COMITATO SCIENTIFICO:
Elvira Grandone (San Giovanni Rotondo)
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Epidemiologia delle complicanze emorragiche da AVK e Aspirina nella popolazione generale

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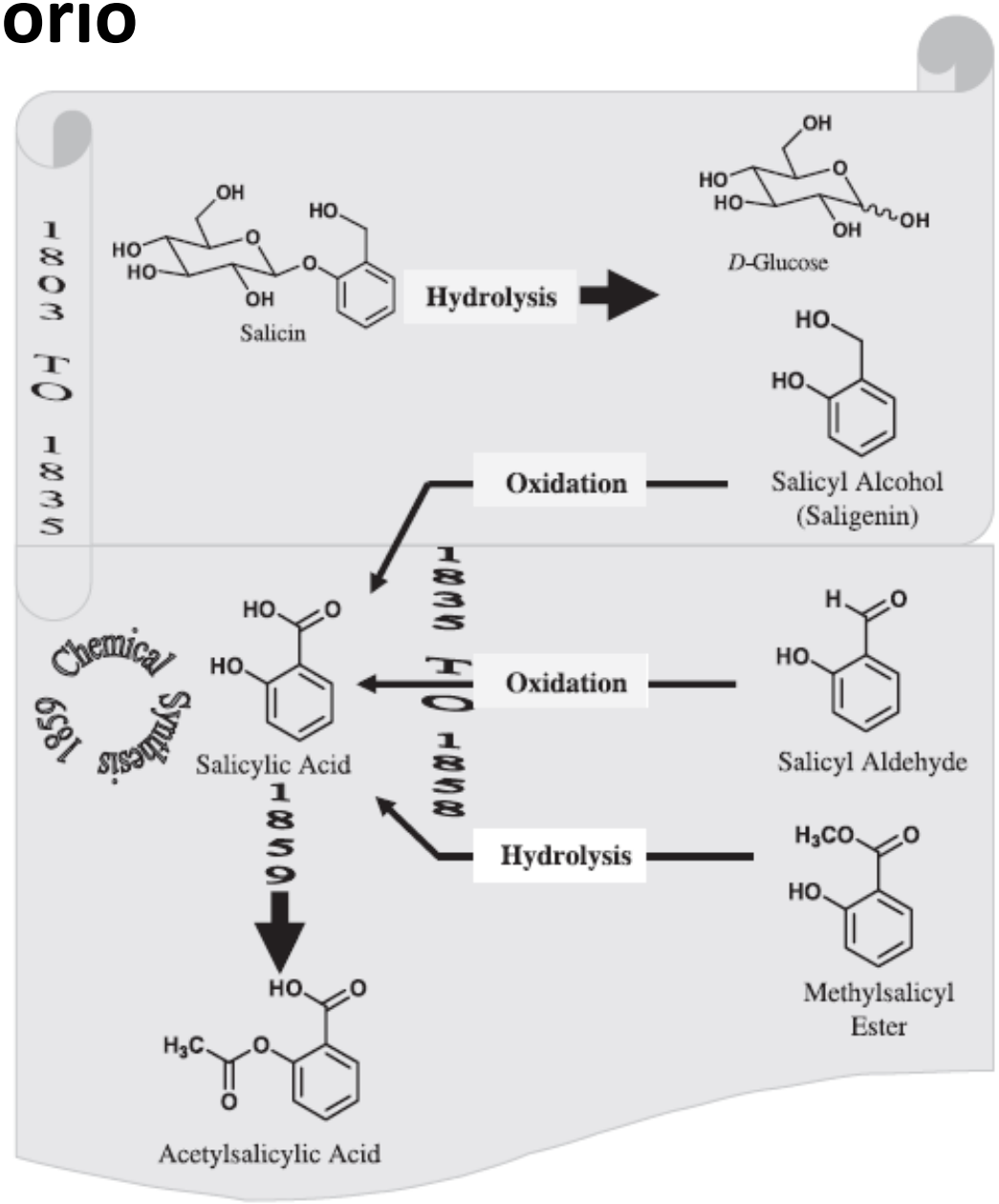
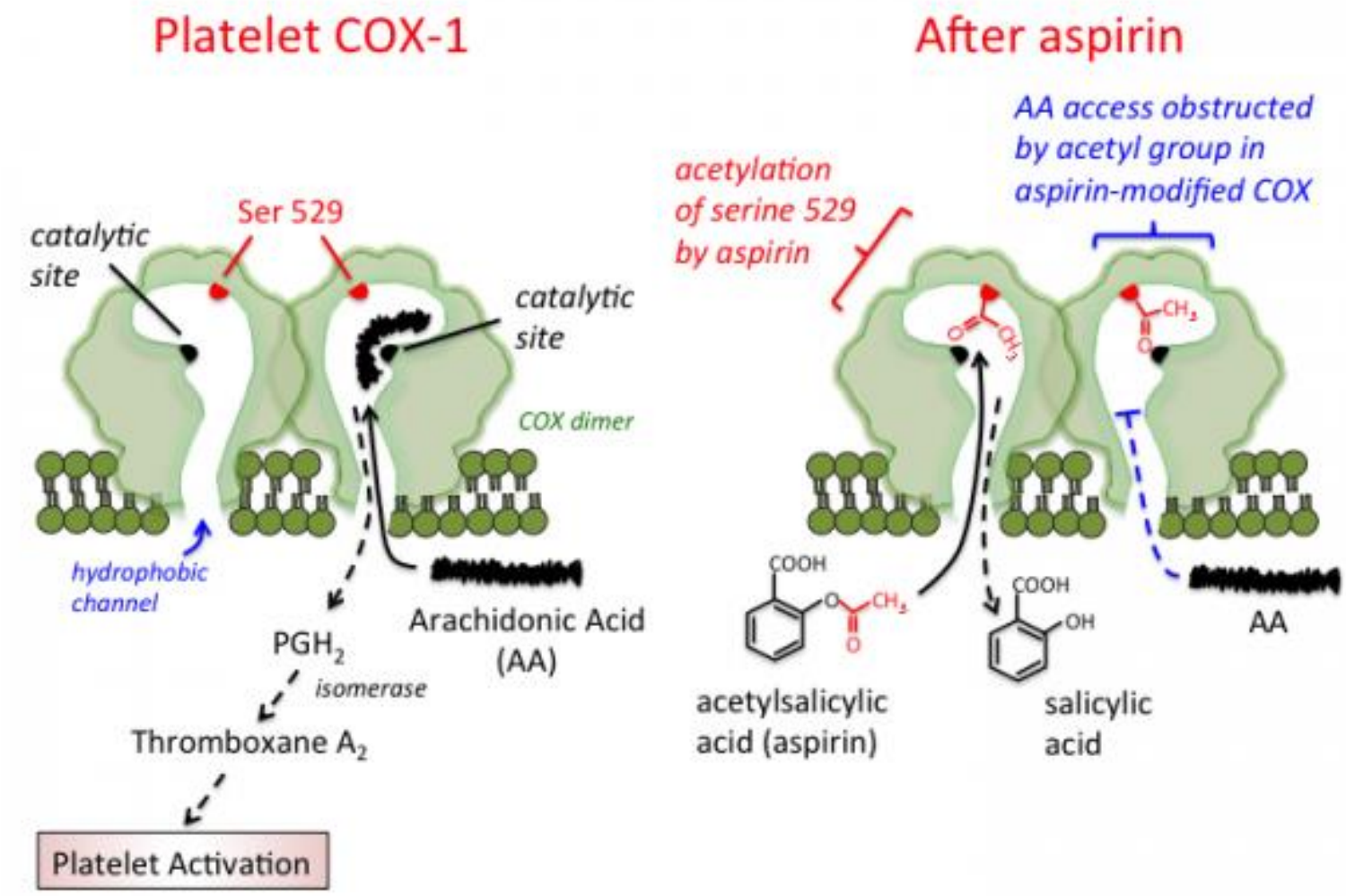
Internal Medicine and Haemocoagulophaties Unit

Prima Anti-infiammatorio
Poi Anti-trombotico

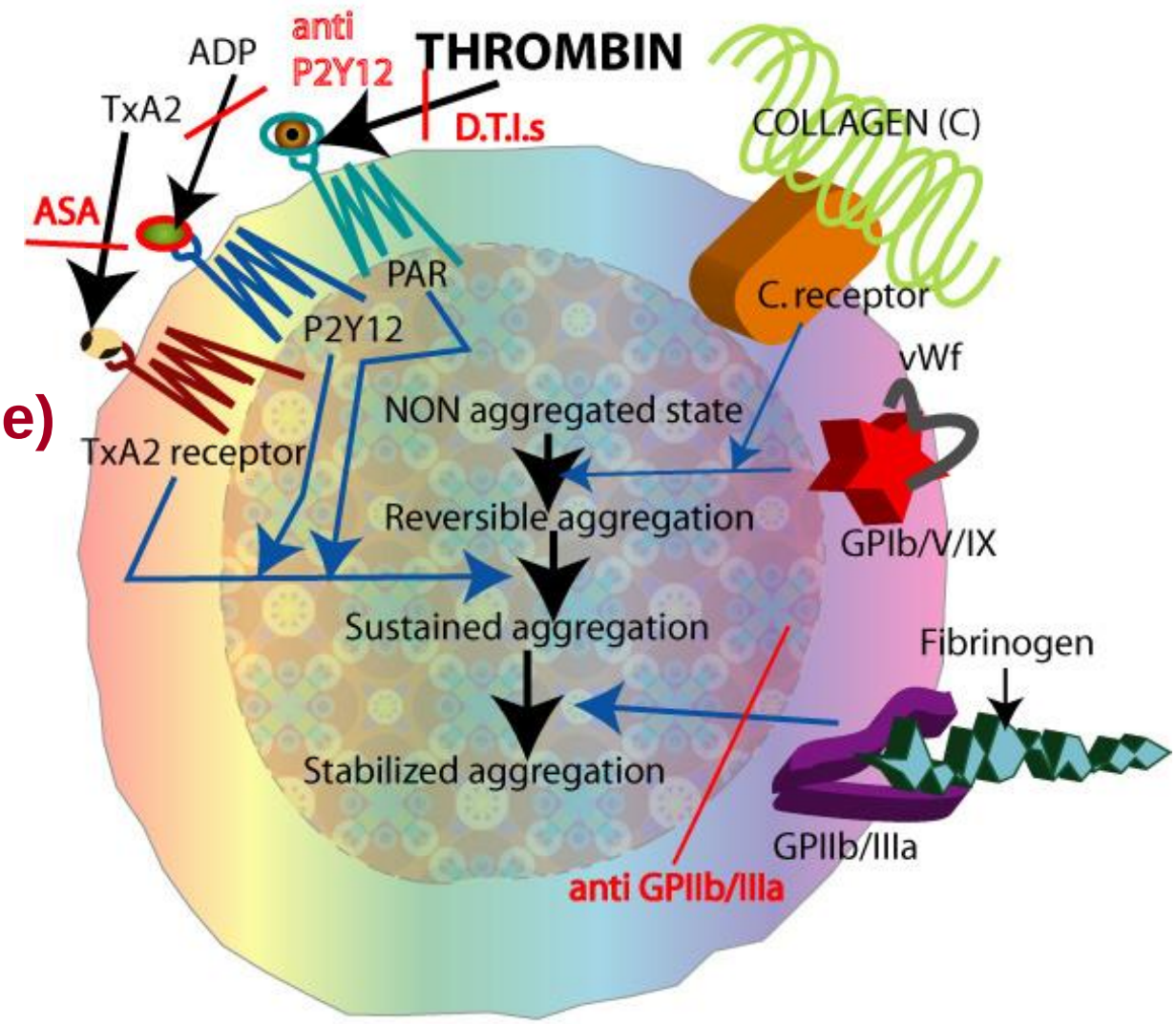


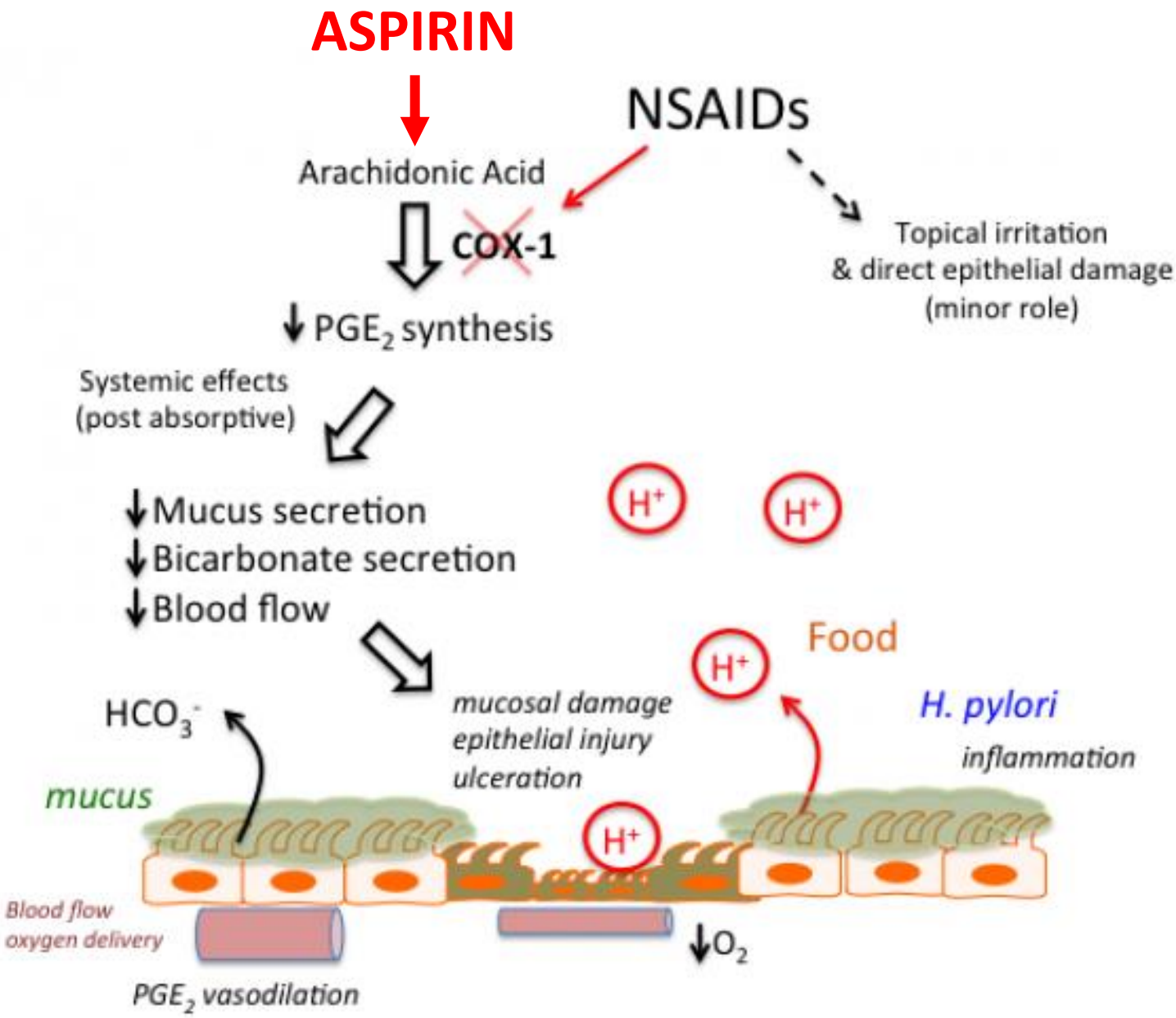
Mahdi JG et al. Cell Prolif 2006; 39: 147-155


Platelet COX-1
After aspirin
Ser 529
catalytic site
catalytic site
COX dimer
hydrophobic channel
Arachidonic Acid (AA)
PGH2
isomerase
Thromboxane A2
Platelet Activation
acetylation of serine 529 by aspirin
AA access obstructed by acetyl group in aspirin-modified COX
COOH
COOH
OH
AA
acetylsalicylic acid (aspirin)
salicylic acid

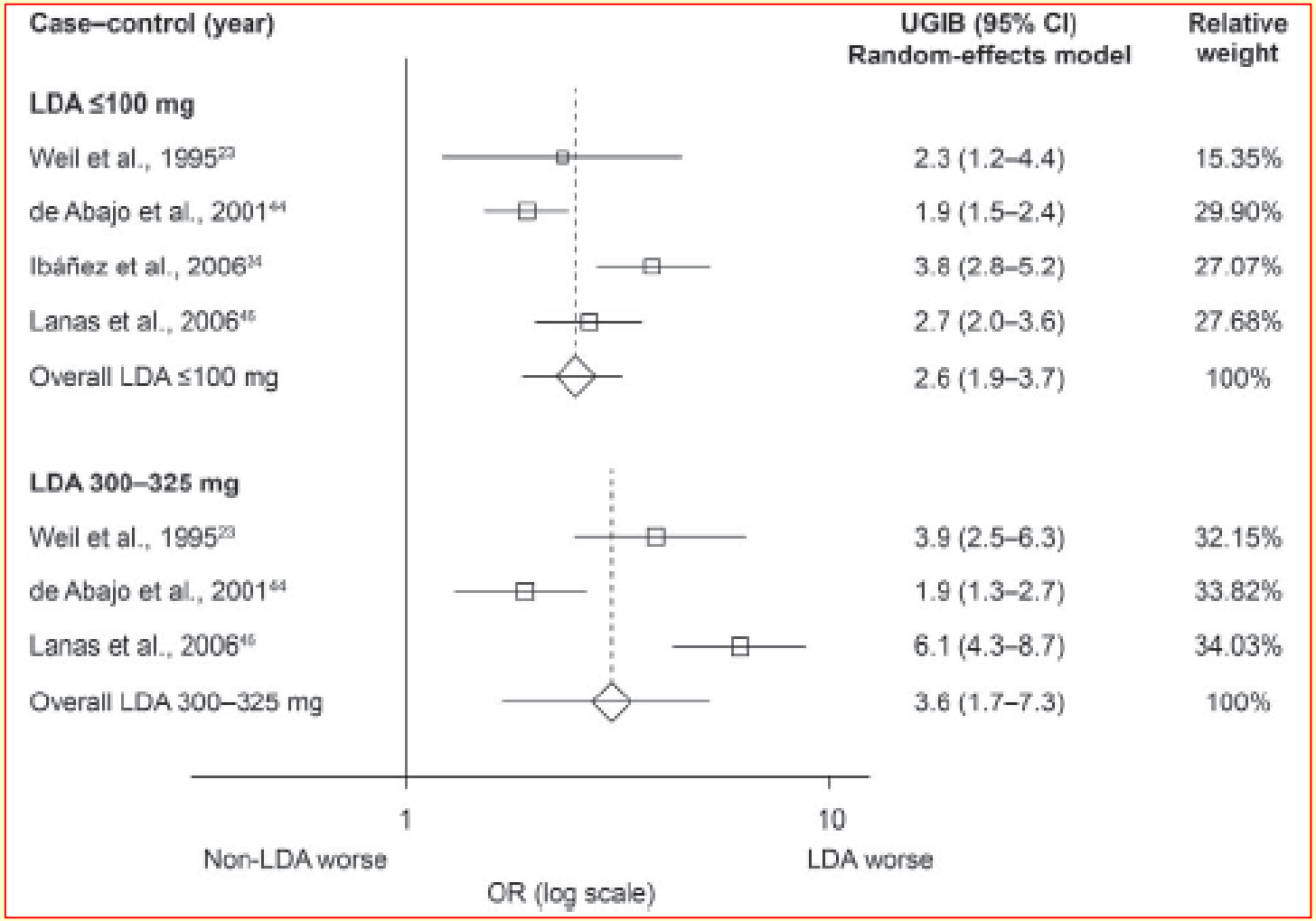
Diverse possibilità di inibizione dell'attività piastrinica:

ASA (Tx produzione)
Anti-recettore Tx
Clopidogrel (ADP)
Prasugrel (ADP)
Ticagrenol (ADP)
Trombina (DTI)
Anti GPIIb/IIIa
Anti vW




ASPIRIN
NSAIDs
Arachidonic Acid
COX-1
Topical irritation
& direct epithelial damage
(minor role)
↓ PGE2 synthesis
Systemic effects
(post absorptive)
↓ Mucus secretion
↓ Bicarbonate secretion
↓ Blood flow
H+
H+
Food
H+
HCO3-
mucosal damage
epithelial injury
ulceration
H. pylori
inflammation
mucus
H+
Blood flow
oxygen delivery
↓ O2
PGE2 vasodilation

Aspirin and Gastrointestinal bleeding



Can J Gastroenterol Vol 27 No 3 March 2013

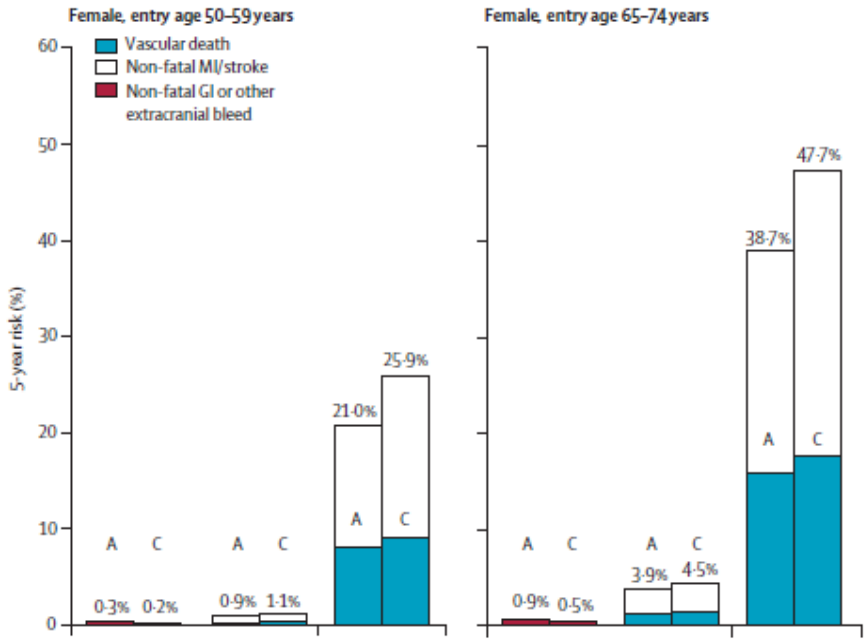
Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

*Antithrombotic Trialists' (ATT) Collaboration**

Outcomes	Primary prevention	Secondary prevention
Any serious vascular event	0.88, 0.82-0.94	0.81, 0.75-0.87
Non fatal MI	0.77, 0.69-0.86	0.69, 0.60-0.80
CHD mortality	0.95, 0.82.1.10	0.87, 0.78-0.98
Stroke ischemic	0.86, 0.74-1.00	0.78, 0.61-0.99
Stroke haemorrhagic	1.32, 1.00-1.75	1.67, 0.97-2.90
Extracranial bleed	1.54, 1.30-1.82	2.69, 1.25-5.76

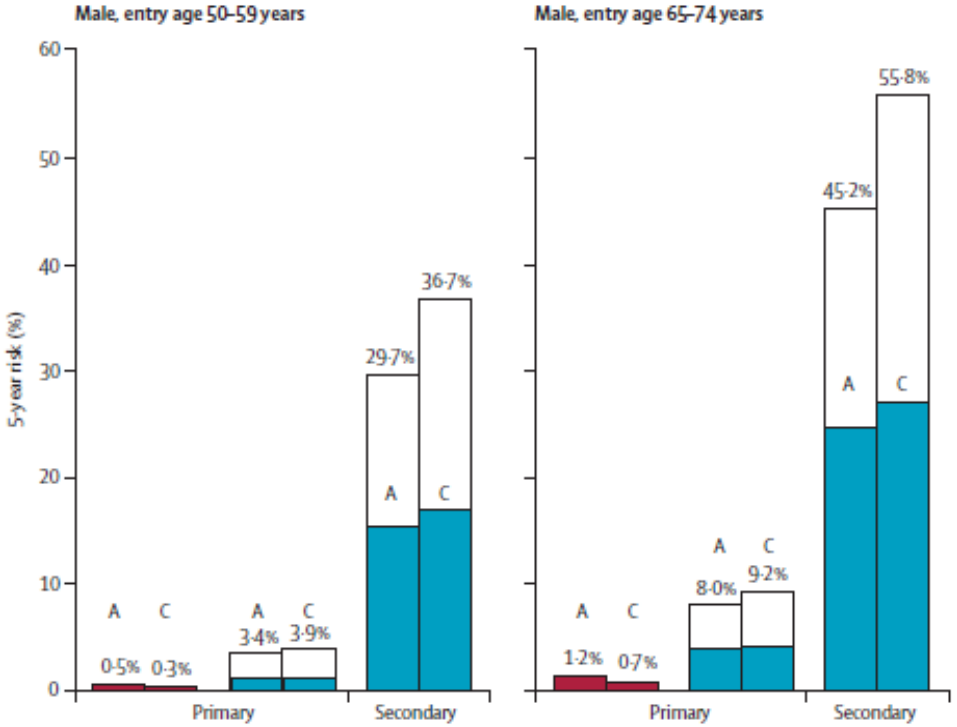
ASA in primary prevention: not so convenient

Lancet 2009; 373: 1849–60



Not a significant gain of function (anti-thrombotic) in primary prevention.

Good results in secondary prevention



Lancet 2009; 373: 1849–60

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

Outcome	Warfarin alone n=34851	Warfarin + ASA n=4311
Major bleeding	2.04, 1.92-2.16 %	3.07, 2.70-2.44 %
Intracranial	0.41, 0.35-0.46 %	0.62, 0.45-0.79 %
GI bleeding	0.67, 0.60-0.74 %	1.18, 0.95-1.41 %

Bleeding is increased adding aspirin to warfarin

JAMA Cardiol. 2016;1(2):172-180.

Insorgenza di FA con storia di SCA da più di 1 anno

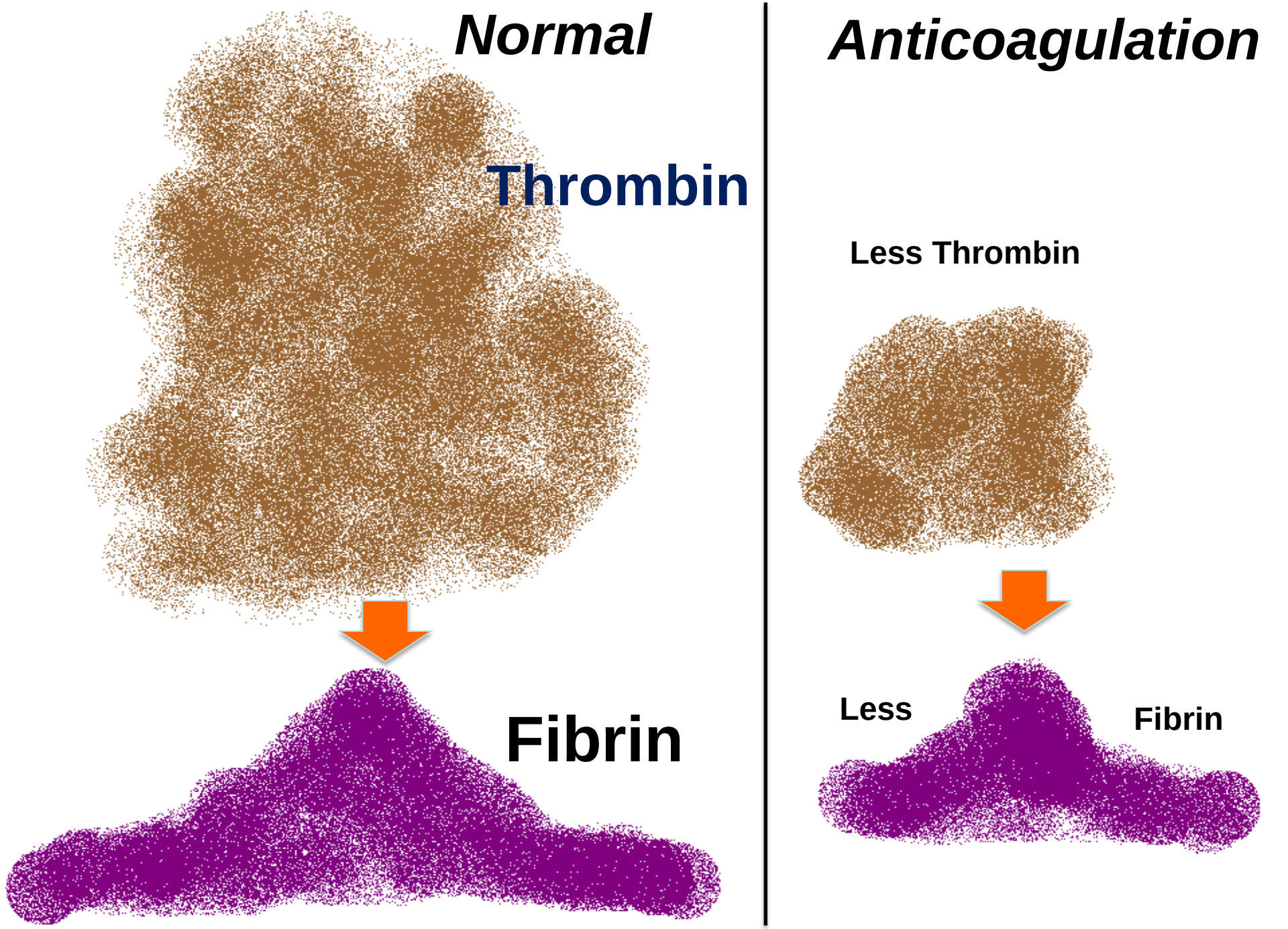
1 VKA come monoterapia (WARIS II)
2 Utilizzo dei DOAC possibile ma evidenza indiretta (*Trials*)

Evento	ASA	Warfarin	Warfarin + ASA
Reinfarto	117/1206	90/1216	69/1208

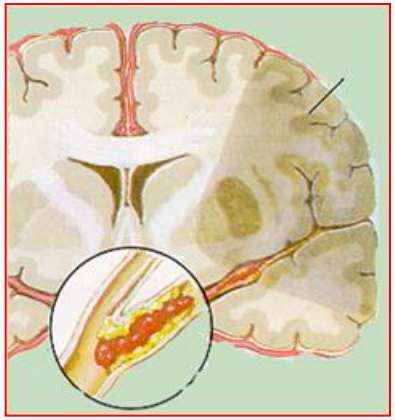
WARIS II

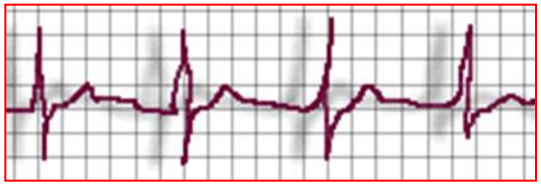
W + ASA versus ASA: 0.56, 0.41-0.78
W versus ASA: 0.74, 0.55-0.98
W versus W + ASA: 0.77, 0.56-1.04

Europace 2015;17:1467-507
N Engl J Med 2002;347:969-74

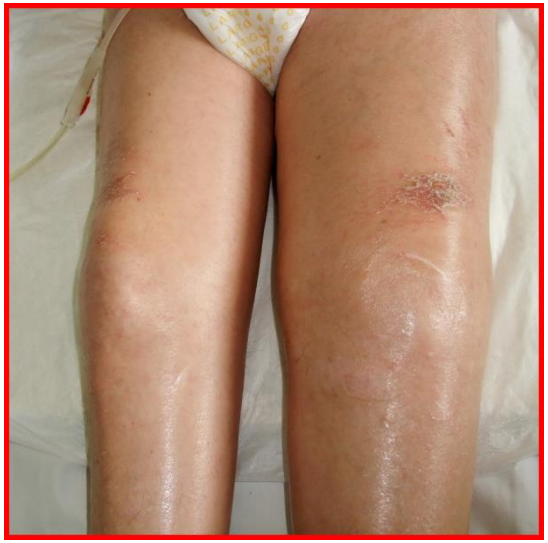

Normal
Thrombin
Fibrin
Anticoagulation
Less Thrombin
Less
Fibrin

…..but for which pathological conditions ?





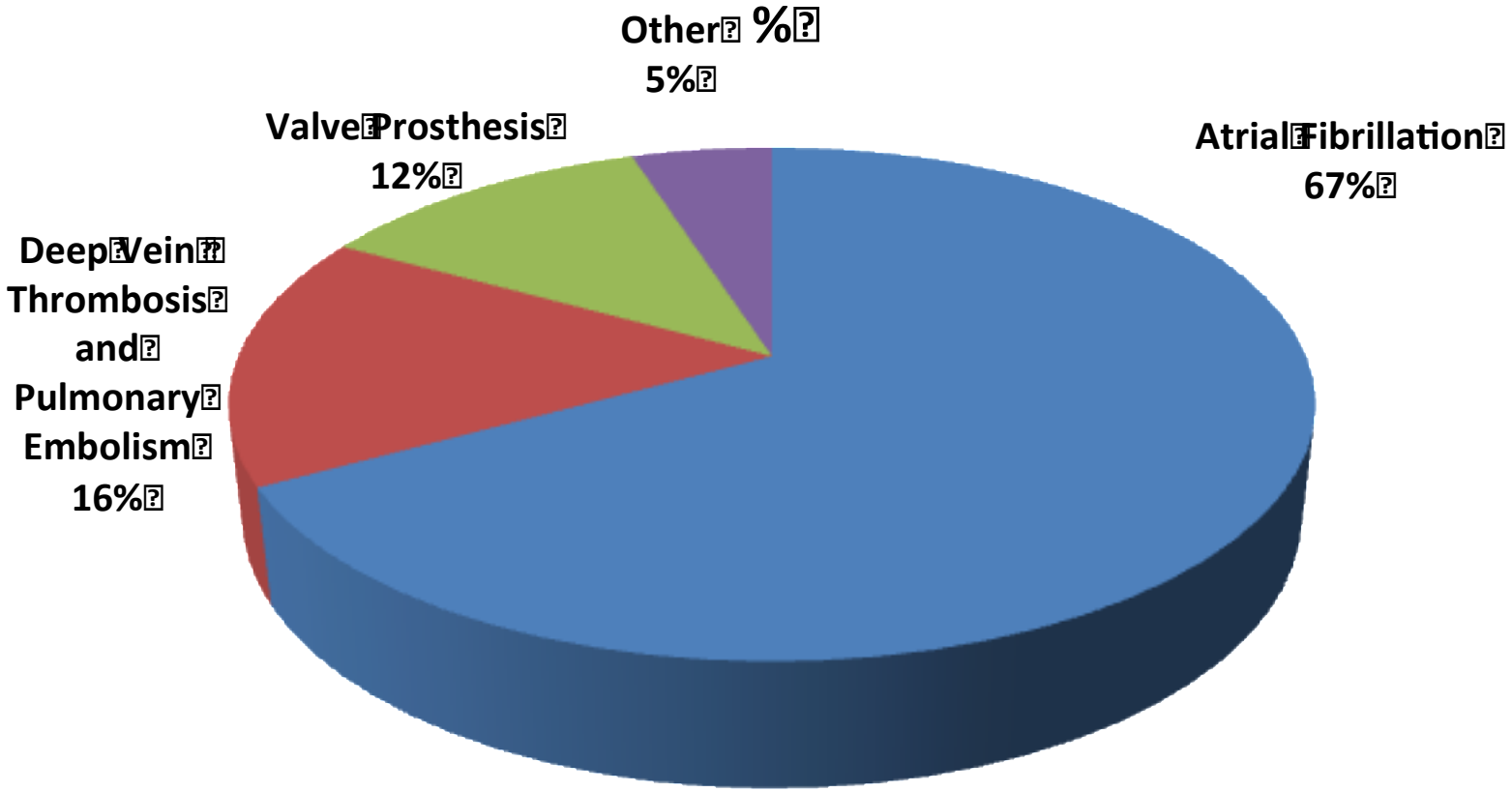
Cardioembolic stroke from Atrial Fibrillaton

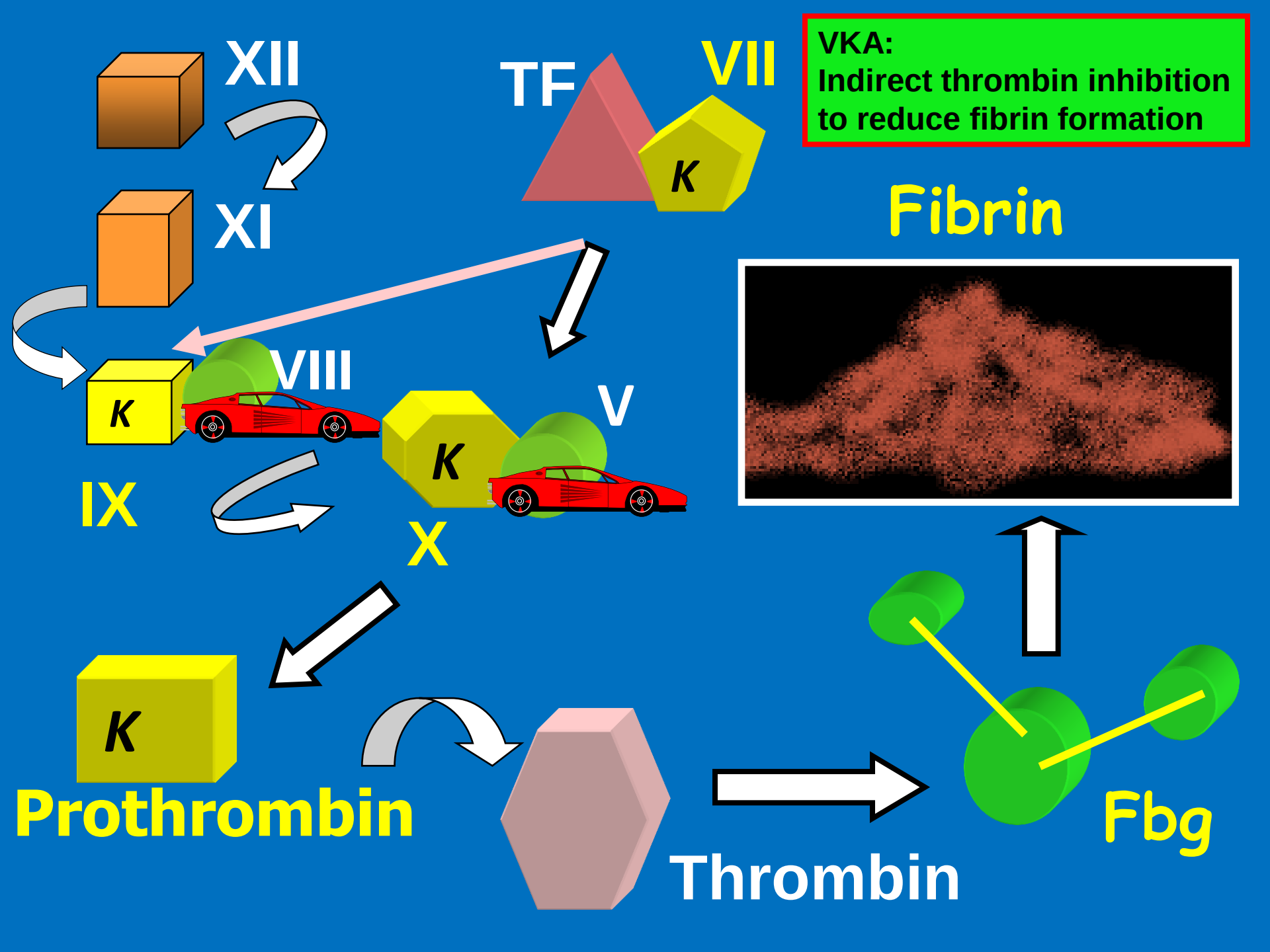


Deep Vein Thrombosis and Pulmonary Embolism after a LMWH course

Mechanical heart valves VKA only

Oral anticoagulation (VKA) can reduce the risk of thromboembolism by 64-90 %


Other 5%
Valve Prosthesis 12%
Atrial Fibrillation 67%
Deep Vein Thrombosis and Pulmonary Embolism 16%


XII
XI
TF
VII
K
VKA:
Indirect thrombin inhibition
to reduce fibrin formation
Fibrin
VIII
K
V
K
IX
X
K
Prothrombin
Thrombin
Fbg

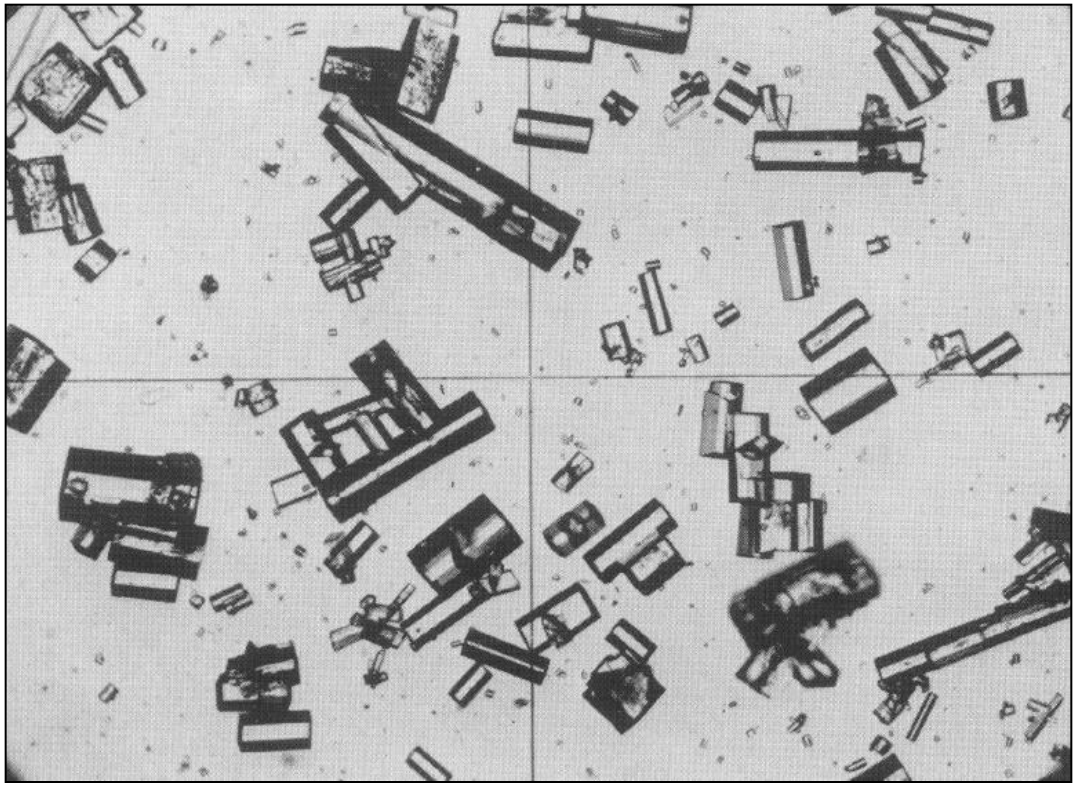
Sweetclover

In 1920 a substance contained in the spoiled sweetclover was identified to induce the haemarrhagic disease of the cattle.

Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. Circulation 1994; 89: 432-49.

That substance, dicoumarol, was identified in 1940. Warfarin was then isolated by Link

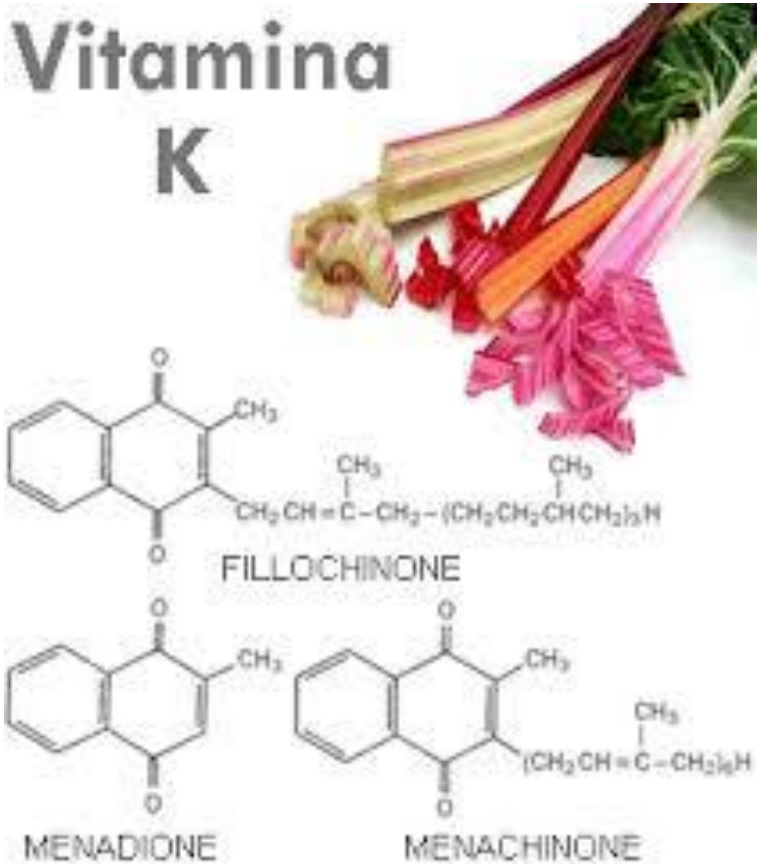
Kark Paul Link (1901-1978)



Warfarin

But Link's research was planned to get a rat killer. He announced his final results in 1948

Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. Br J Haematol 2008;141:757-63



In the same years Link demonstrated that the effect of coumarins was antagonized by vitamin K contained almost in vegetables.

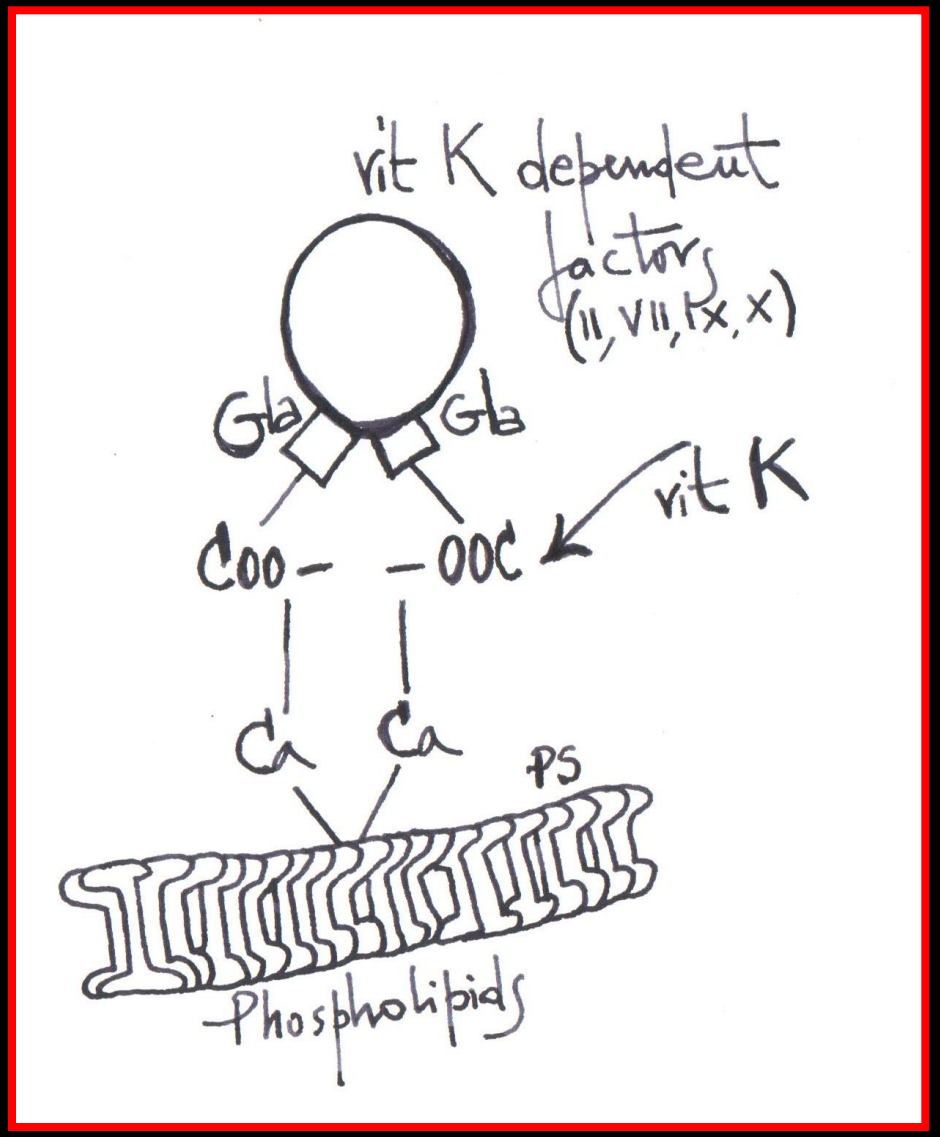
But the mechanism of action of coumarins was discovered by Suttie only in 1978.

Vitamin K comes from diet (vegetables mainly).

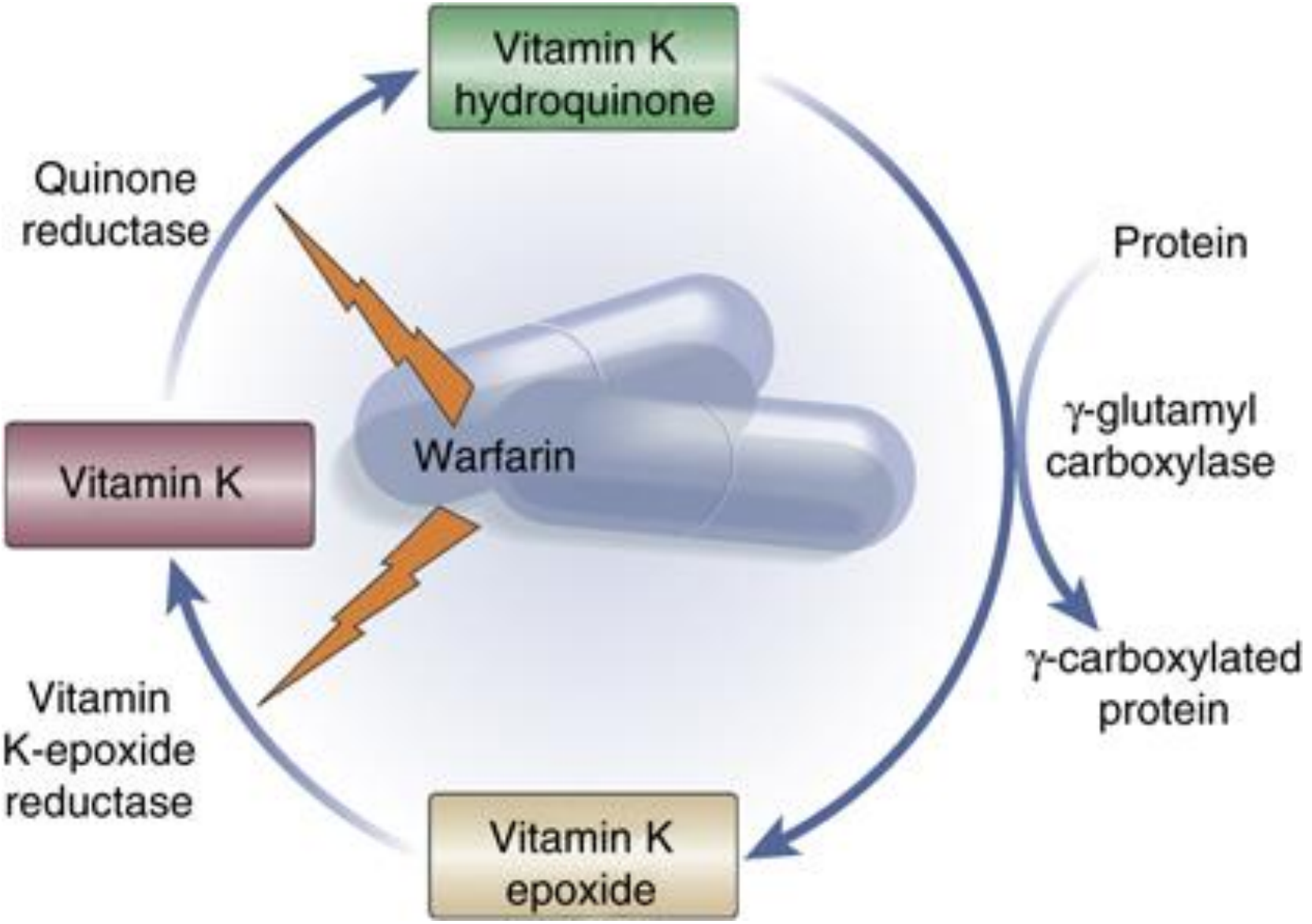
It can drive a carboxylase which induces carboxylation of the Gla residues common to all vitamin K coagulative factors (II, VII, IX and X).

This is essential for their function because in this way they can be anchored to phospholipids of platelet membrane.

In other words they can be “coagulated”.

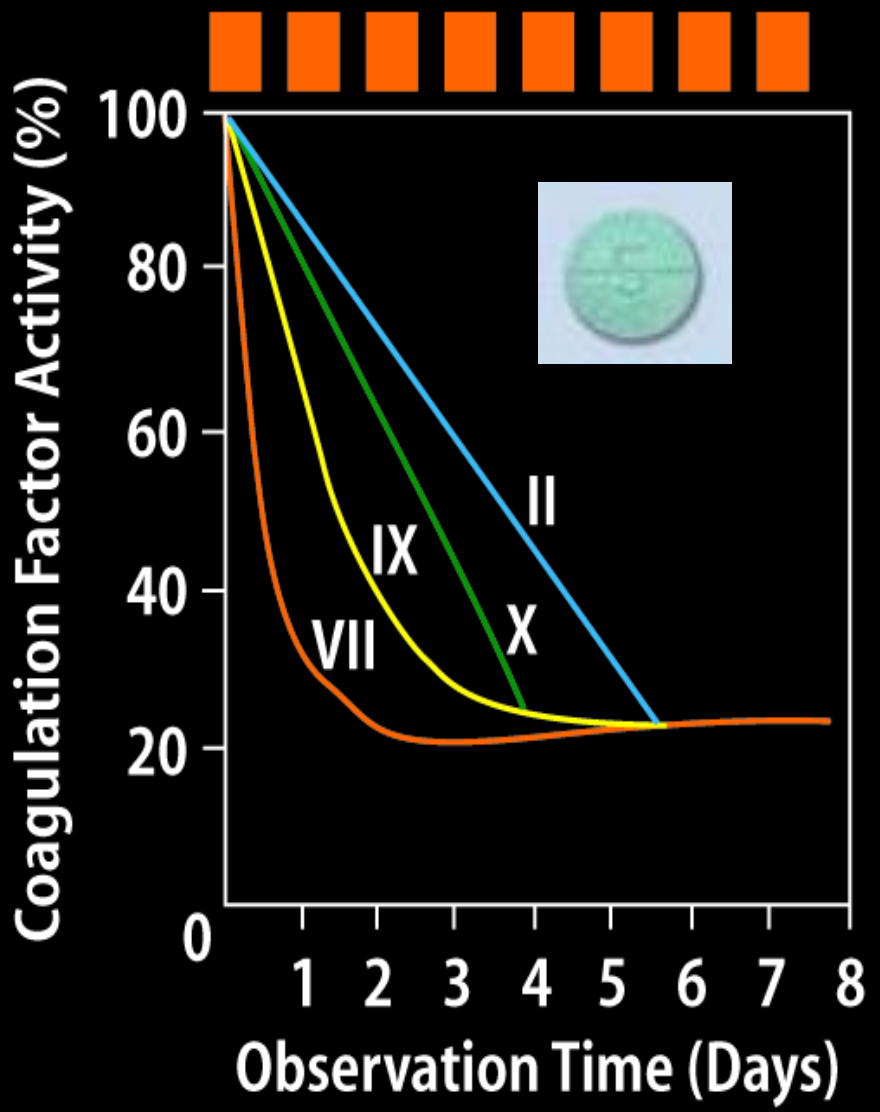


Biochemistry 1978; 17: 1371


Vitamin K
hydroquinone
Quinone
reductase
Protein
γ-glutamyl
carboxylase
Warfarin
Vitamin K
γ-carboxylated
protein
Vitamin
K-epoxide
reductase
Vitamin K
epoxide

The slow onset of action of AVK is due to the very different clearance of the Vitamin K dependent factors (II, VII, IX and X) ranging from 6 to 60 h.

A full anticoagulation can be therefore reached after several days.



AVK need to be monitored by means of a lab test: Prothrombin Time (PT)

$$PT_{Ratio} = \frac{PT\ patients}{MNPT}$$

$$INR = (PT_{Ratio})^{ISI}$$

PT is expressed as INR (International Normalized Ratio)

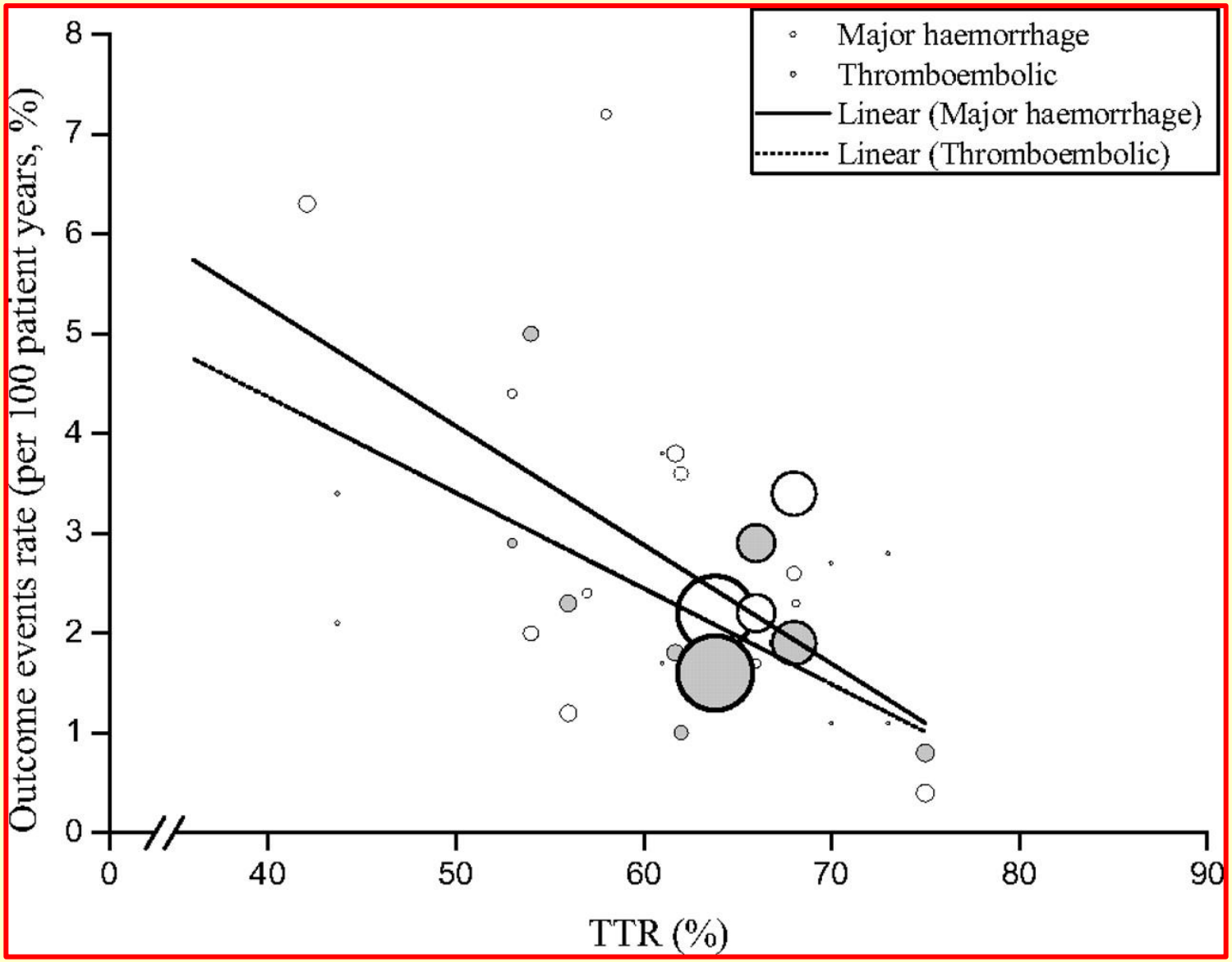
Each anticoagulated patient should stay within an INR range: 2.0-3.0 for all indications (target 2.5).

Mitral mechanical valves: 2.5-3.5 (target 3.0)

Normal subjects: INR around 1.0

The Time spent within the therapeutic range (TTR) is a measure which evaluates the quality of the therapy: patients should have a TTR ≥ 70 %.

TTR versus adverse events (weighted by sample size) for all studies



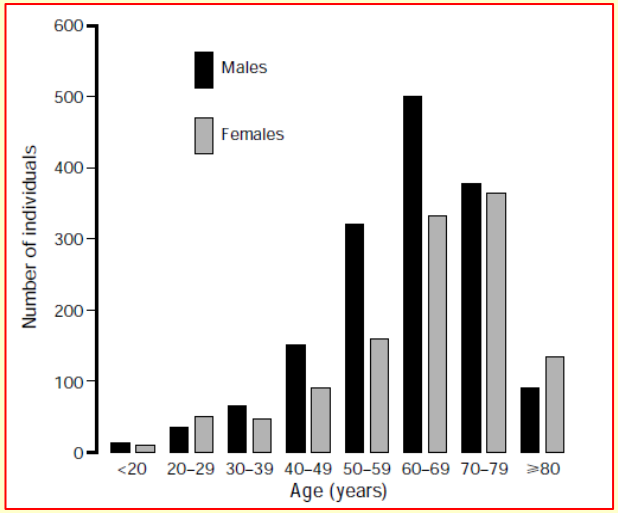
Wan, Y. et al. Circ Cardiovasc Qual Outcomes 2008;1:84-91

Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)

*Gualtiero Palareti, Nicoletta Leali, Sergio Coccheri, Mario Poggi, Cesare Manotti, Armando D'Angelo, Vittorio Pengo, Nicoletta Erba, Marco Moia, Nicola Ciavarella, Gianluigi Devoto, Mauro Berrettini, Serena Musolesi, on behalf of the Italian Study on Complications of Oral Anticoagulant Therapy**

Venous thromboembolism	892 (32·5%)
Non-ischaemic heart disease	661 (24·1%)
Dilated cardiomyopathy	136
Atrial fibrillation	462
Endocavitary thrombosis	24
Other	39
Ischaemic heart disease	403 (14·7%)
Post-myocardial infarction	144
After ACBP or PTCA	135
Other	124
Atrial vascular disease	281 (10·2%)
Peripheral	48
Cerebral	93
After vascular surgery	80
After peripheral emboli	44
Other	16
Heart-valve prosthesis	296 (10·8%)
Biological	34
Mechanical	262
Heart-valve disease	183 (6·7%)
Other diagnoses	29 (1·1%)
Total	2745

ACBP=aorto-coronary bypass, PTCA=percutaneous transluminal coronary angioplasty.



2745 pazienti

***Follow-up*: 2011 anni/paz**

All	153 (7·6)*	**Minor**	125 (6·2)
Fatal (all cerebral, 4 women)	5 (0·25)	32 haematuria 25 proctorrhagia	
Major	23 (1·1)	16 uterine bleeding	
7 digestive		14 gastrointestinal bleeding	
5 ocular (2 with diabetic retinopathy)		14 haematoma	
4 cerebral		13 large bruising	
3 haemarthrosis		2 epistaxis	
2 haemoptysis		9 other or multiple sites	
1 retroperitoneal		6 with two minor bleeding episodes	
1 haematuria		4 with three minor bleeding episodes	

*Per 100 patient-years.

Lancet 1996; **348:** 423–28

NOA versus Warfarin in Atrial Fibrillation

Anticoagulant	Major Bleeding	ICH	GI Bleeding
Dabigatran 150 mg	3.11	0.10	1.51
Dabigatran 110 mg	2.71	0.12	1.12
Warfarin	3.36	0.38	1.02
Rivaroxaban 20 mg	3.60	0.50	2.00
Warfarin 2.0-3.0 INR	3.40	0.70	1.24
Apixaban 5 mg	2.13	0.24	0.76
Warfarin	3.09	0.47	0.86
Edoxaban 60 mg	2.75	0.26	1.51
Edoxaban 30 mg	1.61	0.16	0.82
Warfarin	3.43	0.47	1.23

Am J Med 2016 Aug 29. pii: S0002-9343(16)30652-0

%/year

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

Outcome	Warfarin ≥ 70 n=22185	Warfarin <70 % n=19428
Major bleeding	1.61, 1.49-1.73 %	3.81, 3.51- 4.11 %
Intracranial	0.34, 0.28-0.39 %	0.72, 0.59-0.85 %
GI bleeding	0.56, 0.49-0.63 %	1.26, 1.09-1.43 %

An optimal management of the therapy induces a low bleeding risk

JAMA Cardiol. 2016;1(2):172-180.

Good clinical results in warfarin-treated patients managed in italian anticoagulation clinics (the ISCOAT 2016 study). Comparison with the ISCOAT study published 20 years ago

Palareti G et al. 2016 (Manuscript submitted)

Patients n.	**5707**
Males n (%)	**3029 (53)**
Age mean (range) y	**73.0 (19.0)**
Age n (%) <70	**2069 (36.2)**
≥70	**3638 (63.8)**
>80	**1605 (28.1)**
Indication for anticoagulation n (%)	
Venous Thromboembolism	**1593 (28.0)**
Atrial fibrillation	**3516 (61.6)**
Heart-valve prosthesis	**219 (3.5)**
Biological	**115 (53.8)**
Mechanical	**101 (46.2)**
Heart-valve disease	**32 (0.56)**
Other	**347 (6.08)**

Quality of anticoagulation control	
median (IQR) percent time spent in relation to the therapeutic range (2.0-3.0 INR)	
Below	**21.0 (12.0-33.0)**
Within (TTR)	**66.0 (53.0-77.0)**
Above	**9.0 (3.0-16.0)**
median (IQR) TTR in patients according the indication for treatment	**67.0 (54.0-77.0)**
AF	**65.0 (50.0-76.0)**
VTE	**51.0 (33.0-68.0)**
Other	
TTR in relation to age median (IQR)	
≤ 80 y	**65.0 (50.0-76.0)**
> 80	**66.0 (54.0-76.5)**

Events n. (rate % annually)	Bleeding complications	Thrombotic complications
Major events	123 (1.38)	47 (0.53)
Fatal	10 (0.11)	4 (0.04)
	Intracranial 38 (0.43; 7 fatal)	Stroke 12 (0.13; 4 fatal)
	Digestive 29 (0.32.6; 3 fatal)	TIA 12
	Haematuria 7	AMI 9 (0.10)
	Haemarthrosis 3	Recurrent VTE 7
	Other 45	SVT 5
		Arterial embolism 2
Sex		
Males	71 (1.48)	22 (0.46)
Females	52 (1.24)	25 (0.60)
Age		
<70	30 (1.0)	17 (0.58)
≥70	93 (1.55)	30 (0.50)
RR	1.50 (1.0-2.4) p=0.04	

Anticoagulant	Major Bleeding	ICH
Dabigatran 150 mg	3.11	0.10
Dabigatran 110 mg	2.71	0.12
Warfarin	3.36	0.38
Rivaroxaban 20 mg	3.60	0.50
Warfarin 2.0-3.0 INR	3.40	0.70
Apixaban 5 mg	2.13	0.24
Warfarin	3.09	0.47
Edoxaban 60 mg	2.75	0.26
Edoxaban 30 mg	1.61	0.16
Warfarin	3.43	0.47

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation

Daniela Poli, MD; Emilia Antonucci, MD; Sophie Testa, MD; Alberto Tosetto, MD; Walter Ageno, MD; Gualtiero Palareti, MD; for the Italian Federation of Anticoagulation Clinics (FCSA)

4093 pazienti (80-100 anni)
di cui 3015 (73.7 % con FA)

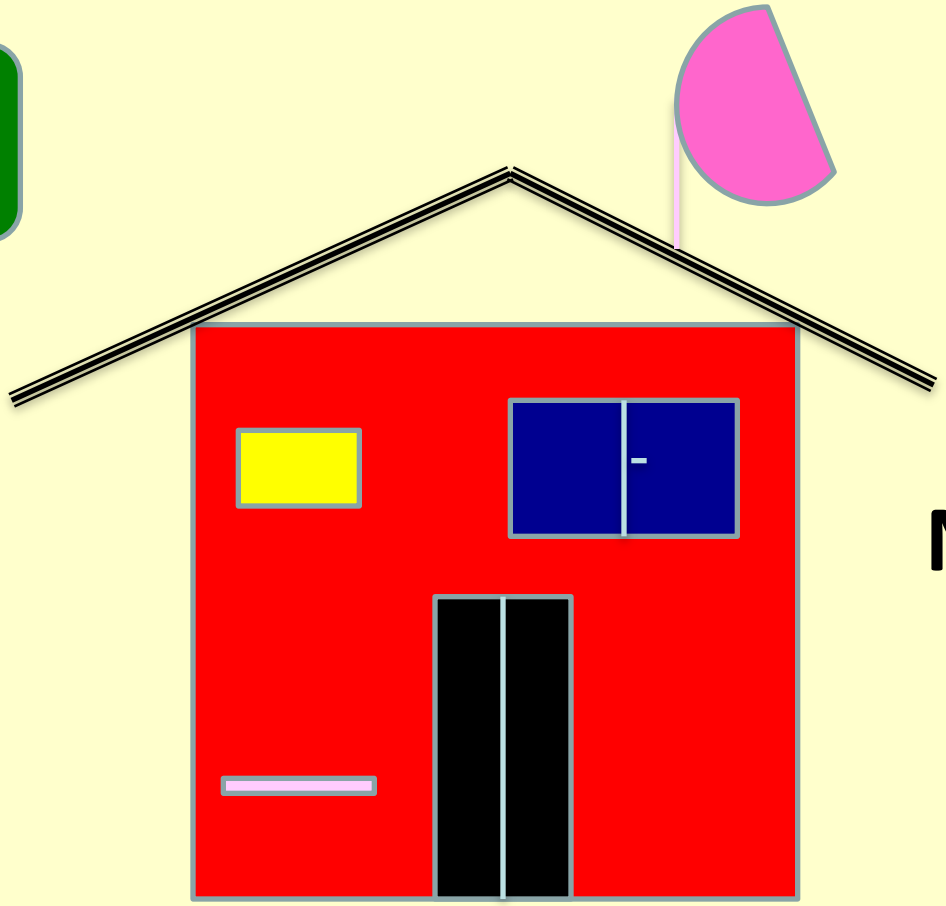
Fibrillazione Atriale
Sanguinamento maggiore
1.73 % anni/paz

Sanguinamento cerebrale
0.55 % anni/paz

Circulation 2011;124:824-29

	ISCOAT 2016	ISCOAT 1996
Major bleeding n. (% annually) [fatal]	123 (1.38)	28 (1.39)
Fatal	10 (0.11)	5 (0.25)
ICH	38 (0.43) [7]	9 (0.45) [5]
Gastrointestinal	29 (0.32) [3]	7 (0.35) [/]
Other	56 (45.5) [/]	12 (0.60) [/]
Major + NMCRB events occurring during the first 90 days of treatment n/N (%)	78/267 (29.2)	62/153 (40.5)

Centri Trombosi



AVK

Nei Centri FCSA

Sanguinamento cerebrale in linea con i Trials

Sanguinamento maggiore:

50 % inferiore a quello dei Trials

Conclusioni

1 I Centri Trombosi italiani hanno dimostrato di aver ben operato negli ultimi 20 anni in considerazione dell'incremento dell'età dei pazienti di circa 10 anni.

2 Vantaggio importante dei NOA per l'emorragia cerebrale (-50 %)

3 Quando però gli AVK sono ben gestiti (TTR >70 %) il sanguinamento maggiore risulta nettamente inferiore a quello ottenuto dai NOA negli studi clinici.

4 L'aspirina non conveniente in profilassi primaria

5 Raddoppio del rischio emorragico quando ASA è associata agli AVK (spesso inutilmente).