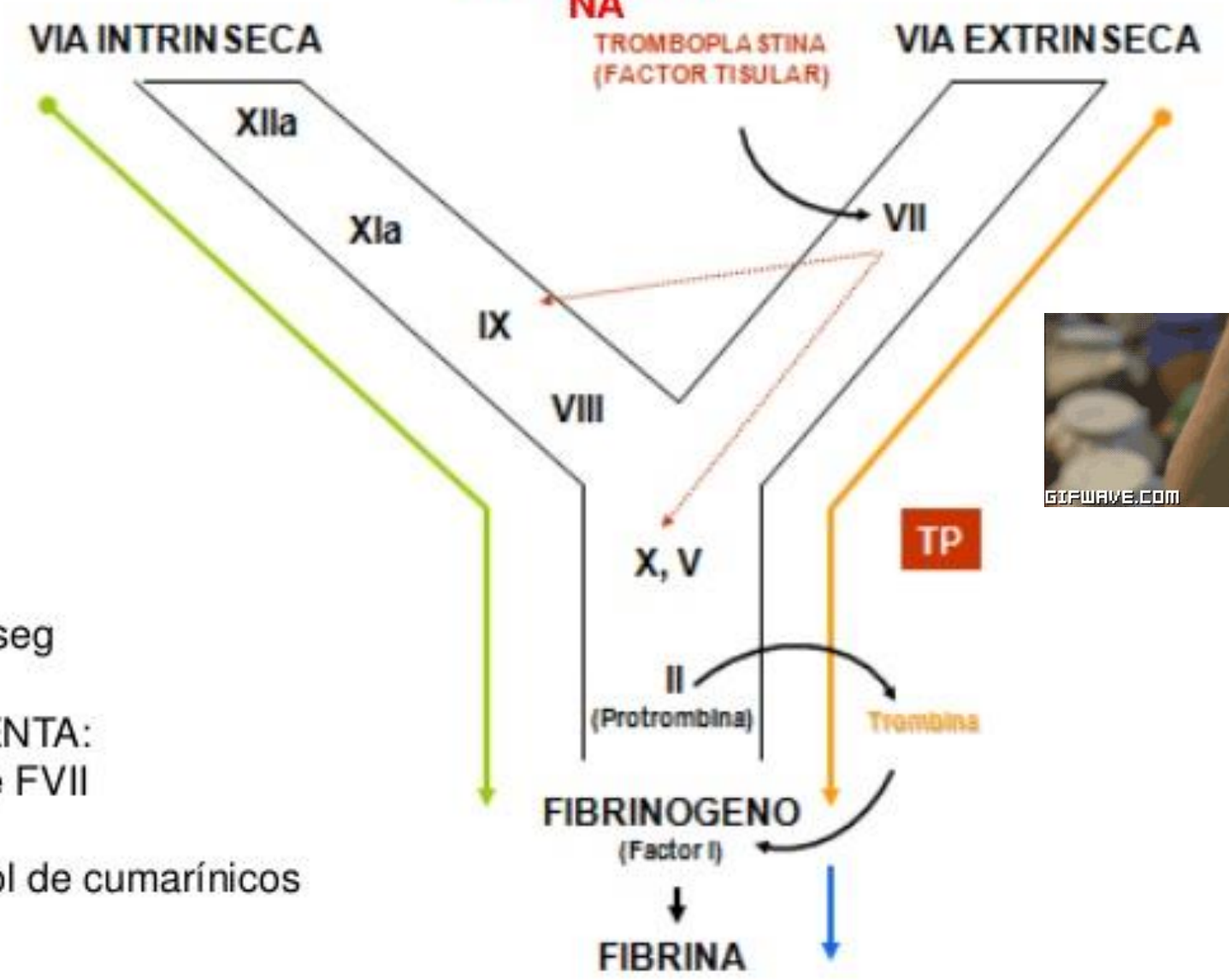
Xa



Efecto multiplicador



TIEMPO DE PROTROMBINA



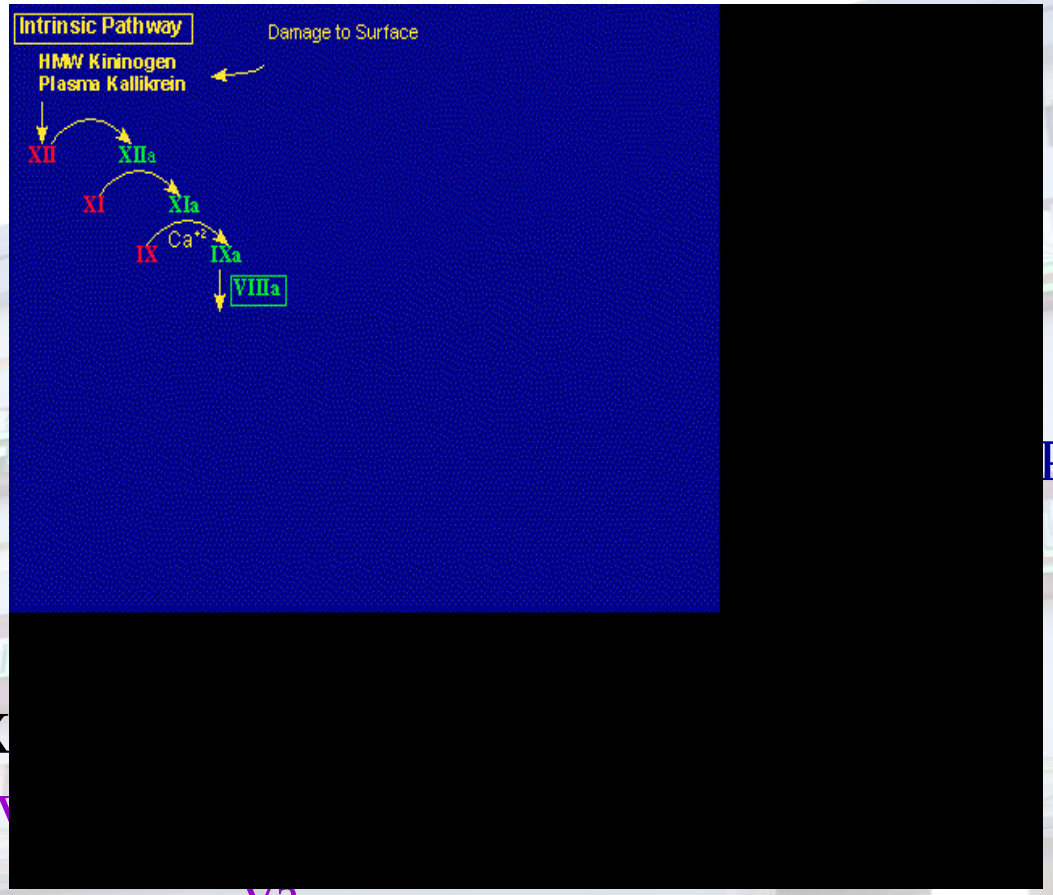
12-14seg
INR
AUMENTA:
Def de FVII
CID
Control de cumarínicos

FIBRINÓGENO

- Se cuantifica por el método coagulométrico (técnica de Clauss)
- Los valores normales son de 2 a 4 g/L (200 a 400 mg/dL)
- ↓ de 100 mg/dl pueden limitar de manera significativa la formación de fibrina

- Se incrementa fisiológicamente en el embarazo y en algunas infecciones o procesos inflamatorios o estados pretrombóticos, e incluso en el infarto al miocardio.
- Disminuido en hepatopatías graves, disfibrinogenemia, CID o fibrinólisis

Intrinsic pathway



XIIa

XIa

IX

Va

Pathway

Trombina

Fibrinogen
o

Fibrina

Coagulo blando

XIIIa

Fibrina

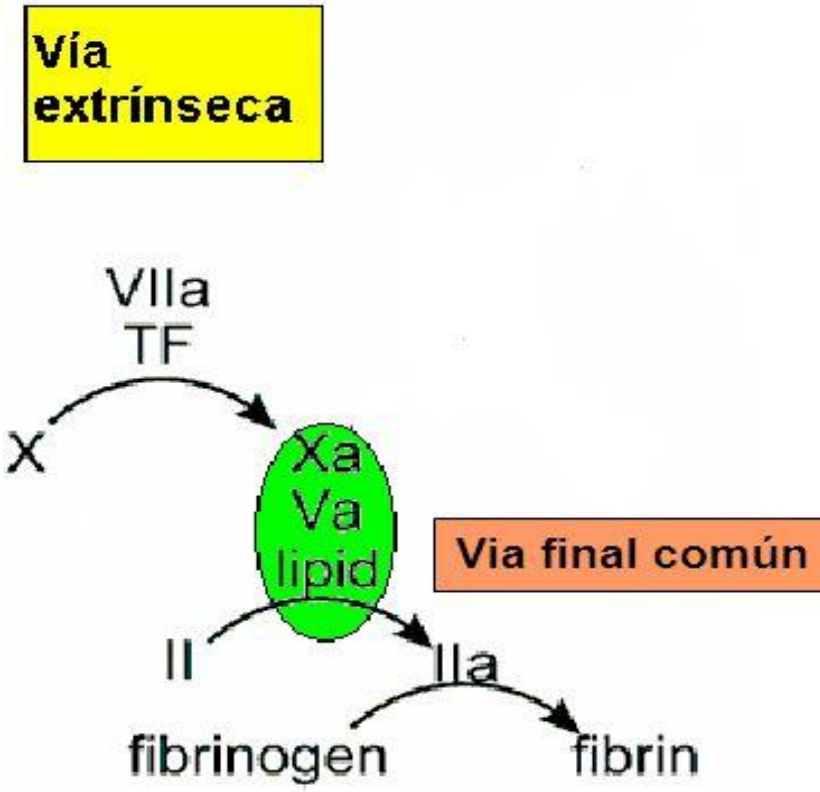
Coagulo estable

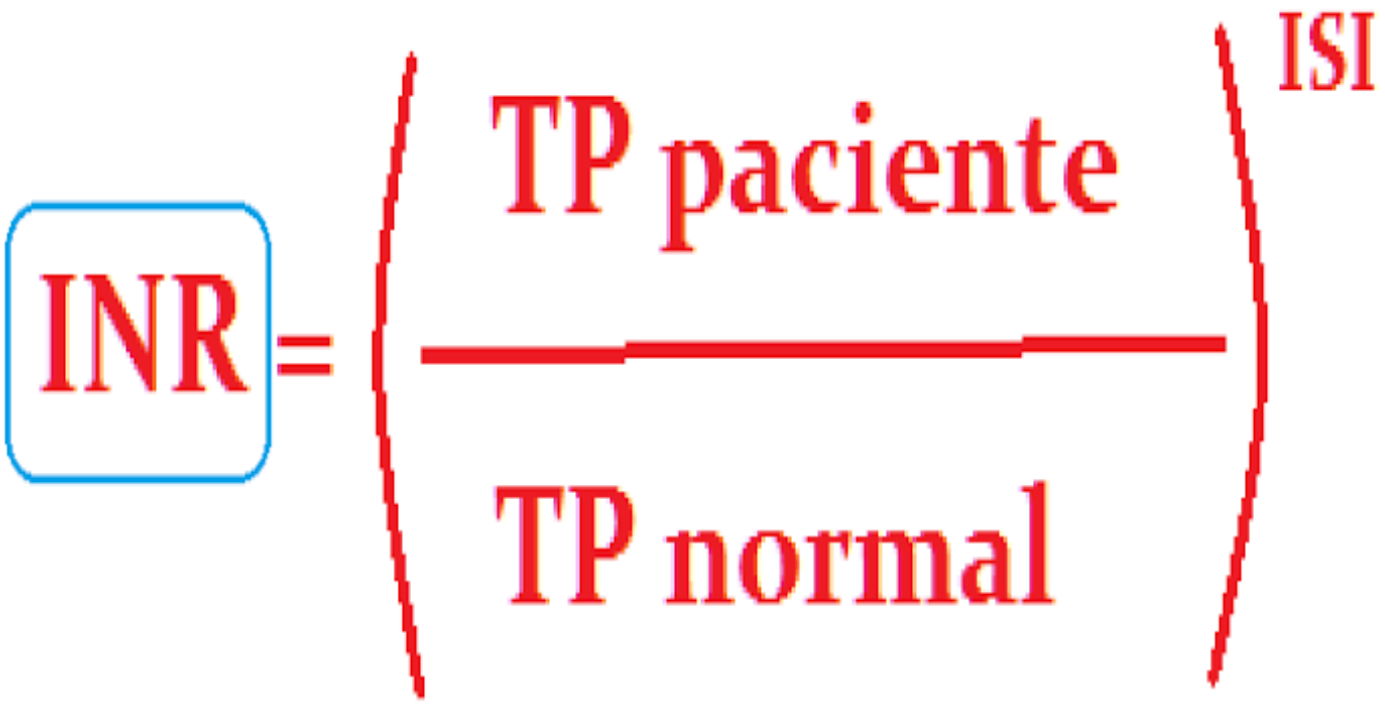
KPTT

- La anticoagulacion se mide por el KPTT (tiempo de tromboplastina parcial activada) y estamos en la dosis correcta cuando se ha duplicado
- KPTT: Es un examen que mide la capacidad de la sangre para coagular.
- Mide la eficacia de la vias intrinsecas (factor IX y cofactores) y la via comun de la coagulacion(factor X y II y cofactores

TIEMPO de PROTOMBINA O QUICK

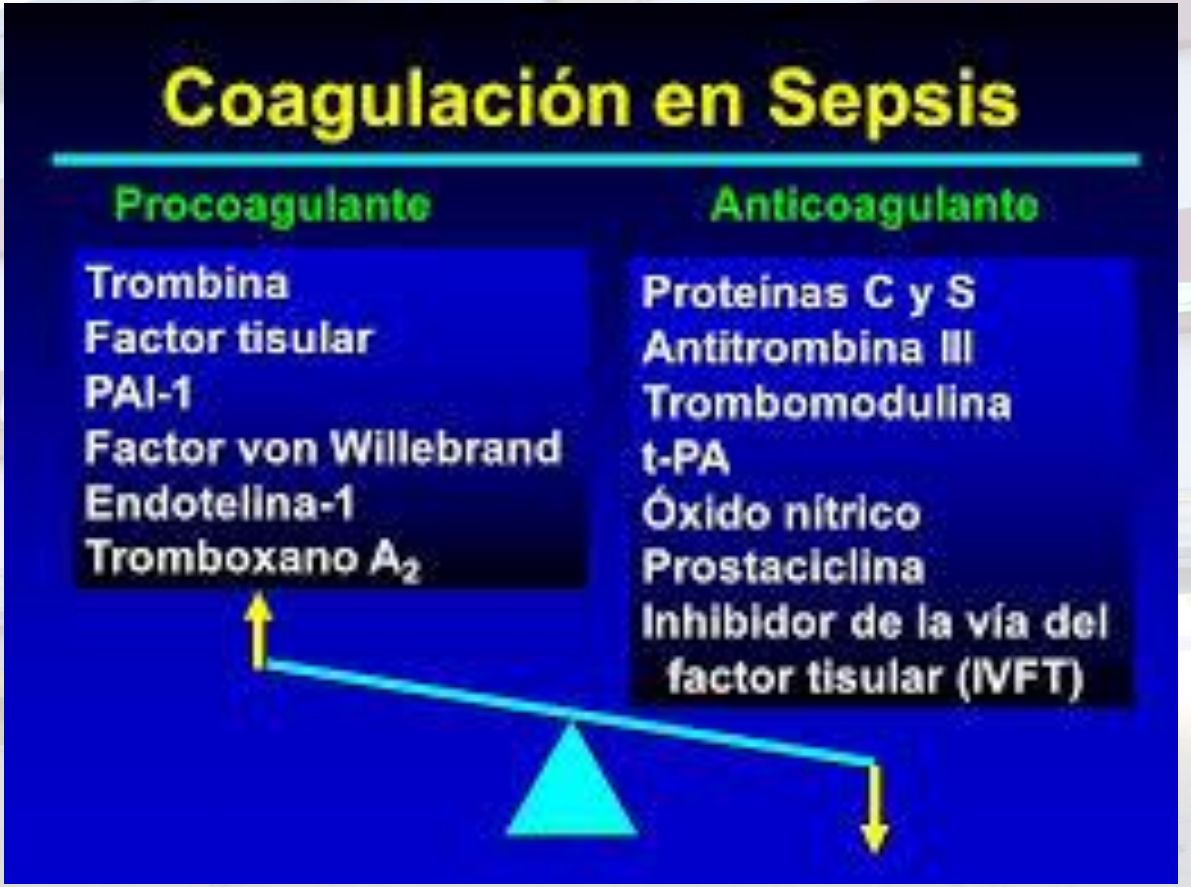
- EVALUA VIA EXTRINSECA (FVII, FX, FV Y FII)
- TIEMPO DE COAGULACION CON TROMBOPLASTINA / CALCIO
- SE EXPRESA COMO:
  - % DE ACTIVIDAD
  - INR (PACIENTES ANTICOAGULADOS)
- VN: 70-120%
- SENSIBLE A ↑ CONCENTRACION DE HEPARINA




INR = (TP paciente / TP normal)^ISI

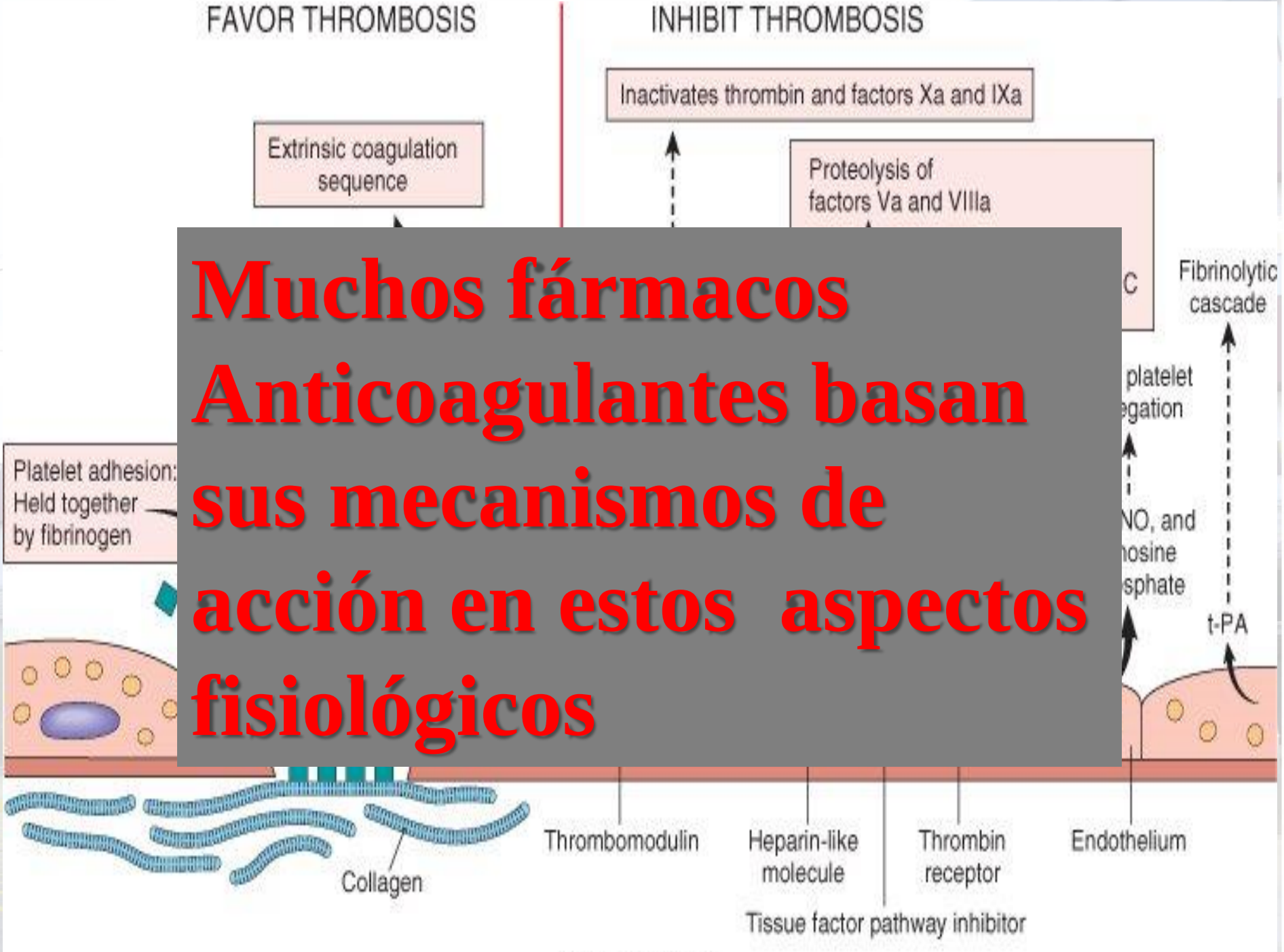
Equilibrio Trombosis

Anti trombosis


Coagulación en Sepsis
Procoagulante
Trombina
Factor tisular
PAI-1
Factor von Willebrand
Endotelina-1
Tromboxano A_2
Anticoagulante
Proteínas C y S
Antitrombina III
Trombomodulina
t-PA
Óxido nítrico
Prostaciclina
Inhibidor de la vía del factor tisular (IVFT)

ROL ANTICOAGULANTE DE LAS CELULAS ENDOTELIALES

Action	Result
Normally provide an intact barrier between the blood and subendothelial connective tissue	Platelet aggregation and the formation of tissue factor/factor VIIa complexes are not triggered
Synthesize and release PGI_2 and nitric oxide	These inhibit platelet activation and aggregation
Secrete tissue factor pathway inhibitor	Inhibits the ability of tissue factor/factor VIIa complexes to generate factor Xa
Bind thrombin (via thrombomodulin), which then activates protein C	Active protein C inactivates clotting factors VIII and V
Display heparin molecules on the surfaces of the plasma membranes	Heparin binds antithrombin III, and this molecule then inactivates thrombin and several other clotting factors
Secrete tissue plasminogen activator	Tissue plasminogen activator catalyzes the formation of plasmin, which dissolves clots



Muchos fármacos Anticoagulantes basan sus mecanismos de acción en estos aspectos fisiológicos

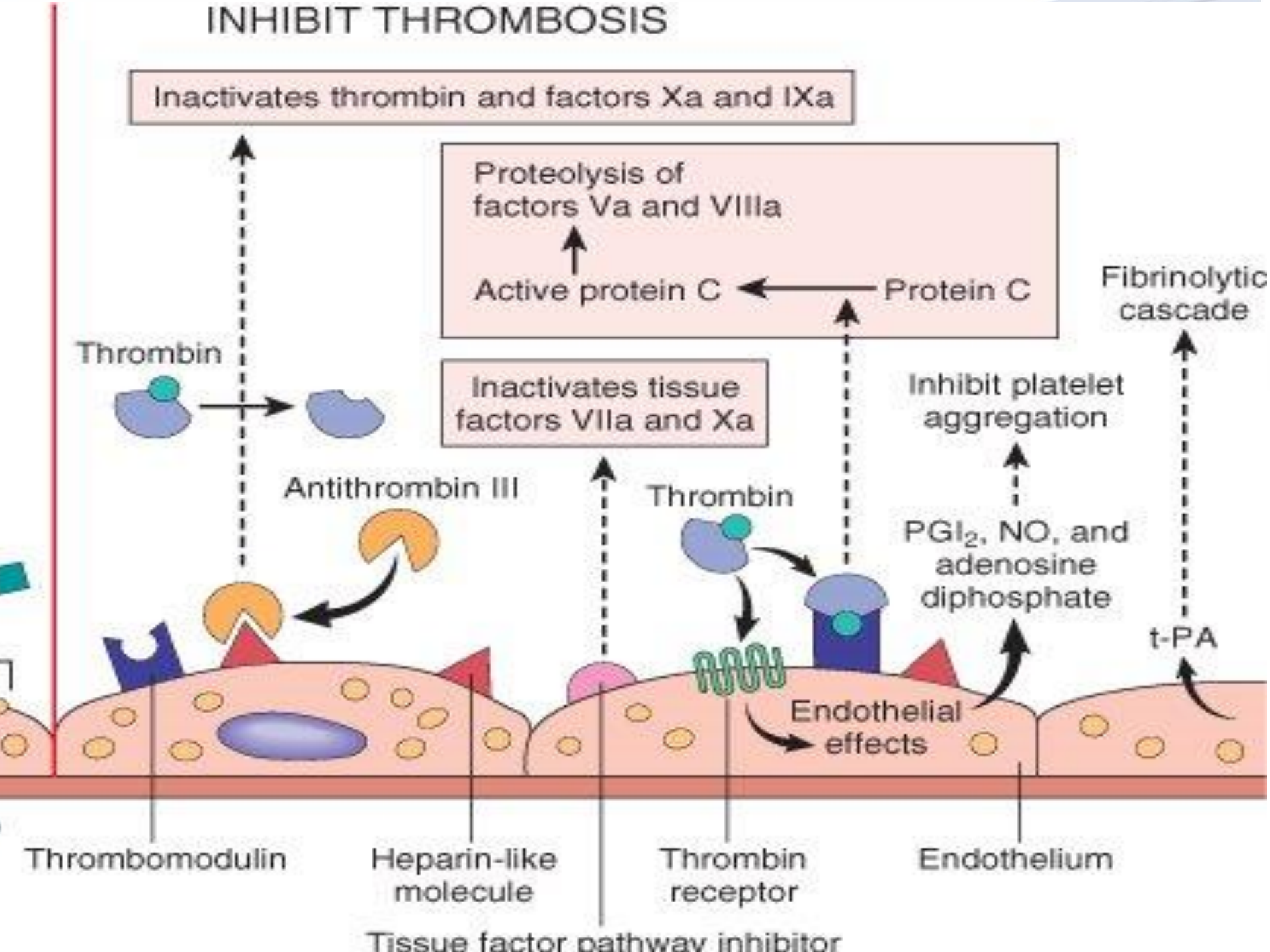
FACRORES FISIOLOGICOS ANTICOAGULANTES Y FIBRINOLITICOS

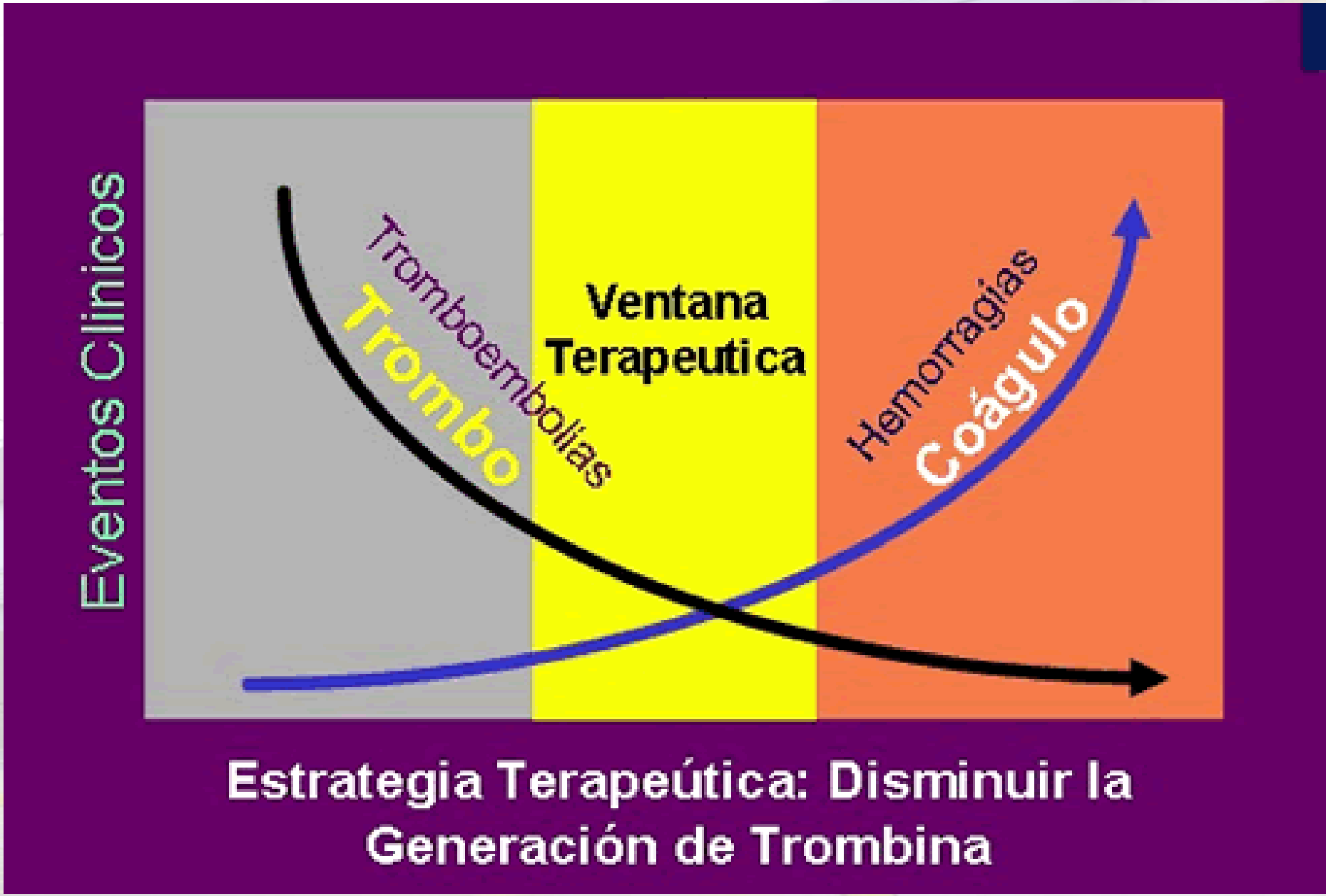
ANTICOAGULANTES ENDOGENOS

- TROMBOMODULINA
- ANTITROMBINA III
- INHIBIDORES DEL FACTOR TISULAR
- EFECTO ANTITROMBOTICO DE LA TROMBINA

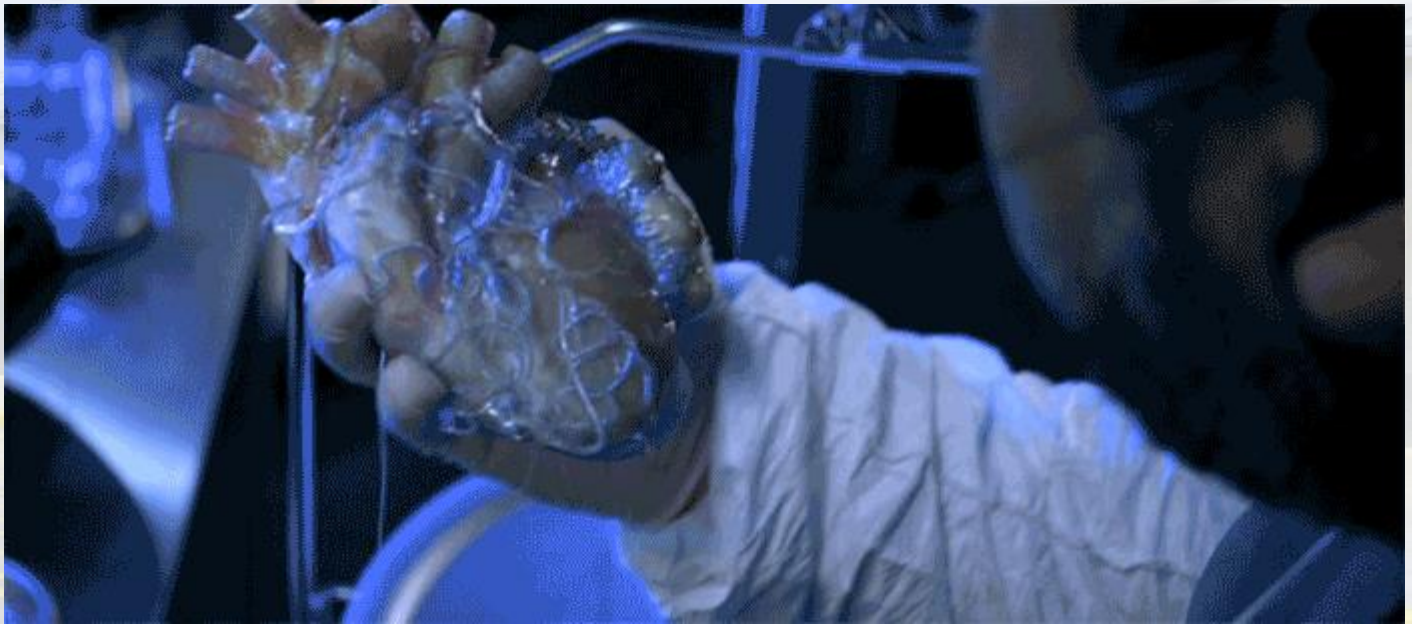
FIBRINOLISIS

- ACTIVADOR DEL PLASMINOGENO EN PLASMINA


INHIBIT THROMBOSIS
Inactivates thrombin and factors Xa and IXa
Proteolysis of factors Va and VIIIa
Active protein C
Protein C
Fibrinolytic cascade
Thrombin
Inactivates tissue factors VIIa and Xa
Inhibit platelet aggregation
Antithrombin III
Thrombin
PGI2, NO, and adenosine diphosphate
t-PA
Endothelial effects
Thrombomodulin
Heparin-like molecule
Thrombin receptor
Endothelium
Tissue factor pathway inhibitor


Eventos Clinicos
Tromboembolias
Trombo
Ventana
Terapeutica
Hemorragias
Coágulo
Estrategia Terapeútica: Disminuir la
Generación de Trombina

TRATAMIENTO ANTICOAGULANTE EN AFECCIONES CARDIOVASCULARES



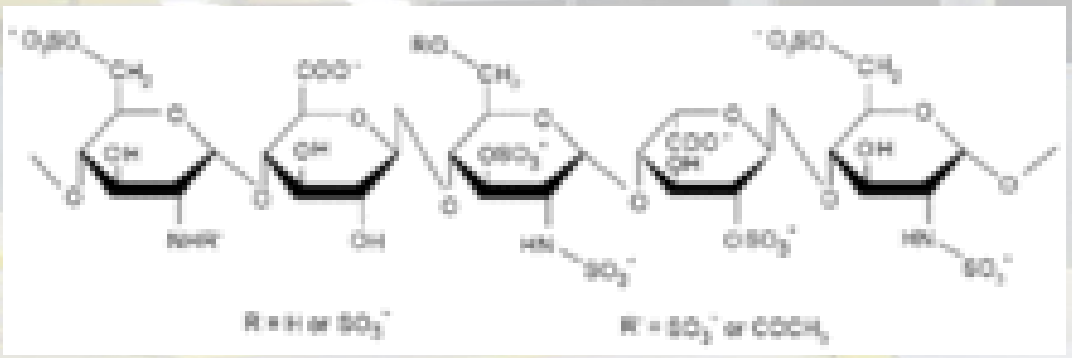
Anticoagulantes clásicos

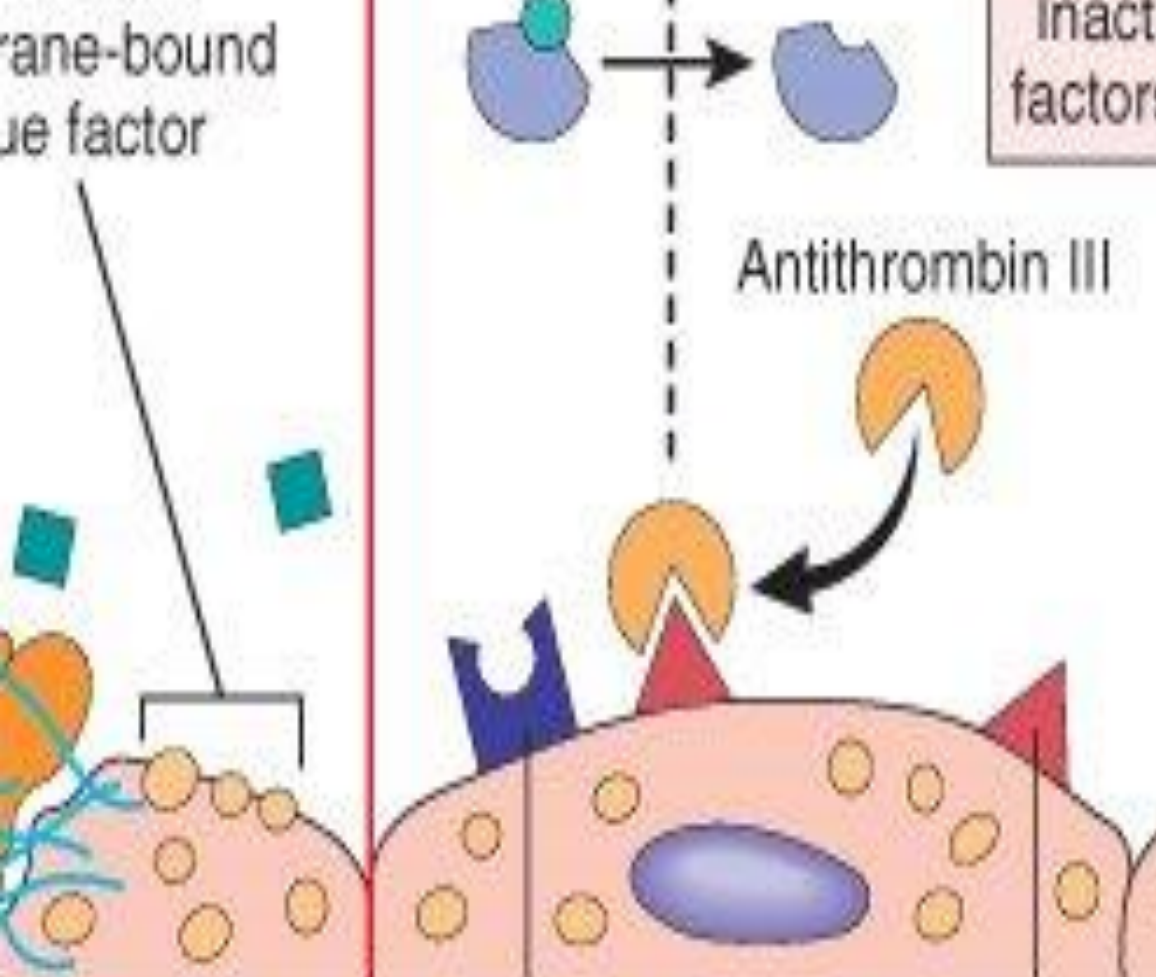
Heparina sódica

Antagonistas de la vitamina k

Heparina

La **heparina** (del griego *ἥπαρ*, hepar,"hígado")





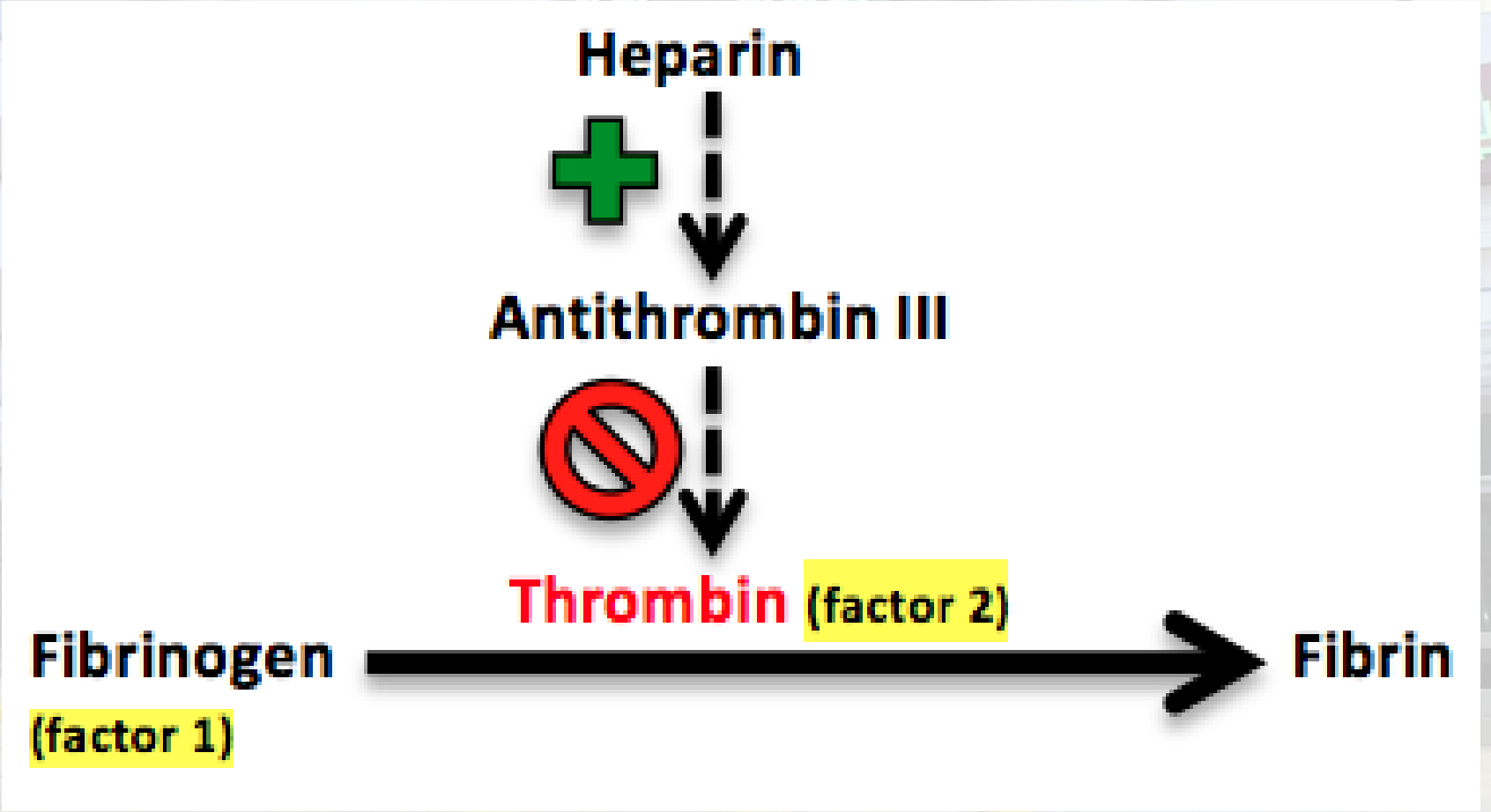
La antitrombina es una pequeña molécula que desactiva varias enzimas de la coagulación. La afinidad por éstas (su efectividad) está potenciada por la heparina. Acelerando la acción de la antitrombina III en 1000 veces.

En la insuficiencia renal (especialmente en el síndrome nefrótico), la antitrombina se pierde en la orina, lo cual lleva a una mayor actividad del Factor II y del Factor X, y a una marcada propensión a la trombosis.

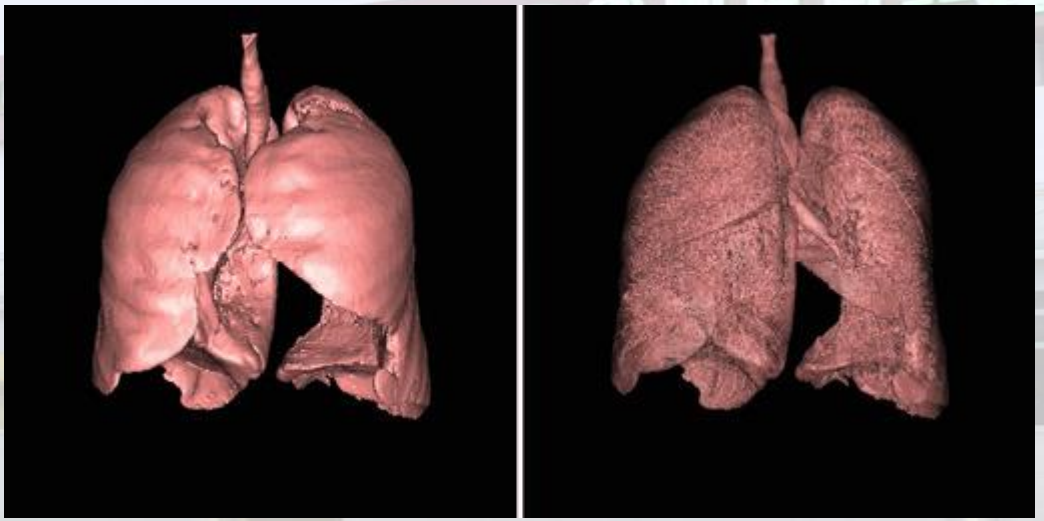
HEPARINA SODICA

La heparina clásica ejerce su efecto anticoagulante acelerando la formación de complejos moleculares entre la antitrombina III y los factores II (trombina), IX, X, XI y XII, que quedan inactivados. Tiene particular importancia la acción ejercida sobre la trombina y el factor X.

Se encuentra naturalmente en pulmones, hígado, piel y células cebadas (mastocitos).



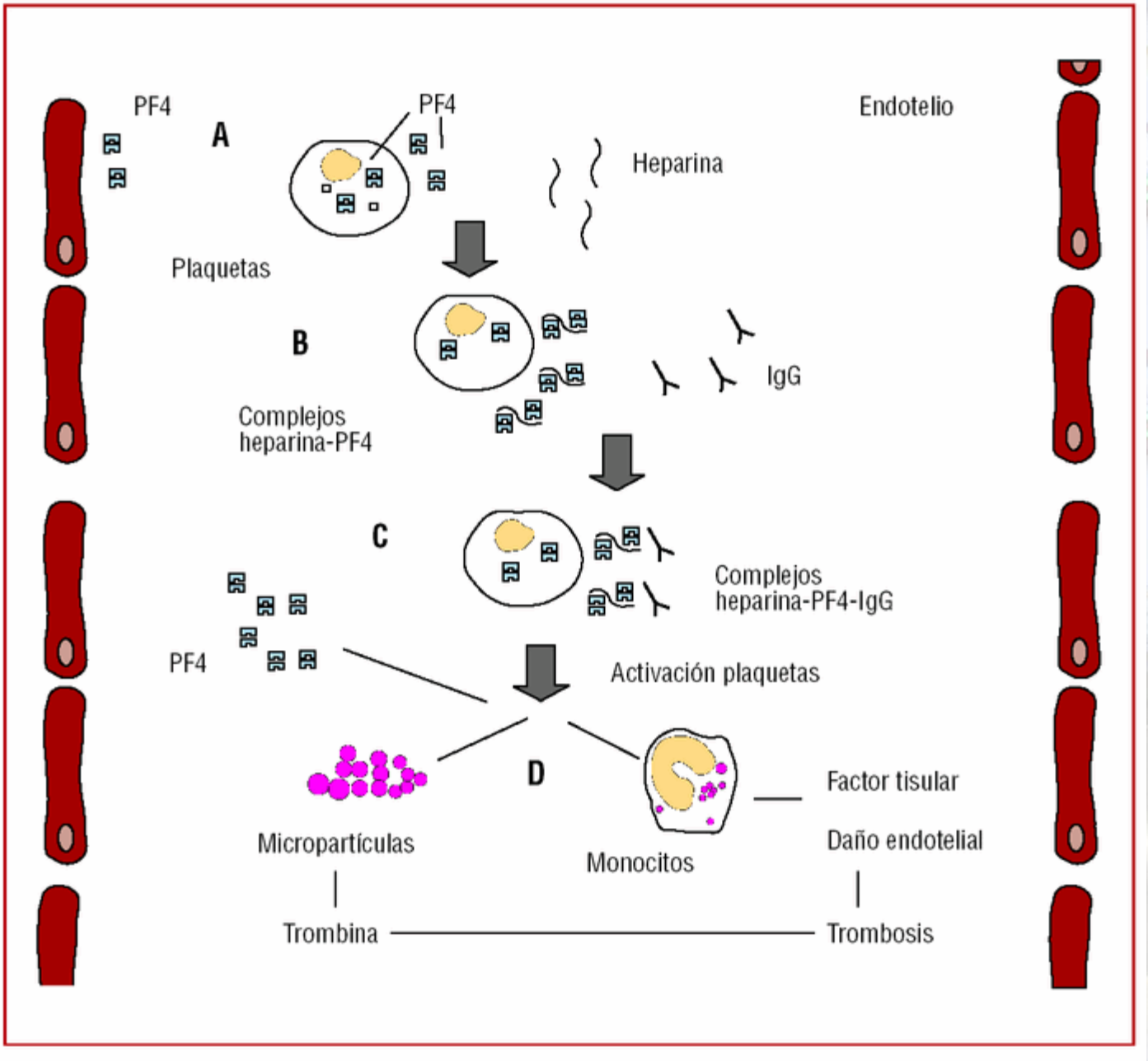
La Heparina en el Tratamiento farmacológico actual del trombo embolismo pulmonar



Trombocitopenia inducida por heparina

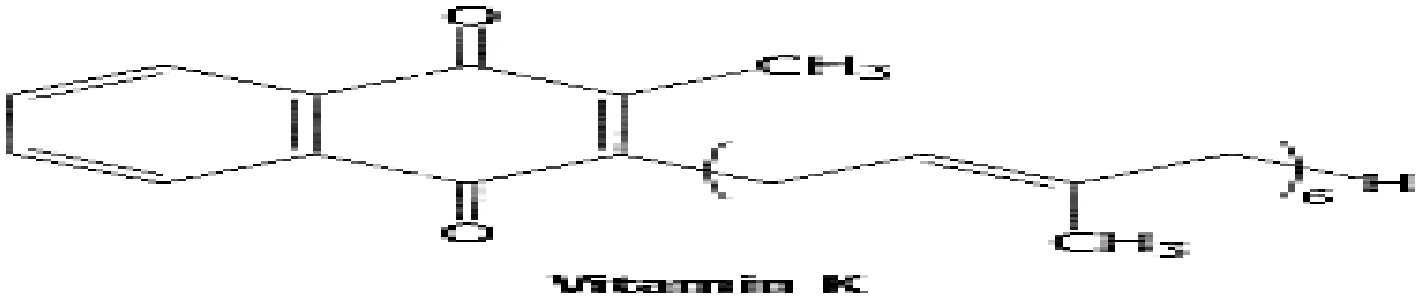
La heparina tiene una gran afinidad por el factor 4 plaquetario (PF4), en los gránulos alfa de las plaquetas y en la superficie de algunas células como las endoteliales y las plaquetas.

Cuando la heparina y el PF4 se unen forman un complejo heparina-PF4 que sufre un cambio conformacional y expone nuevos epítropes, que actúan como inmunógenos

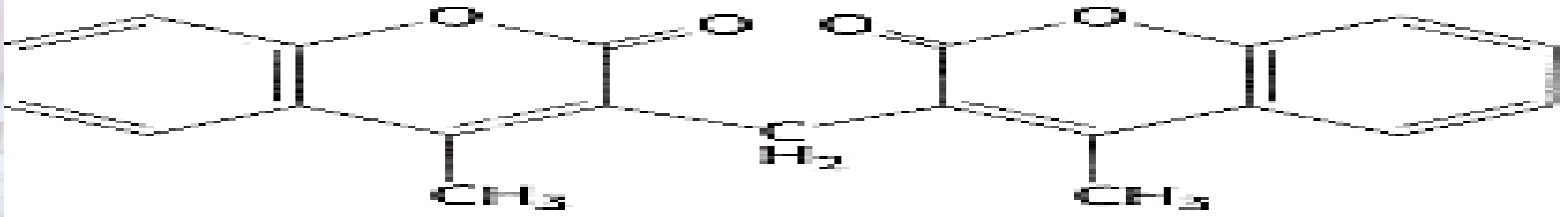

PF4
A
PF4
Endotelio
Heparina
Plaquetas
B
IgG
Complejos
heparina-PF4
C
Complejos
heparina-PF4-IgG
PF4
Activación plaquetas
D
Factor tisular
Micropartículas
Daño endotelial
Monocitos
Trombina
Trombosis

Antagonistas de la vitamina K

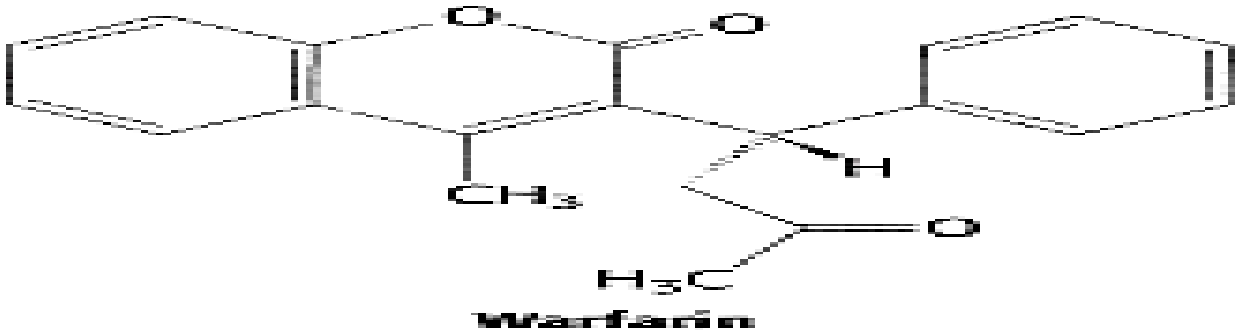
Rol del la vitamina K



Vitamin K

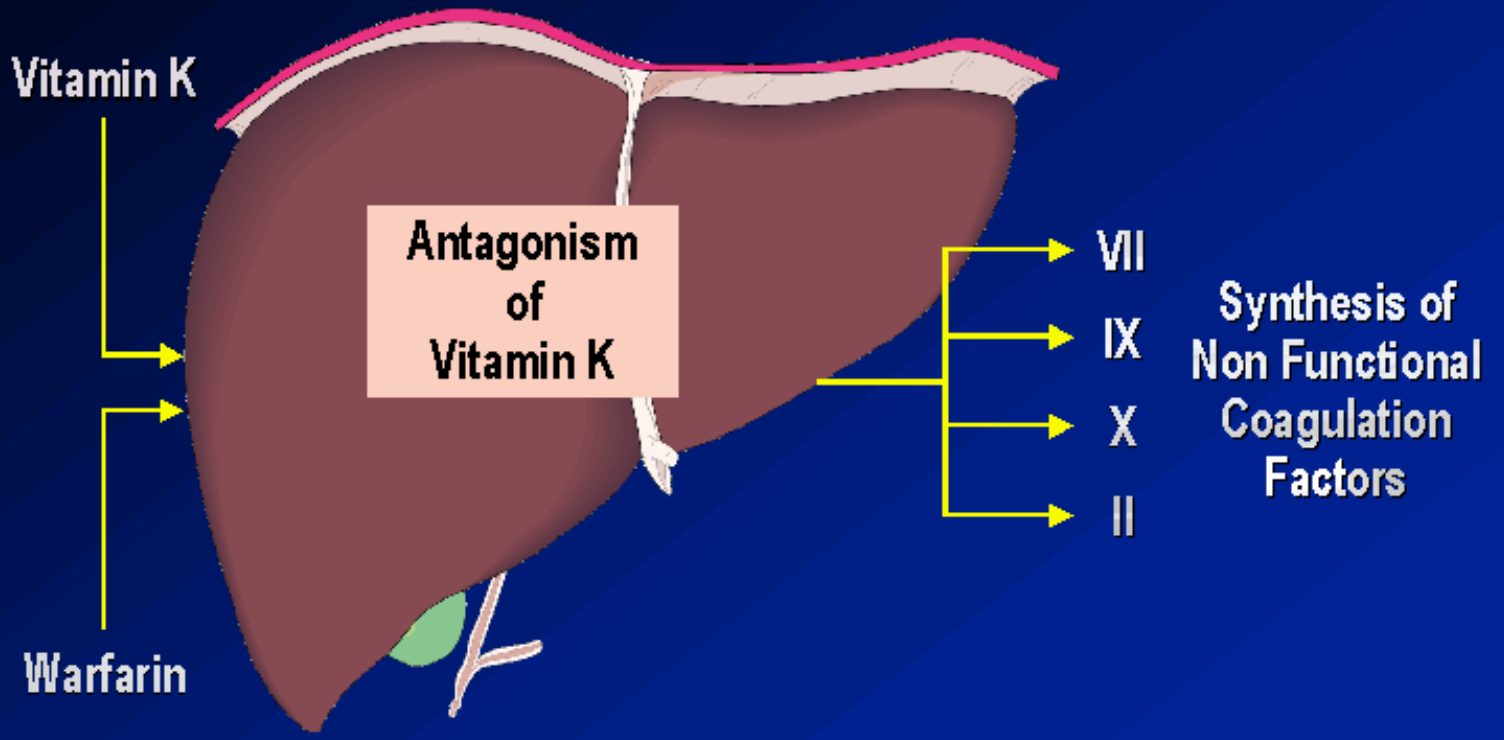


Dicoumarol



Warfarin

Warfarin Mechanism of Action

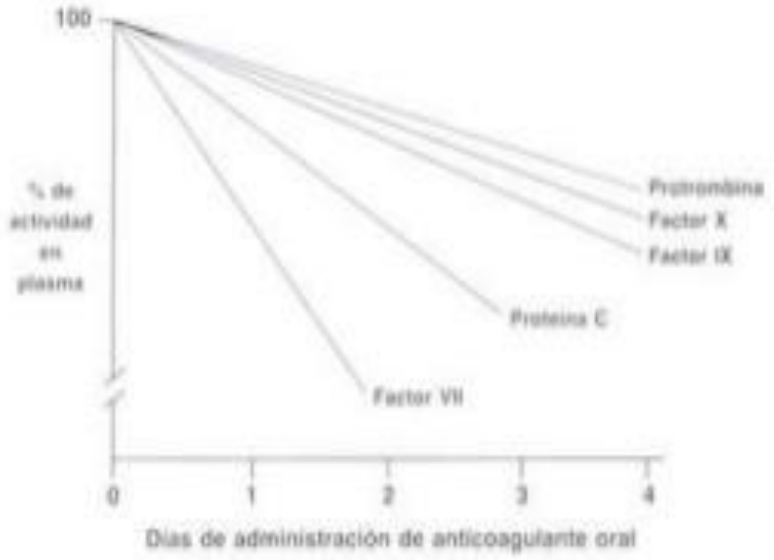


Warfarina

Fármaco	Biodisponibilidad	Metabolimso del primer paso	Vida media hrs	Unión a proteinas	Volumen de distribución	pKa	eliminación
Warfarina	99%	Si	48 (r) 31 (s)	97%	0,14/kg	5	Renal Heces

Interacciones:

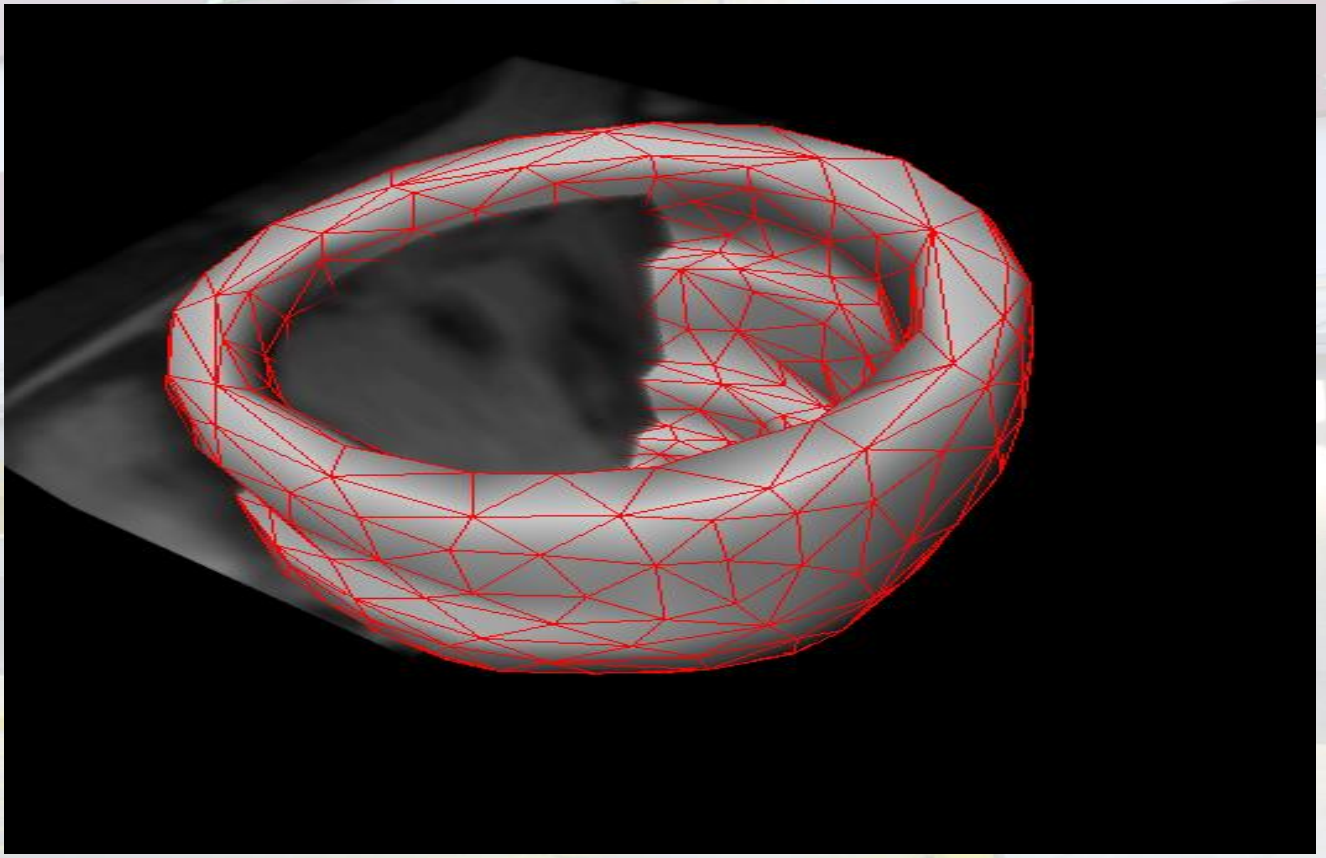
- Aumentan:
  - Amiodarona
  - Metronidazol
  - TMP/SMX
- Disminuyen:
  - Fenobarbital
  - Rifampicina
  - Carbamazepina



Antagonistas de la Vitamina K

- Miocardiopatía dilatada

Anticoagulación en miocardiopatía dilatada



- EL 1,6 % DE LOS PACIENTES CON INSUFICIENCIA CARDÍACA MUEREN POR ACCIDENTE CEREBRO VASCULAR EN EL GLOBAL

- 7% con Fey inferior al 35%

Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction

Clinical PI: Shunichi Homma, MD Statistical PI: JLP (Seamus) Thompson, PhD

WARCEF

is a two-arm double blind randomized multicenter clinical trial (target enrollment 3201 patients at 140 clinical sites in North America , Europe, and Argentina) designed to test the primary null hypothesis of no difference between warfarin and aspirin in 2-6 year survival for the composite endpoint death or recurrent stroke or intracerebral hemorrhage among patients with low EF

Sponsors and Collaborators

Columbia University

National Institute of Neurological Disorders and Stroke (NINDS)

Original Article

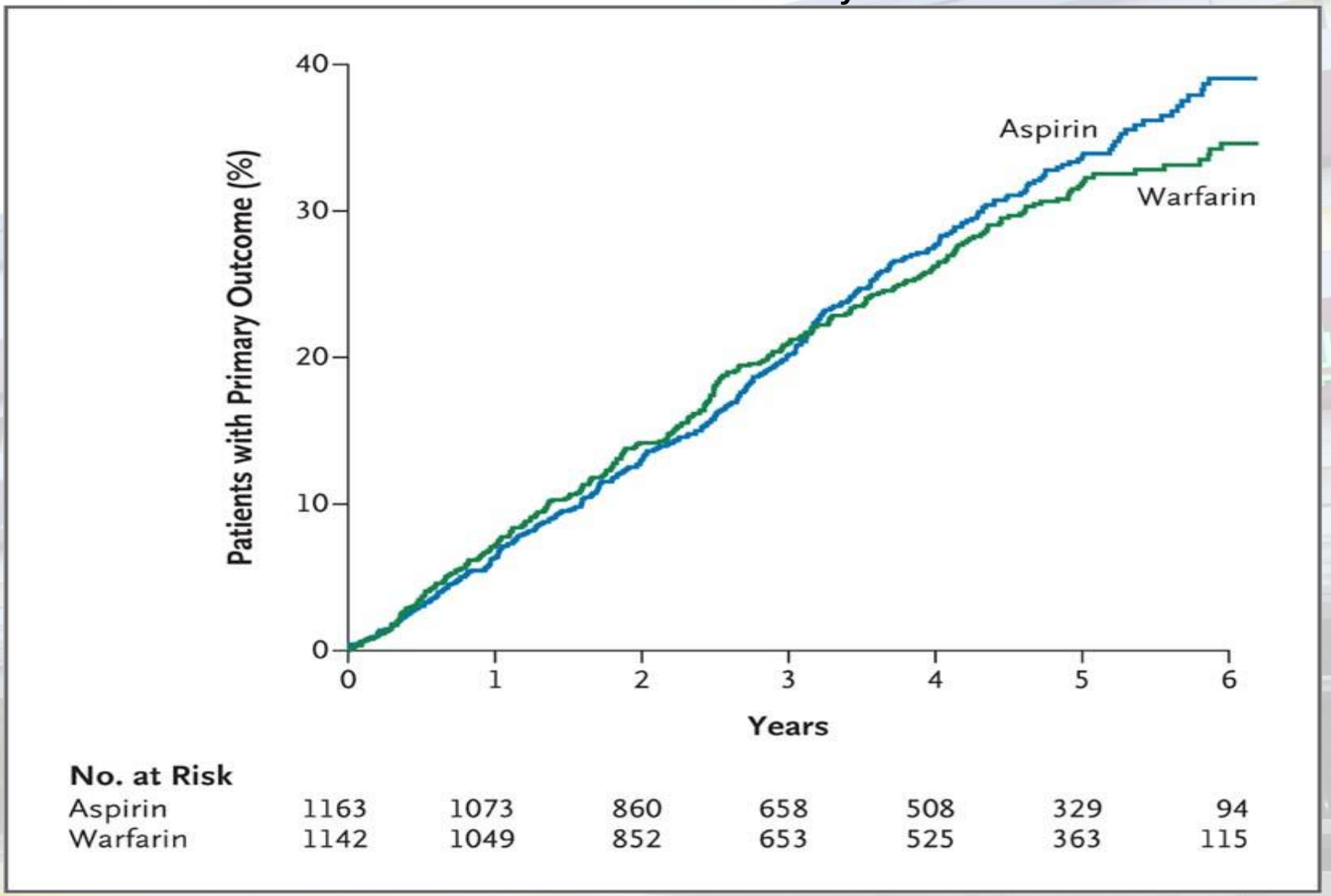
Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Shunichi Homma, M.D., John L.P. Thompson, Ph.D., Patrick M. Pullicino, M.D., Bruce Levin, Ph.D., Ronald S. Freudenberger, M.D., John R. Teerlink, M.D., Susan E. Ammon, N.P., Susan Graham, M.D., Ralph L. Sacco, M.D., Douglas L. Mann, M.D., J.P. Mohr, M.D., Barry M. Massie, M.D., Arthur J. Labovitz, M.D., Stefan D. Anker, M.D., Ph.D., Dirk J. Lok, M.D., Piotr Ponikowski, M.D., Ph.D., Conrado J. Estol, M.D., Ph.D., Gregory Y.H. Lip, M.D., Marco R. Di Tullio, M.D., Alexandra R. Sanford, M.S., Vilma Mejia, B.S., Andre P. Gabriel, M.D., Mirna L. del Valle, B.S., Richard Buchsbaum, for the WARCEF Investigators

N Engl J Med
Volume 366(20):1859-1869
May 17, 2012

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidence of the Primary Outcome



No. at Risk							
Aspirin	1163	1073	860	658	508	329	94
Warfarin	1142	1049	852	653	525	363	115

Homma S et al. N Engl J Med 2012;366:1859-1869

The NEW ENGLAND JOURNAL of MEDICINE

Among patients with reduced LVEF who were in sinus rhythm, there was **no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin.** A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The choice between warfarin and aspirin should be individualized. (Funded by the National Institute of Neurological Disorders and Stroke; WARCEF ClinicalTrials.gov number,

Conclusions

- **Among patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin.**
- **A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage.**
- **The choice between warfarin and aspirin should be individualized.**

The NEW ENGLAND JOURNAL of MEDICINE

COMMANDER HF

Cardiovascular Outcome Modification, Measurement AND Evaluation of Rivaroxaban in patients with Heart Failure

European Journal of Heart Failure (2015)
doi:10.1002/ejhf.266

COMMANDER HF

Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

Faiez Zannad[1], Barry Greenberg[2], John G.F. Cleland[3], Mihai Gheorghiade[4], Dirk J. van Veldhuisen[5], Mandeep R. Mehra[6], William M. Byra[7], Min Fu[7], and Roger M. Mills[7]*

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www.clinicaltrials.gov/ct2/show/NCT01877915

The currently ongoing COMMANDER-HF trial has been designed to address this issue. In this chapter we review evidence of existence of a prothombotic state in HF, the pharmacodynamics and clinical trials of the NOACs and the outcomes from NOAC substudies in the HF subgroup. We also discuss the rationale for using anticoagulation in HF independent of arrhythmia burd

Pharmacological Treatment for Stage C HF*r*EF (cont.)

IIaIIbIII
C

The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized rate therapeutic ration if the patient has been taking warfarin.

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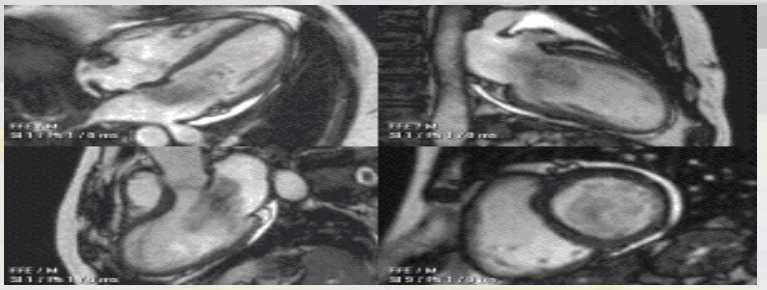
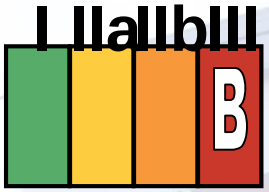
B

Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke (in the absence of contraindications to anticoagulation).



Pharmacological Treatment for Stage C HF*r*EF (cont.)

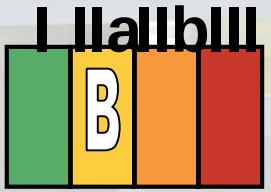


No Benefit

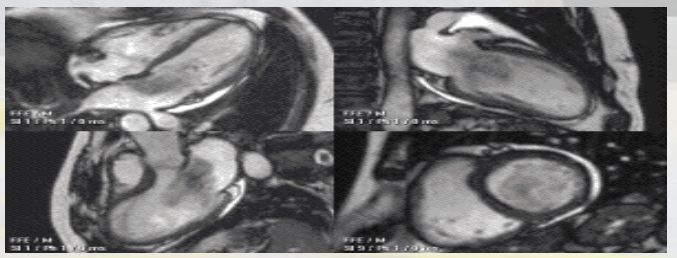
Anticoagulation is not recommended in patients with chronic HF*r*EF without AF, a prior thromboembolic event, or a cardioembolic source.

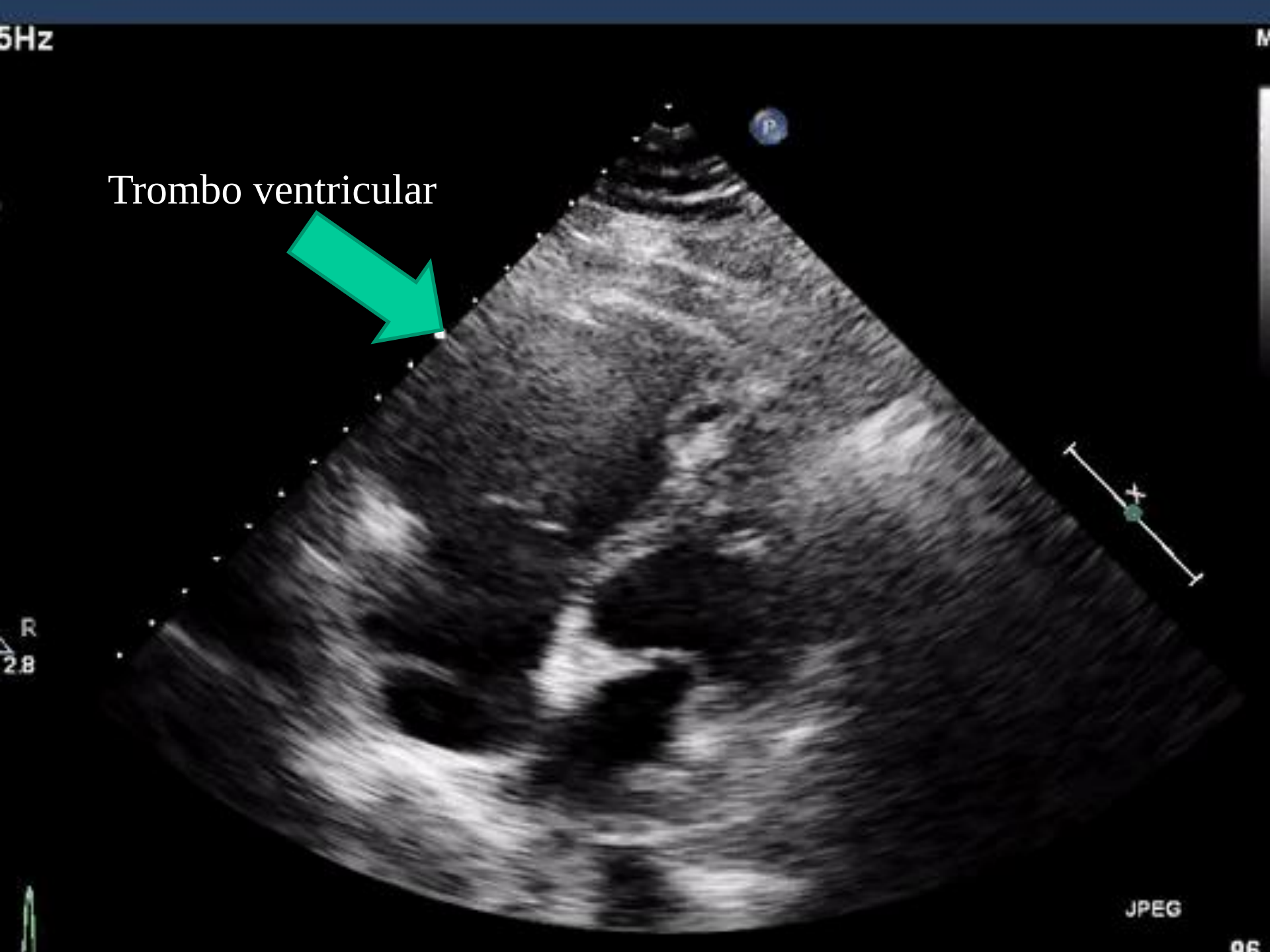
No Benefit

Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.



Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HF*r*EF or HF*p*EF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.

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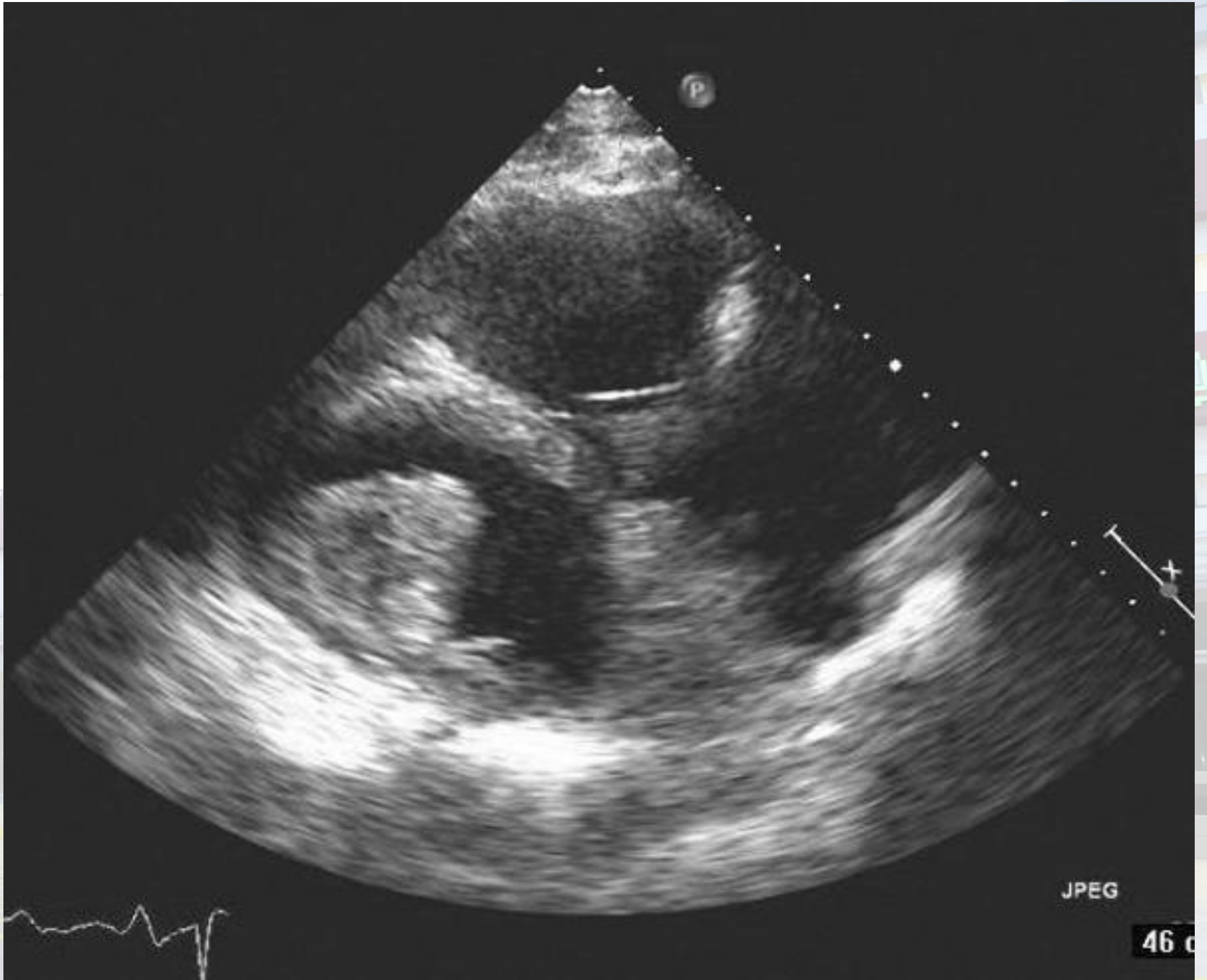
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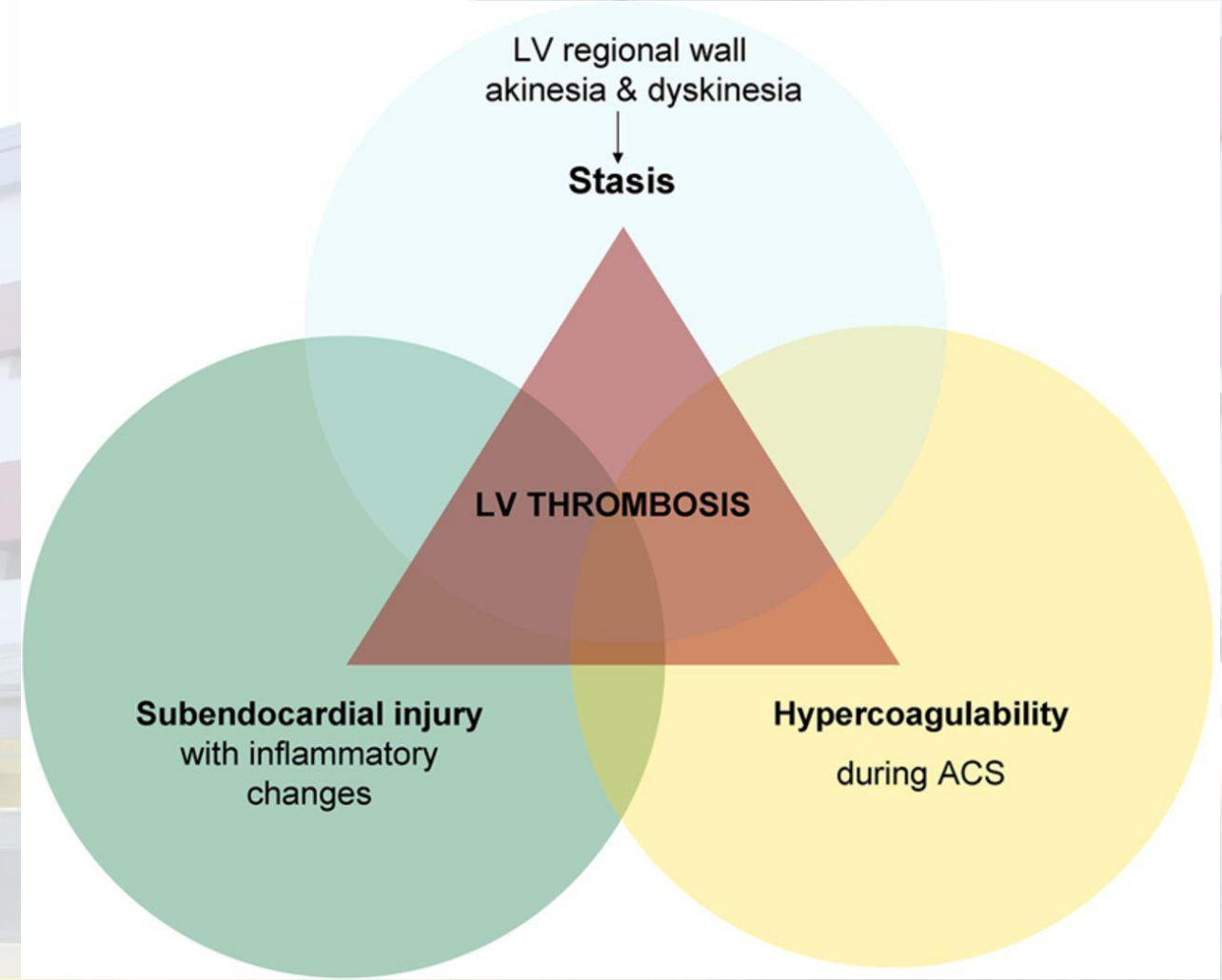
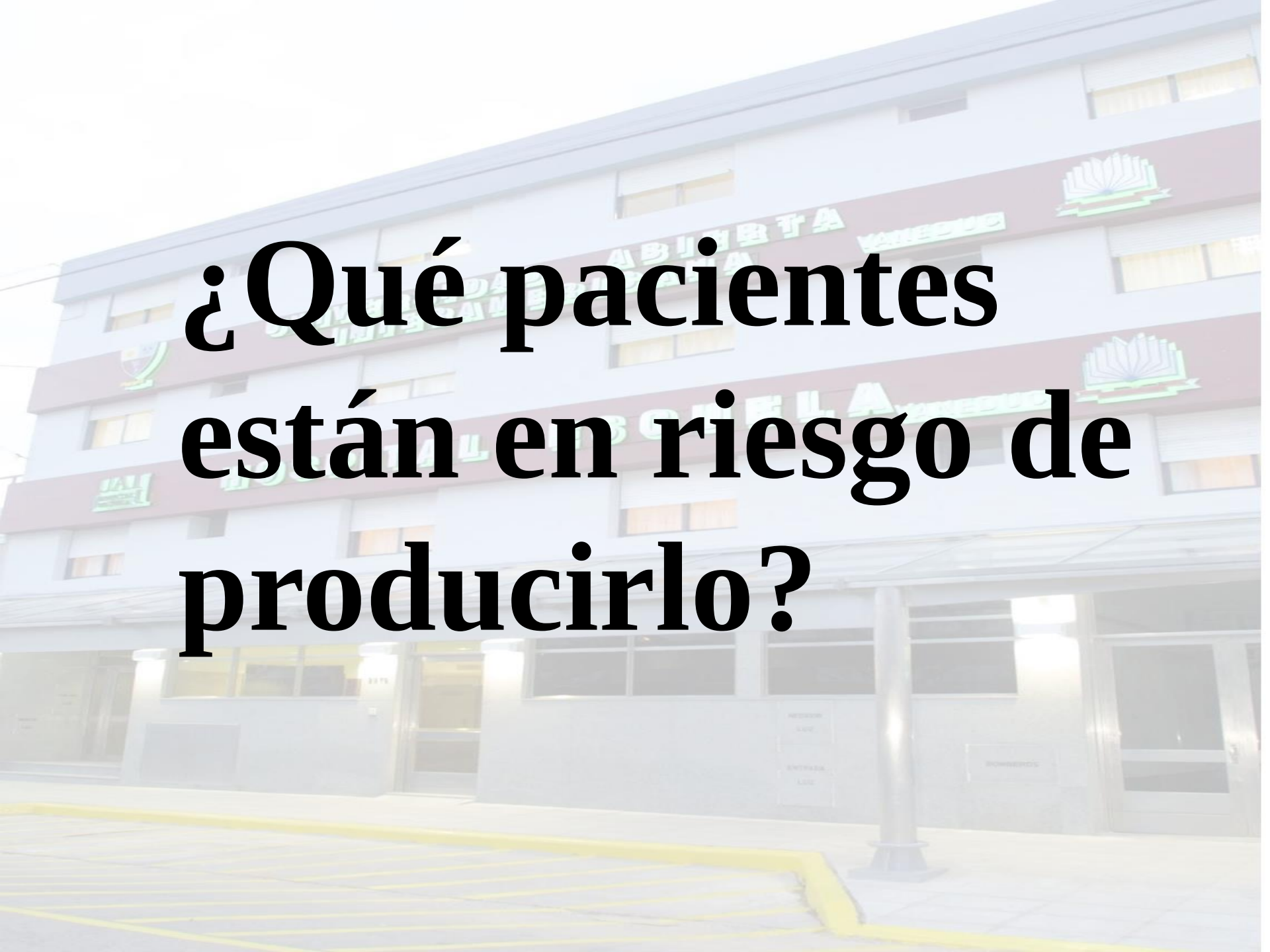
¿Como y cuando se produce produce?

The three components of the Virchow's triad in left ventricular thrombus formation.



Ronak Delewi et al. Heart 2012;98:1743-1749

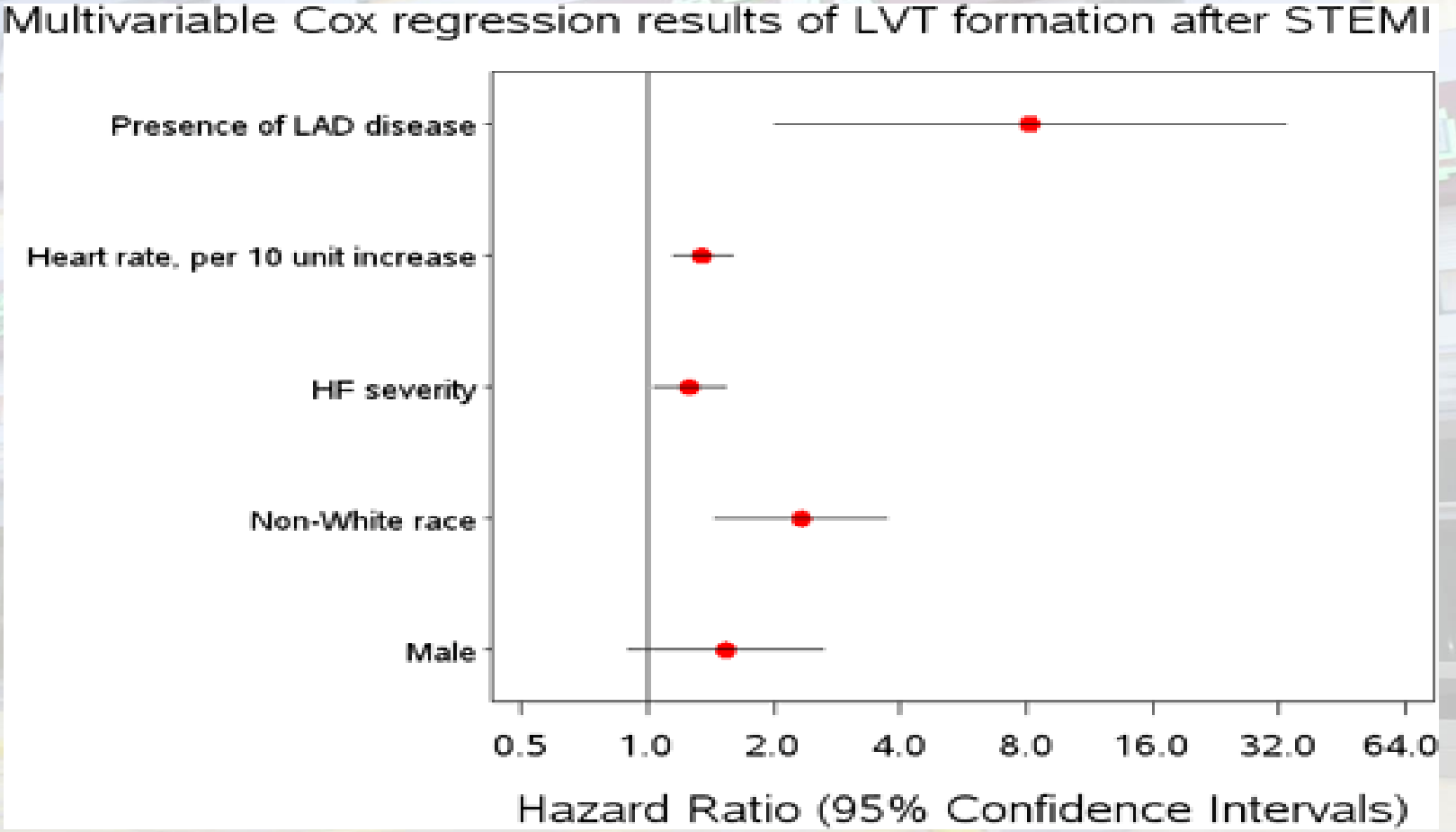
Heart

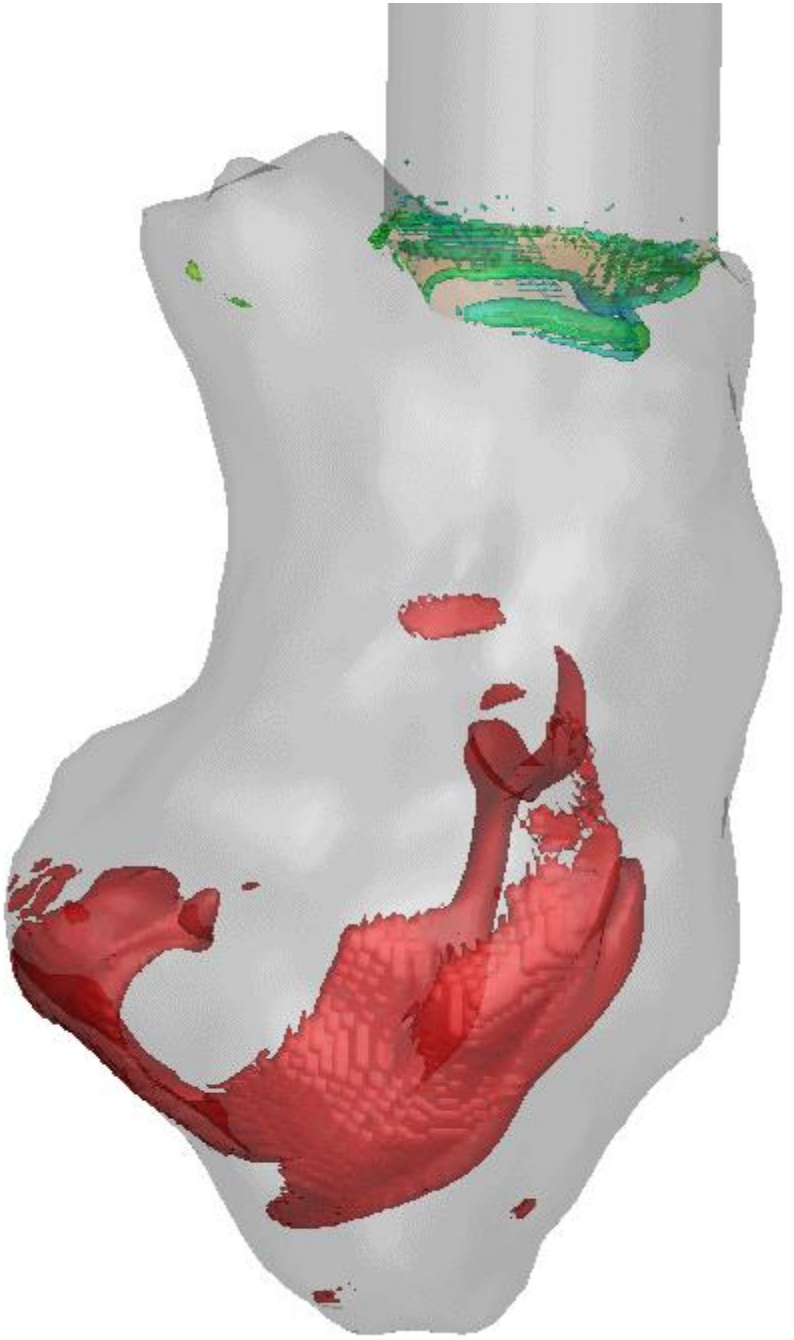


¿Qué pacientes están en riesgo de producirlo?

*Large anterior ST-elevation myocardial infarction with
*Anteroapical aneurysm formation.
*Left anterior descending coronary artery
*5.4% and 7.1% of patients with acute anterior wall myocardial infarctions

Riesgo de desarrollar trombo interventricular post infarto





¿Cómo prevenirlo?

Heparina

In a randomised controlled trial, AMI survivors who were treated with high dose heparin (12 500 units subcutaneously every 12 h) showed a lower incidence of LV thrombus formation than those administered a low dose (5000 units subcutaneously every 12 h**) (11% vs 32%, p<0.001) during a 10 day period**

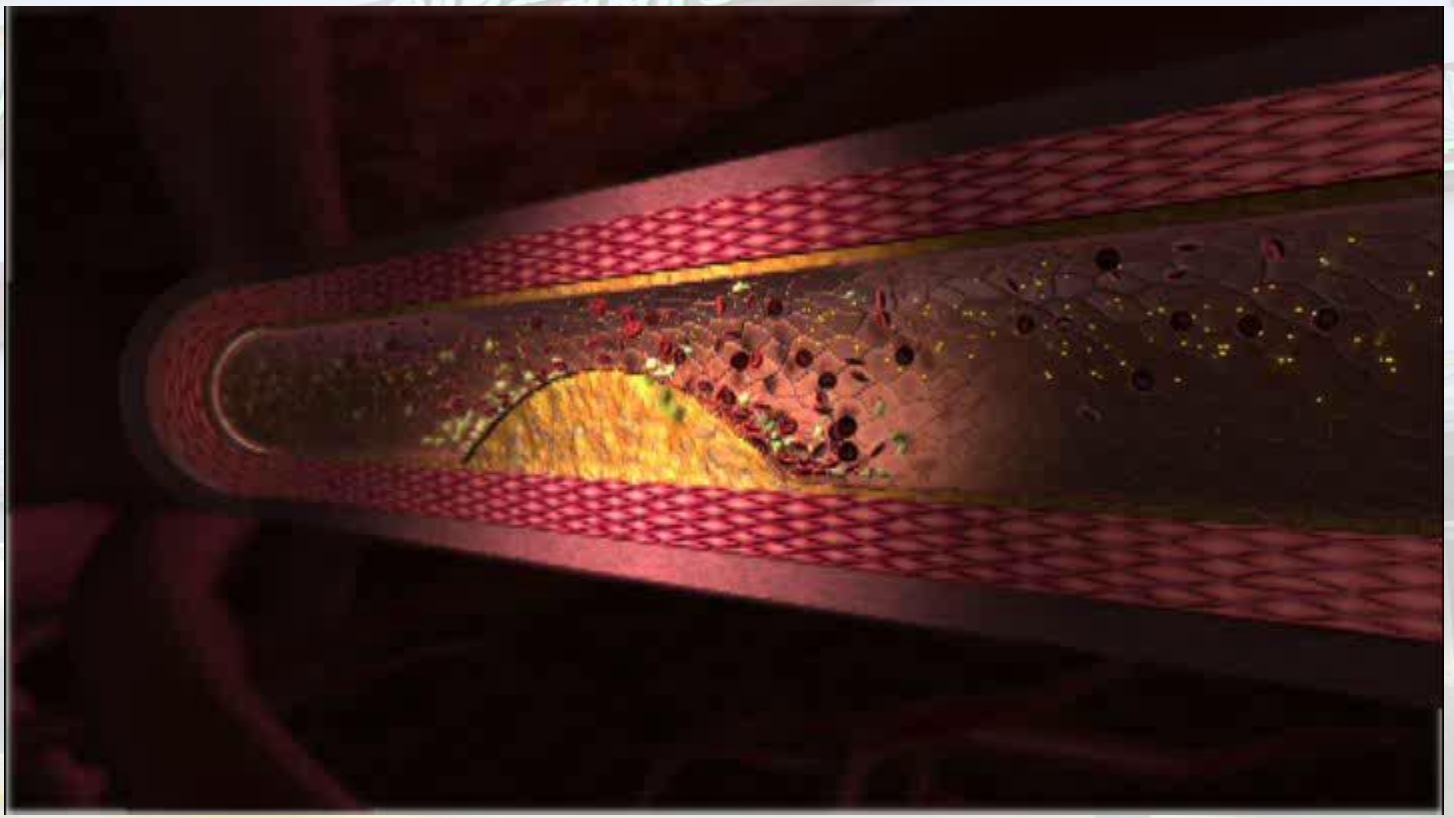
¿CómoTratarlo?

Tanto los consensos europeos y americanos coinciden el la utilización de antagonistas de la vitamina k en forma crónica

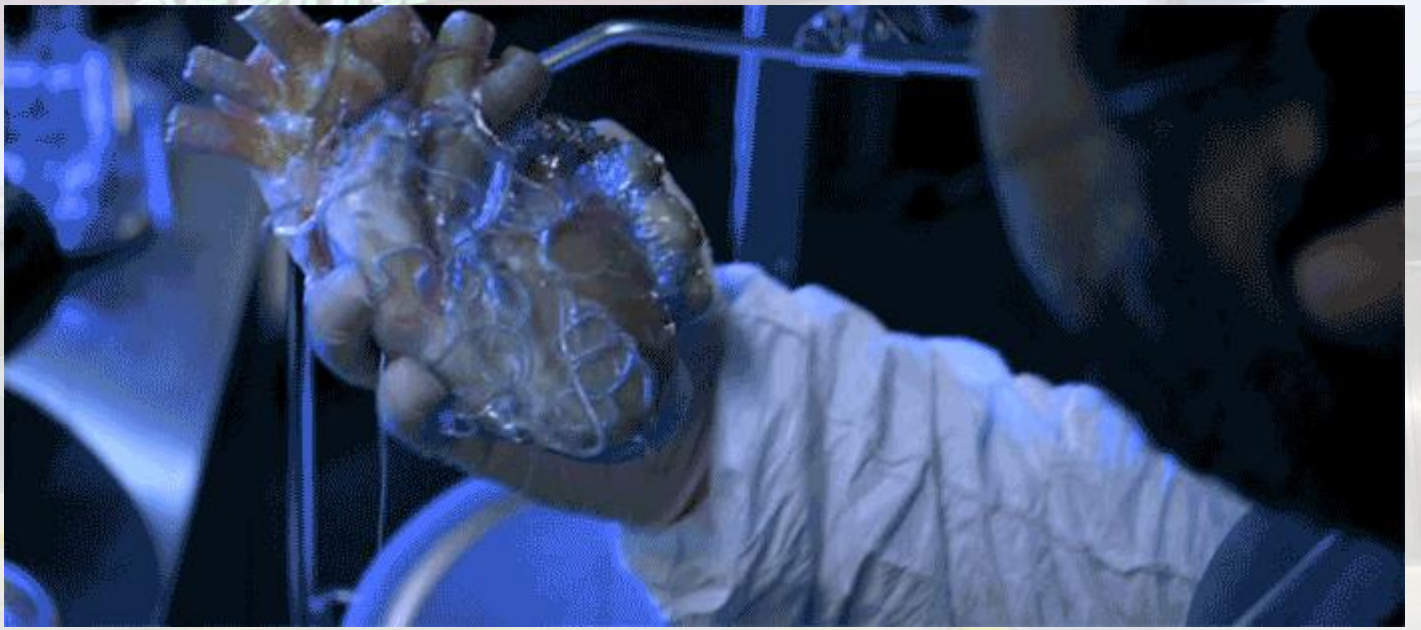
A pesar de ello no se ha demostrado que esto acelere la resolución del coagulo

- Assess LV thrombus within the first month after AMI, preferably with CMR in high risk patients, ***and start vitamin K antagonist*** when LV thrombus is present and no contraindication exists
- **Re-evaluate LV thrombus formation after 6 months** since data show that LV thrombus resolution in the initial months is very common, also in patients treated with vitamin K antagonists[w43]
- ***When LV thrombus is not present and there is no other indication for vitamin K antagonist, assess bleeding risk and consider stopping therapy***

Anticoagulación y Enfermedad Coronaria



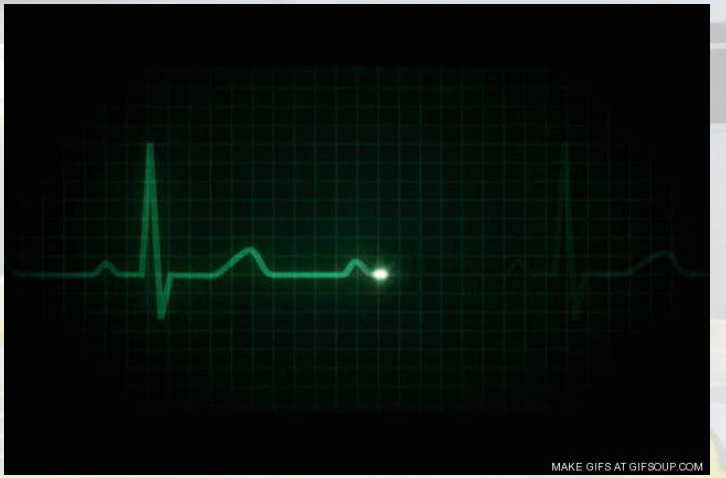
ANRTICOAGULACIÓN EN PREVENCIÓN SECUNDARIA DE LA ENFERMEDAD CORONARIA CRÓNICA



ANTICOAGULACIÓN SIN ANTGIAGREGACIÓN

- IGUAL REDUCCIÓN DE EVENTOS MAYORES QUE LA ASPIRINA **RIN 3**
- MAYOR RIESGO DE SANGRADO
- MAYOR DIFICULTAD OPERATIVA

ANTICOAGULACIÓN MAS ANTIAGREGACIÓN EN PREVECNCÍON SECUNDARIA DE ENFERMEDAD CORONARIA



Asociación improductiva

- **No hay evidencia de utilidad** en la asociación por debajo de rin de 3
- Mayor riesgo