

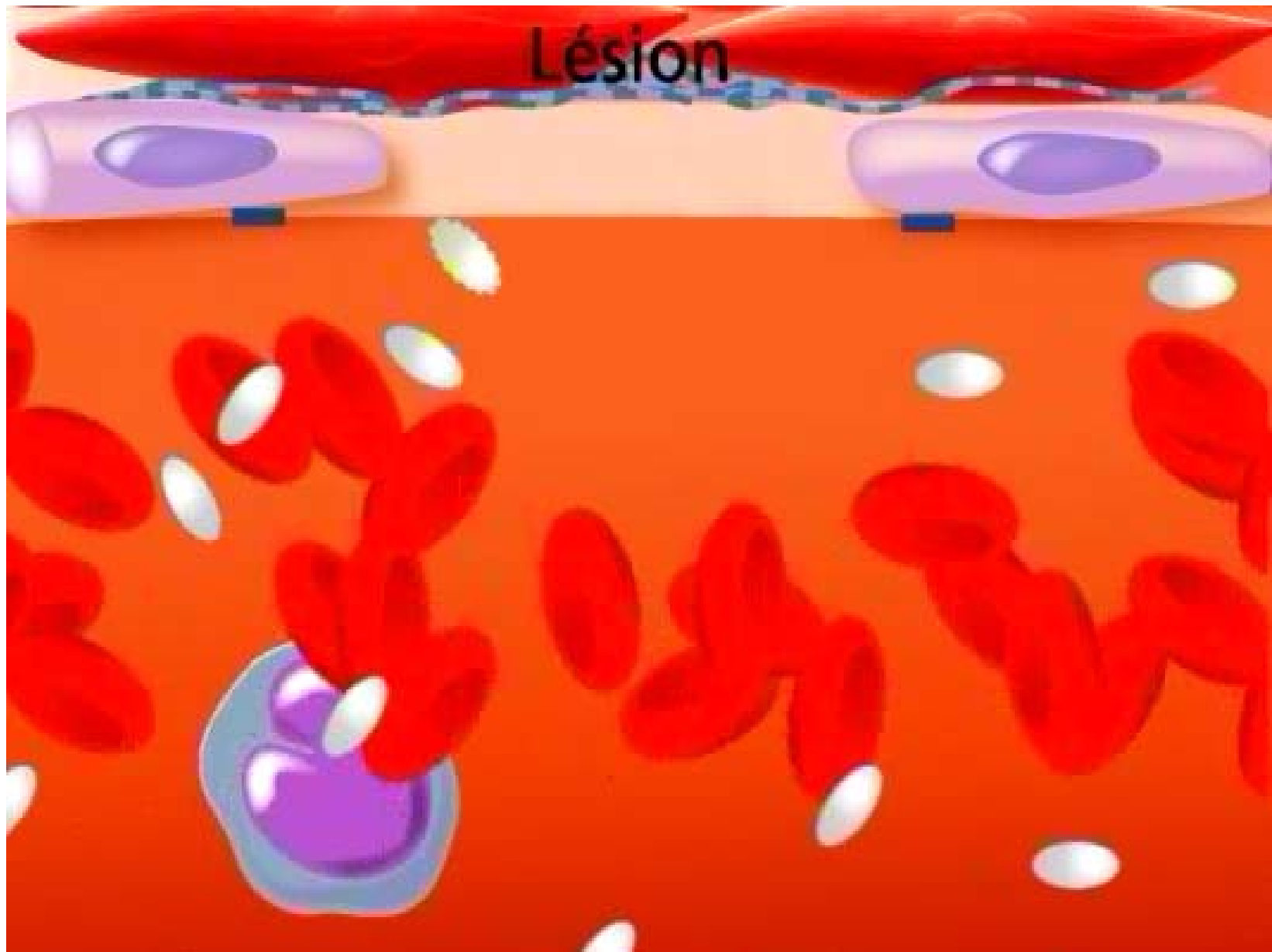
***Séminaire thromboses et
antithrombotiques***

***Les
antiplaquettaires***

14-15 octobre 2005

*Ludovic DROUET
(Angio-Hématologie, Hôpital Lariboisière-Paris)*

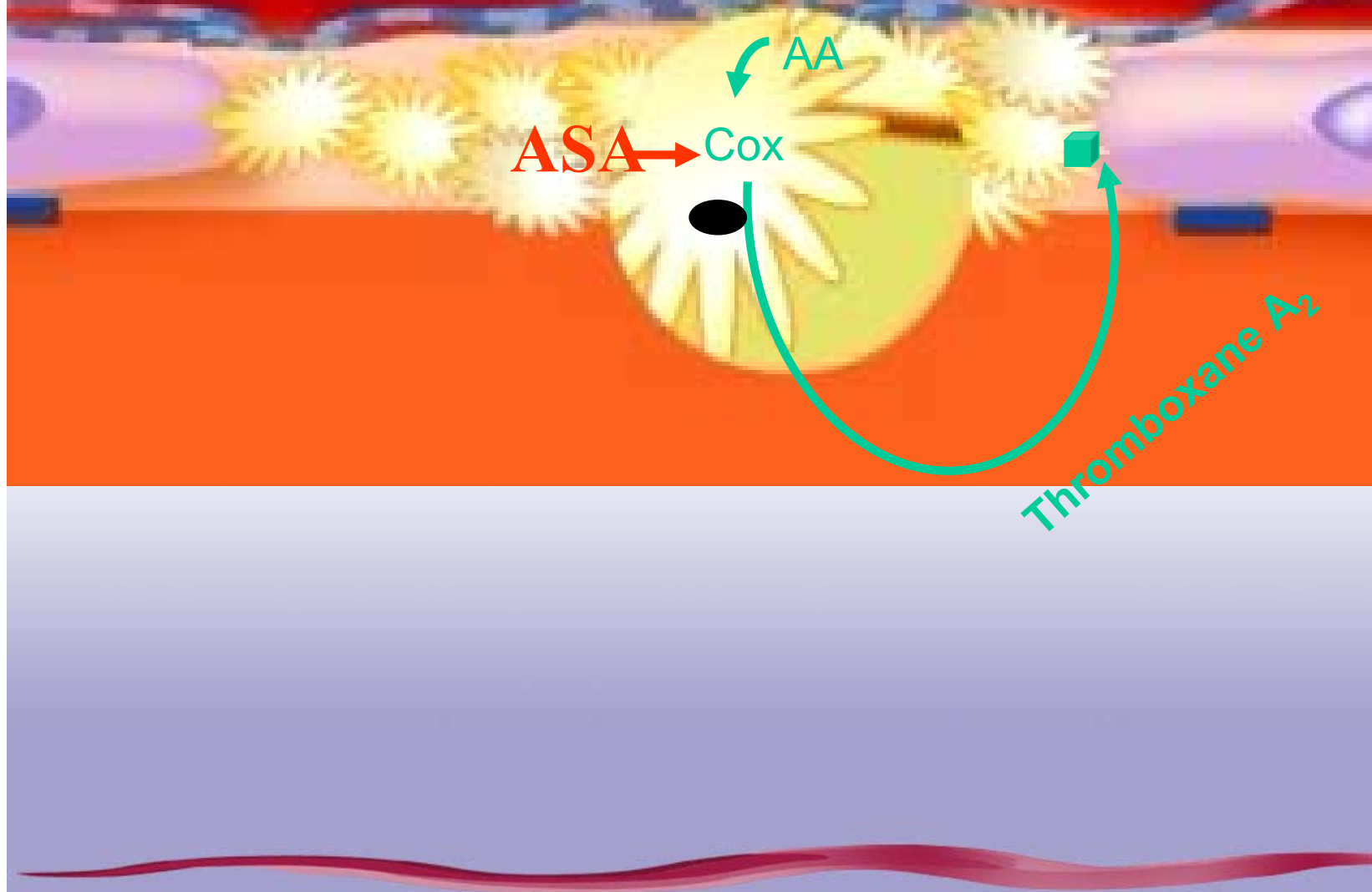
Lésion



Lésion

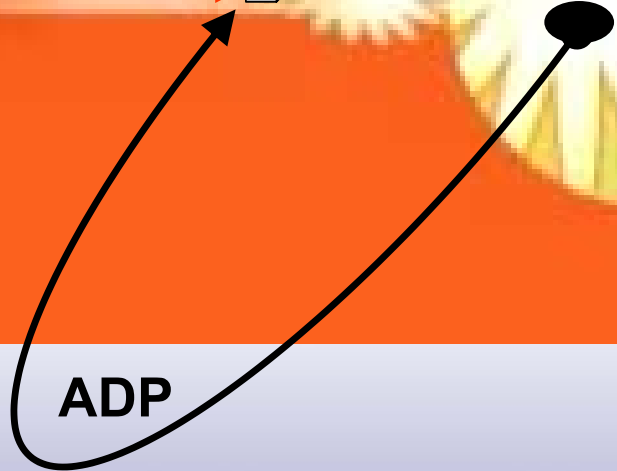


Lésion

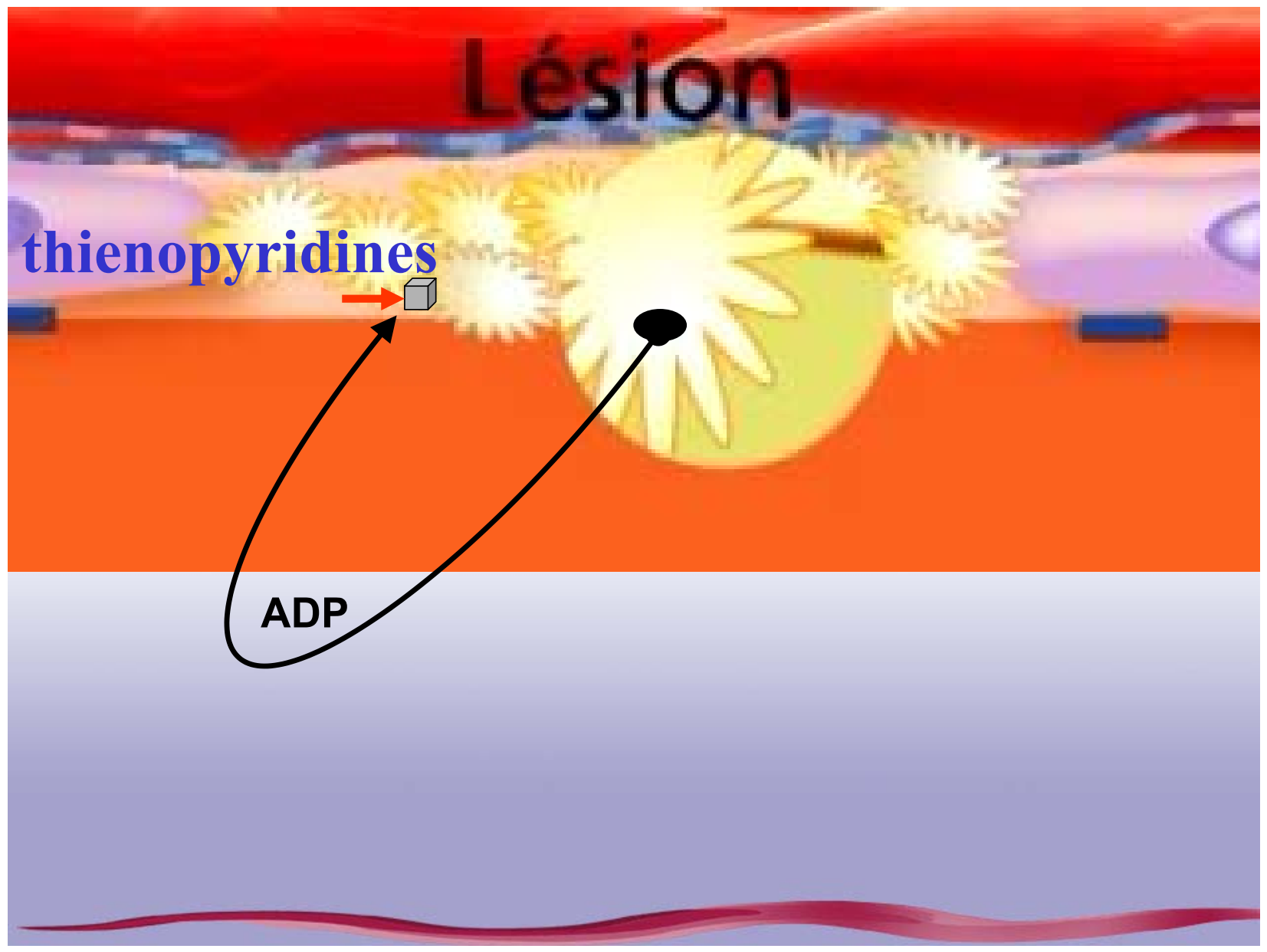


Lésion

thienopyridines



ADP



Lésion

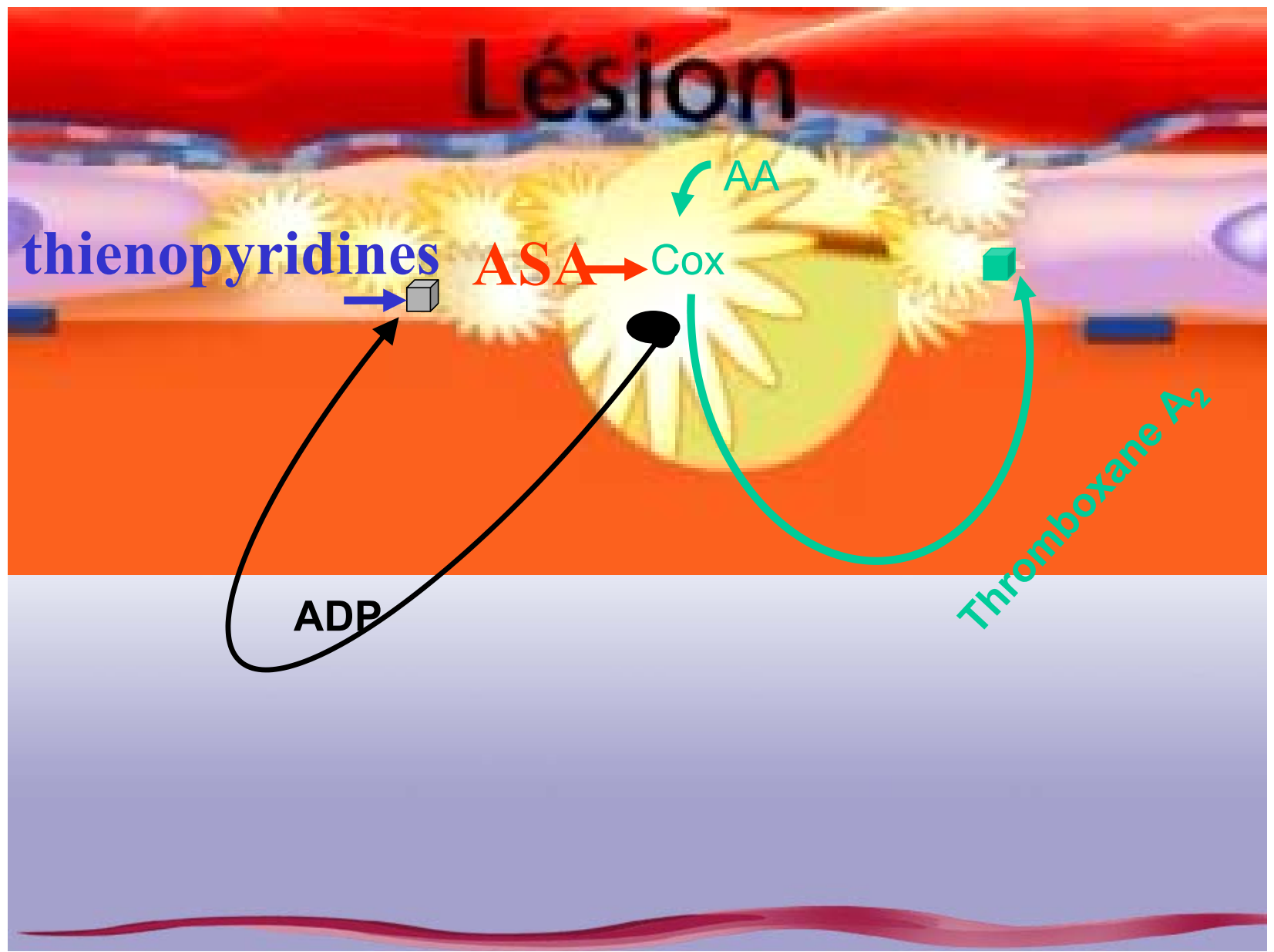
thienopyridines

ASA → Cox

AA

Thromboxane A₂

ADP



Lésion



== GPIIb
GPIIIa

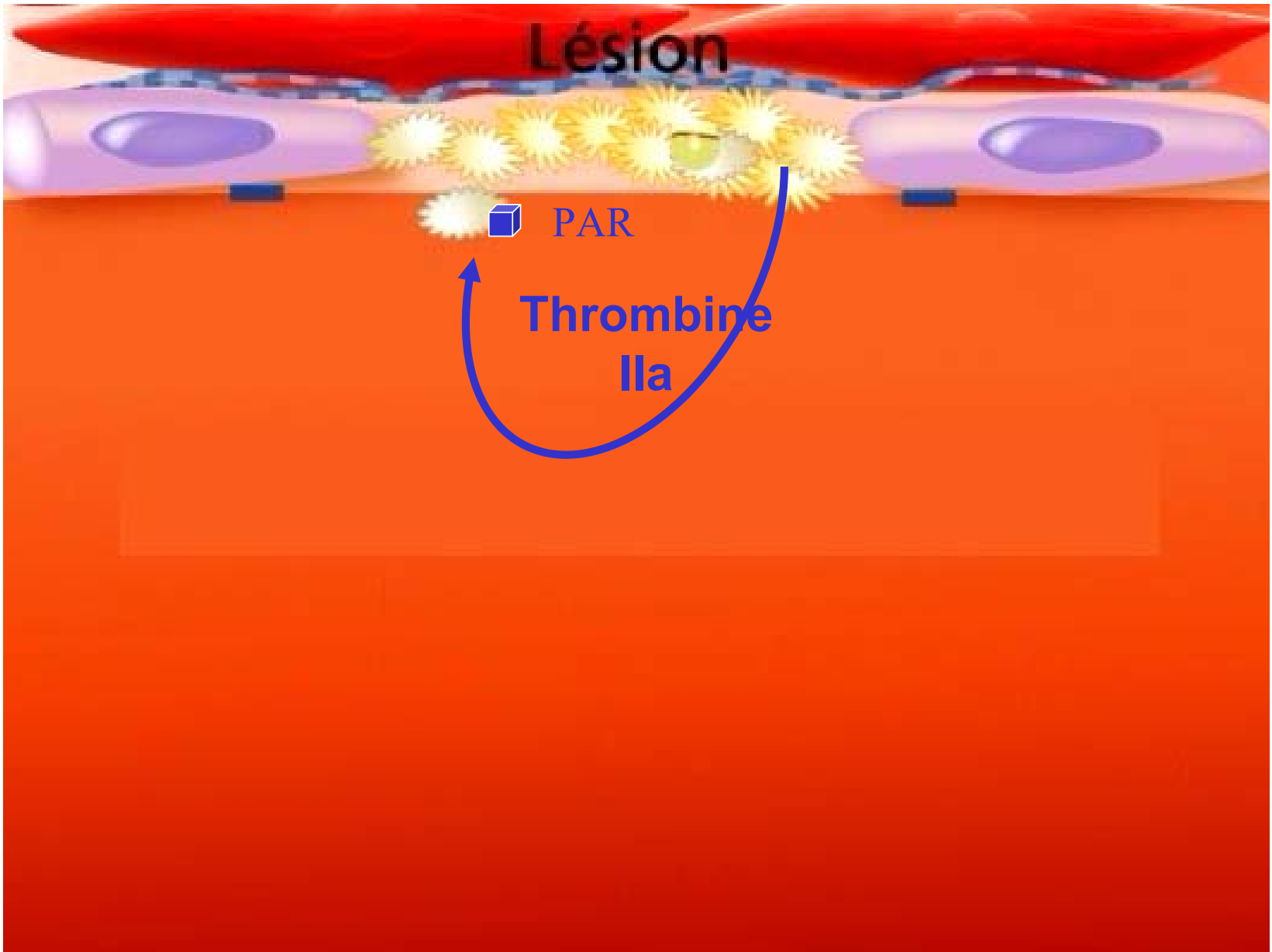
Fibrinogène

Lésion



PAR

Thrombine
IIa



Prévenir les thromboses

Artère

Veine

- Lutter contre les facteurs de risque

Athérosclérose
HTA, Hyper
cholestérolémie,
Tabac,...

Immobilisation +++

- Agir sur le principal mécanisme en cause

**ANTI-AGREGANTS
PLAQUETTAIRES**

ANTICOAGULANTS

A vie

Tant que le risque persiste

Traiter les thromboses

Artère

Veine

- Désobstruer le vaisseau
(si risque vital ou organique majeur)

Angioplastie

(Thrombectomie)

THROMBOLYTIQUES

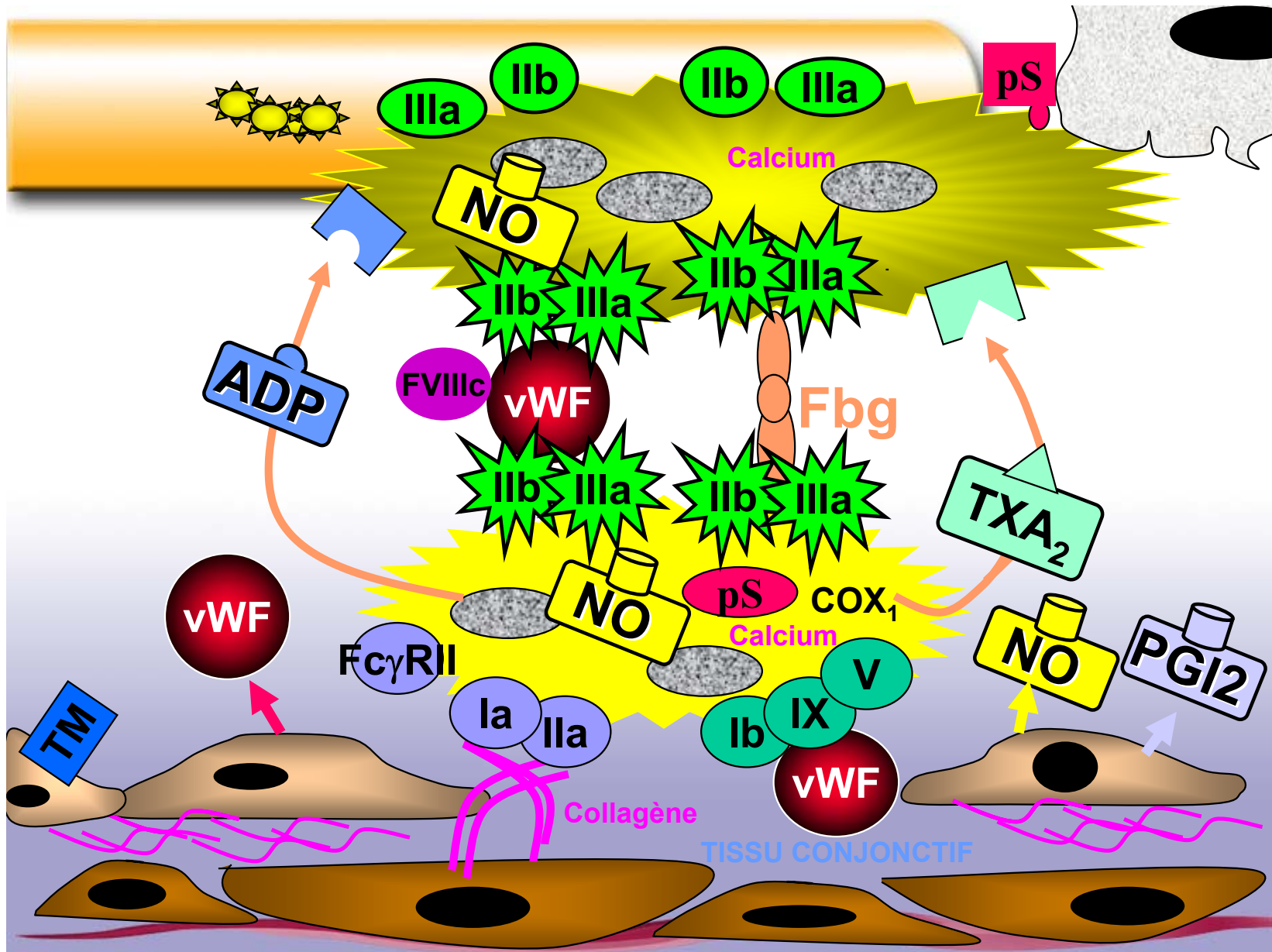
- Empêcher l'extension, prévenir la récurrence

Antiagrégants

ANTICOAGULANTS

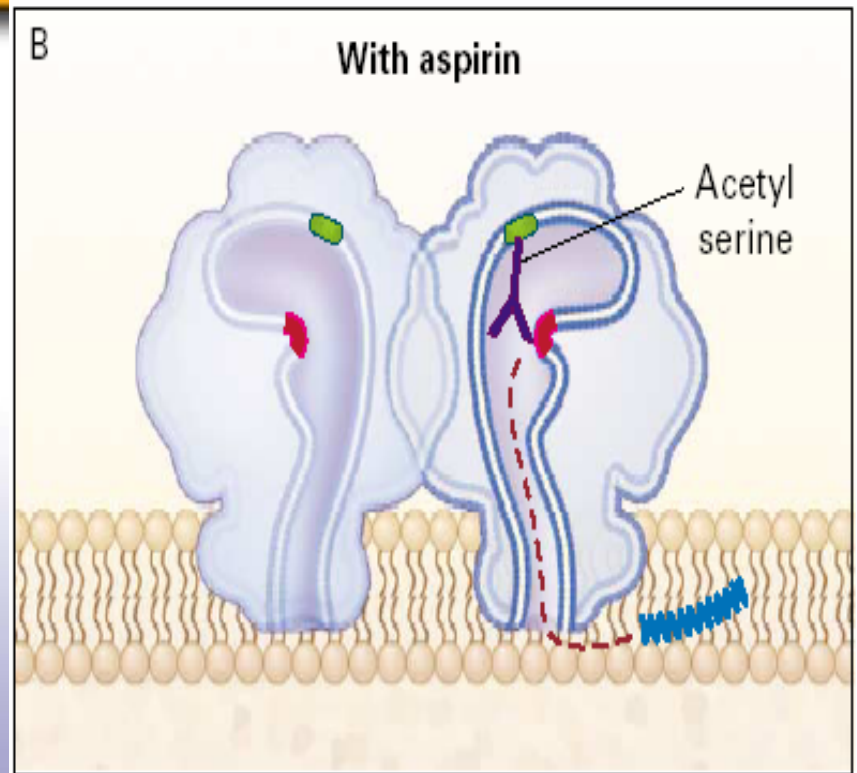
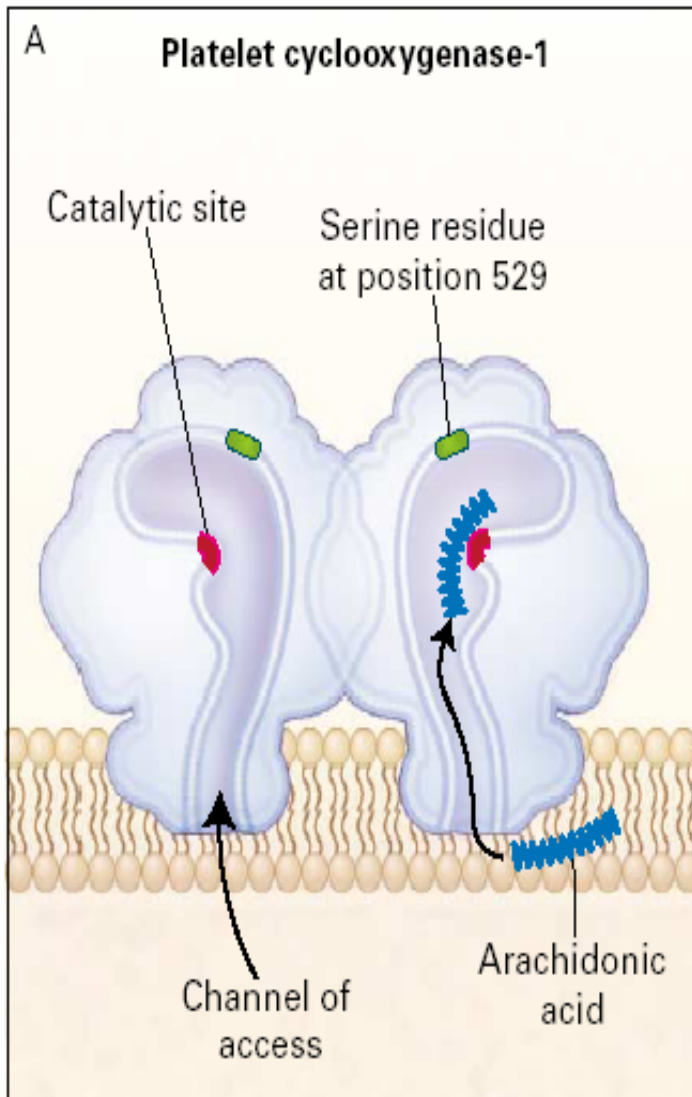
AAP : principales indications

- **Prévention artérielle ++**
 - prévention au long cours des complications ischémiques (thrombotiques) « l'athérombose » prévention primaire, prévention secondaire et prévention primo-secondaire
 - après un premier accident (IDM, angor instable, AVC, etc...)
 - ◆ ASPIRINE, (TICLID), PLAVIX : administration orale
- **Phase aiguë des syndromes coronaires**
 - Angor instable
 - Angioplasties
 - ◆ ASPIRINE, (TICLID) PLAVIX (+ASPIRINE) : administration orale
 - ◆ Anti GPIIb IIIa : perfusion IV
- **Post angioplastie + stenting**
 - coronaire
 - Autres territoires
 - ◆ ASPIRINE, (TICLID) PLAVIX (+ASPIRINE) : administration orale
 - Durée ≤ 12 mois (Plavix+aspirine)



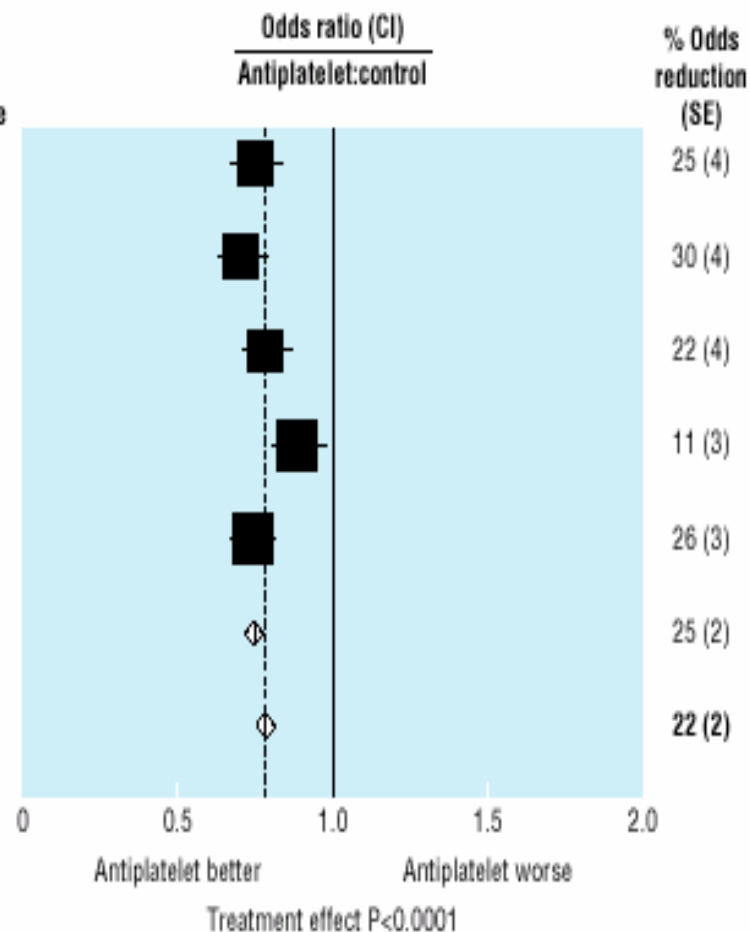
Lésion





Antiplatelet Therapy on vascular events (MI, stroke or vascular death)

Category of trial	No of trials with data	No (%) of vascular events		Observed-expected	Variance	Odds ratio (CI)		% Odds reduction (SE)
		Allocated antiplatelet	Adjusted control			Antiplatelet:control		
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6			25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2			30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8			22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3			11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0			26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6			25 (2)
All trials	195	7705/71 912 (10.7)	9502/72 139 (13.2)	-810.3	3244.9			22 (2)



Heterogeneity of odds reductions between:

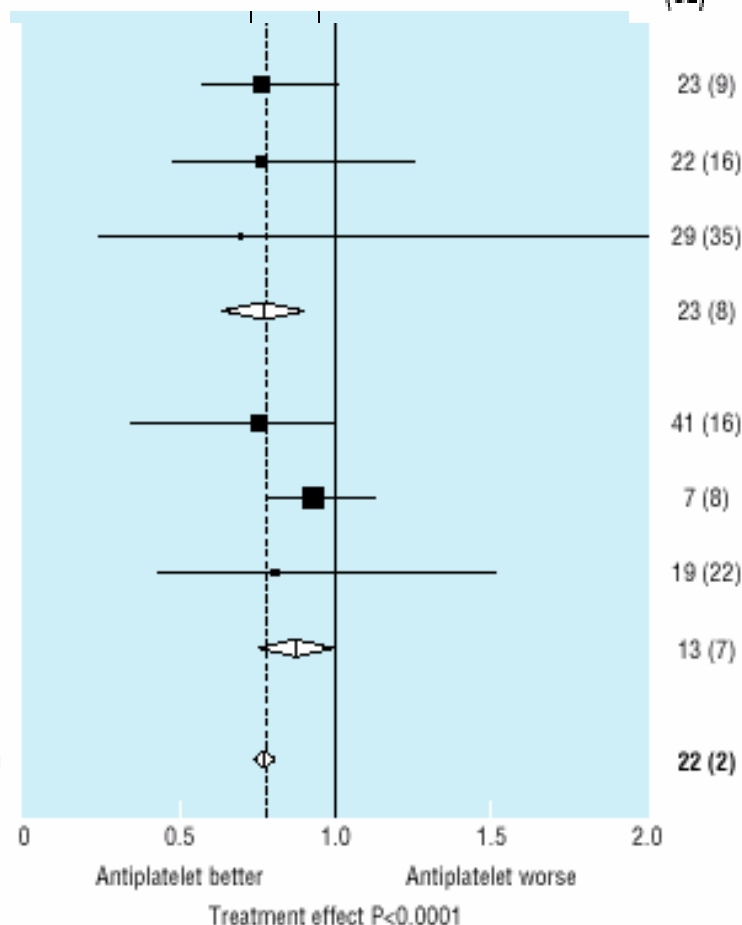
5 categories of trial: $\bullet^2=21.4$, $df=4$; $P=0.0003$

Acute stroke v other: $\bullet^2=18.0$, $df=1$; $P=0.00002$

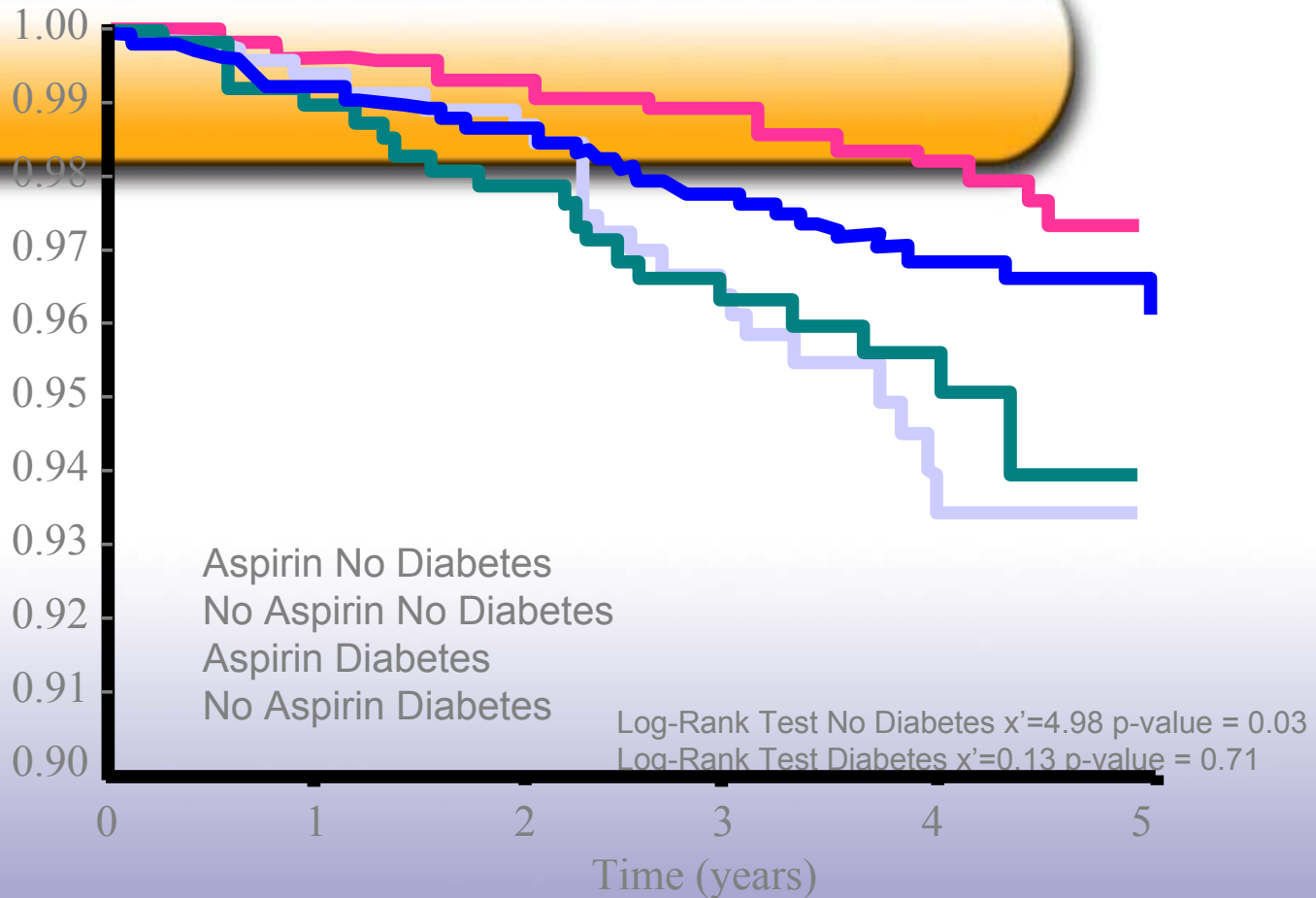
**Antithrombotic Trialists' Collaboration,
Meta-analysis of antiplatelet therapy for prevention of death, MI, stroke, BMJ, 2002**

Antiplatelet therapy on vascular events in 195 trials in high risk patients f(disease) –ATC BMJ 2002-

Category of trial	No of trials with data	No (%) of vascular events		Observed-expected	Variance	Odds ratio (CI)		% Odds reduction (SE)
		Allocated antiplatelet	Adjusted control			Antiplatelet:control		
Peripheral arterial disease:								
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6			23 (9)
Peripheral grafting	12	67/1249 (5.4)	81/1248 (6.5)	-7.3	29.1			22 (16)
Peripheral angioplasty	4	12/472 (2.5)	17/474 (3.6)	-2.0	5.8			29 (35)
Subtotal	42	280/4844 (5.8)	347/4862 (7.1)	-31.6	121.5			23 (8)
Other high risk conditions:								
Haemodialysis	14	38/1333 (2.9)	67/1371 (4.9)	-12.2	23.4			41 (16)
Diabetes	9	403/2568 (15.7)	426/2558 (16.7)	-12.7	164.4			7 (8)
Carotid disease	6	36/339 (10.6)	43/337 (12.8)	-3.6	17.1			19 (22)
Subtotal	29	477/4240 (11.3)	536/4266 (12.6)	-28.5	204.9			13 (7)
All trials	195	7705/71 912 (10.7)	9502/72 139 (13.2)	-811.4	3244.9			22 (2)



Heterogeneity between 7 subtotals other than acute stroke: $\bullet^2=15.4$, $df=6$; $P=0.02$

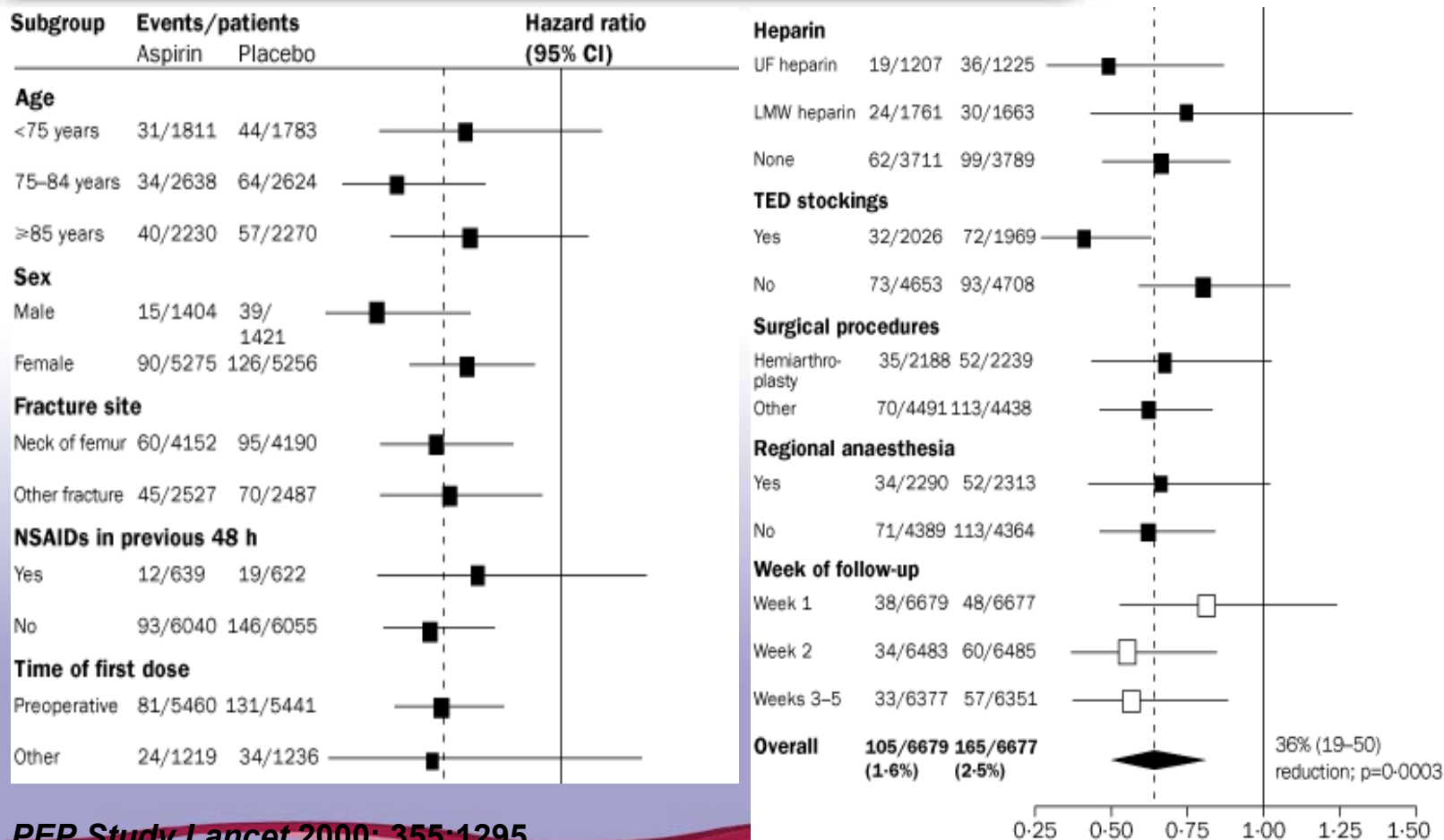


Primary Prevention of Cardiovascular Events With Low-Dose aspirin and Vitamin E in Type 2 Diabetic Patients, Results of the Primary Prevention Project (PPP) trial
 M. SACCO, et al *Diabetes Care* 26:3264–3272, 2003.

Antiagrégants plaquettaires

- **L'aspirine a-t-elle une place en prévention de la thrombose veineuse**

Aspirine & Thrombose veineuse

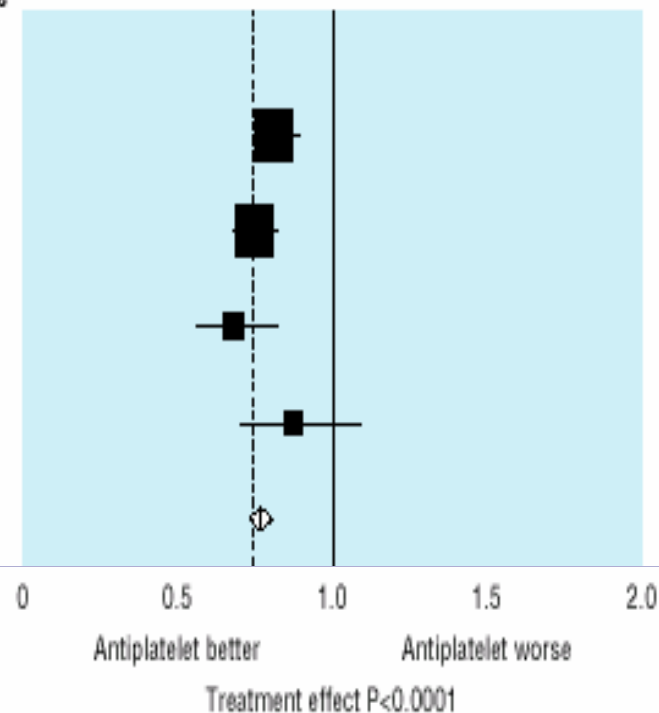


Anti agrég(e)ant plaquettaire

- **L'aspirine en pathologie artérielle atherothrombotique: « oui » mais quelle(s) dose(s) ?**
 - En phase chronique
 - À la phase aiguë

Indirect comparisons of aspirin dosages on vascular events in high risk patients (excluding those with acute stroke)

Category of trial	No of trials with data	No (%) of vascular events		Observed-expected	Variance	Odds ratio (CI)		% Odds reduction (SE)
		Allocated antiplatelet	Adjusted control			Antiplatelet : control		
Aspirin alone (mg daily):								
500-1500	34	1621/11 215 (14.5)	1930/11 236 (17.2)	-147.1	707.8			19 (3)
160-325	19	1526/13 240 (11.5)	1963/13 273 (14.8)	-219.9	742.6			26 (3)
75-150	12	366/3370 (10.9)	517/3406 (15.2)	-72.0	183.8			32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	-18.9	136.5			13 (8)
Any aspirin*	65	3829/29 652 (12.9)	4764/29 743 (16.0)	-452.3	1717.0			23 (2)



Heterogeneity of odds reductions between:

Different aspirin doses: $\chi^2=7.7$, $df=3$; $P=0.05$

Other antiplatelet v any aspirin: $\chi^2=10.8$, $df=8$; $P>0.1$

*Antithrombotic Trialists' Collaboration,
Meta-analysis of antiplatelet therapy for prevention of death, MI, stroke, BMJ, 2002*

Dose-response relationship with ASA

ASA dose

% odds reduction

500–1500 mg daily

160–325 mg daily

75–150 mg daily

<75 mg daily

Any ASA dose

23% ±2 (p<0.0001)

**CURE: ASA
group bleeds**

>200 mg	4.02%
100-200 mg	2.27%
<100 mg	2.03%

0.0

0.5

1.0

1.5

2.0

ASA better

Control better

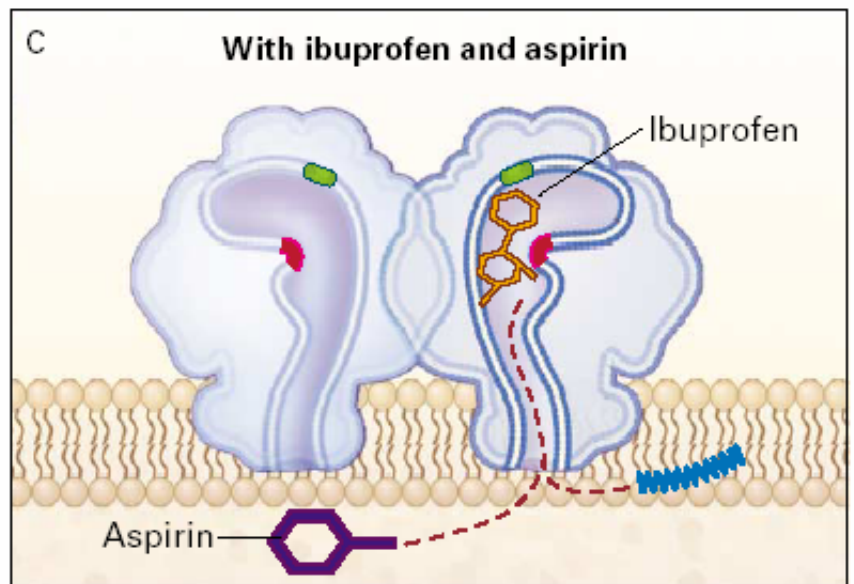
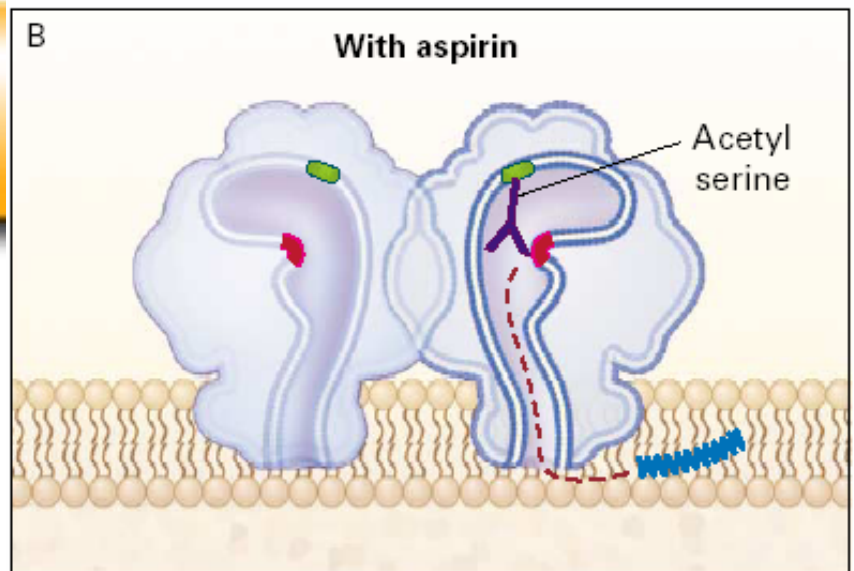
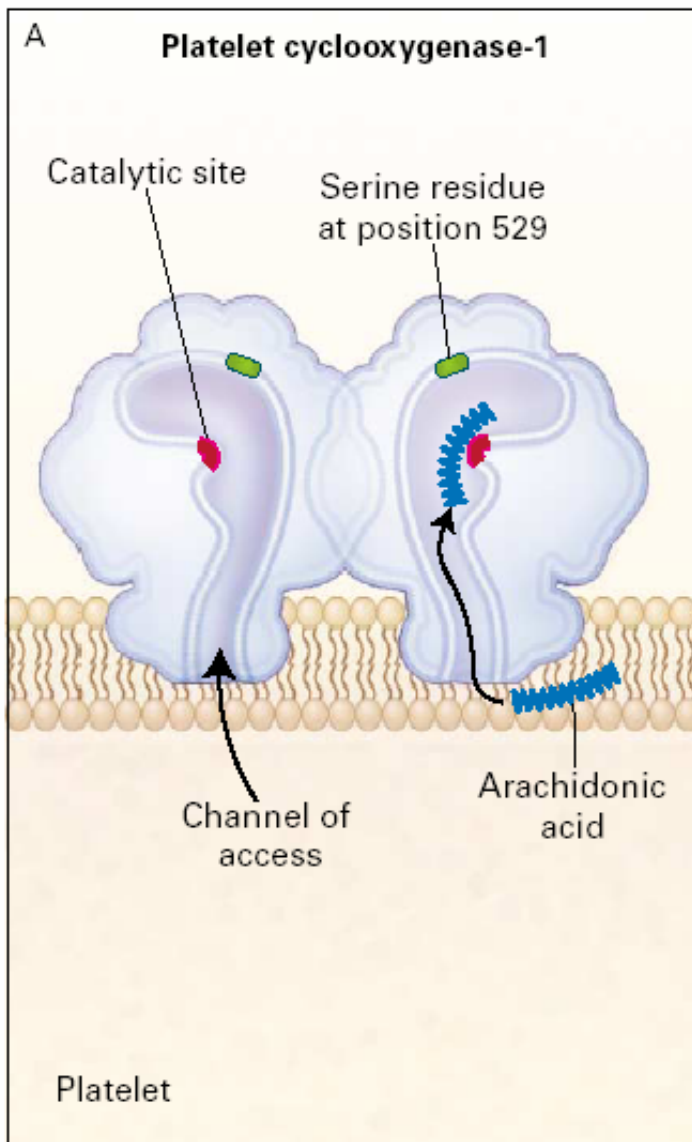
N~60,000



PATHOLOGIE	Dose minimale d'aspirine (mg) ayant démontré une efficacité
Hommes à haut risque cardiovasculaire	75
Hypertendus	75
Angor stable	75
Angor instable	75
Infarctus aigu du myocarde	160
Accidents vasculaires cérébraux ischémiques (constitués et transitoires)	50
Sténose sévère de la carotide	75
Accidents vasculaires cérébraux ischémiques constitués (période aiguë)	160

Aspirine: une notion nouvelle la résistance à l'aspirine

- **Définition de la résistance : clinique / biologique**
- **Observance**
- **Interactions médicamenteuses**
- **Dose(s)**



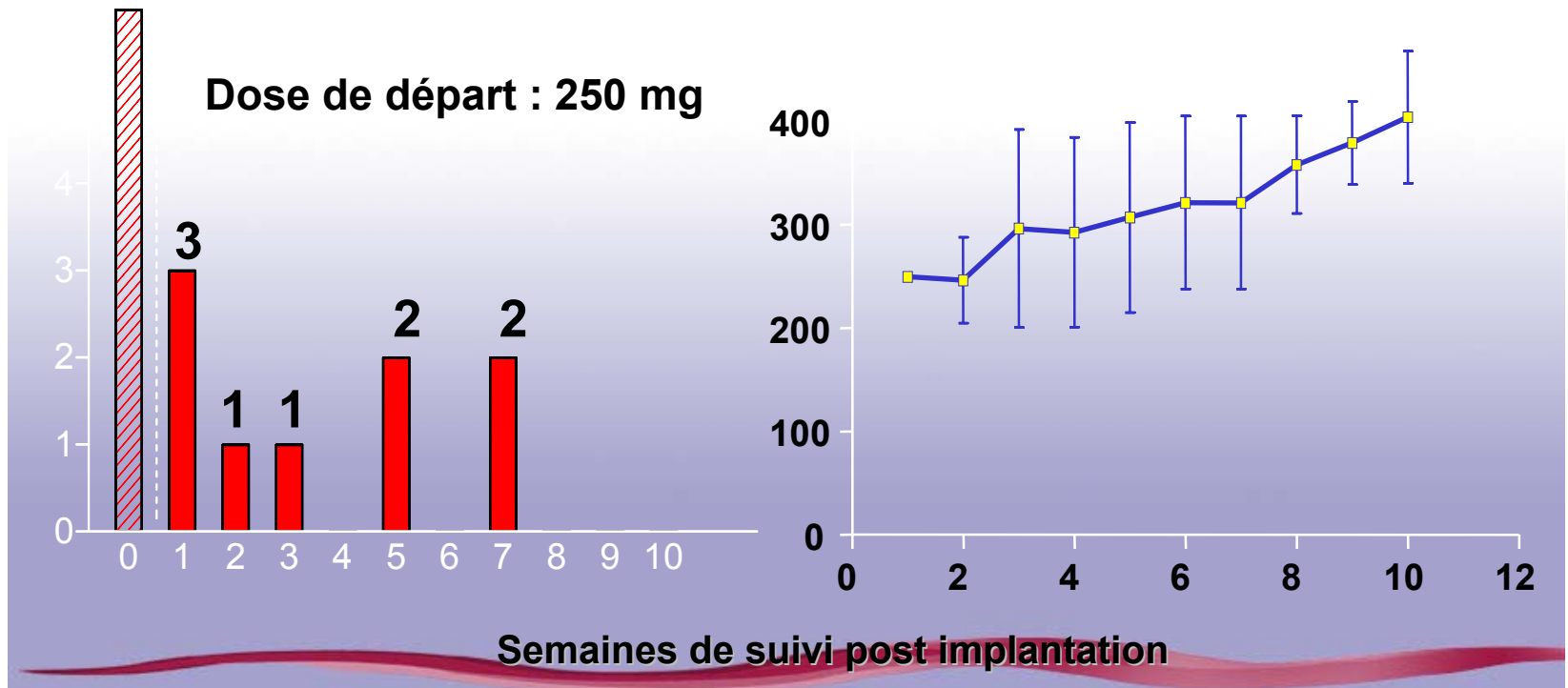
Catella-Lawson F, Fitzgerald GA & al, NEJL

Résistance à l'aspirine

Le modèle exemplaire des assistances cardio-circulatoires chroniques

Nombre de patients
présentant une agrégation plaquettaire
- activation par l'AA-

Doses d'aspirine par jour



Aspirine: les effets secondaires

- **Toxicité digestive**
 - Gastralgies
 - Hémorragies digestives
- **Allergie**

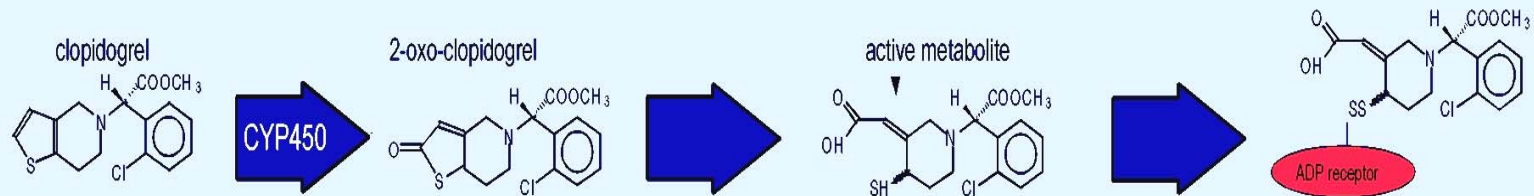
CAPRIE : safety

events incidence (%)

	Aspirin 325 mg/j (n = 9 586)	Plavix 75 mg/j (n = 9 599)	P
Hemorrhages (all bleedings)	9,3	9,3	0,976
GI	2,7	2,0	0,002
other	6,5	7,3	0,024
intra-cranial	0,5	0,4	0,146
GI symptoms (all events)	29,8	27,8	≤ 0,001
GI ulcers	1,2	0,7	0,001
diarrheas	3,4	4,5	≤ 0,001
severe diarrheas	0,1	0,2	≥ 0,05
Blood count abnormalities			
severe Neutropenia (<0,45 x 10 ⁹)	0,02	0,04	≥ 0,4
severe Thrombopenia (<80 x 10 ⁹)	0,1	0,2	≥ 0,255
Other adverse effects			
headaches, vertigos	23,8	22,3	0,016
skin	13,1	15,8	≤ 0,001
severe rashes	0,07	0,13	≥ 0,05
severe itching	0	0,13	≥ 0,05

Clopidogrel Plavix®

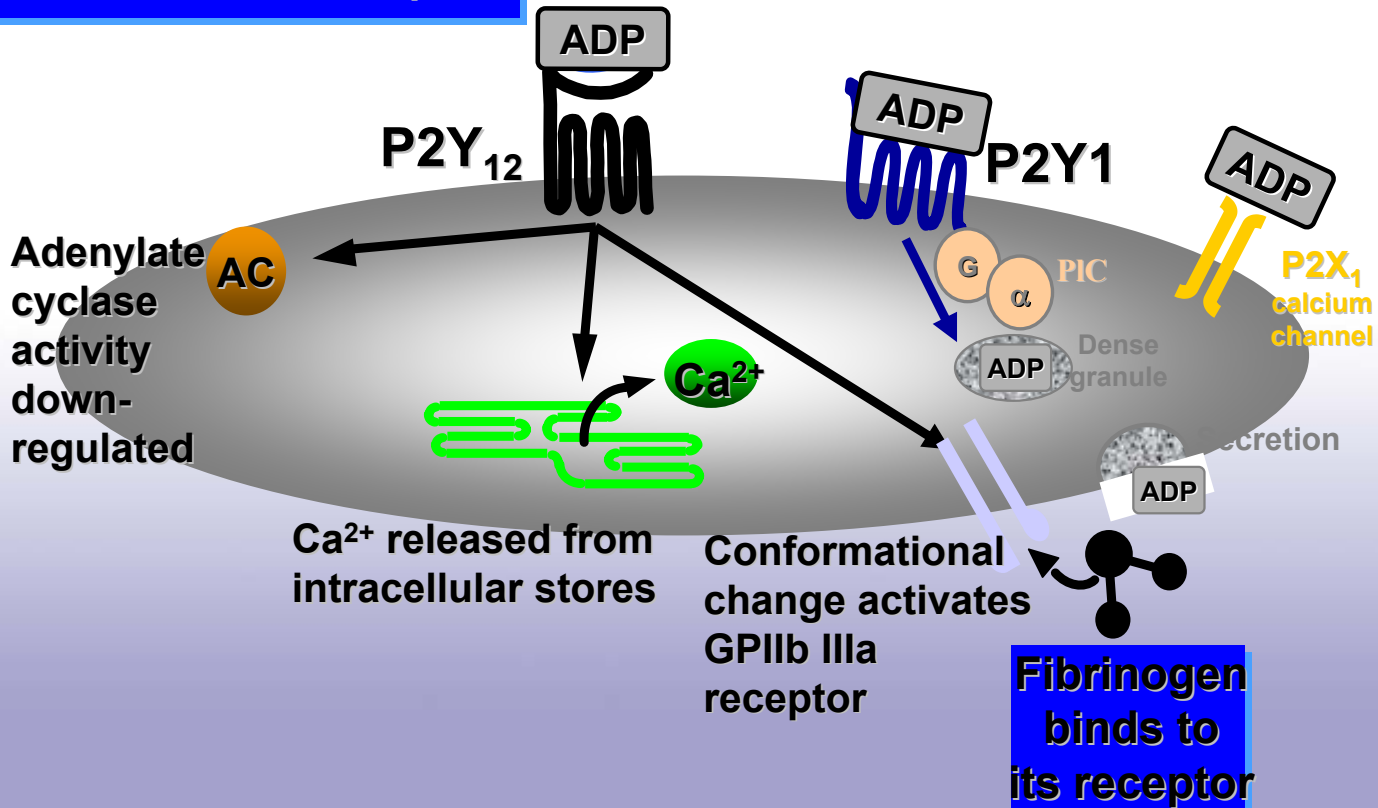
- **prodrogue**
- **active metabolite: Identified , very short half live**



- **Acts by irreversible SS bridges with P2Y₁₂ receptor (one the 3 platelet ADP receptors)**

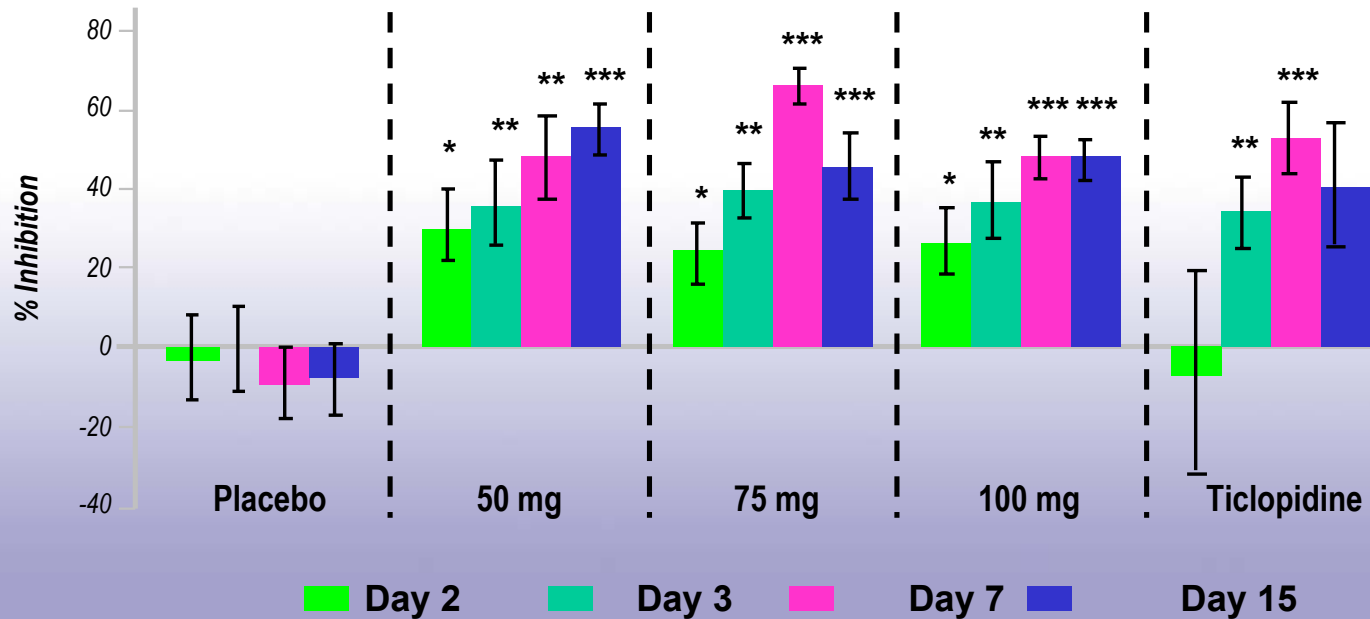
Platelet ADP pathway

ADP binds to its receptor



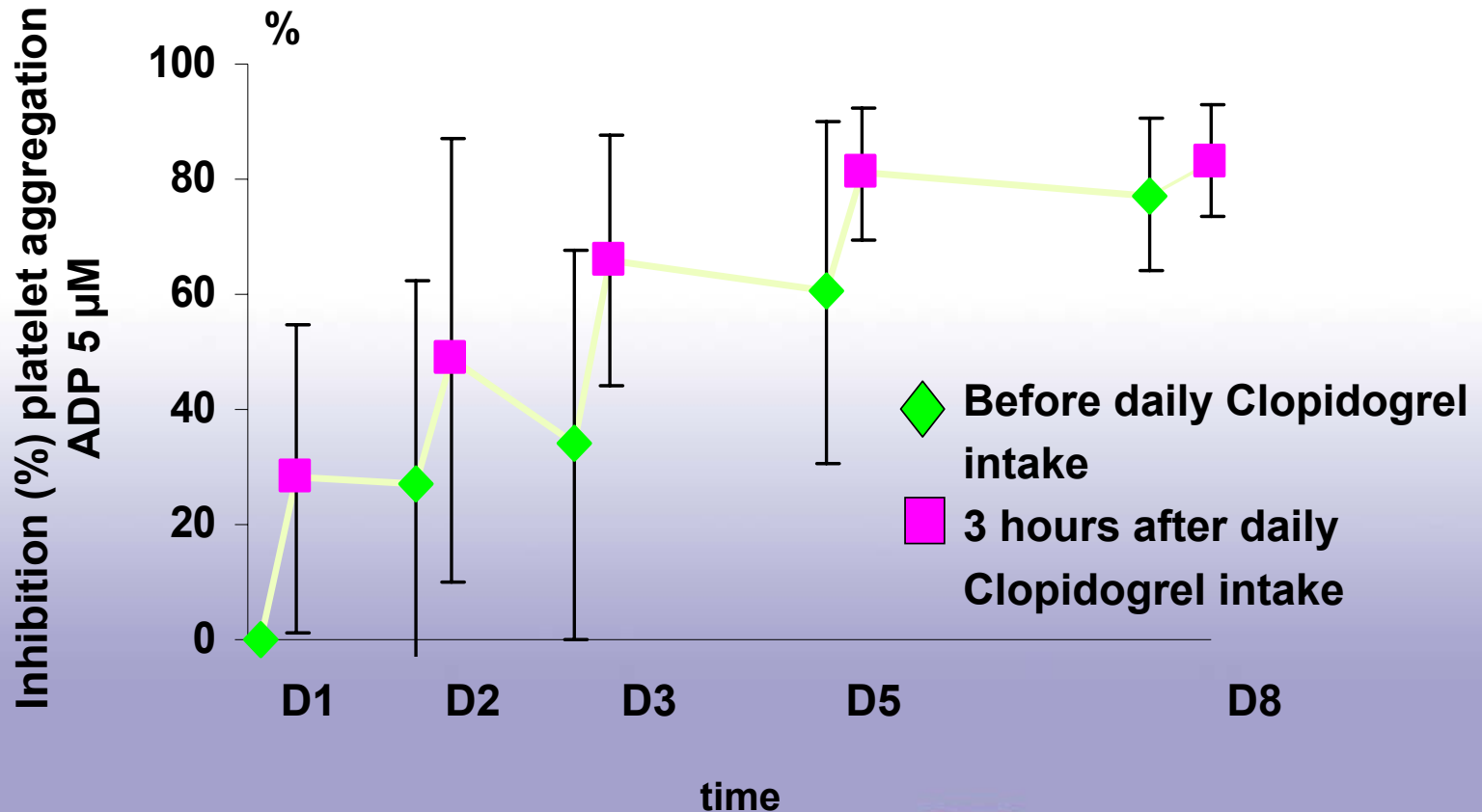
Clopidogrel: Kinetics of antiplatelet activity

Mean (\pm SEM) inhibition of platelet aggregation induced by 5 μ M

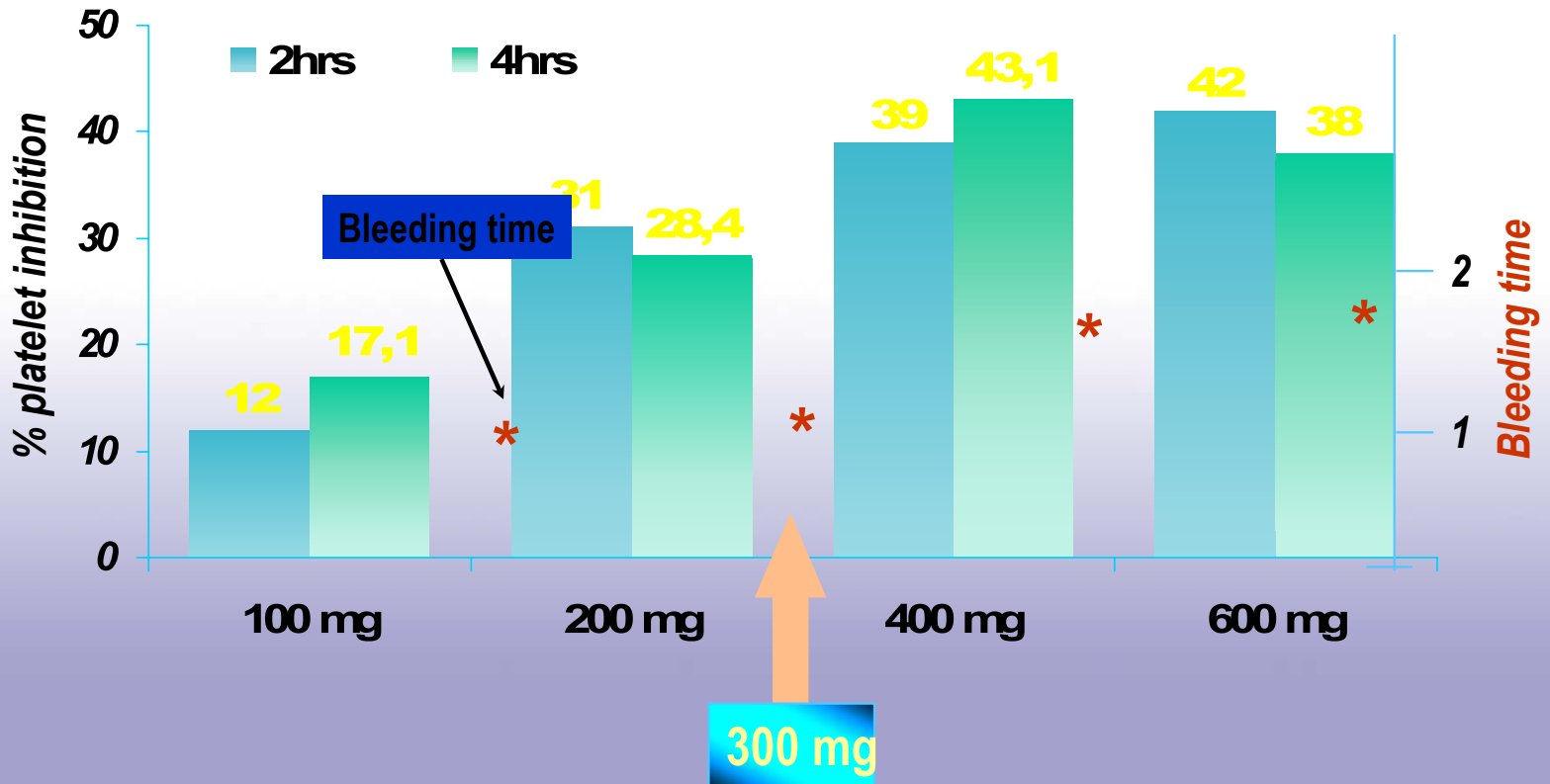


* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

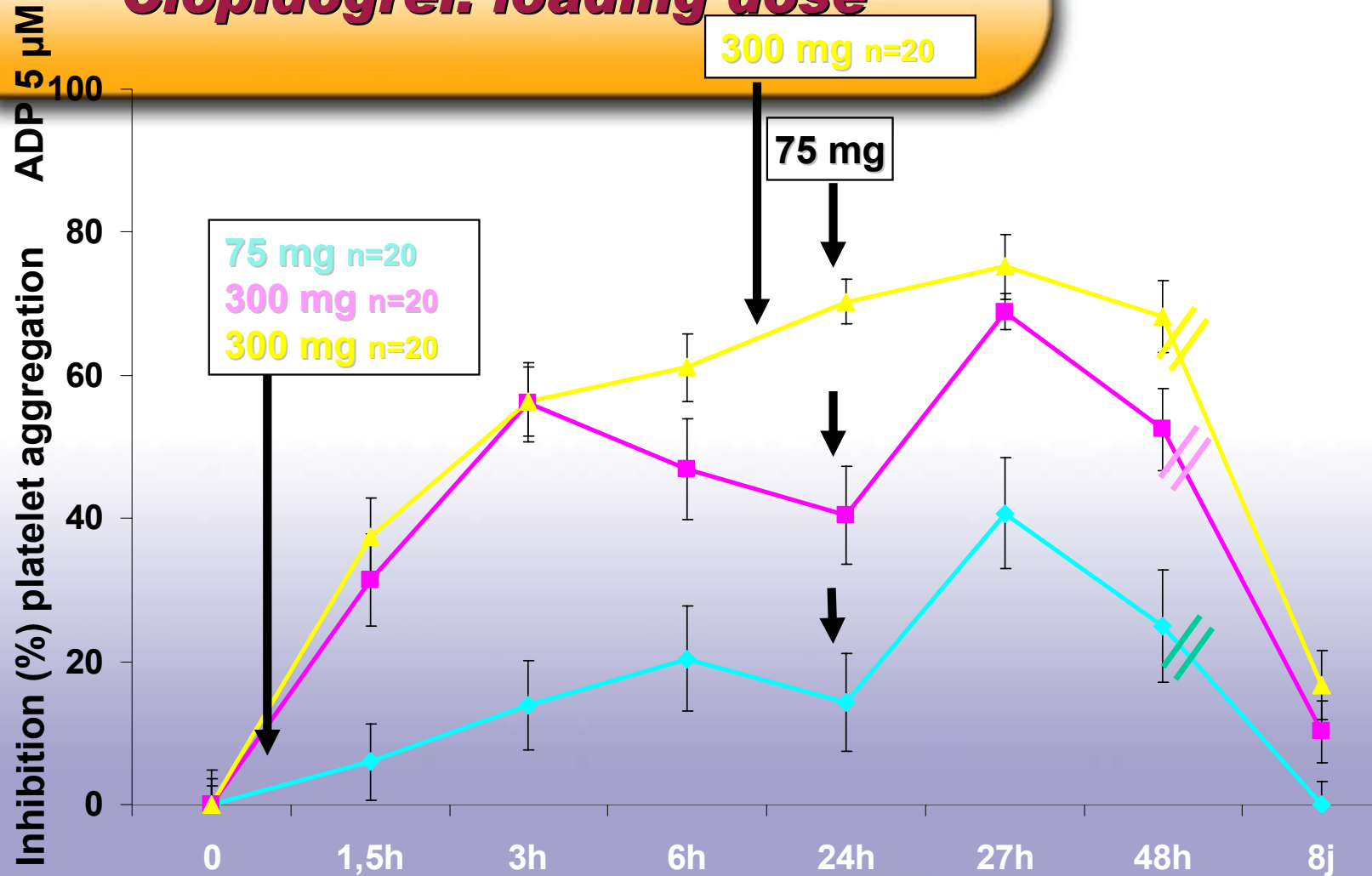
Kinetics of antiplatelet activity of clopidogrel 75 mg/d for 8d in healthy volunteers (n=12)



Clopidogrel loading dose



Clopidogrel: loading dose



CAPRIE : safety

events incidence (%)

	Aspirin 325 mg/j (n = 9 586)	Plavix 75 mg/j (n = 9 599)	P
Hemorrhages (all bleedings)	9,3	9,3	0,976
GI	2,7	2,0	0,002
other	6,5	7,3	0,024
intra-cranial	0,5	0,4	0,146
GI symptoms (all events)	29,8	27,8	≤ 0,001
GI ulcers	1,2	0,7	0,001
diarrheas	3,4	4,5	≤ 0,001
severe diarrheas	0,1	0,2	≥ 0,05
Blood count abnormalities			
severe Neutropenia (<0,45 x 10 ⁹)	0,02	0,04	≥ 0,4
severe Thrombopenia (<80 x 10 ⁹)	0,1	0,2	≥ 0,255
Other adverse effects			
headaches, vertigos	23,8	22,3	0,016
skin	13,1	15,8	≤ 0,001
severe rashes	0,07	0,13	≥ 0,05
severe itching	0	0,13	≥ 0,05

TTP : clinical Experience since beginning of commercialization

20 TTP cases reported on more than 4,7 millions patients treated with PLAVIX.

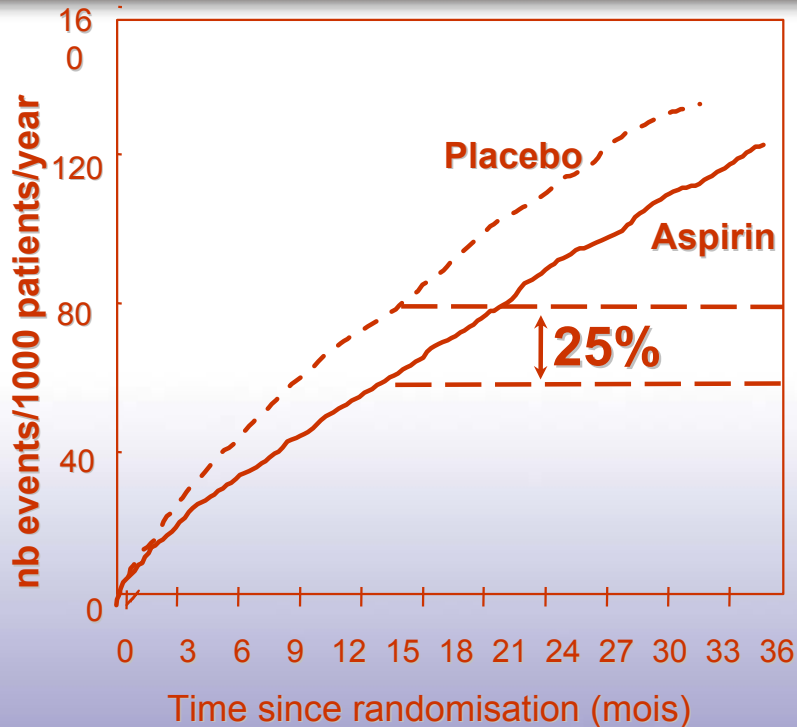
Incidence supposée : 1 / 235 000

- ◆ ***Incidence similar to that of general population***
- ◆ ***Causality to be established***
- ◆ ***No need for systematic blood count monitoring***

Atherothrombose

Evolution des traitements antiplaquettaires

Aspirin prevents 1/4 of ischemic cardio-vascular events



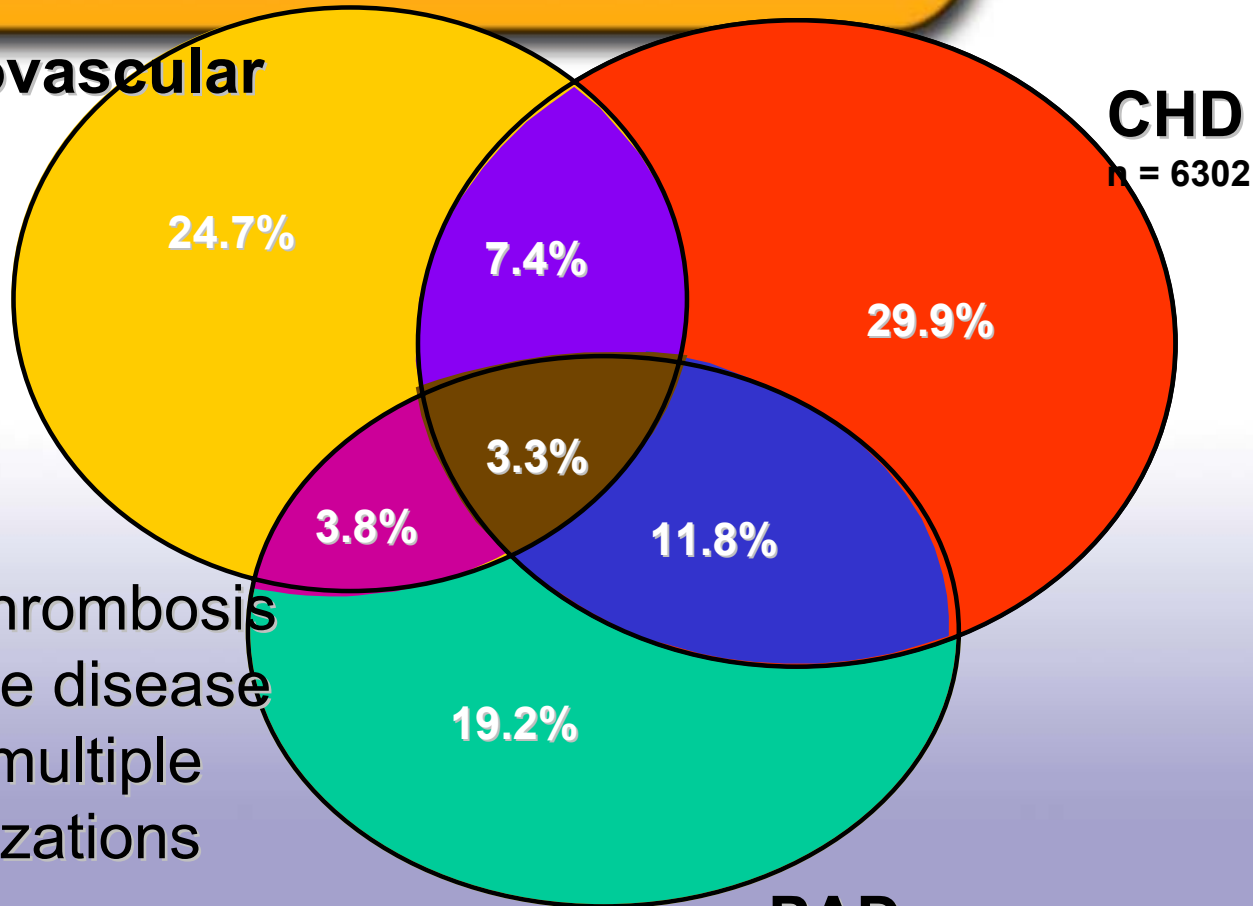
Placebo arm extrapolated from APTC meta-analysis.
Antiplatelet Trialists' Collaboration. BMJ 1994;308:81-106, .

Can an antiplatelet agent be more efficacious?

CAPRIE's patients $n = 19\ 185$

**Cerebrovascular
Disease**

$n = 6431$



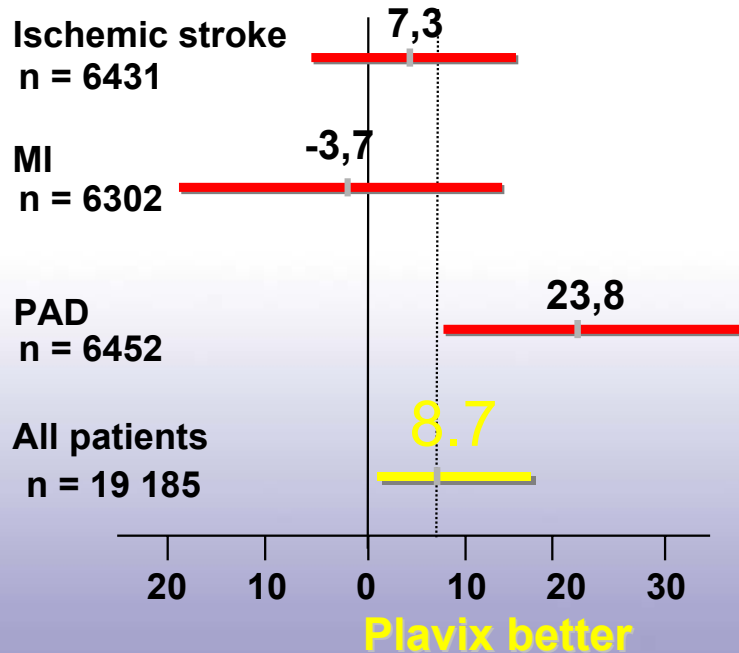
Atherothrombosis
A unique disease
with multiple
localizations

PAD

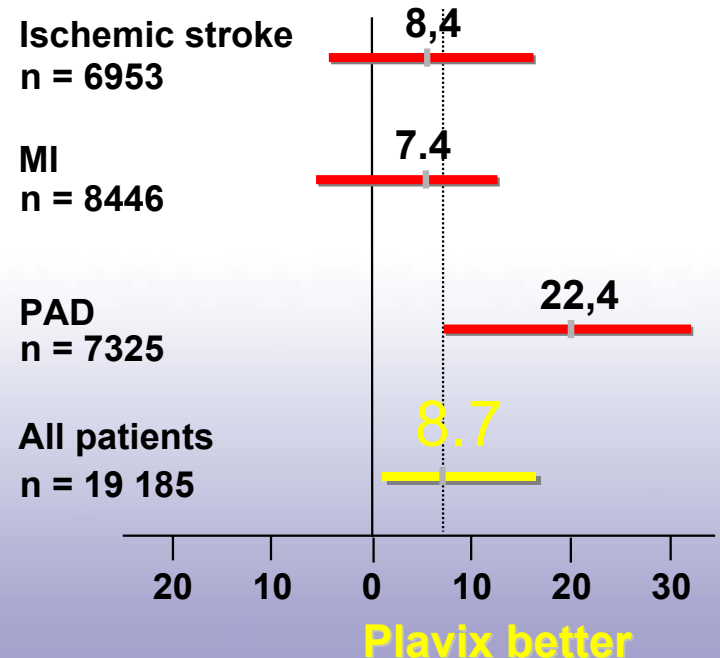
$n = 6452$

CAPRIE : Results analysis

As inclusion criteria:



As real medical history :



CAPRIE Steering Committee. Lancet 1996;348:1329-1339

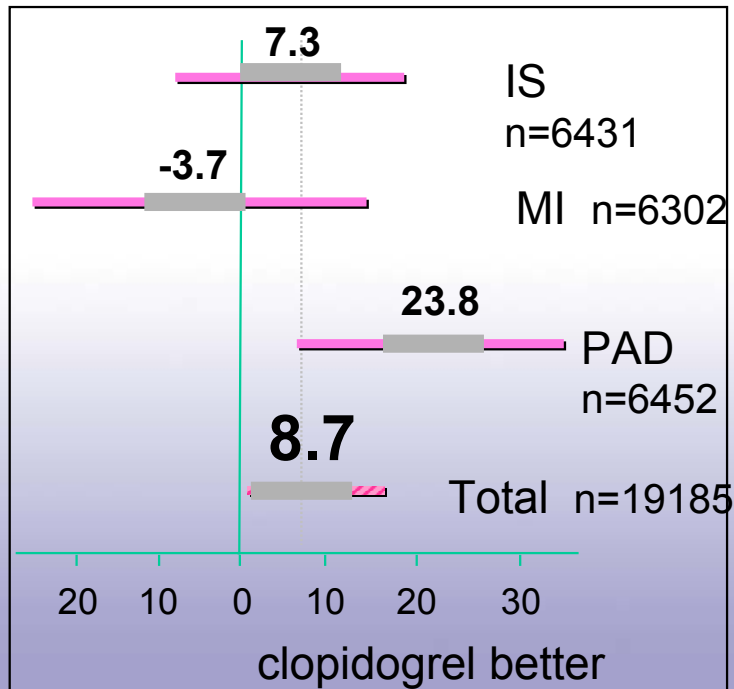
Gent M. Benefit of clopidogrel in patients with coronary disease Circulation 1997, 96(8) suppl

Rupprecht HJ. Consistency of the benefit of clopidogrel across a range of vascular related endpoints: results from CAPRIE.

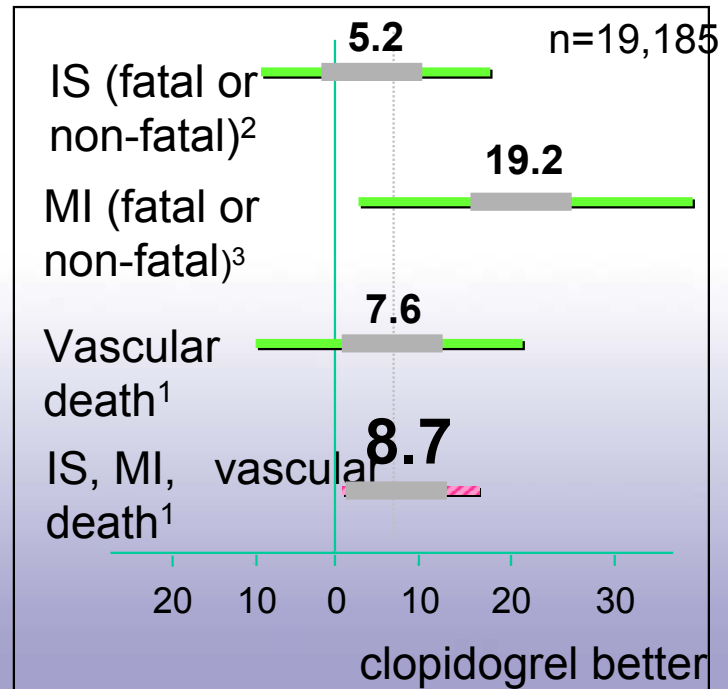
European Society of Cardiology, 1998, Vienne (abstract 53116)

CAPRIE Study: MI Paradox

Relative Risk Reduction* by Qualifying Entry Criteria¹



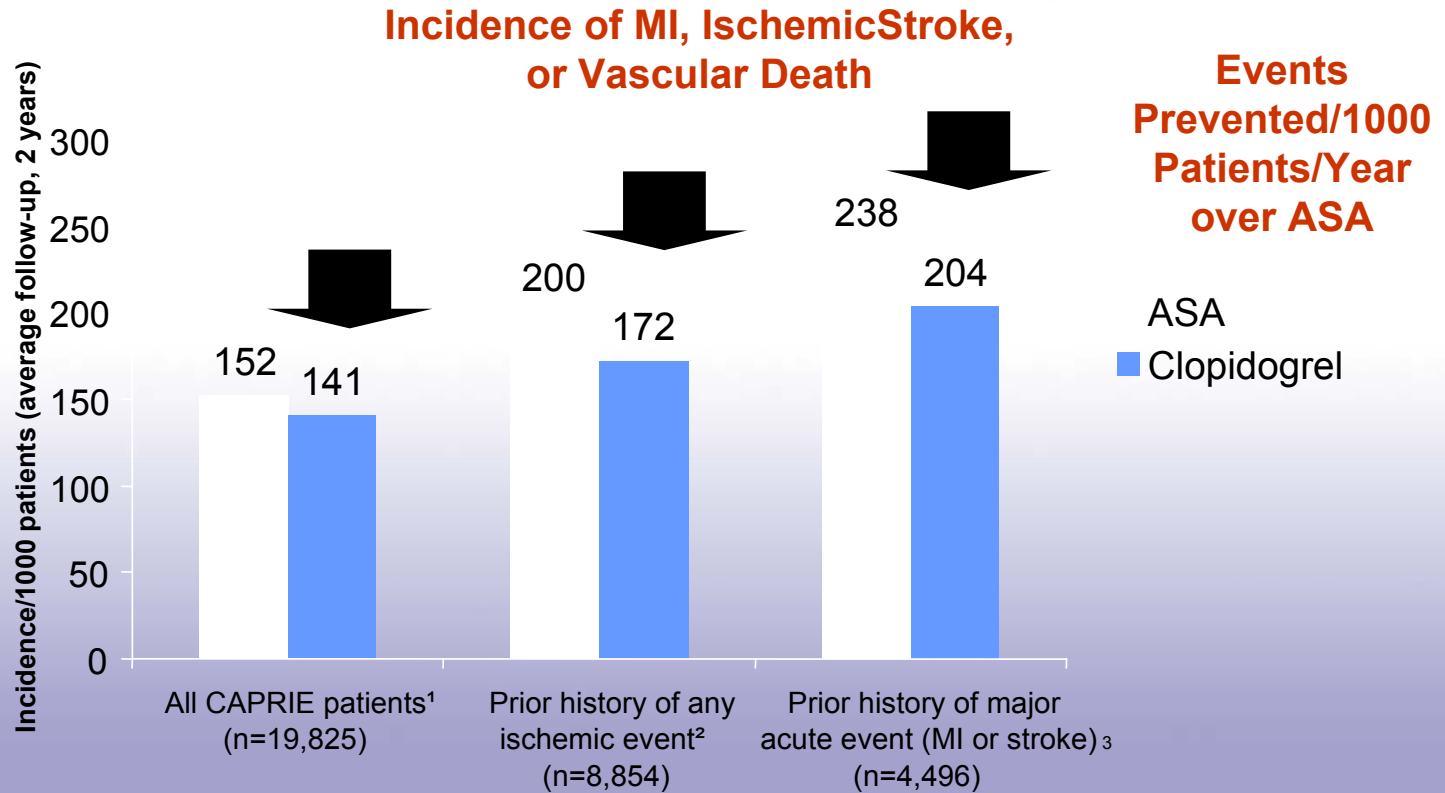
Relative Risk Reduction of Individual End Points



*Cluster of IS, MI, or vascular death. ¹CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

²Easton. Neurology 1998;50(suppl 4):A157. ³Gent. Circulation. 1997;96(suppl):I-467.

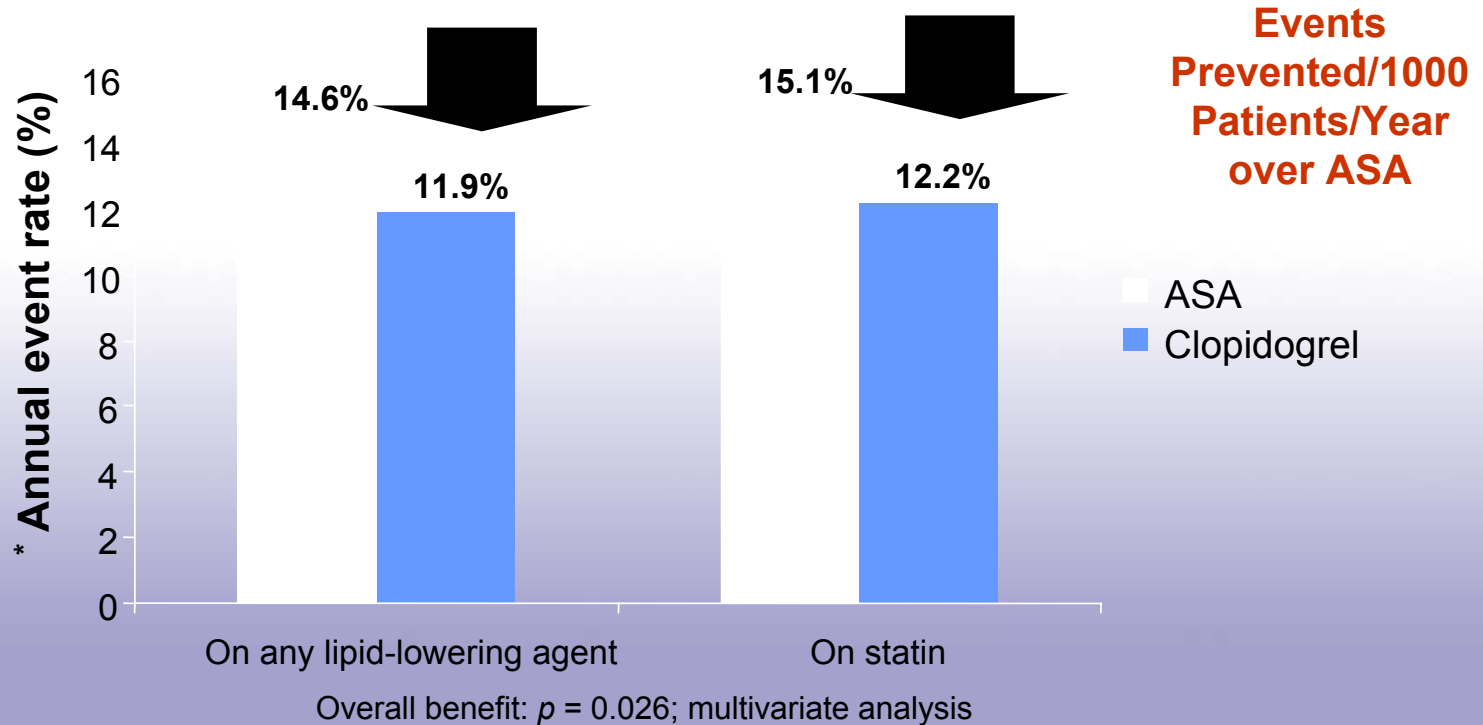
CAPRIE: Amplified Benefit of Clopidogrel in Patients with Higher Vascular Risk¹⁻³



1. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329-39. 2. Jarvis B, Simpson K. *Drugs* 2000; 60: 347-77. 3. Ringleb PA et al. *Eur Heart J* 1999; 20: 666.

CAPRIE: Amplified Benefit of Clopidogrel in Patients with Hypercholesterolemia¹

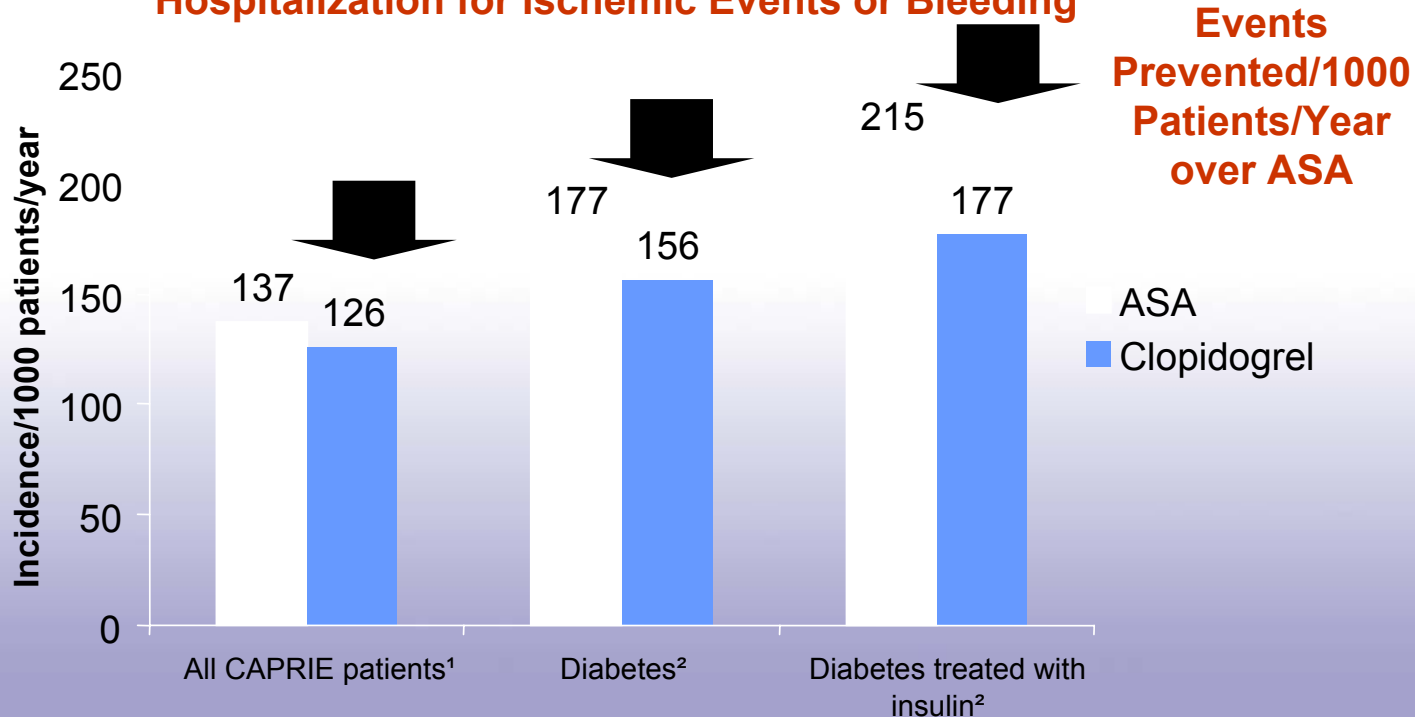
Incidence of Myocardial Infarction, Stroke, Vascular Death or Hospitalization for Ischemic Events or Bleeding



1. Bhatt DL et al. *J Am Coll Cardiol* 2000; 35(suppl A): 326.

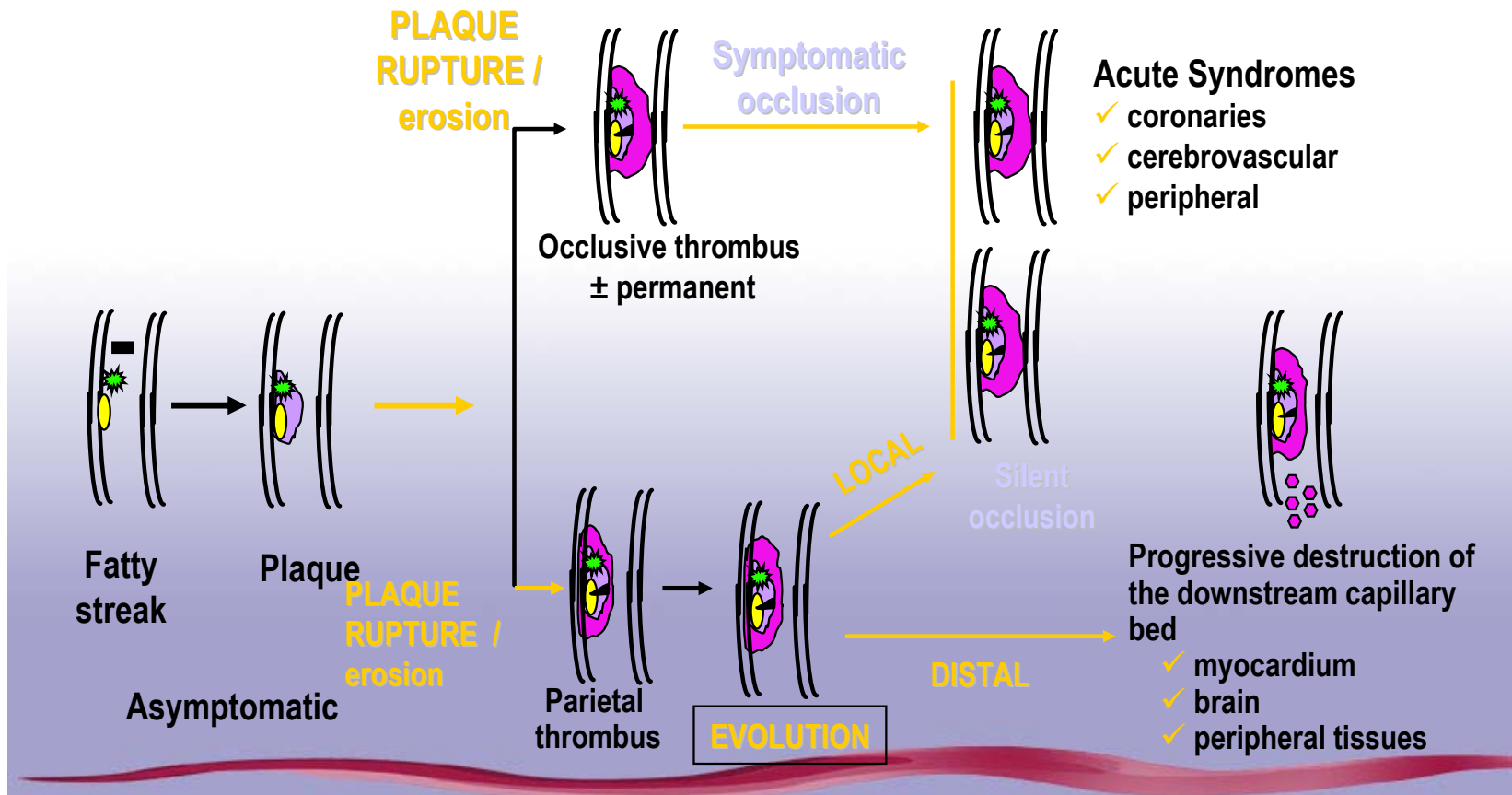
CAPRIE: Amplified Benefit of Clopidogrel in Patients with Additional Risk Factors^{1, 2}

Incidence of Myocardial Infarction, Stroke, Vascular Death or Hospitalization for Ischemic Events or Bleeding

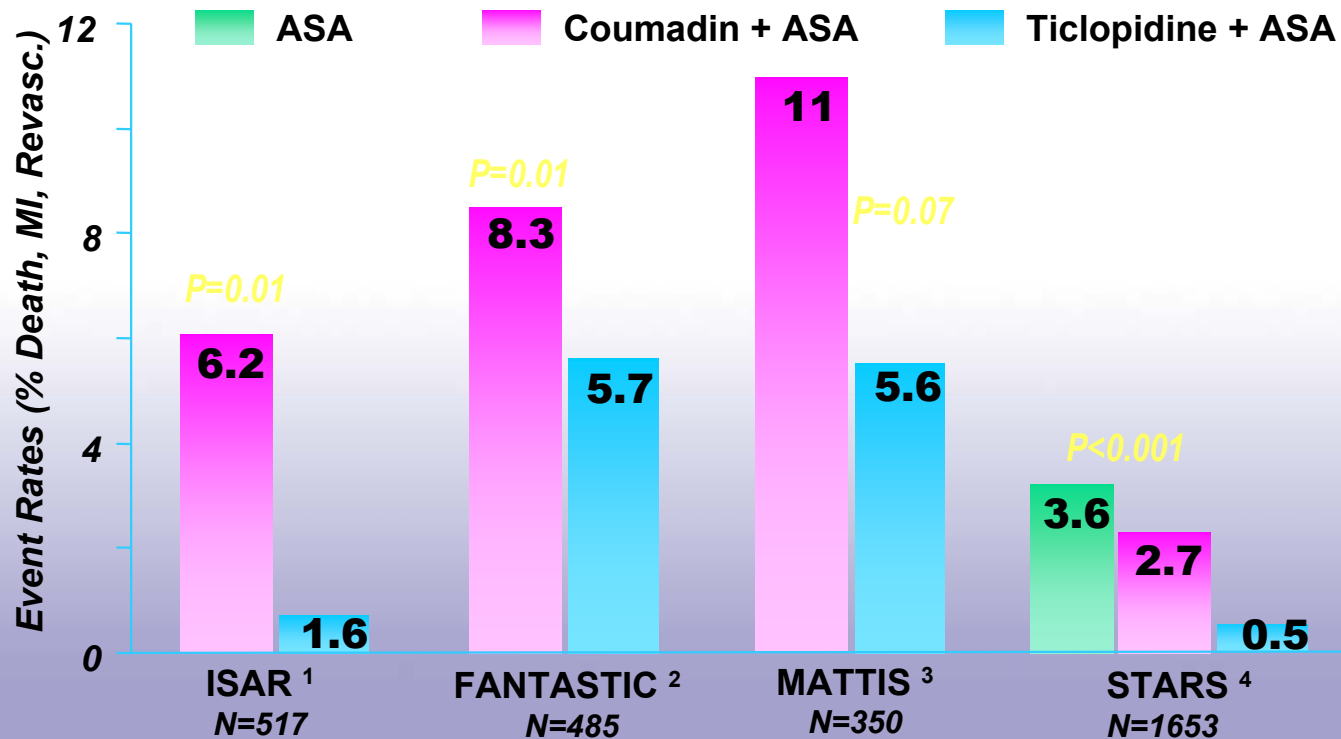


1. Bhatt DL *et al.* *Am Heart J* 2000; 140: 67–73. 2. Jarvis B, Simpson K. *Drugs* 2000; 60: 347–77.

Atherothrombosis is a Generalized Disease

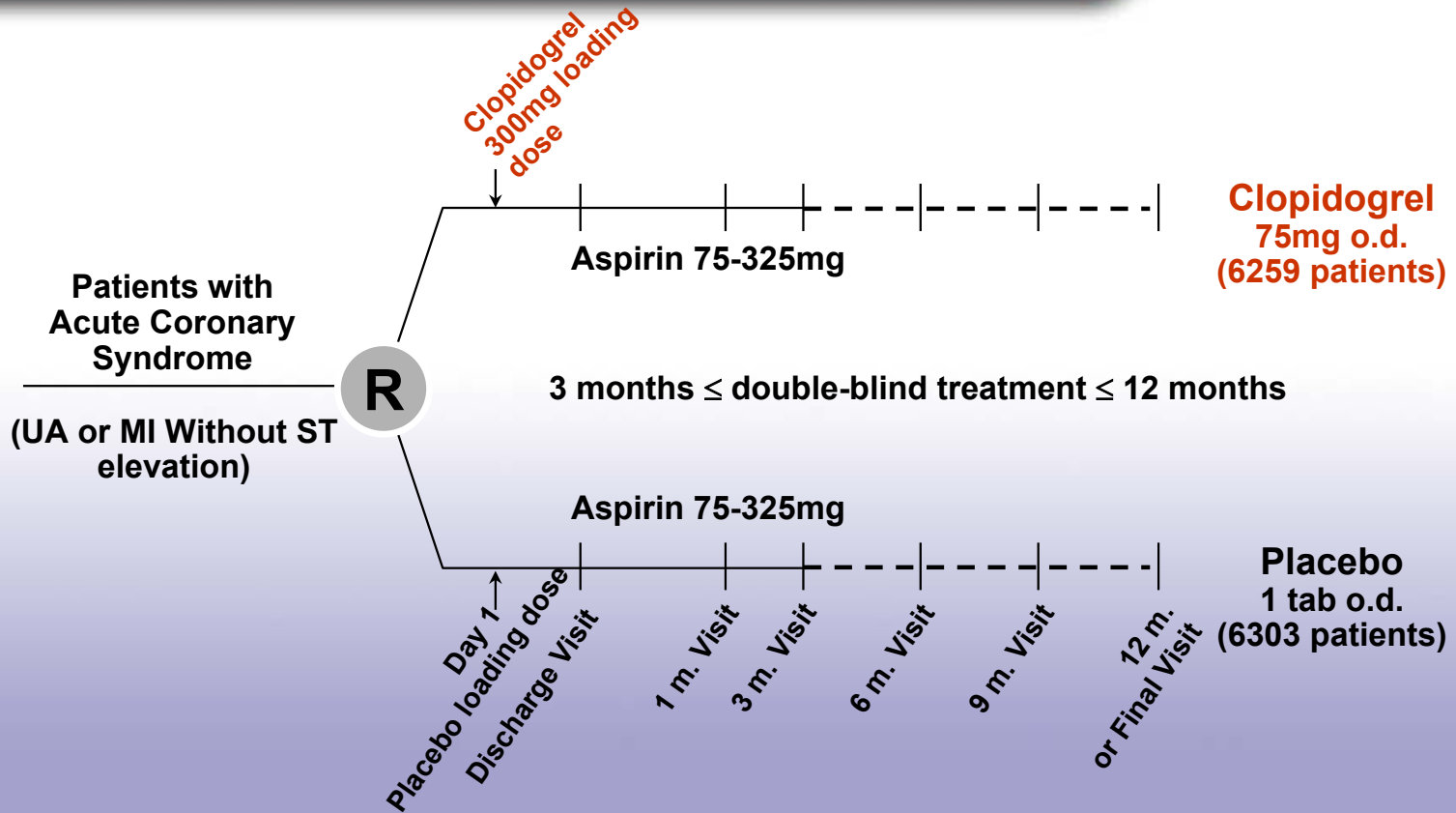


Ticlid + aspirin for prevention of subacute thrombosis on coronary stents



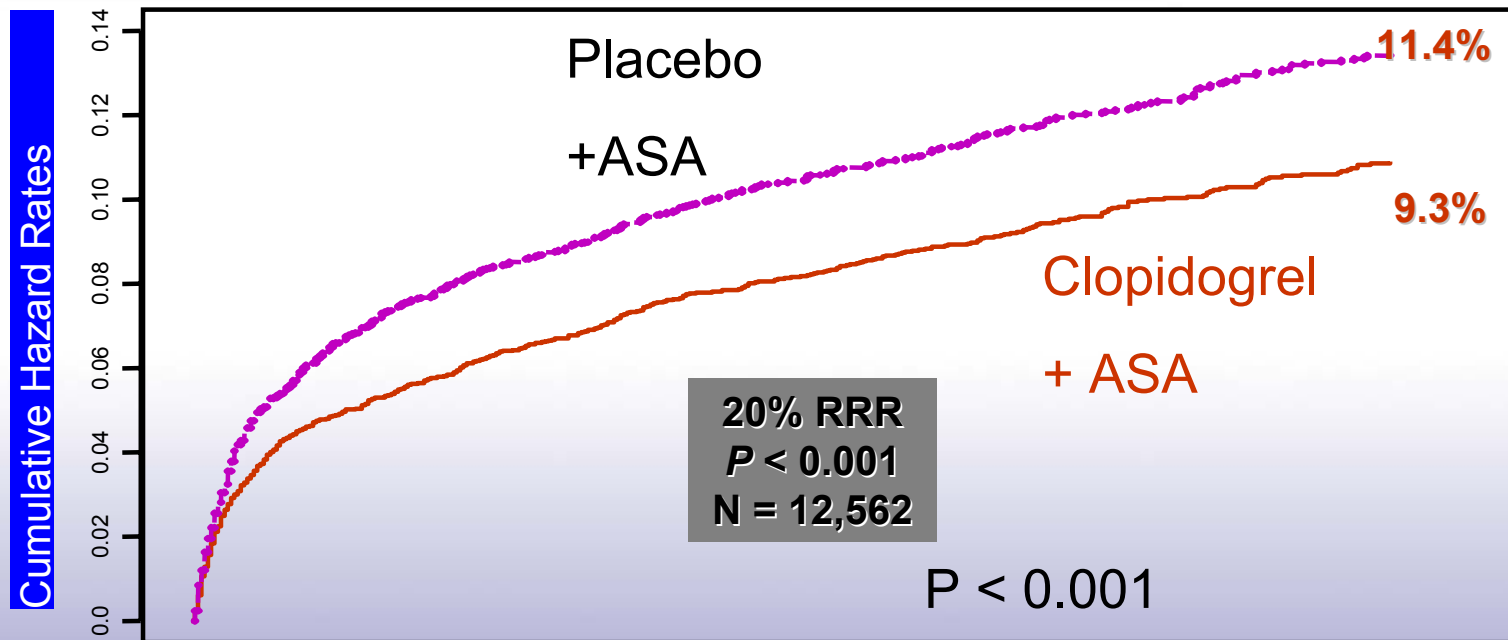
¹ Schömig et al. (1996), ² Bertrand et al. (1998), ³ Urban (1998), ⁴ Leon et al. (1998)

Patient Randomization



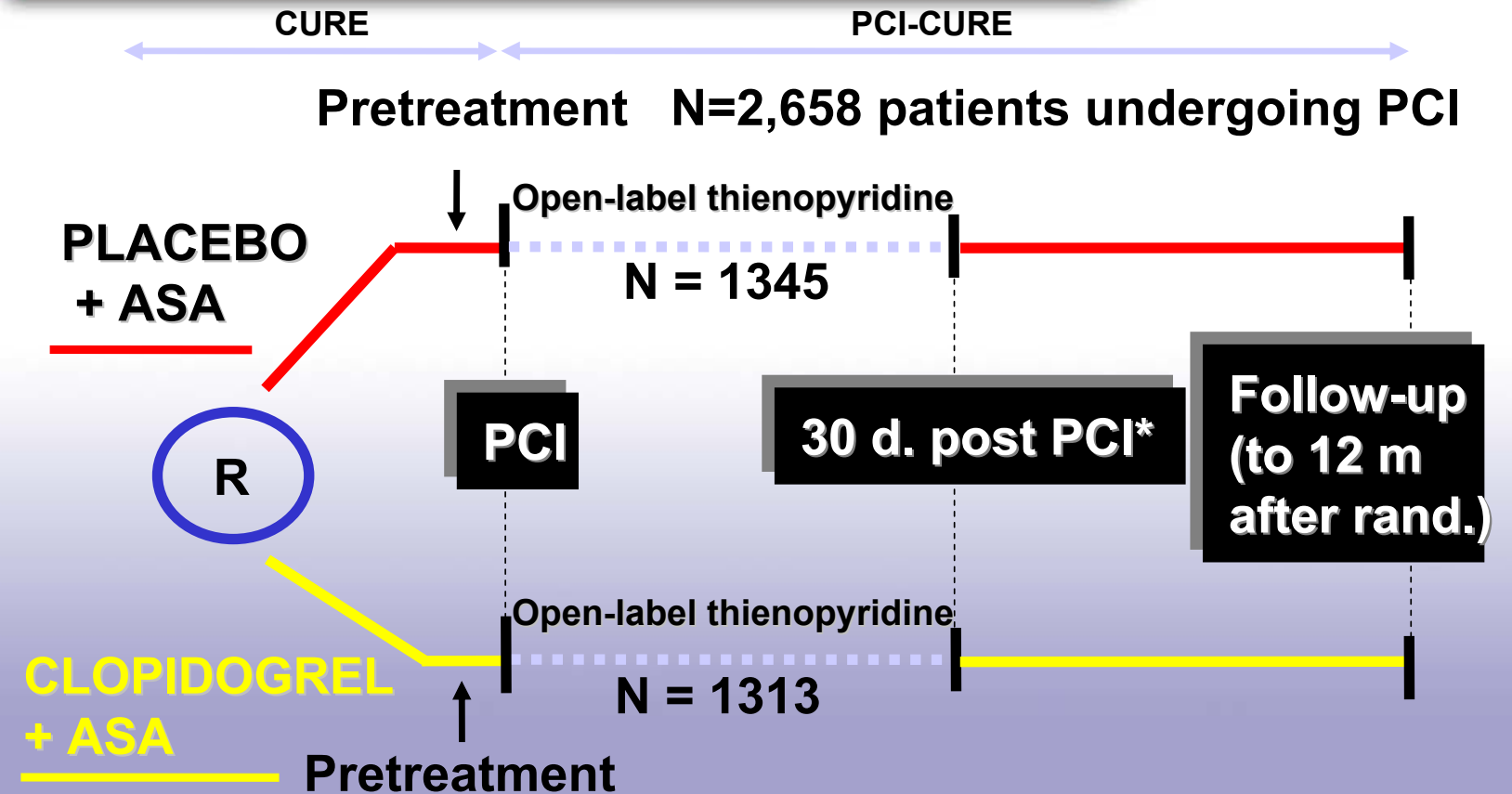
R=Randomization

Cure : Cumulative Hazard Rates for CV Death|MI|Stroke



No of Pts	0	3	6	9	12
Plac	6303	5780	4664	3600	2388
Clop	6259	5866	4779	3644	2418

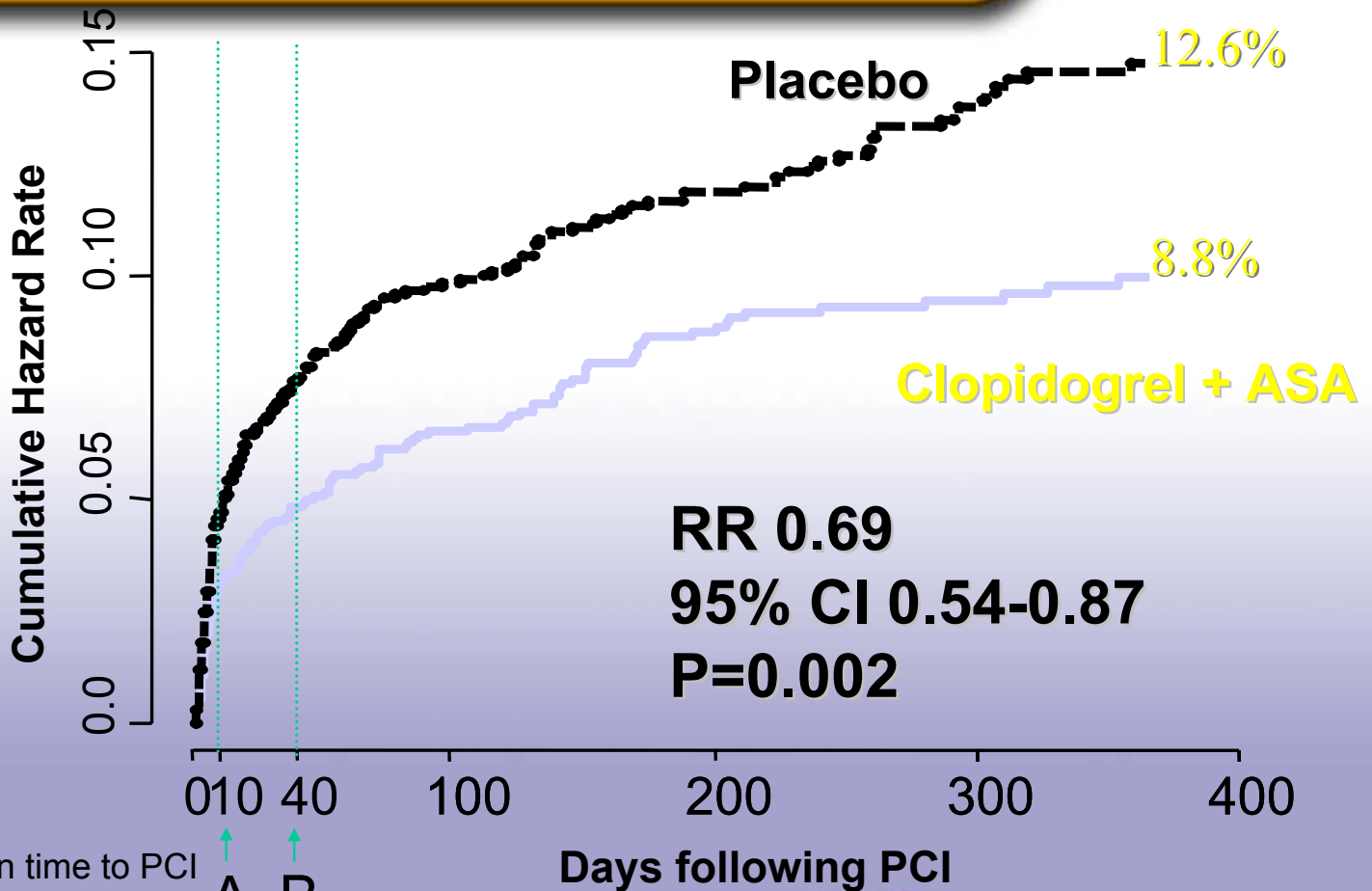
PCI-CURE: Study Design



*1° Outcome: CV Death, MI, Urg Revasc.

Mehta SR et al. *Lancet* 2001;358:527-33

PCI-Cure : Overall Results: CV Death or MI



A=median time to PCI
B=30 days after PCI

A B

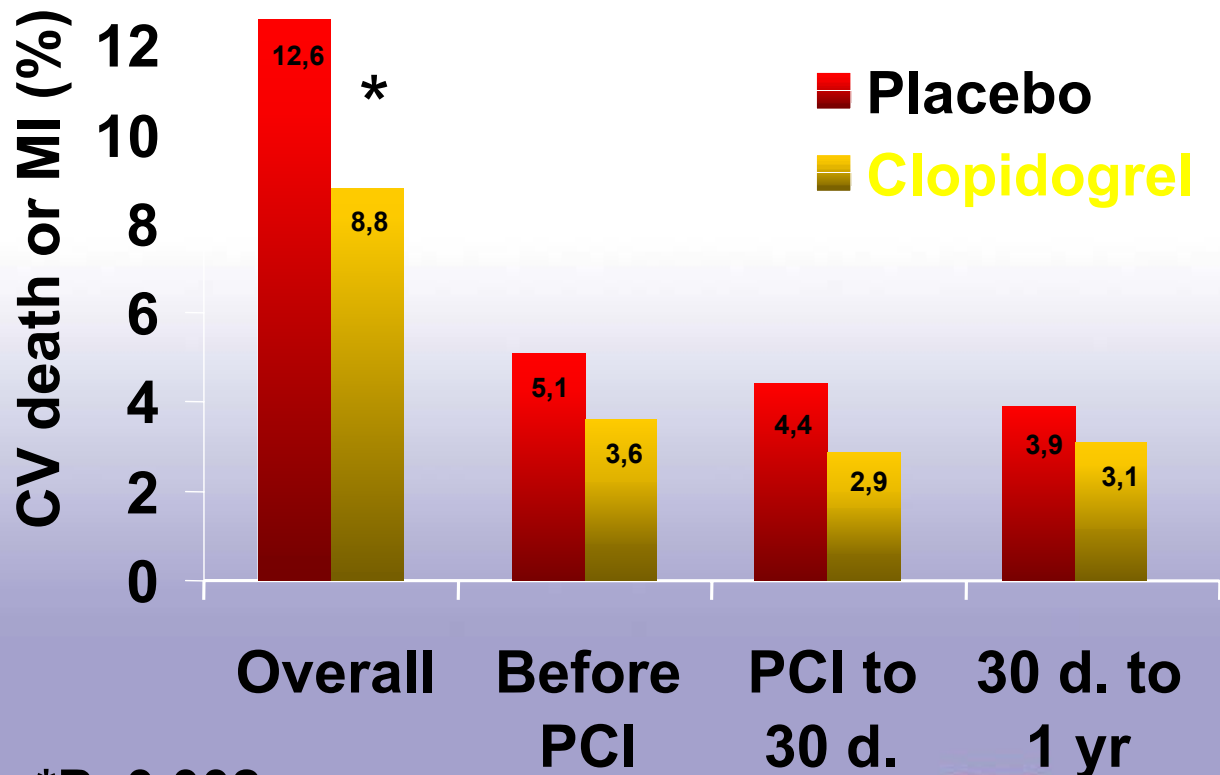
PCI-Cure : CV Death or MI at Various Intervals

RRR: 31%

32%

34%

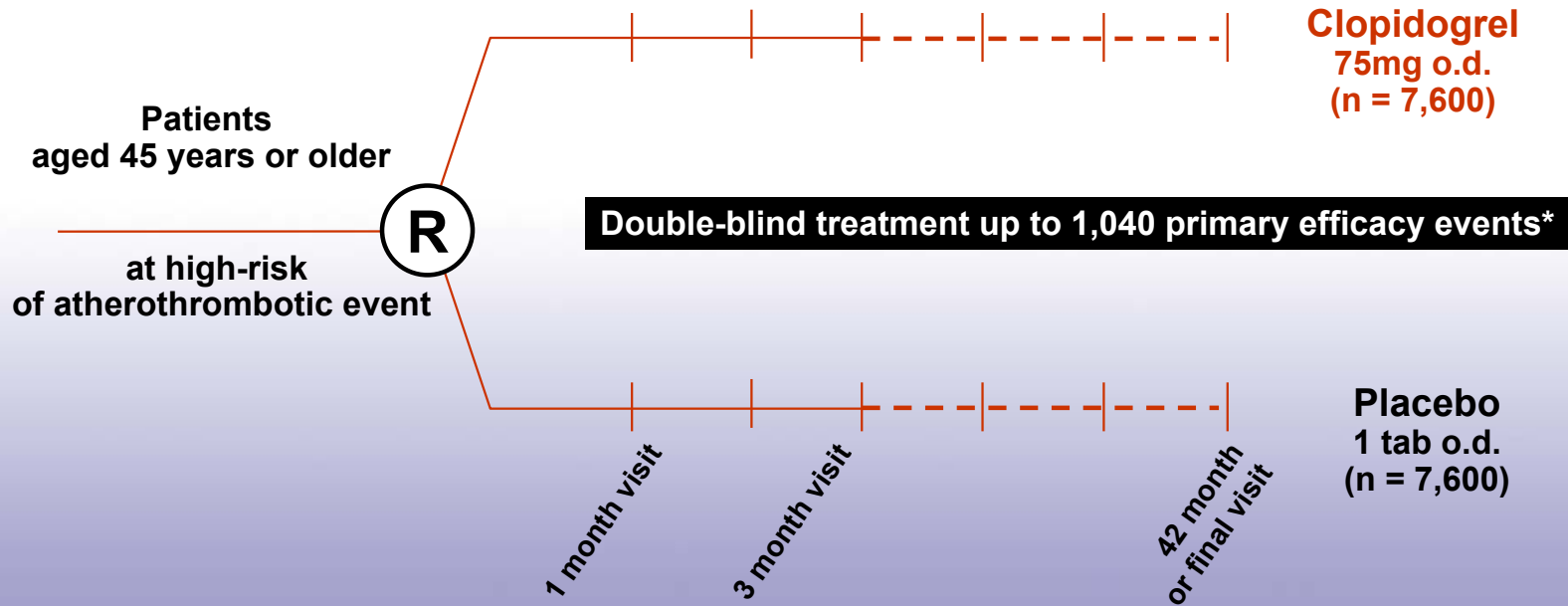
21%



*P=0.002

Mehta SR et al. *Lancet* 2001;358:527-33

CHARISMA - Design



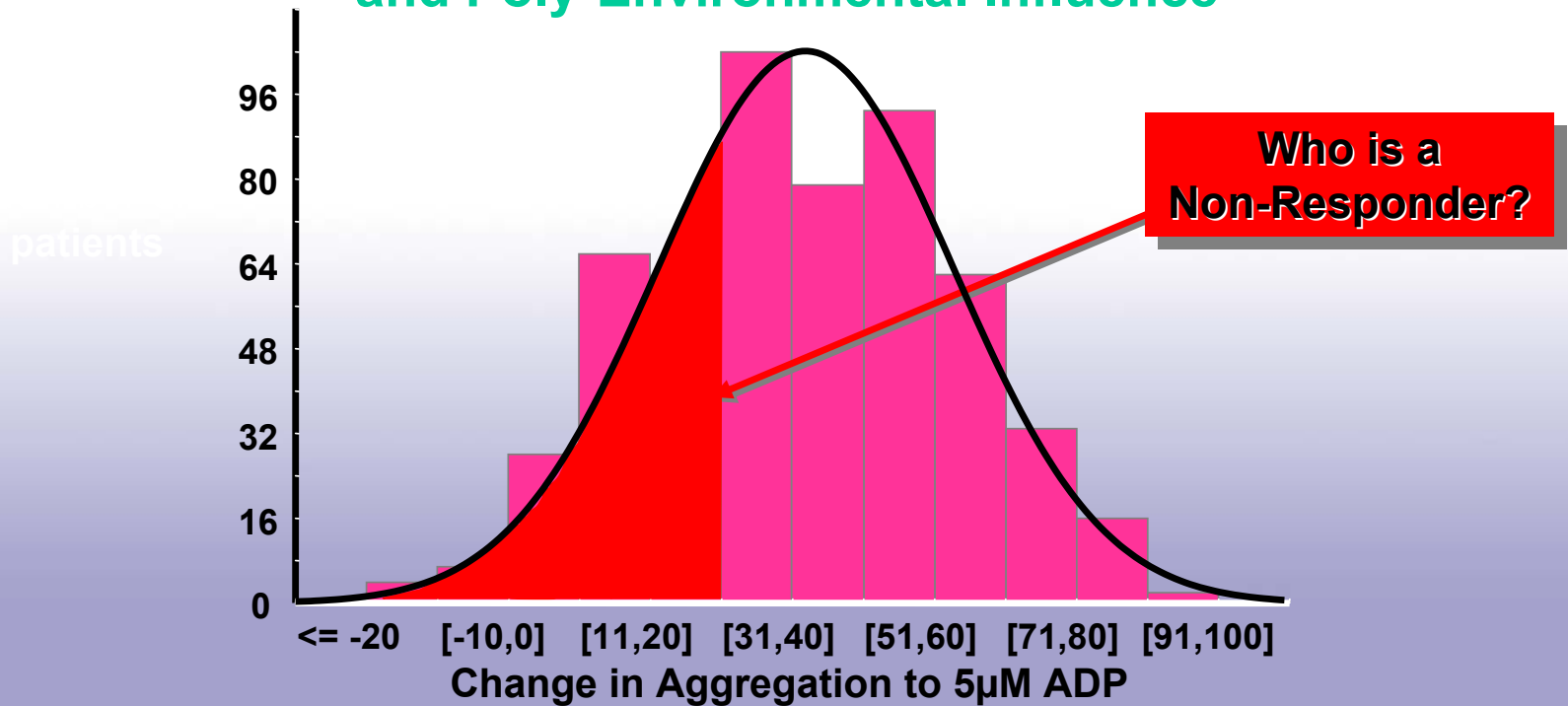
All patients receiving ASA 75–162 mg o.d.

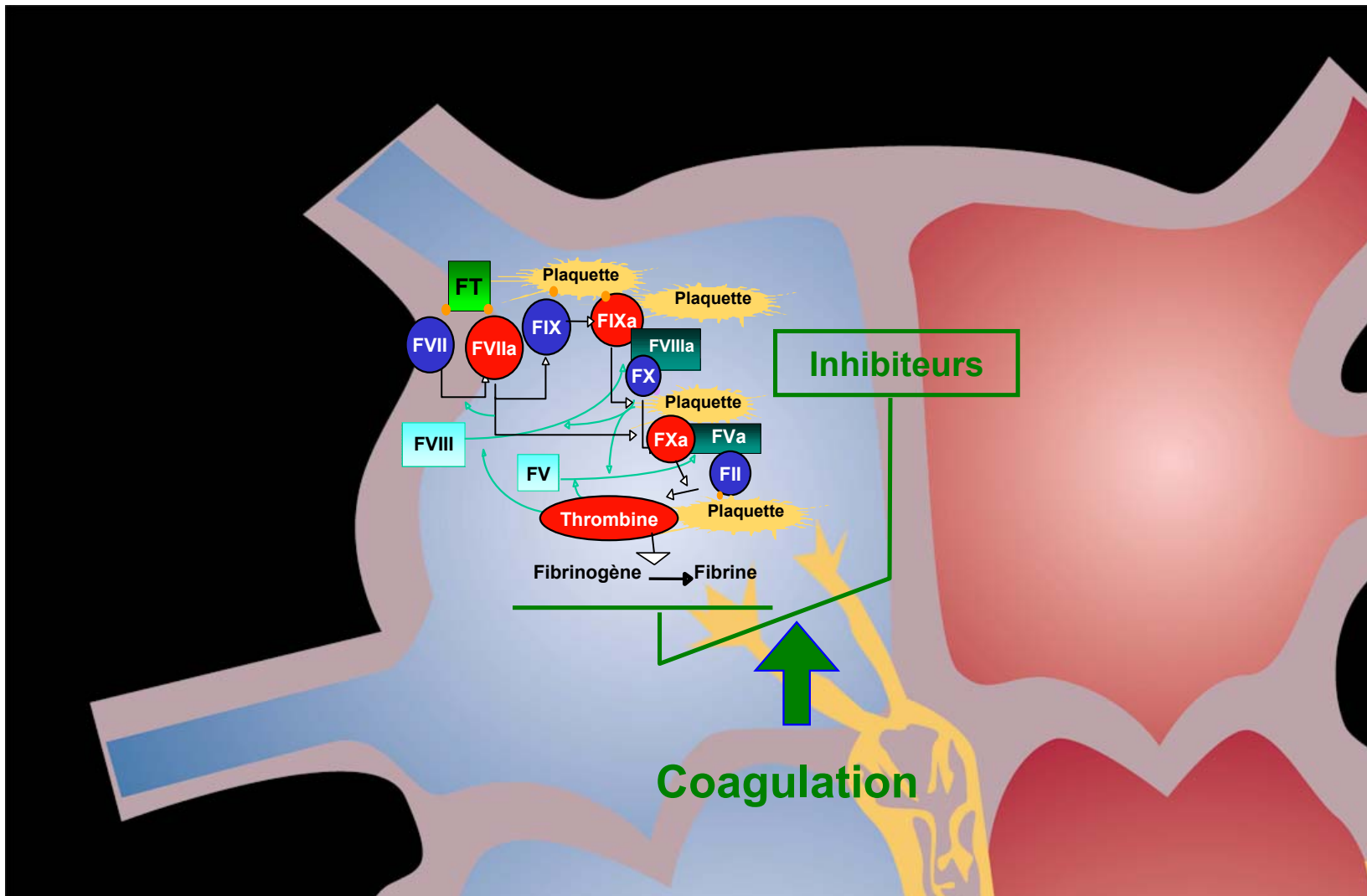
* event driven trial, approximately 15,000 patients

R = Randomization

Distribution of Responsiveness to Clopidogrel in 544 Individuals

A Normal Distribution: Consistent with a Poly-Genetic and Poly-Environmental Influence





Les antiagrégants plaquettaires dans la fibrillation auriculaire