



Raoul, il primo caso riportato (1271) di trombosi venosa profonda

de Saint Pathus, G. (1330-50) *La vie et les Miracles de Saint Louis*. Paris: Bibliothèque National de France

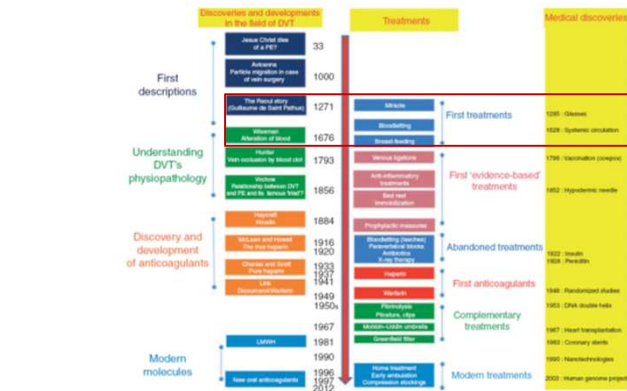
Unlike the situation for varicose veins, leg ulcers, or lower limb edema, to which there are extensive references in antique art and literature, the first description of a case truly compatible with a DVT first appears during the Middle Ages [8,9]. In the manuscript of Guillaume de Saint Pathus entitled 'La vie et les miracles de Saint Louis', it is reported that, in 1271, Raoul, a 20-year-old Norman cobbler suffered unilateral pain and swelling of the right calf that subsequently extended up to the thigh (Fig. 1) [9]. Raoul's surgeon, Henri de Perche, advised him to wait and see. Unfortunately, the patient's symptoms worsened, and he developed a leg ulcer. He visited St Eloi's shrine, without any improvement. After additional unsuccessful unspecified treatment attempts, Raoul was advised to visit the tomb of King Saint Louis. He spent several days praying to the saint, and then he decided to collect the dust that he found below the stone that covered the tomb, and he applied it directly to the ulcer. The story reports that he was miraculously healed after this direct application, and was still alive 11 years later. Thus, this first reported case of effective treatment of DVT might not be the most reproducible. In antiquity,

HISTORICAL SKETCH

The history and historical treatments of deep vein thrombosis

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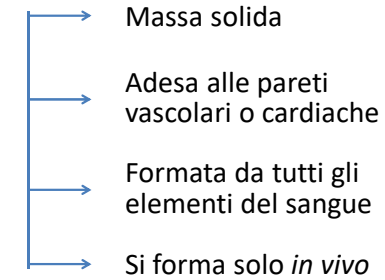


Trombosi

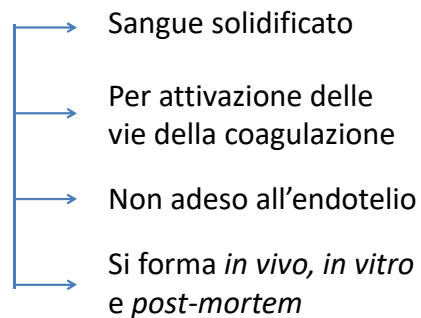
Θρόμβος, grumo

I disegni e molti schemi sono stati realizzati dal prof. Ernesto Damiani

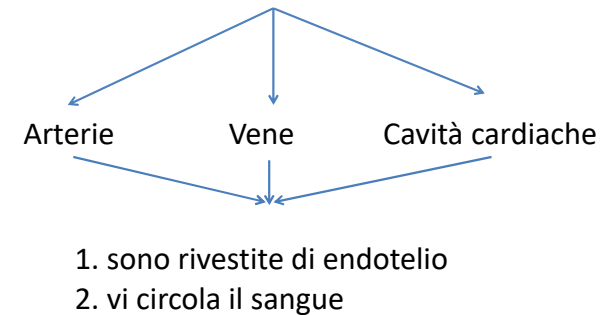
Definizione di trombo



Definizione di coagulo



Localizzazione delle trombosi



Formazione del trombo

- 1-

Formazione del trombo piastrinico

Il trombo piastrinico si forma in tre fasi

- 1 – adesione piastrinica all'endotelio
- 2 – aggregazione piastrinica
- 3 – reazione di rilascio piastrinico

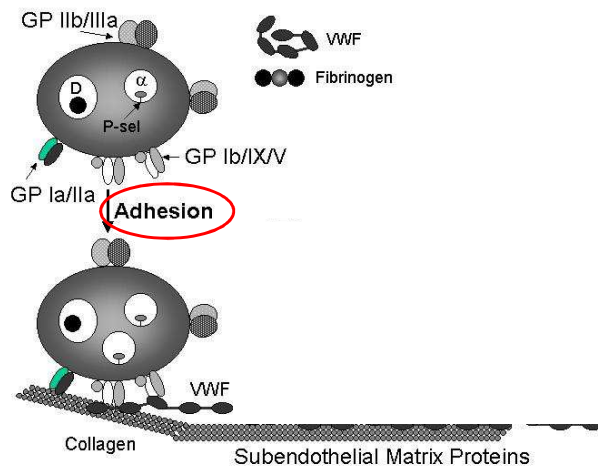
Adesione piastrinica all'endotelio

Il processo di adesione avviene in due fasi

- 1 – adesione instabile
- 2 – adesione stabile

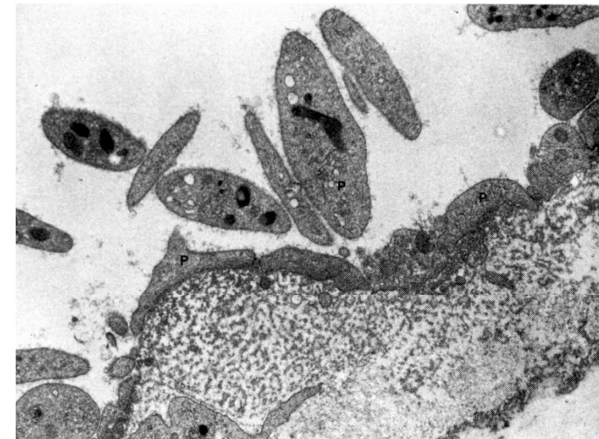
Questa sequenza di fasi è un fenomeno già osservato

Adesione dei polimorfonucleati in corso di infiammazione
 Riflette l'espressione di proteine di adesione di differente affinità



Prima fase
 Adesione delle piastrine al collageno sub-endoteliale della membrana basale

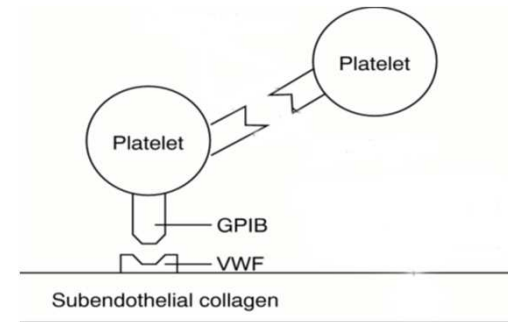
Recettori a bassa affinità



Seconda fase
l'adesione delle piastrine al collageno
è stabilizzata dall'intervento del
fattore di von Willebrand

Legame ad alta affinità

Il vWF si lega a un recettore glicoproteico sulle piastrine

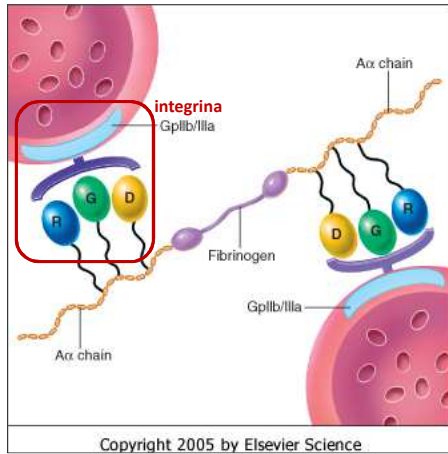


Sindrome di Bernard-Soullier

Manca il recettore piastrinico per in
vWF

Aggregazione piastrinica

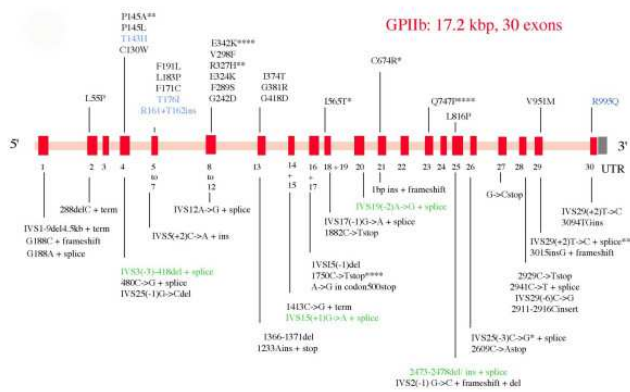
Le piastrine aggregano tra di loro per
intervento del fibrinogeno



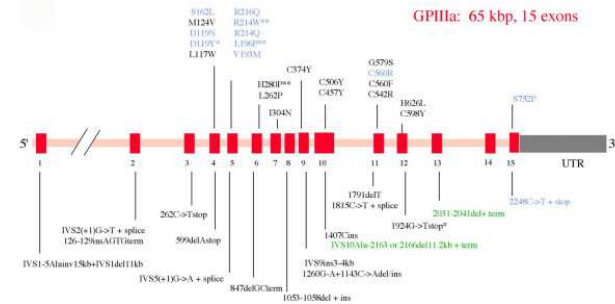
Tromboastenia di Glanzmann

Manca il recettore piastrinico del fibrinogeno

Alterazioni di GPIIb



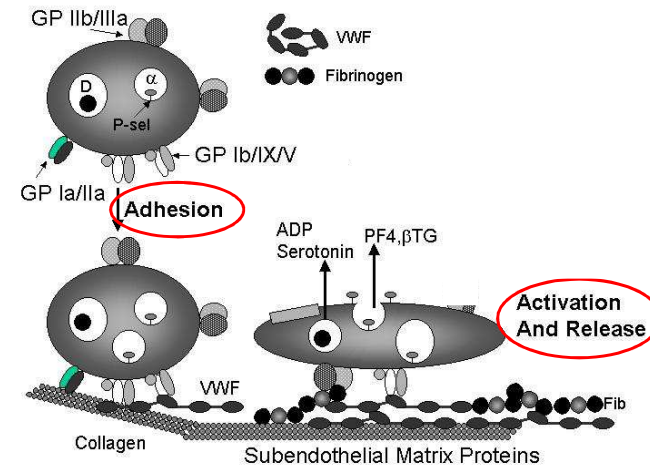
Alterazioni di GPIIIa



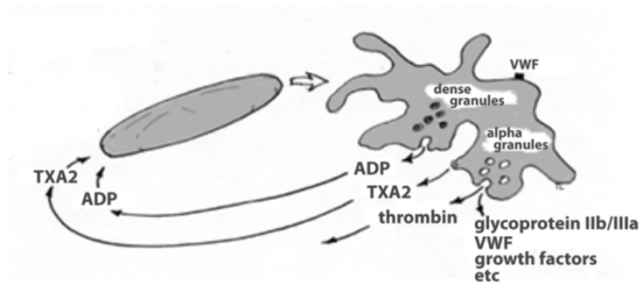
All'aggregazione fa seguito la reazione di rilascio piastrinico

Sono rilasciati tromboxano A2, vWF, ADP

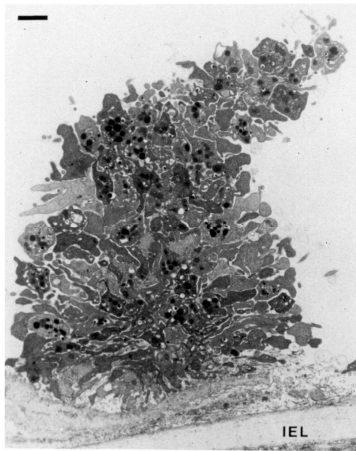
Agiscono in senso autocatalitico



Reazione di rilascio piastrinica



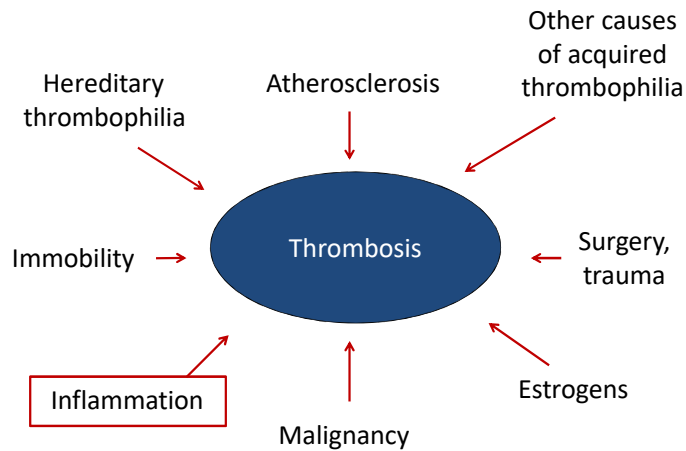
Si è formato il trombo piastrinico bianco



Questo è quello che succede normalmente nell'emostasi capillare

La prima fase del processo di trombosi si sovrappone con l'emostasi capillare (tappo piastrinico)

Risk Factors for Thrombosis



COAGULATION Thienel *et al.*, *Science* **380**, 178–187 (2023) 14 April 2023

Immobility-associated thromboprotection is conserved across mammalian species from bear to human

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Venous thromboembolism (VTE) comprising deep venous thrombosis and pulmonary embolism is a major cause of morbidity and mortality. Short-term immobility-related conditions are a major risk factor for the development of VTE. Paradoxically, long-term immobilized free-ranging hibernating brown bears and paralyzed spinal cord injury (SCI) patients are protected from VTE. We aimed to identify mechanisms of immobility-associated VTE protection in a cross-species approach. Mass spectrometry-based proteomics revealed an antithrombotic signature in platelets of hibernating brown bears with heat shock protein 47 (HSP47) as the most substantially reduced protein. HSP47 down-regulation or ablation attenuated immune cell activation and neutrophil extracellular trap formation, contributing to thromboprotection in bears, SCI patients, and mice. This cross-species conserved platelet signature may give rise to antithrombotic therapeutics and prognostic markers beyond immobility-associated VTE.

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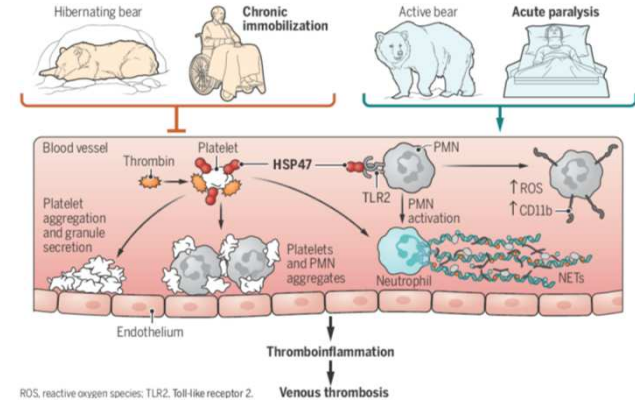
Sleep like a bear

Reduced expression of a platelet protein protects against thrombosis during chronic immobilization

By Mirta Schattner

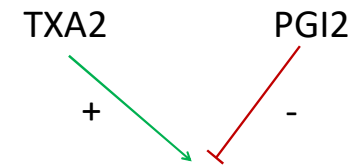
Protection from venous blood clots

Platelet heat shock protein 47 (HSP47) contributes to blood clot formation by recruiting thrombin to platelets and triggering their aggregation and by activating polymorphonuclear leukocytes (PMNs). The latter generates neutrophil extracellular traps (NETs) comprising DNA and proteins that provide a scaffold for red blood cells, platelets, and procoagulant molecules. The expression of HSP47 is down-regulated during chronic immobilization, which protects against thromboinflammation and clot formation.



L'aggregazione piastrinica è influenzata da due metaboliti dell'acido arachidonico

- Tromboxano A2 di produzione piastrinica
- Prostaciline (PGI2) di produzione endoteliale



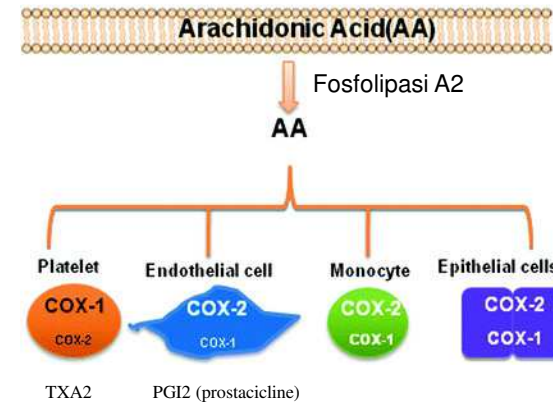
Aggregazione piastrinica

Farmaci anti-infiammatori non steroidei (FANS), piastrine e trombogenesi

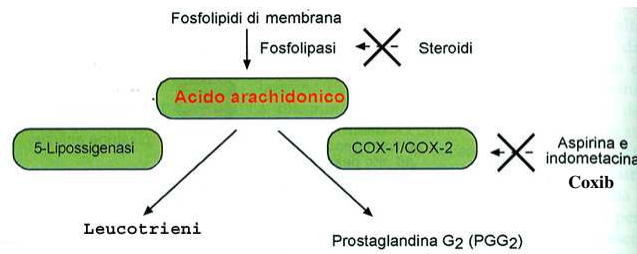
Tutti i metaboliti dell'acido arachidonico sono sintetizzati per azione delle cicloossigenasi (COX1 e COX2)

Take-home message in tema di COX

Le COX sono espresse differenzialmente e distribuite a mosaico nei tessuti



Le COX sono inibite dai FANS (NSAID)



Non-selective (COX-1 and 2) (traditional, conventional)
Aspirin
Acetaminophen
Indomethacin (Indocin)
Ibuprofen (Advil, Motrin)
Naproxen (Aleve, Naprosyn)
Sulindac (Clinoril)
Diclofenac (Voltaren, Cataflam)
Piroxicam (Feldene)
β- Piroxicam (Cycladol)
Meloxicam (Movatec)
Ketoprofen (Profenid)

Hippocrates (440-377 B.C.) prescribed the bark and leaves of salix, the willow tree (rich in salicin), to reduce pain and fever. It also was mentioned by **Dioscorides** (c. 100 A.D.) and later by **Pliny the Elder** and **Galen**. However, it then fell into clinical disuse for centuries until the **Reverend Edward (aka Edwin) Stone (1702-1768) rediscovered its efficacy**. Stone was born in Lacey Green, Princes Risborough, Buckinghamshire. He attended Wadham College, Oxford in 1720 and in 1728 was ordained for the curacy of Charlton-on-Otmoor, where he remained until 1730 when he was elected a Fellow of Wadham. In 1745 he moved to Chipping Norton as chaplain at Bruern Abbey until it was destroyed by fire.

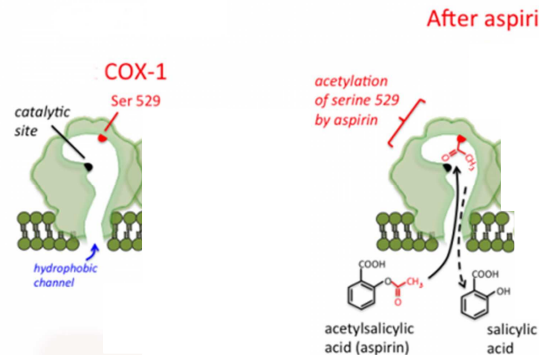
On April 25, 1763, Stone wrote to the president of the Royal Society, George Parker, second earl of Macclesfield, and in his letter read before the Royal Society on June 2, 1763, he described the use of dried willow bark [salix alba] as a remedy for fevers and agues. This landmark paper¹ initiated the discovery of the actions and chemical structure of aspirin² and the development of other non-steroidal anti-inflammatory drugs used worldwide in treating pain, inflammation, and fevers.³

1. Stone E. An account of the success of the bark of the willow in the cure of agues. Phil. Trans. 1763;53, 195-200. <https://royalsocietypublishing.org/doi/10.1098/rstl.1763.0033>.
2. Pearce JMS. Edward Stone and aspirin. World Federation of Neurology Dec 2014. <https://worldneurologyonline.com/article/controversial-story-aspirin/>.
3. Wood JN. From plant extract to molecular panacea: a commentary on Stone (1763) 'An account of the success of the bark of the willow in the cure of the agues'. Philosophical transactions of the Royal Society of London. Series B

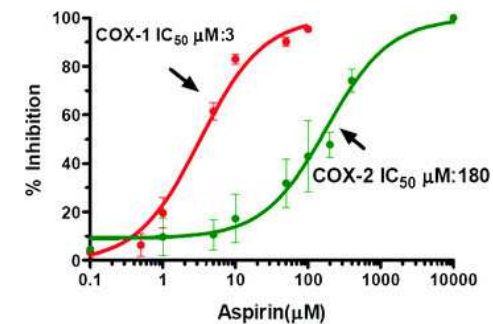
[195]
XXXII. An Account of the Success of the Bark of the Willow in the Cure of Agues.
In a Letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edmund Stone, of Chipping-Norton in Oxfordshire.
 My Lord,
 Read June 2d. 1763.
AMong the many useful discoveries, which this age hath made, there are very few which, better deserve the attention of the public than what I am going to lay before your Lordship.
 There is a bark of an English tree, which I have found by experience to be a powerful astringent, and very efficacious in curing aguish and intermitting disorders.
 About six years ago, I accidentally tasted it, and was surpris'd at its extraordinary bitterness; which immediately rais'd me a suspicion of its having the properties of the Peruvian bark. As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim, that many natural maladies carry their cures along with them, or that their remedies lie not far from their causes, was so very apposite to this particular case, that I could not help applying it; and that this might be the intention of Providence here, I must own had some little weight with me.
 The excessive plenty of this bark furnish'd me, in my speculative disquisitions upon it, with an
 D d 2 argument

[200]
 cinnamon or luteitious colour, which I believe is the case with the Peruvian bark and powder.
 I have no other motives for publishing this valuable specific, than that it may have a fair and full trial in all its variety of circumstances and situations, and that the world may reap the benefits accruing from it. For these purposes I have given this long and minute account of it, and which I would not have troubled your Lordship with, was I not fully persuaded of the wonderful efficacy of this Cortex Salignus in agues and intermitting cafes, and did I not think, that this persuasion was sufficiently supported by the manifold experience, which I have had of it.
 I am, my Lord,
 with the profoundest submission and respect,
 Chipping-Norton, your Lordship's most obedient
 April 25, 1763. humble Servant
 Edward Stone.
 XXXIII. *As*

L'aspirina è l'unico inibitore irreversibile



L'aspirina è un inibitore non selettivo



Ma inibisce la COX-1 con maggiore affinità

Tossicità gastrointestinale dei FANS

TABELLA 10
ODDS RATIO (CI 95%) PER SANGUINAMENTO GASTROINTESTINALE E PERFORAZIONE (1) O SANGUINAMENTO GASTROINTESTINALE ACUTO (2)

	Ratio (95% CI) (1)	Ratio (95% CI) (2)
Ibuprofene	2,9 (1,8 – 5,0)	2,0 (1,4 – 2,8)
Diclofenac	3,9 (2,3 – 6,5)	4,2 (2,6 – 6,8)
Naproxene	3,1 (1,7 – 5,9)	9,1 (5,5 – 15,1)
Indometacina	6,3 (3,3 – 12,2)	11,3 (6,3 – 20,3)
Ketoprofene	5,4 (2,6 – 11,3)	23,7 (7,6 – 74,2)
Piroxicam	18,0 (8,2 – 39,6)	13,7 (7,1 – 26,3)
Azapropazone	23,4 (6,9 – 79,5)	31,5 (10,3 – 96,9)
Totali	4,7 (3,8 – 5,7)	4,5 (3,6 – 5,6)
Bassi dosaggi	2,6 (1,8 – 3,8)	2,5 (1,7 – 3,8)
Dosaggi intermedi	–	4,5 (3,3 – 6,0)
Alti dosaggi	7,0 (5,2 – 9,6)	8,6 (5,8 – 12,6)

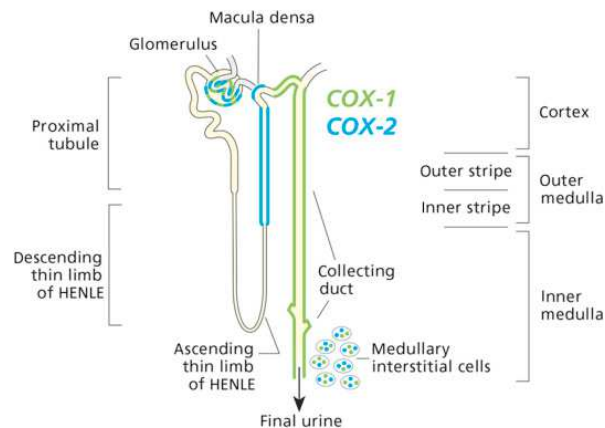
1. Garcia Rodriguez, *Lancet* 1994; 343, 769-772
2. Lagman, *Lancet* 1994; 343, 1075-1078

COX2-inibitori (Coxib)

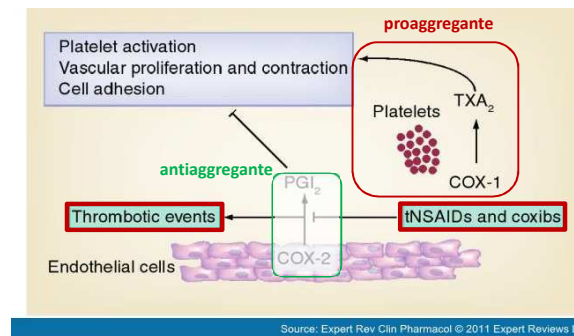
Selectives (COX-2) COXIBs	
Rofecoxib	Ridotta tossicità gastrointestinale
Valdecoxib	
Parecoxib	
Celecoxib	Ma nefrotossicità
Etoricoxib	
Lumiracoxib	

Inibiscono selettivamente la COX2

Espressione delle isoforme di COX nelle differenti parti del nefrone



Aumentato rischio di eventi trombotici da Coxib



La Merck ritira il Vioxx, aumenta i rischi d'infarto

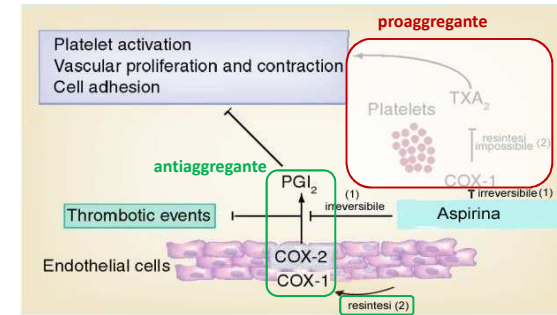
- La Merck, una delle più importanti case farmaceutiche del mondo, ha disposto il ritiro immediato dal commercio del Vioxx, un antinfiammatorio. Il Vioxx (principio attivo **rofecoxib**) provocherebbe un aumento del rischio d'infarto nelle persone che lo prendono
- La decisione, secondo quanto riporta un comunicato stampa della società newyorkese, è basata sui risultati di un recente studio clinico, secondo il quale Vioxx aumenta considerevolmente i rischi di problemi cardiaci, come infarti e attacchi cardiaci, nei pazienti in cura da più di 18 mesi

Formazione del trombo

- 2-

Evoluzione del trombo piastrinico
bianco in trombo rosso

Uso specifico dell'aspirina come anti-aggregante piastrinico



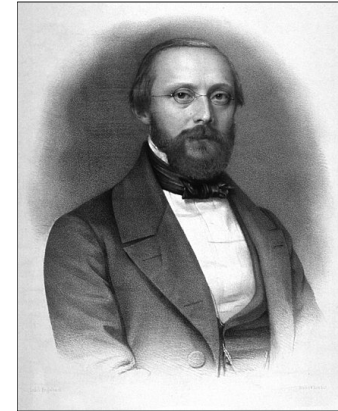
Nonostante la coagulazione non sia implicata nel meccanismo di formazione del trombo piastrinico, ben presto il sistema della coagulazione è attivato e si forma fibrina che deposita sul trombo piastrinico, stabilizzandolo.

Nelle maglie di fibrina restano intrappolati globuli rossi e leucociti. Sulla superficie di fibrina depositano ulteriori piastrine.

A questo punto, il trombo è formato da tutti gli elementi del sangue, è **misto** per composizione e **rosso** per colore

Questa sequenza è comune a tutte le trombosi, arteriose, venose e cardiache

L'ingrandimento del trombo facilita l'ulteriore ingrandimento del trombo, perché rallenta il flusso fino eventualmente all'occlusione

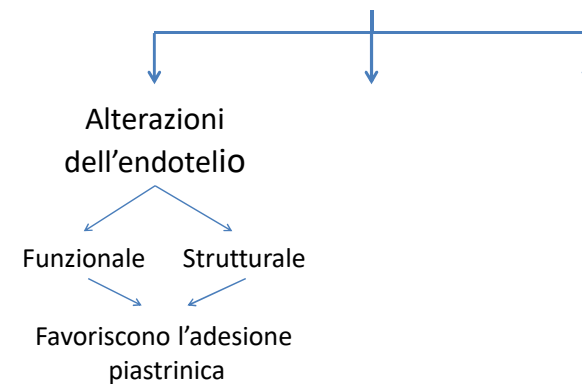


Rudolf Ludwig Karl Virchow (1821-1902)

Patogenesi della trombosi



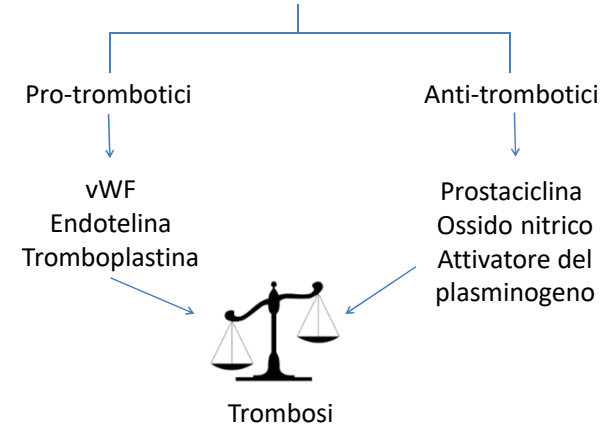
Triade di Virchow



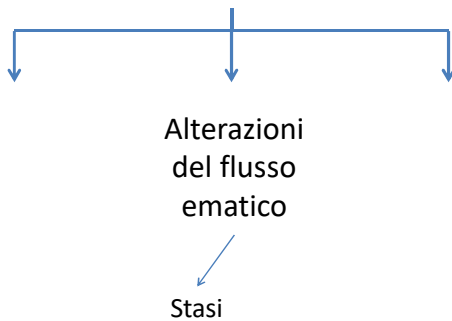
Danno funzionale endoteliale



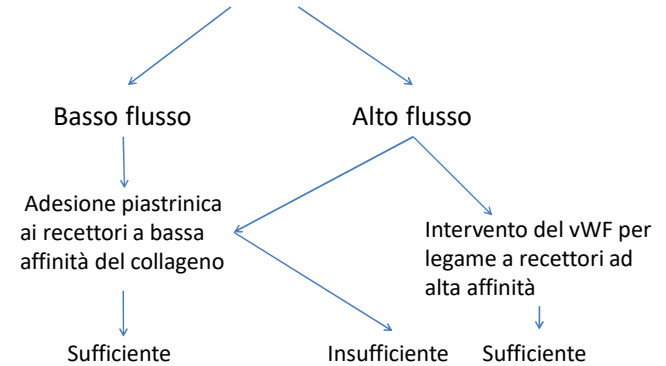
L'endotelio produce fattori

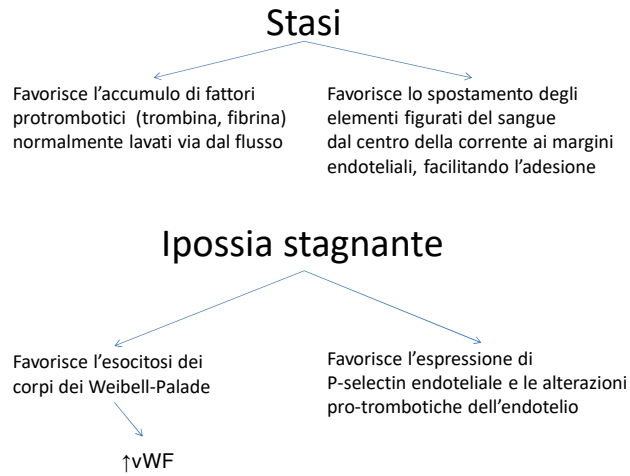


Triade di Virchow



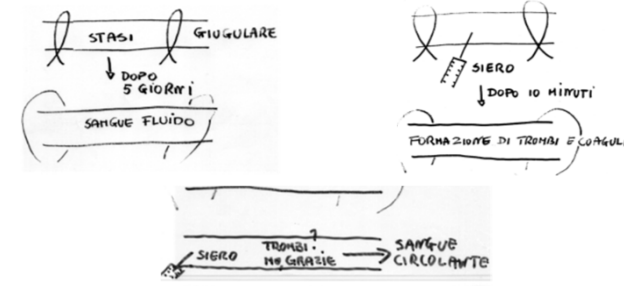
La stasi facilita il processo di formazione del trombo piastrinico





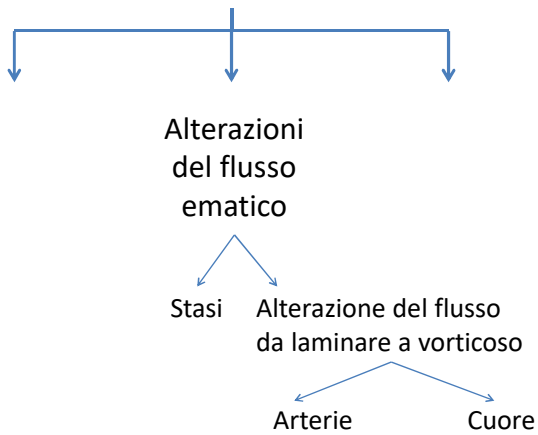
E' sufficiente la stasi per innescare il processo trombotico?

Esperimenti di Zahn

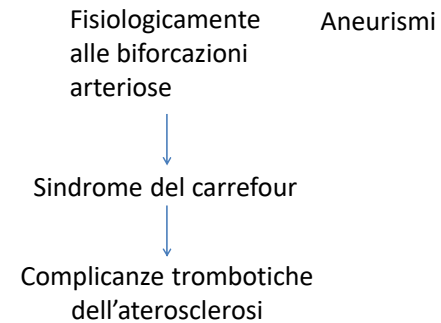


Necessaria, ma non sufficiente

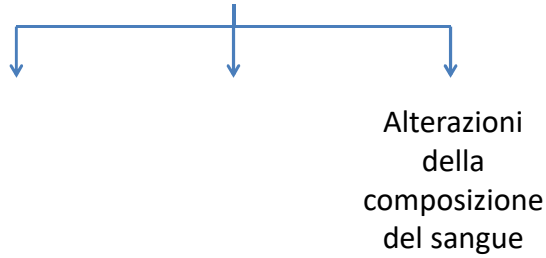
Triade di Virchow



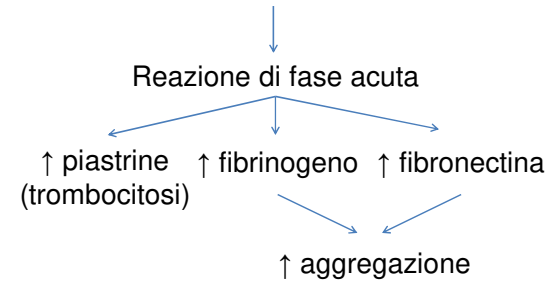
Flusso vorticoso



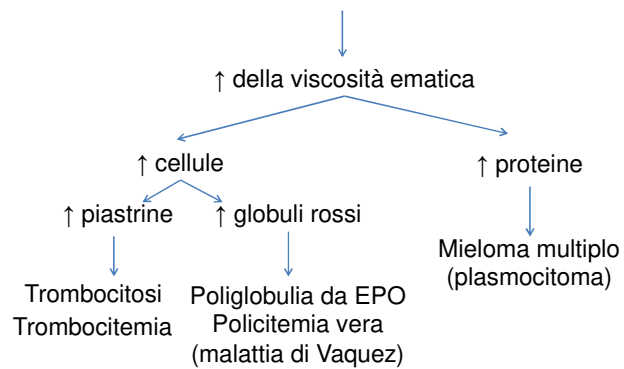
Triade di Virchow



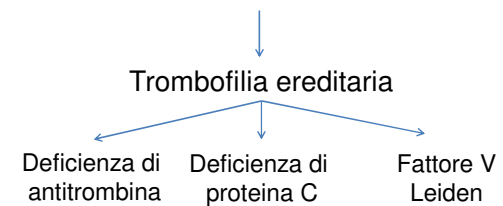
Alterazioni della composizione del sangue



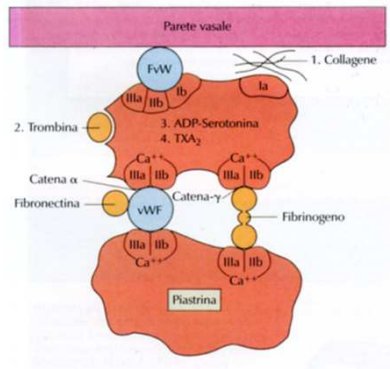
Alterazioni della composizione del sangue



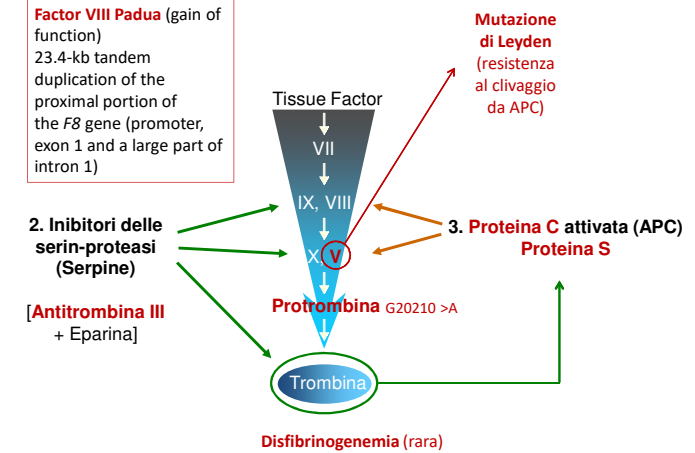
Alterazioni della composizione del sangue



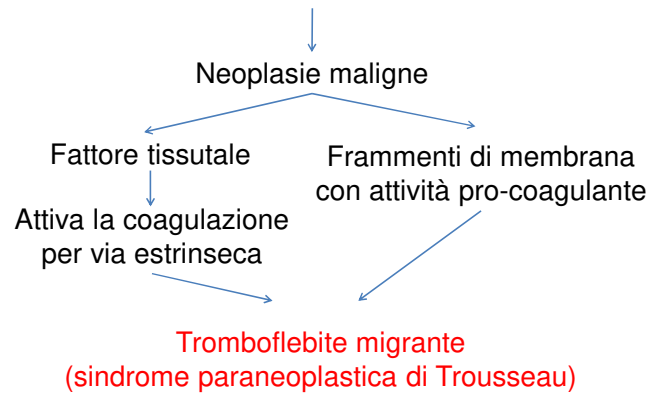
La trombina attiva l'adesione e l'aggregazione piastrinica



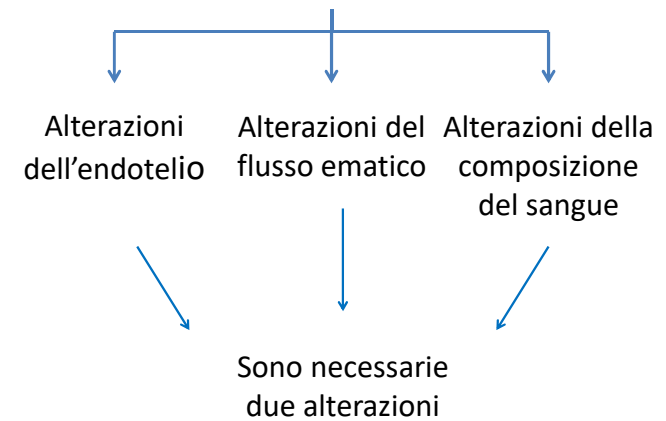
Le trombofilie ereditarie



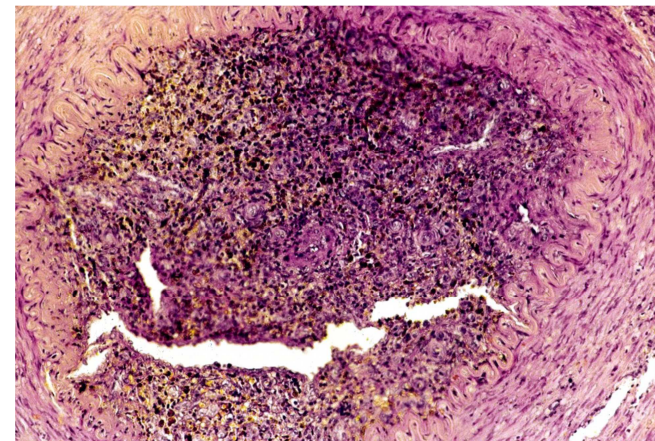
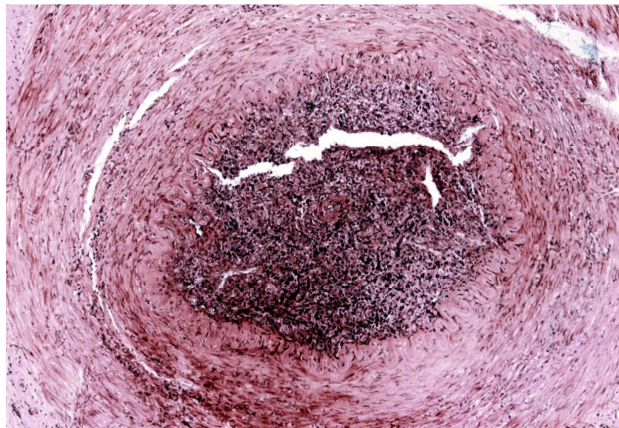
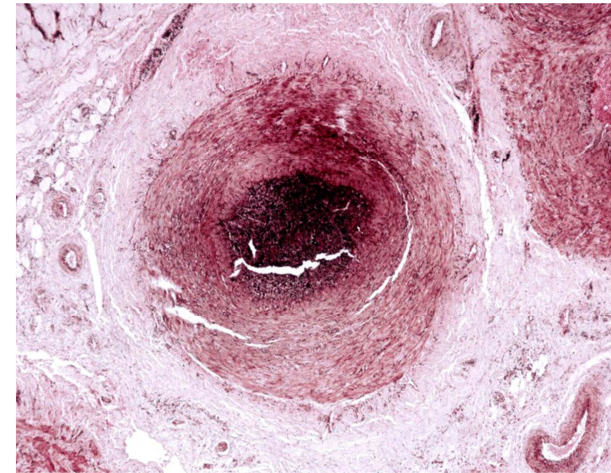
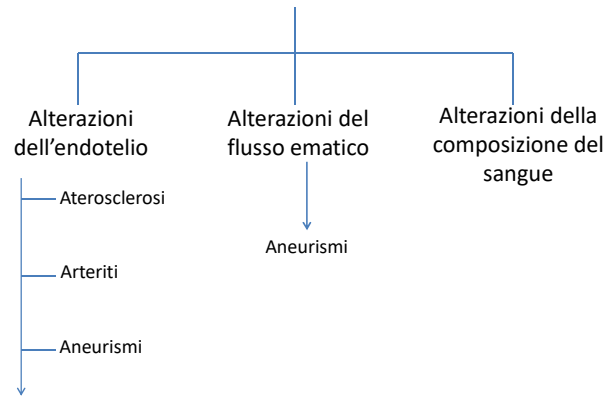
Alterazioni della composizione del sangue



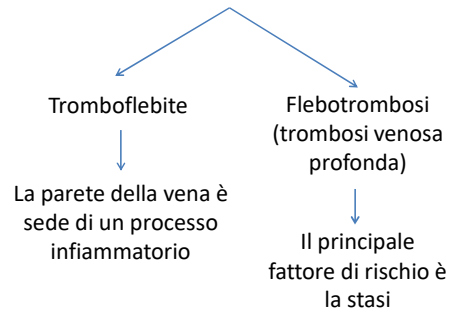
Triade di Virchow



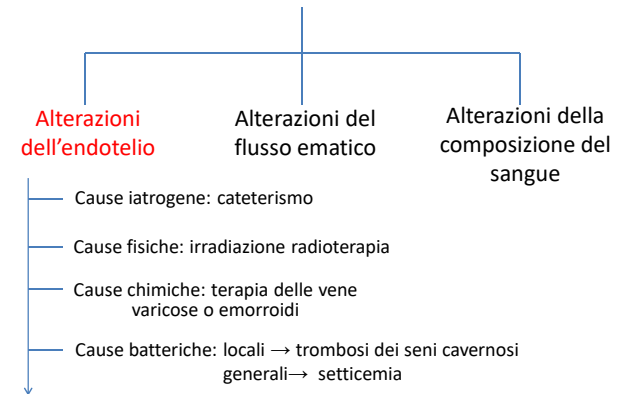
Trombosi arteriose



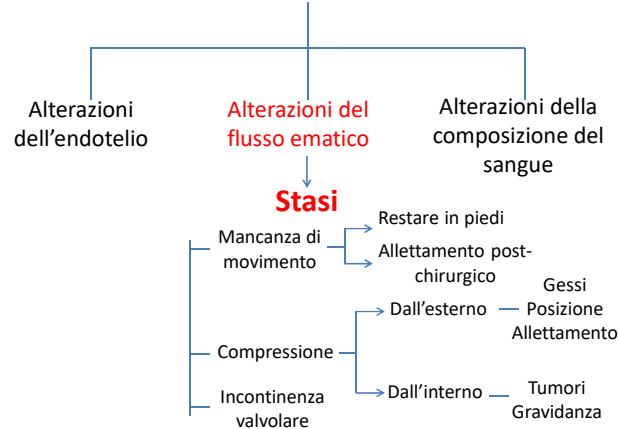
Trombosi venose



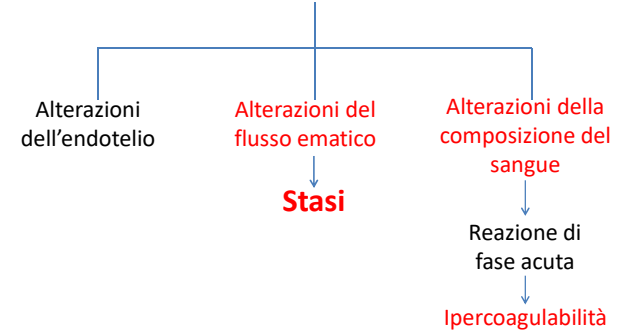
Tromboflebite



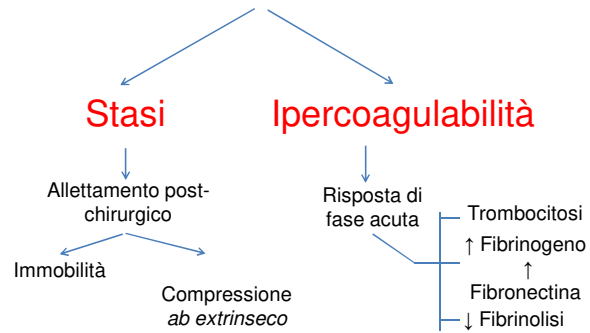
Flebotrombosi



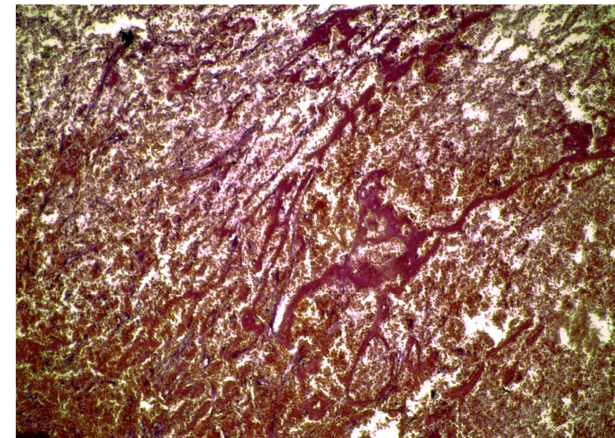
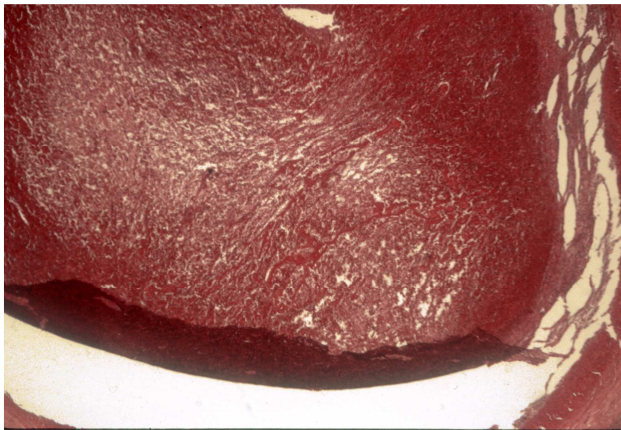
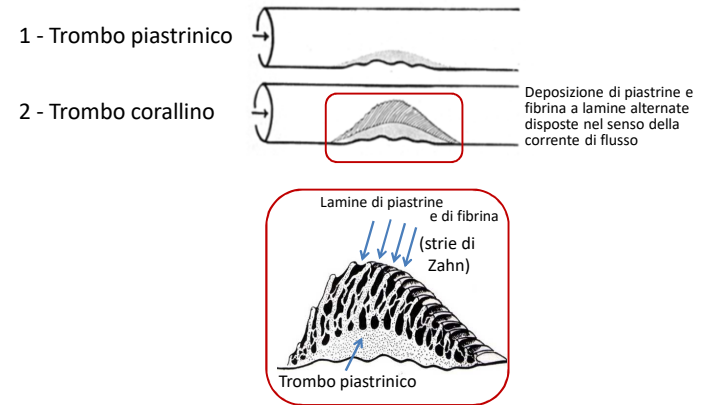
Flebotrombosi

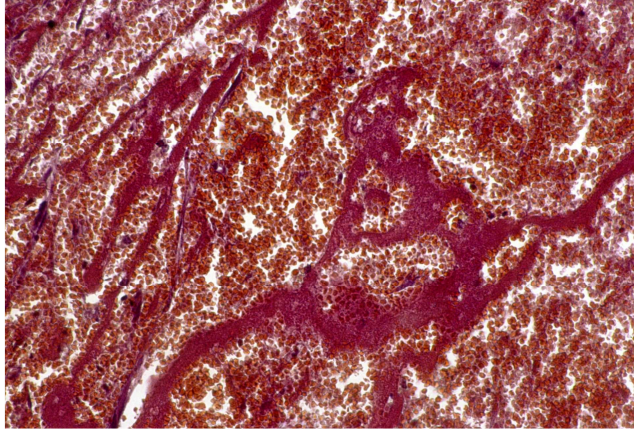


Il paziente post-chirurgico è un paziente a rischio di flebotrombosi

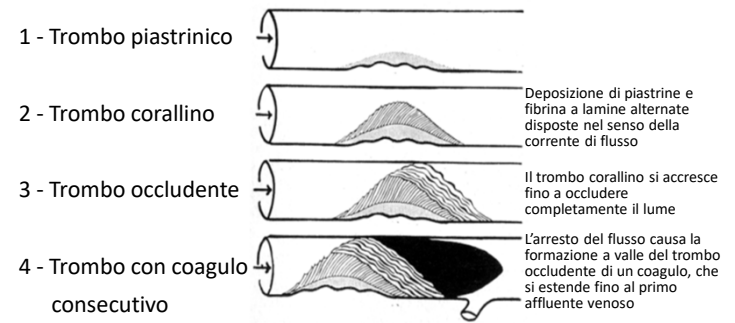


Fasi della formazione della flebotrombosi

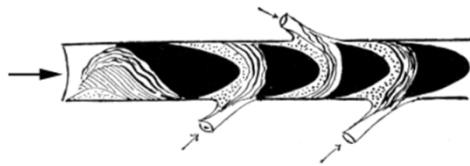




Fasi della formazione della flebotrombosi



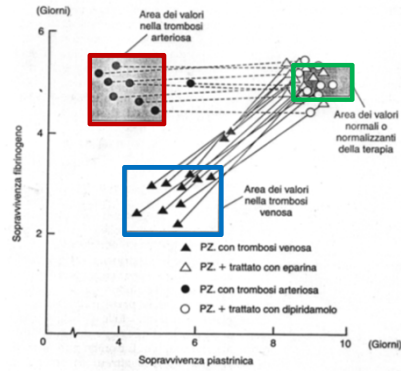
Coagulo propagato



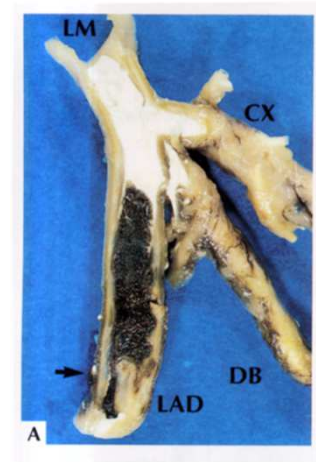
A livello degli affluenti venosi, la concomitanza di flusso lento e coagulazione può portare alla formazione di un nuovo trombo, la cui formazione ripete la sequenza precedente. Sul secondo trombo si riforma il coagulo consecutivo, e così via per ogni affluente venoso.

Date le caratteristiche del flusso, i fenomeni coagulativi sono tipici delle trombosi venose, e non delle trombosi arteriose.

Le trombosi arteriose consumano piastrine, ma non fibrinogeno

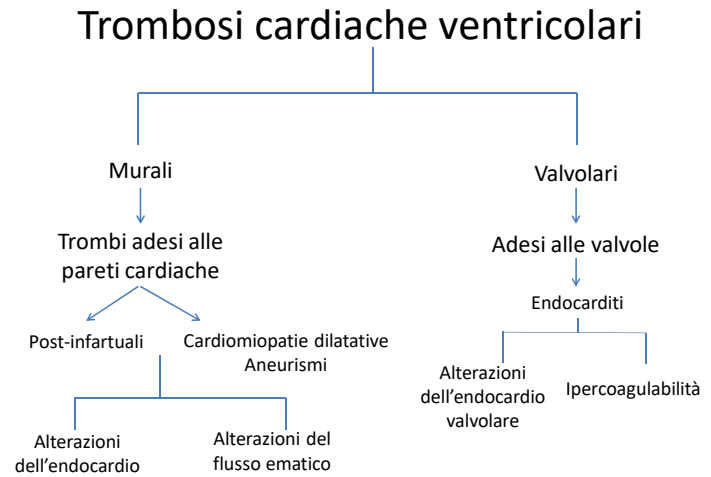


Nella trombosi coronarica, secondariamente al blocco del flusso può sviluppare un coagulo retrogrado, che si può propagare fino alla biforcazione.



Trombosi cardiache

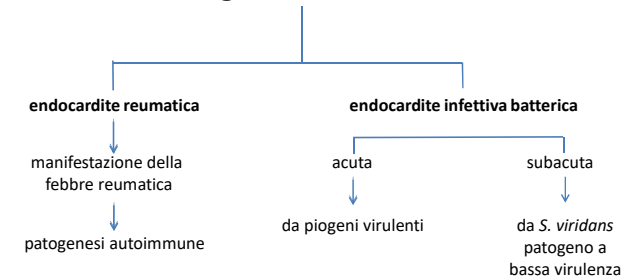
Ventricolari
Atriali



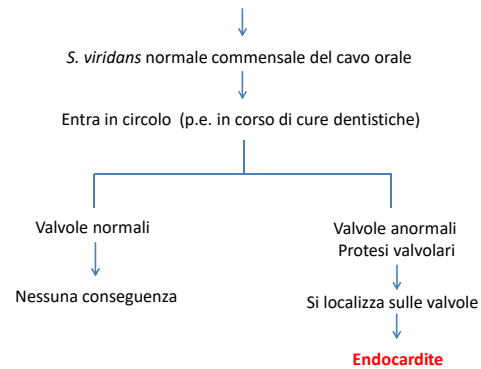
Endocardite

Inflammatione che coinvolge l'endocardio valvolare e più raramente quello parietale.

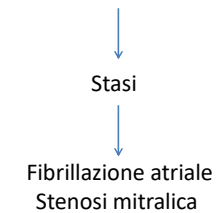
In rapporto all'origine si distinguono le seguenti forme:



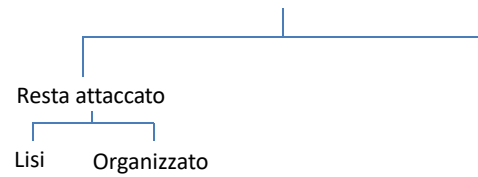
Endocardite batterica subacuta



Trombosi cardiache atriali



Evoluzione dei trombi



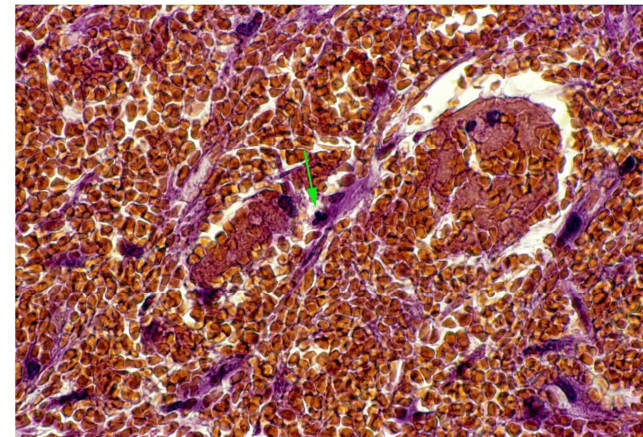
Il processo di organizzazione avviene in maniera identica alla riparazione

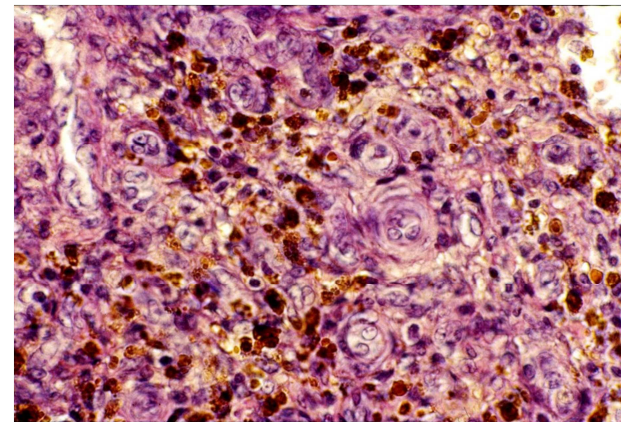
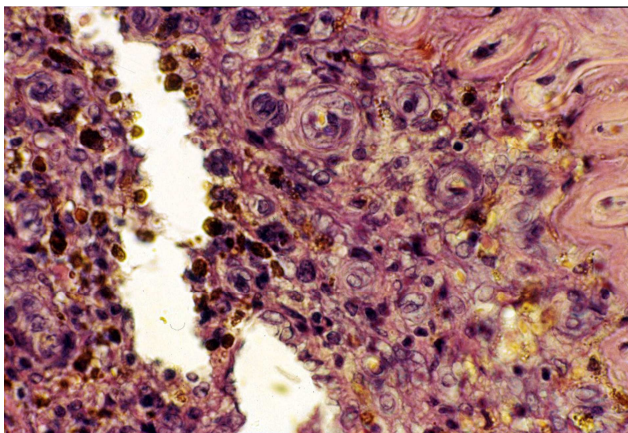
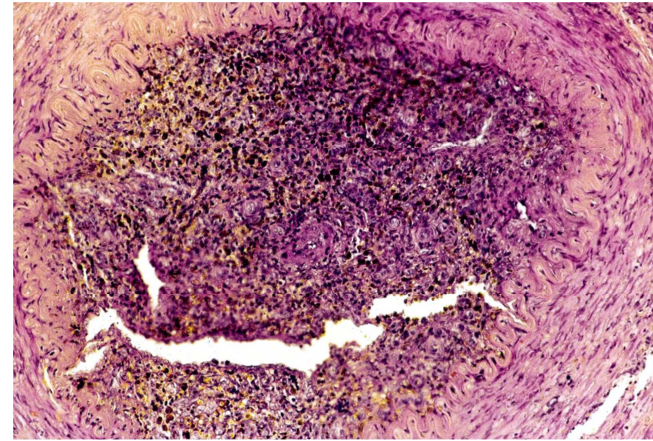
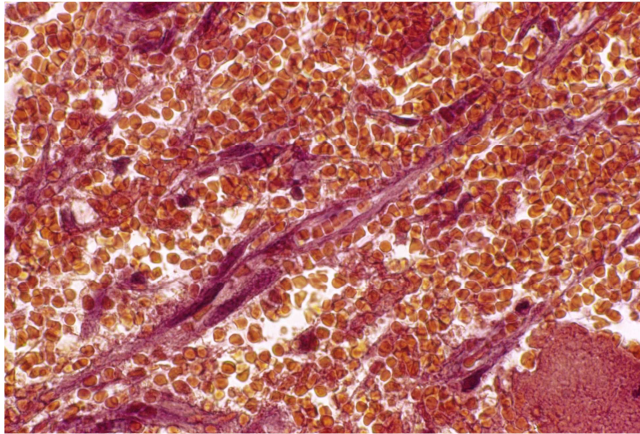
Organizzazione

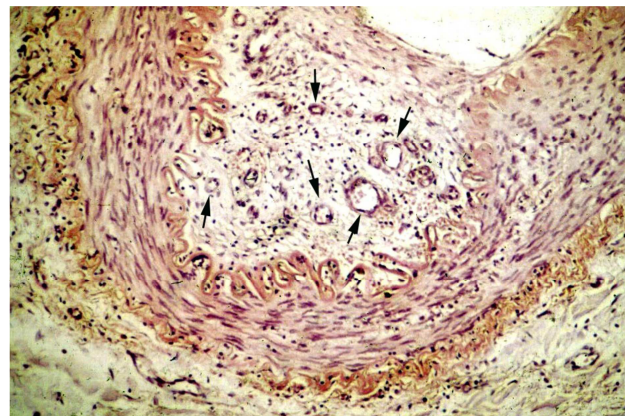
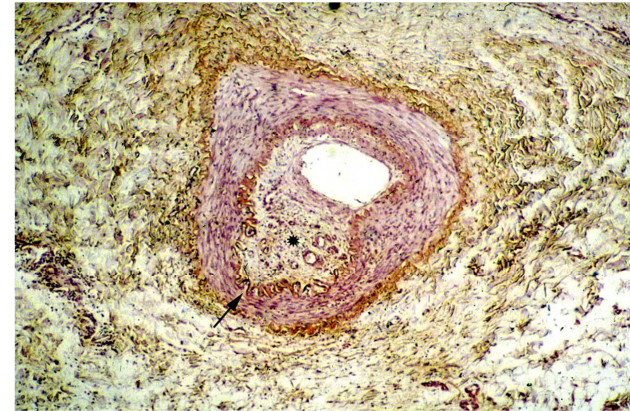
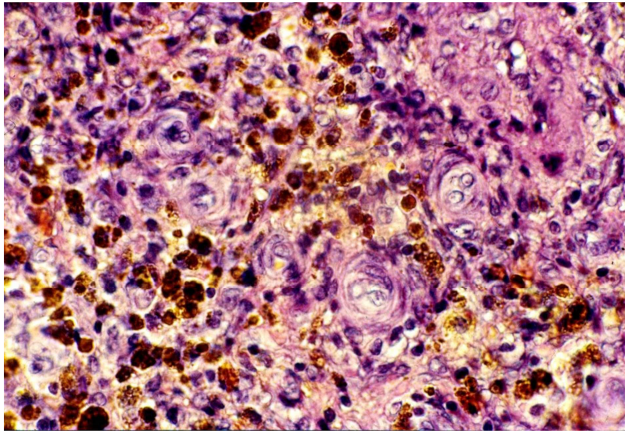
La sostituzione con tessuto connettivo riparativo di un:

- trombo
- embolo
- coagulo
- area necrotica
- essudato

Tutti materiali non viventi



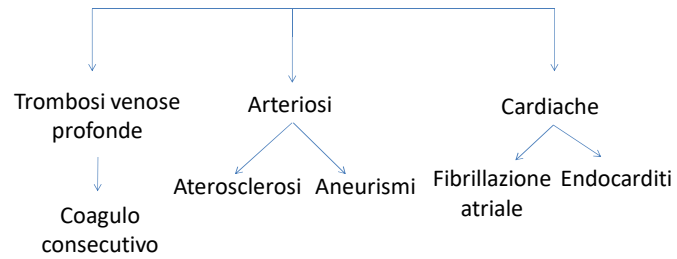




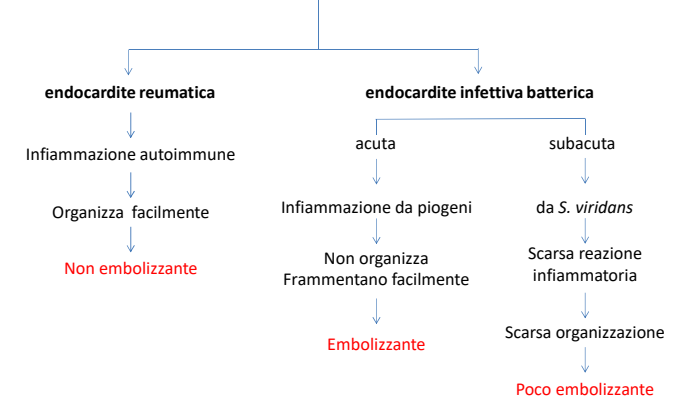
Evoluzione dei trombi



Embolia da distacco di trombi



Capacità embolizzante delle endocarditi



Gli emboli da trombosi infettive batteriche sono infetti

Emboli micotici