Les AAP: la nouvelle donne en 2013

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Potential conflicts of interest

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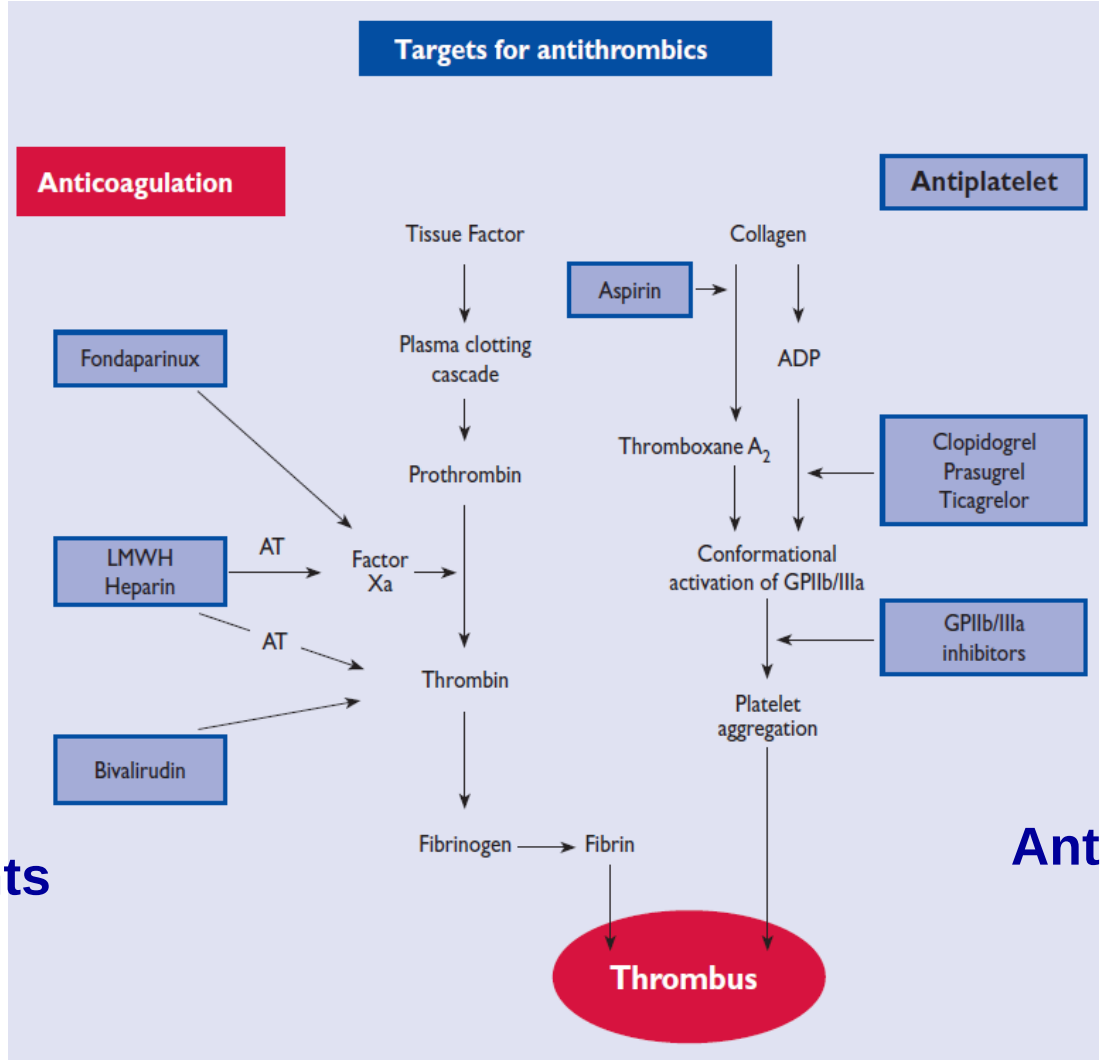
I have the following potential conflicts of interest to report:

- ***x*** **Research grants: Astra Zeneca, BMS, Sanofi , Eli Lilly**
- ***x*** **Lecteure fees: Astra Zeneca, Eli lilly, BMS, Sanofi**

Antithrombotiques



Anticoagulants

Antiplaquettaires

Aspirine: Est- ce un AAP ?

En prévention primaire ? Méta analyse…

En prévention secondaire ? Méta-analyse…..

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

Antithrombotic Trialists' (ATT) Collaboration*

Lancet 2009; 373: 1849–60

See Comment page 1821

*Collaborators listed at end of Article

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ATT Collaboration, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Richard Doll Building, University of Oxford, Oxford OX3 7LF, UK
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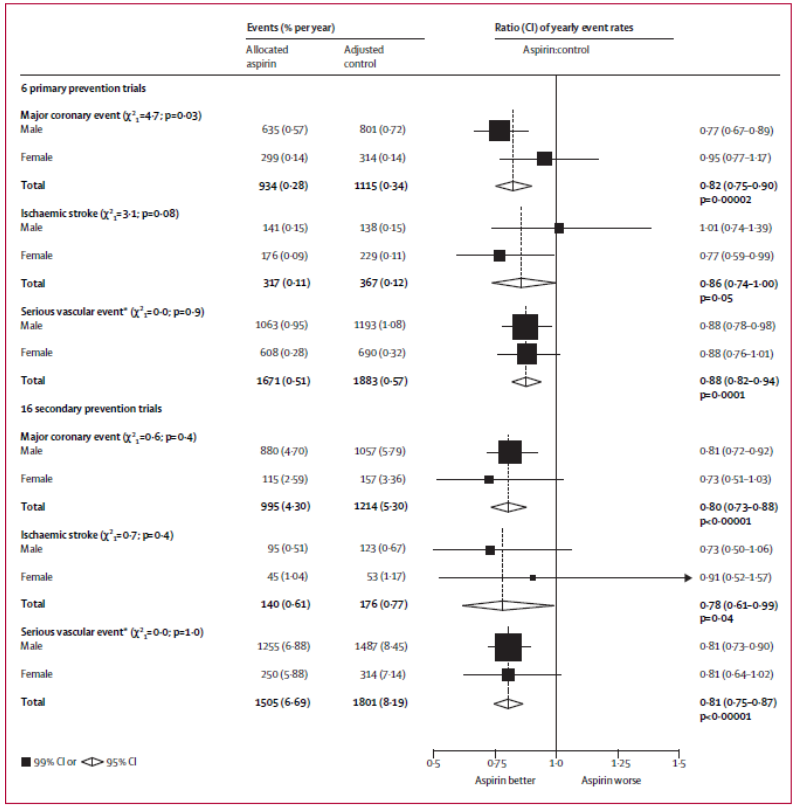


Figure 3: **Selected outcomes in primary and secondary prevention trials of aspirin, by sex**
Actual numbers for aspirin-allocated trial participants, and adjusted numbers for control-allocated trial participants, are presented together with the corresponding mean yearly event rate (in parentheses). Rate ratios (RRs) for all trials are indicated by squares and their 99% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares or diamonds to the left of the solid line indicate benefit. *Myocardial infarction, stroke (haemorrhagic or other), or vascular death.

Recommandations ESC 2011-2012

STEMI

Table 36 Antithrombotic treatment options in myocardial revascularization

STEMI			
Antiplatelet therapy			
	ASA	I	B

NSTEMI

Recommendations for oral antiplatelet agents

Recommendations	Class [a]	Level [b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A

Table 14 Checklist of antithrombotic treatments prior to PCI

Aspirin	Confirm loading dose prior to PCI.

Articles

A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)

*CAPRIE Steering Committee**

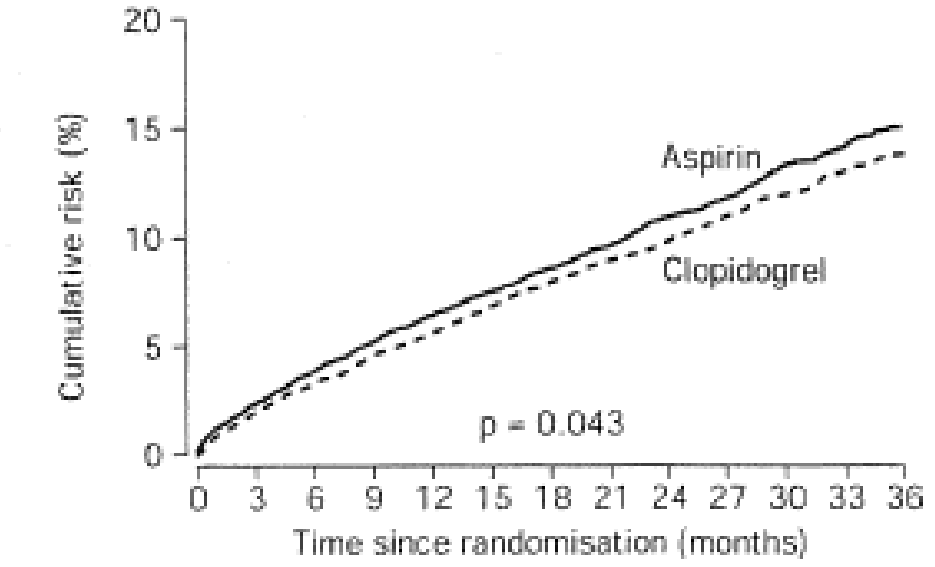
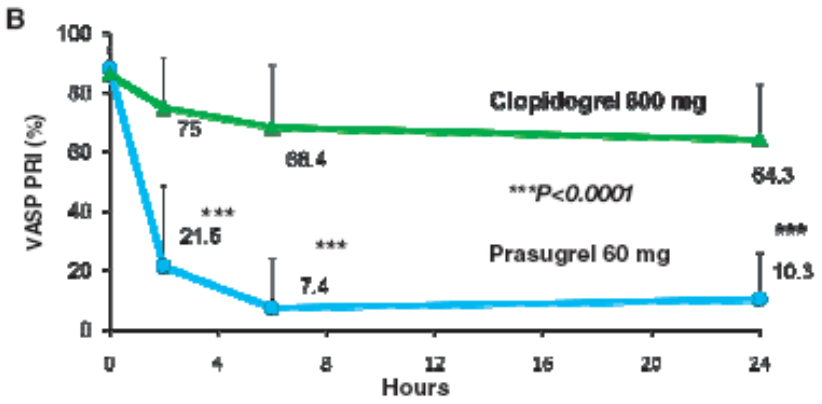
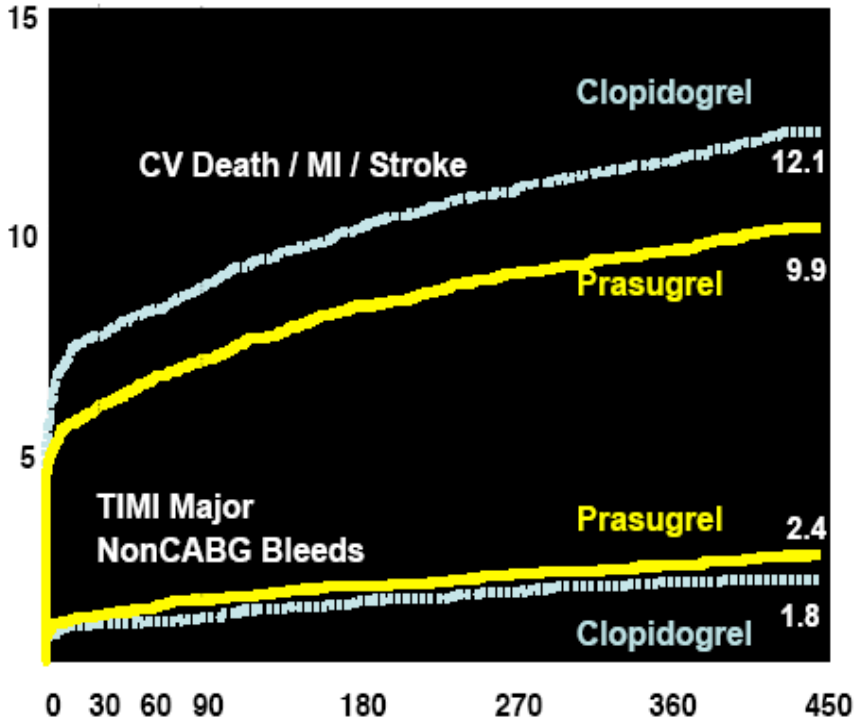


Figure 3: **Cumulative risk of ischaemic stroke, myocardial infarction, or vascular death**
A=aspirin; C=clopidogrel.

Etude TRITON (Prasugrel)





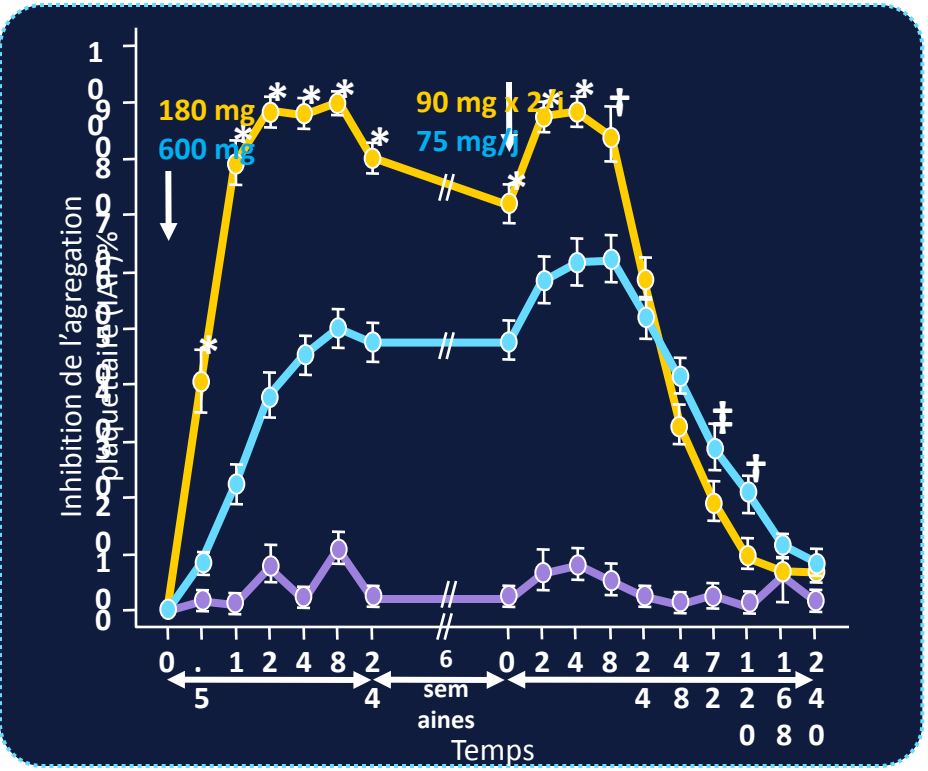
Plus puissant, plus rapide

Réduction des événements thrombotiques

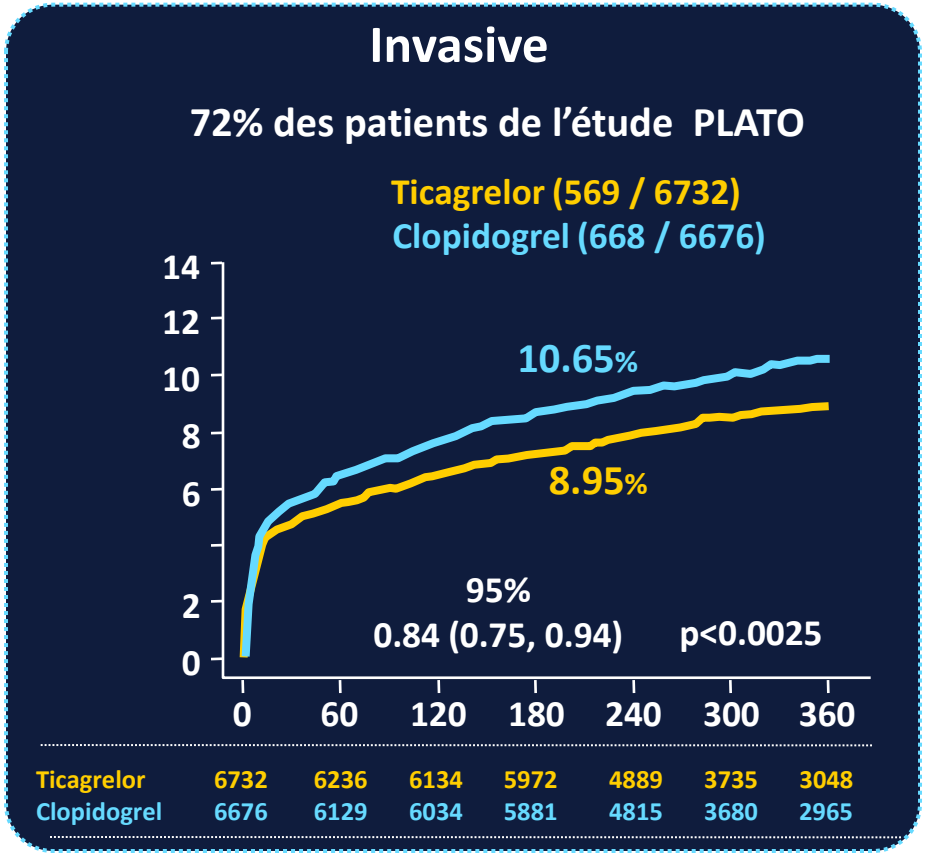
Excès d'hémorragie majeures/mineures non CABG

Principle TIMI 44 circ. 2006. Triton TIMI 38 2007

PLATO (Ticagrelor)



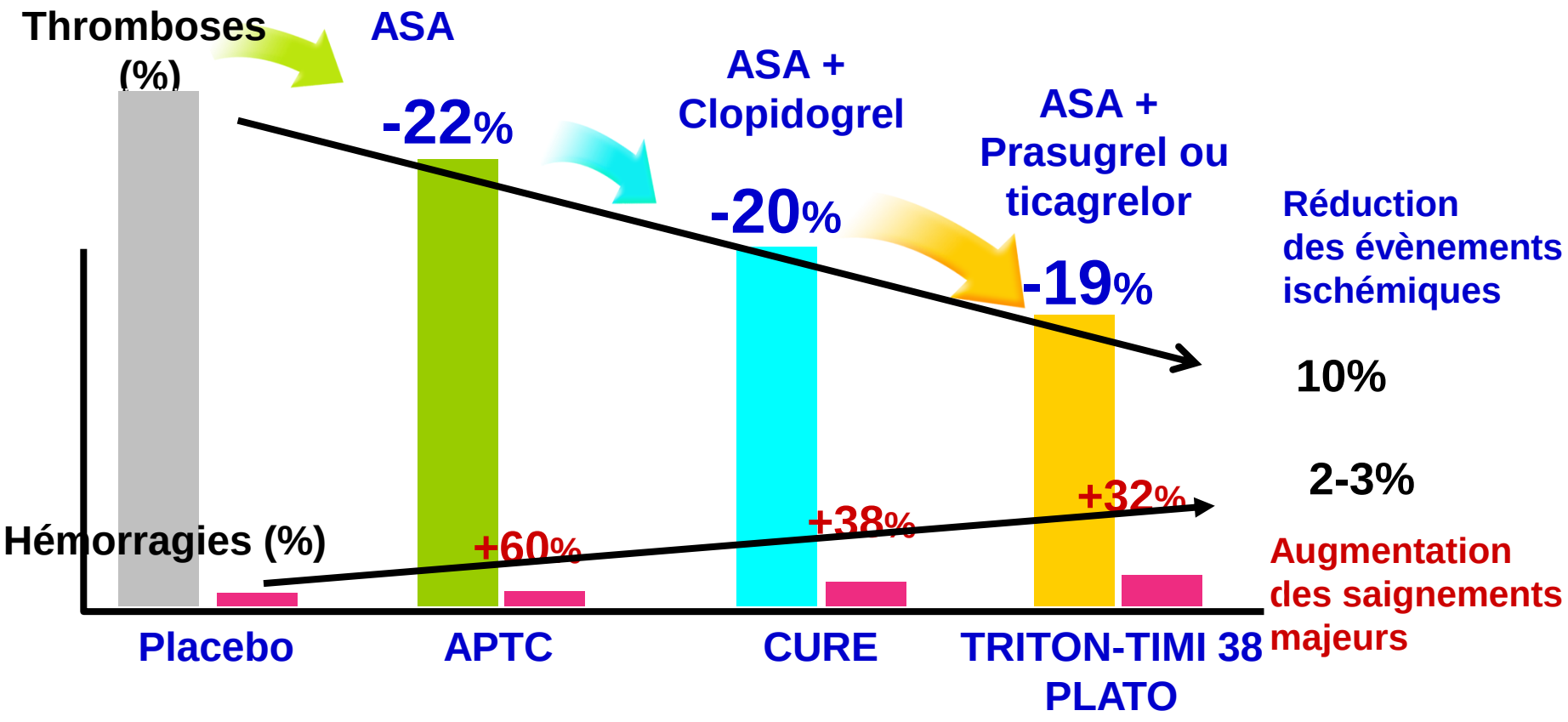
Inhibition plaquettaire
-plus rapide
-plus intense



Réduction des MACE
Augmentation des hémorragies

Gurbel Circ 2010; Cannon Lancet 2010

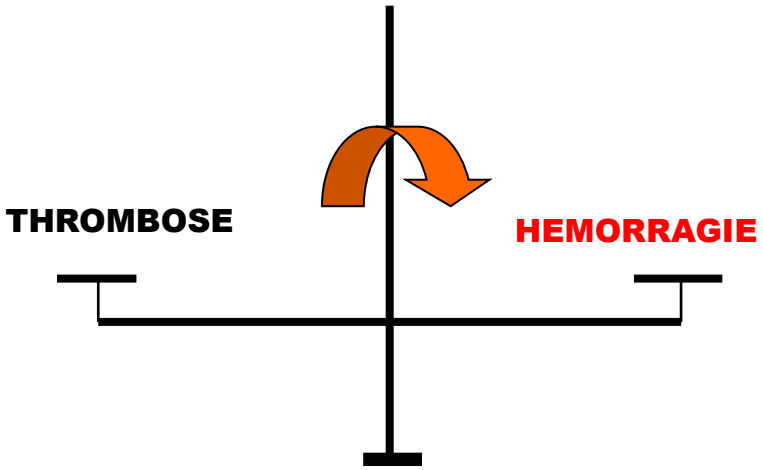
La nouvelle donne

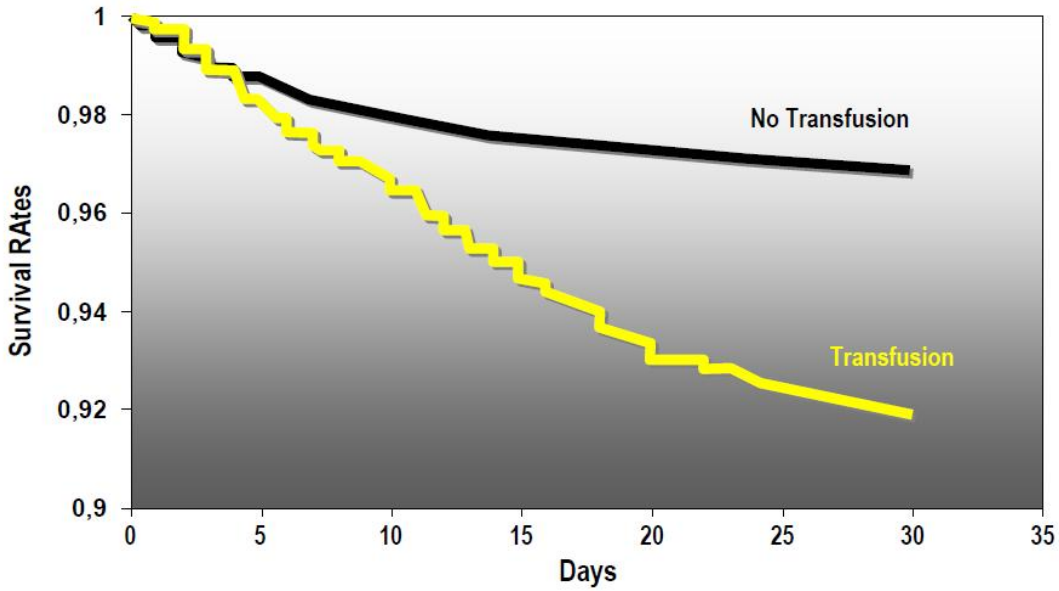


Balance bénéfice – risque

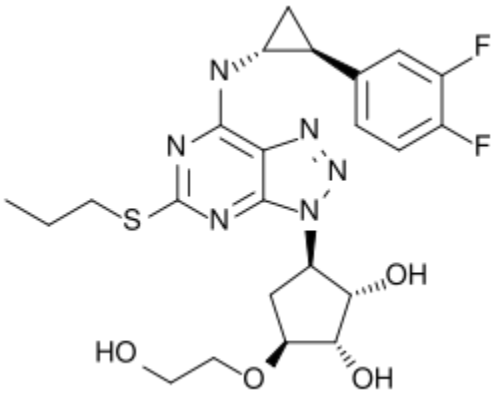
1. APTC : BMJ. 2002 12;324(7329):71-86.
2. CURE : N Engl J Med. 2001 16;345(7):494-502
3. TRITON : N Engl J Med 2007;357:2001-15

Balance bénéfice / risque avec les antagonistes du P2Y12

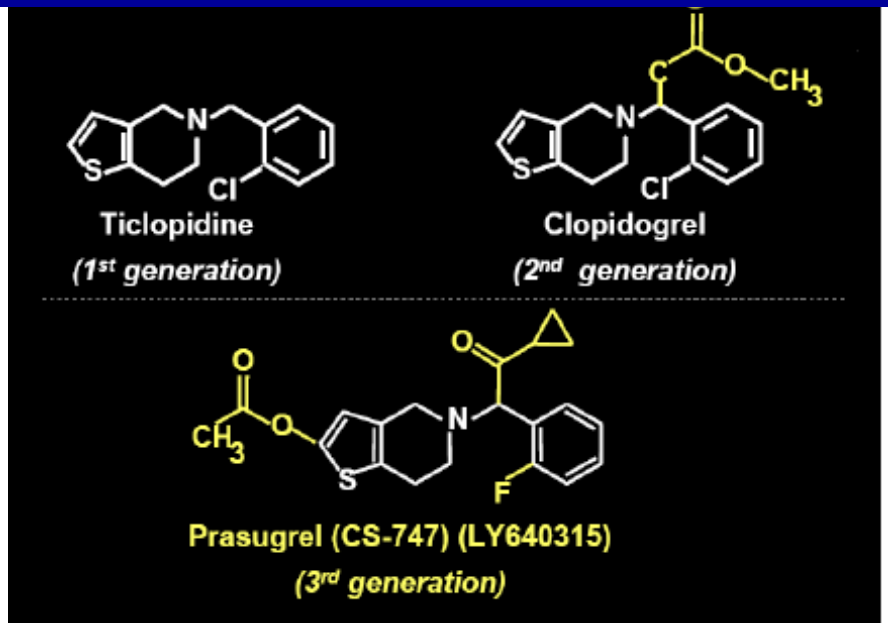




Nouveaux antagonistes des récepteurs P2Y12 à l'ADP



Ticagrelor

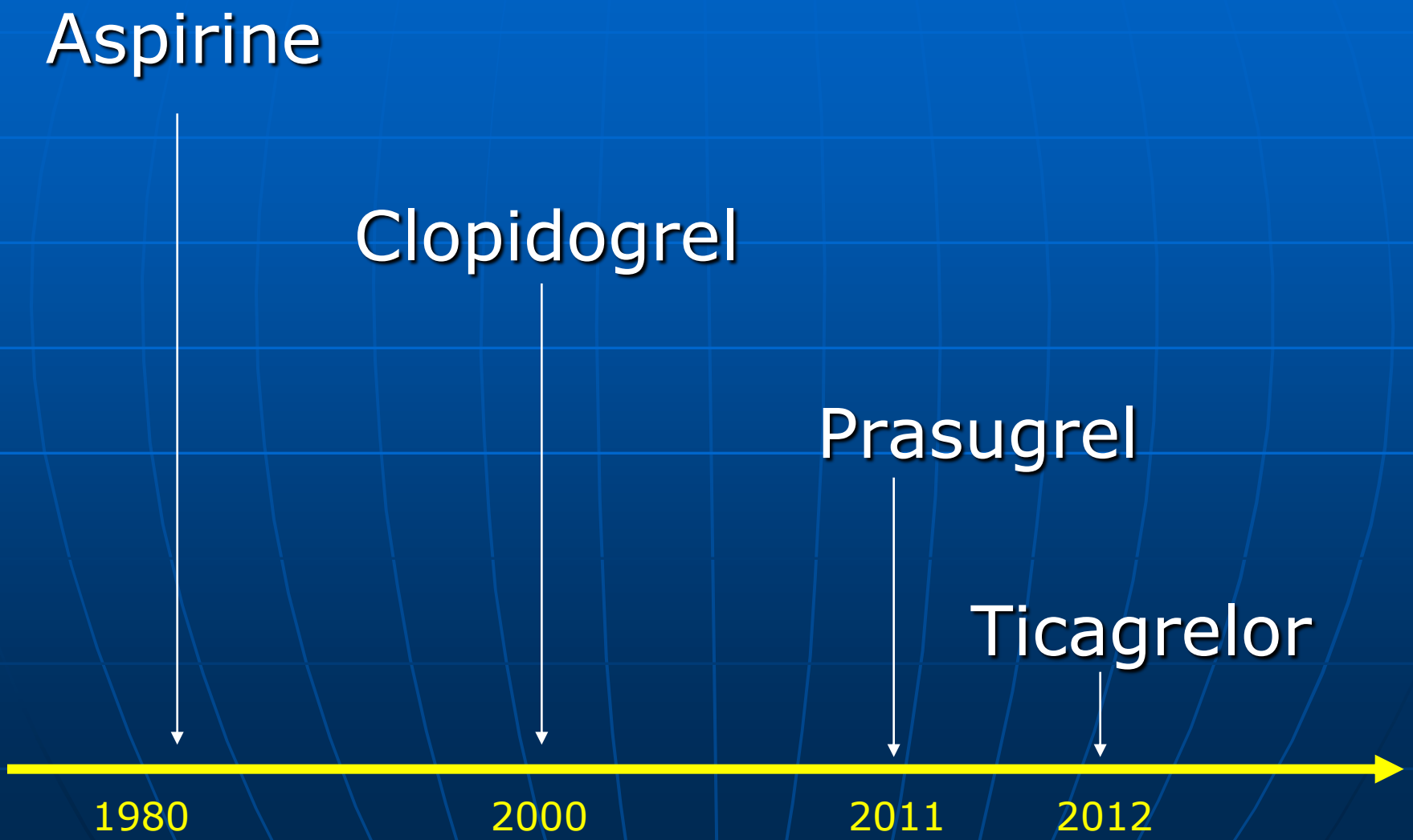


Molécule	Classe	Administration	Métabolisme	Pic d'effet	Réversibilité	½ vie
Ticolpidine	Thiénopyridine	Orale	Conversion prodrogue médiée par le	4jours	Irréversible	NP
Clopidogrel		Orale		2-6heures		
Prasugrel		Orale		1 heure		
Cangrelor	ATP analogue	Intraveineuse	N'est pas une prodrogue	30minutes	Réversible	3 – 5mn
Ticagrelor	CPTP*	Orale		2 heures		12heures

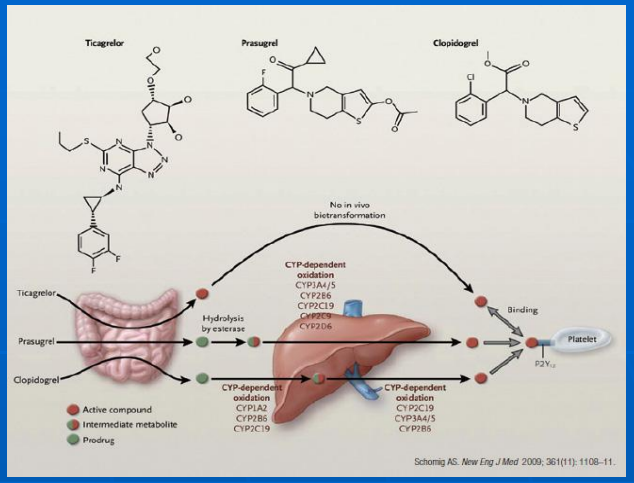
Quel AAP? Prasugrel ou Ticagrelor

- Historique
- Pharmacologie
- Effet indésirable
- Efficacité
- taux de résistance
- Population étudiée
- Sécurité hémorragique
- Recommandations
- Prix
- En pratique…

Par l'historique

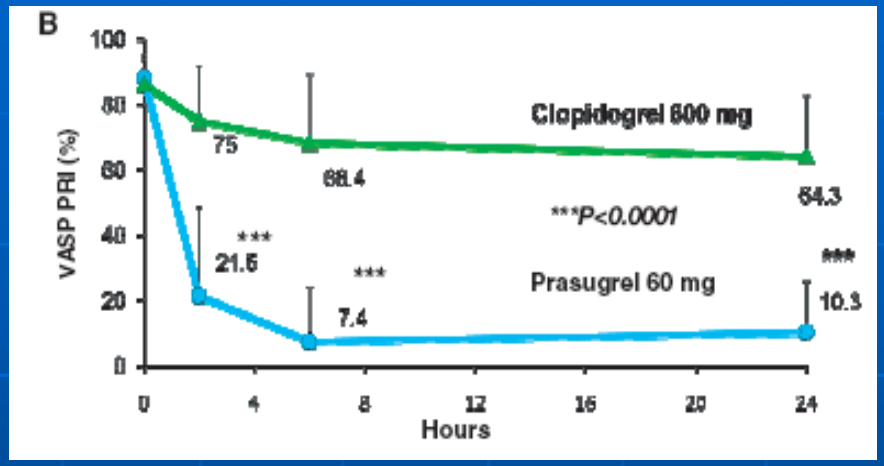


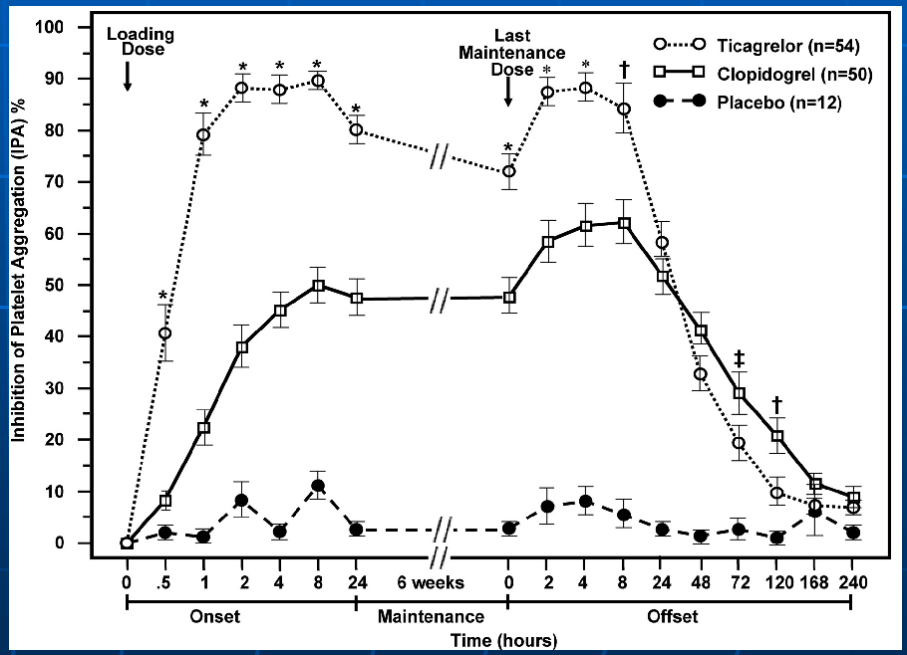
Par la pharmacologie



Inhibiteurs des P2Y12			
	Clopidogrel	Prasugrel	Ticagrelor
Classe	Thienopyridine	Thienopyridine	Triazolopyrimidine
Réversibilité	Non	Non	oui
Activation	Prodrogue	Prodrogue	Drogue active
Début d'effet	≥ 2-4 h	30 min	30 min

Par efficacité biologique





Taux de résistance au VASP

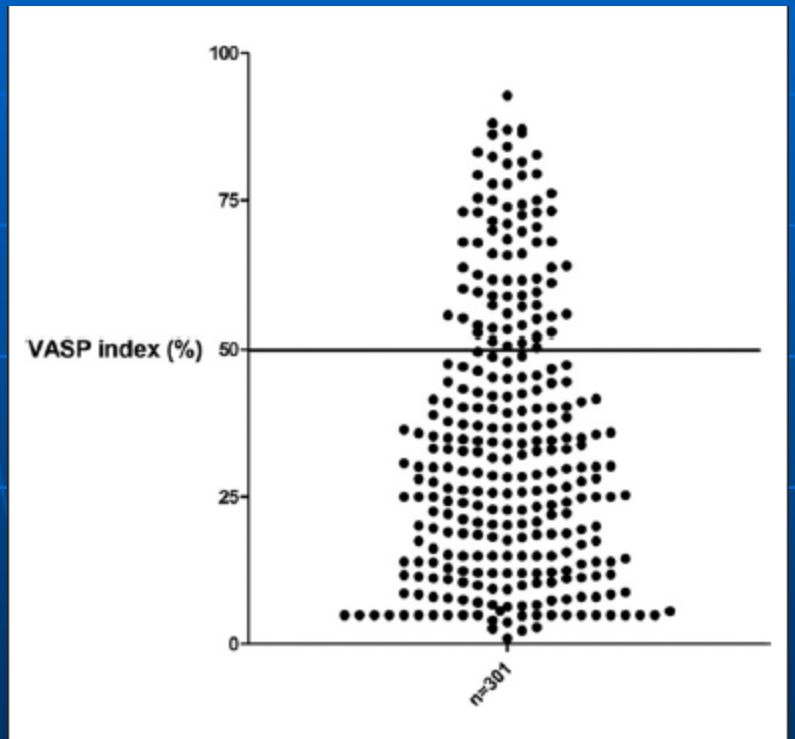
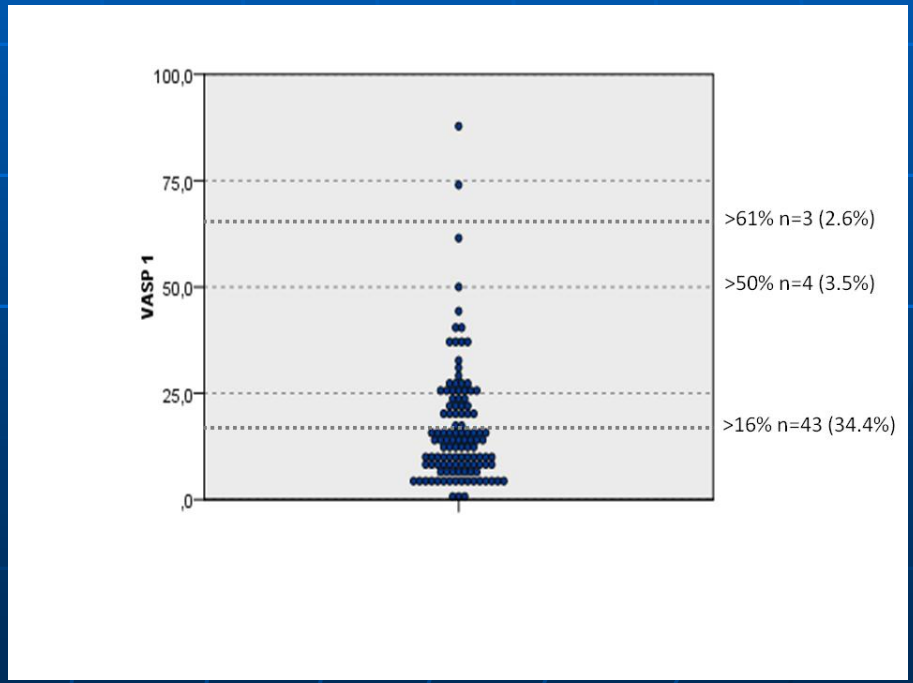
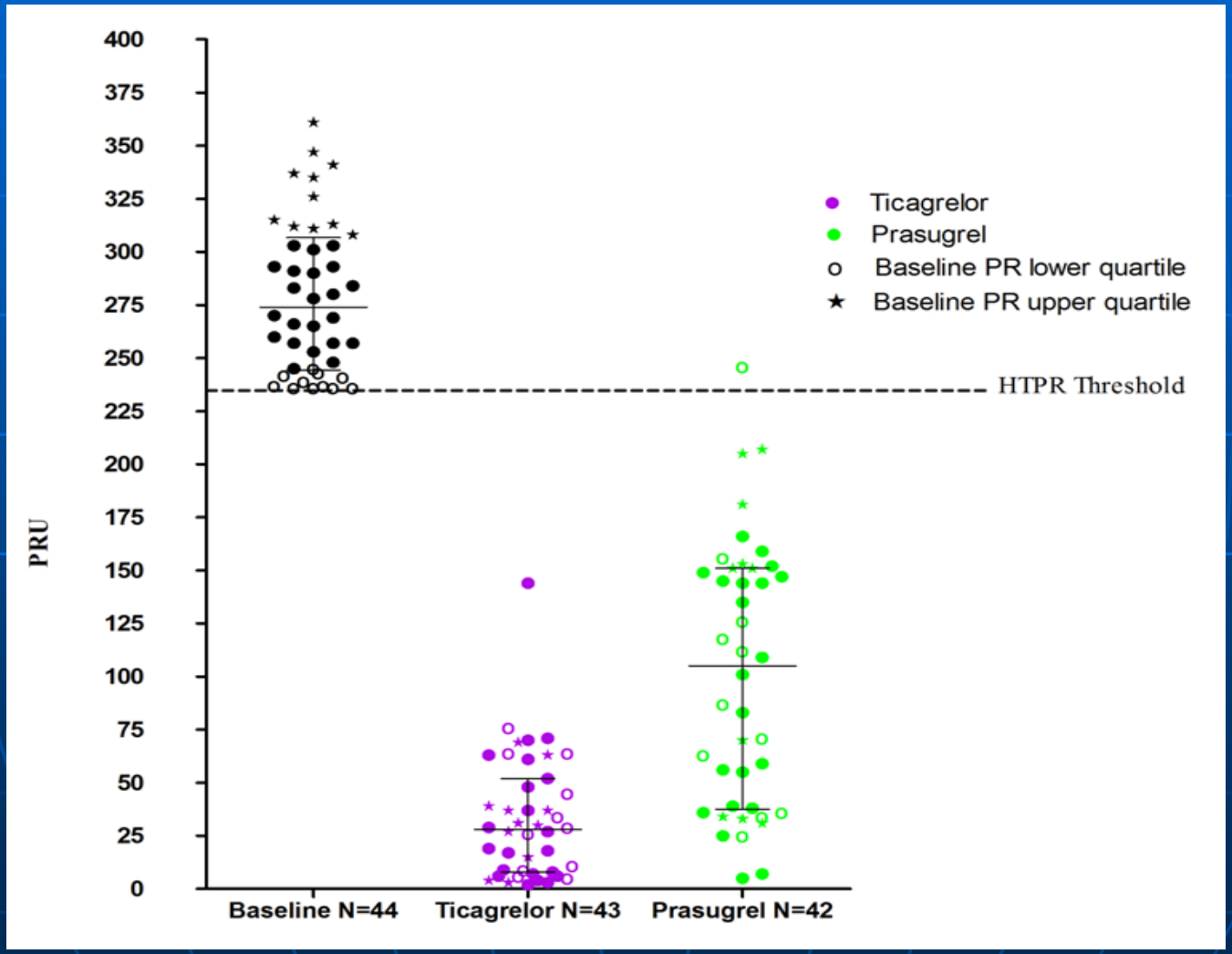


Figure 1 **VASP Index After Prasugrel LD**

Although the vast majority of patients had platelet reactivity (PR) below 50%, 25.2% were considered to have high on-treatment platelet reactivity (HTPR). LD = loading dose; VASP = vasodilator-stimulated phosphoprotein.



Resistance VerifyNow (>235)



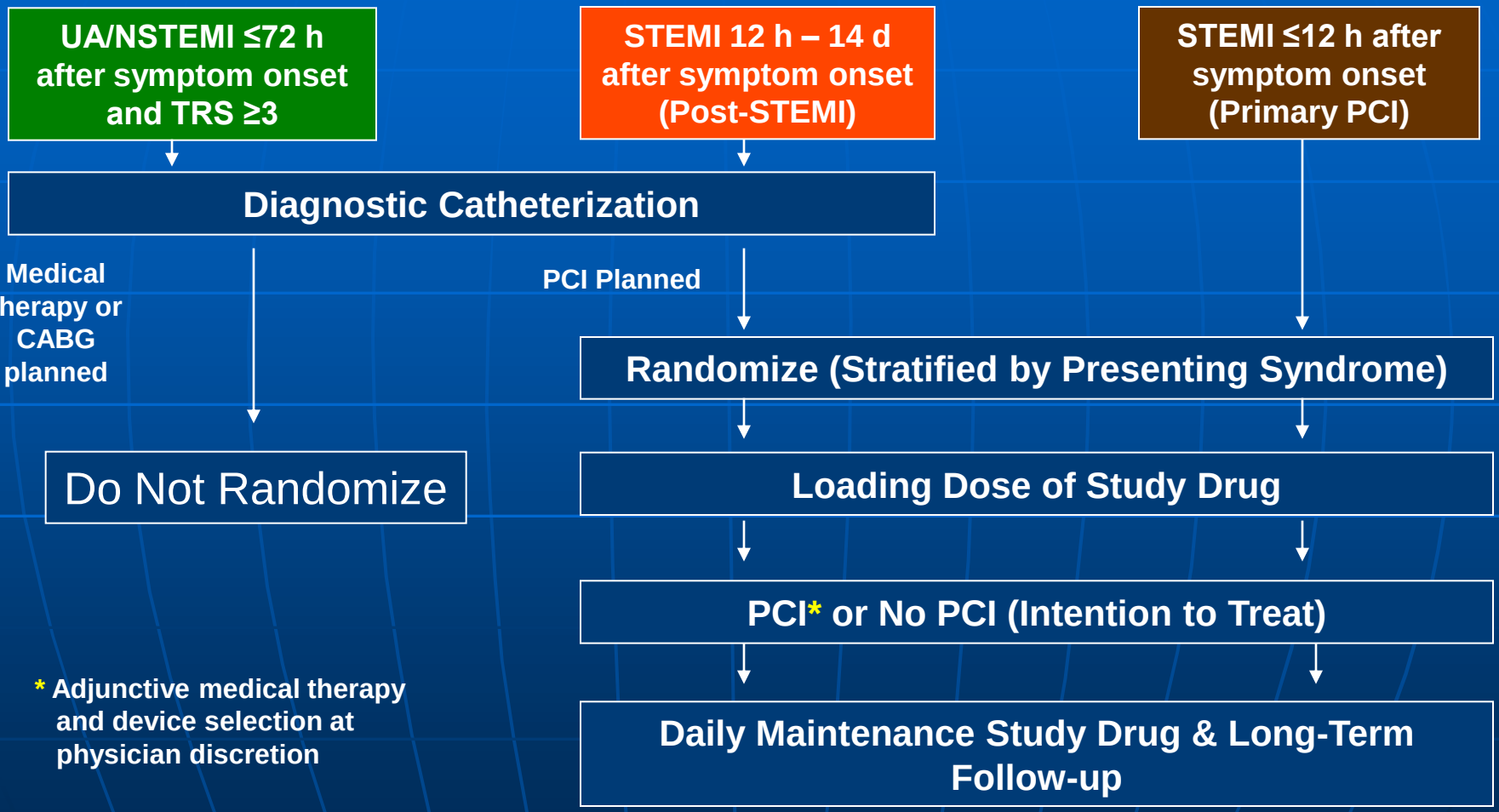
Par effet indésirable

Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

Par le profil des patients

Prasugrel = ACTP
Ticagrelor = que les hauts risque

Prasugrel : AAP de angioplastie



CABG=Coronary Artery Bypass Graft surgery; NSTEMI=Non–ST-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; STEMI=ST-Elevation Myocardial Infarction; TRS=TIMI Risk Score; UA=Unstable Angina

Wiviott SD et al. *Am Heart J* 2006;152:627-635

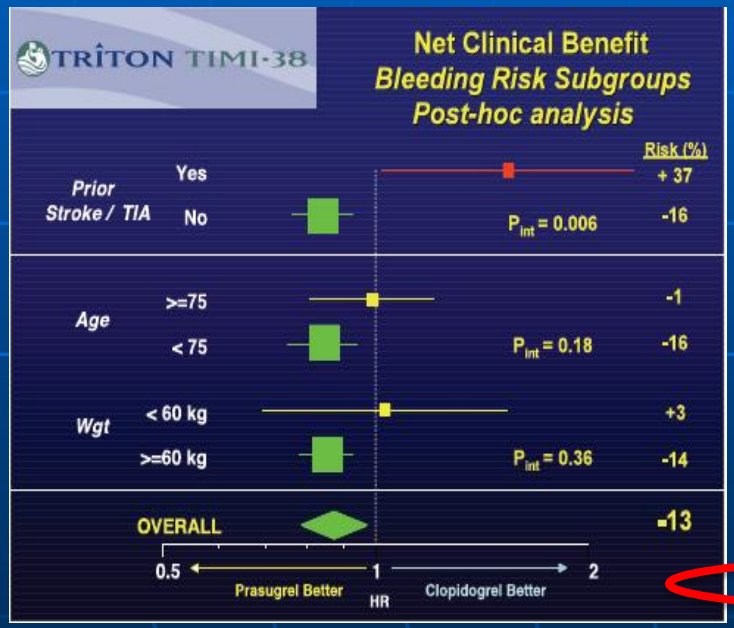
Ticagrelor : AAP du traitement chirurgical, médical et angioplastie mais ….

Que des patients à haut risque

SCA non ST + [AI/NSTEMI] (risque modéré à élevé)
SCA ST+ [STEMI] (uniquement si ICP* I^{aire})

C'est patients uniquement à haut risque ……

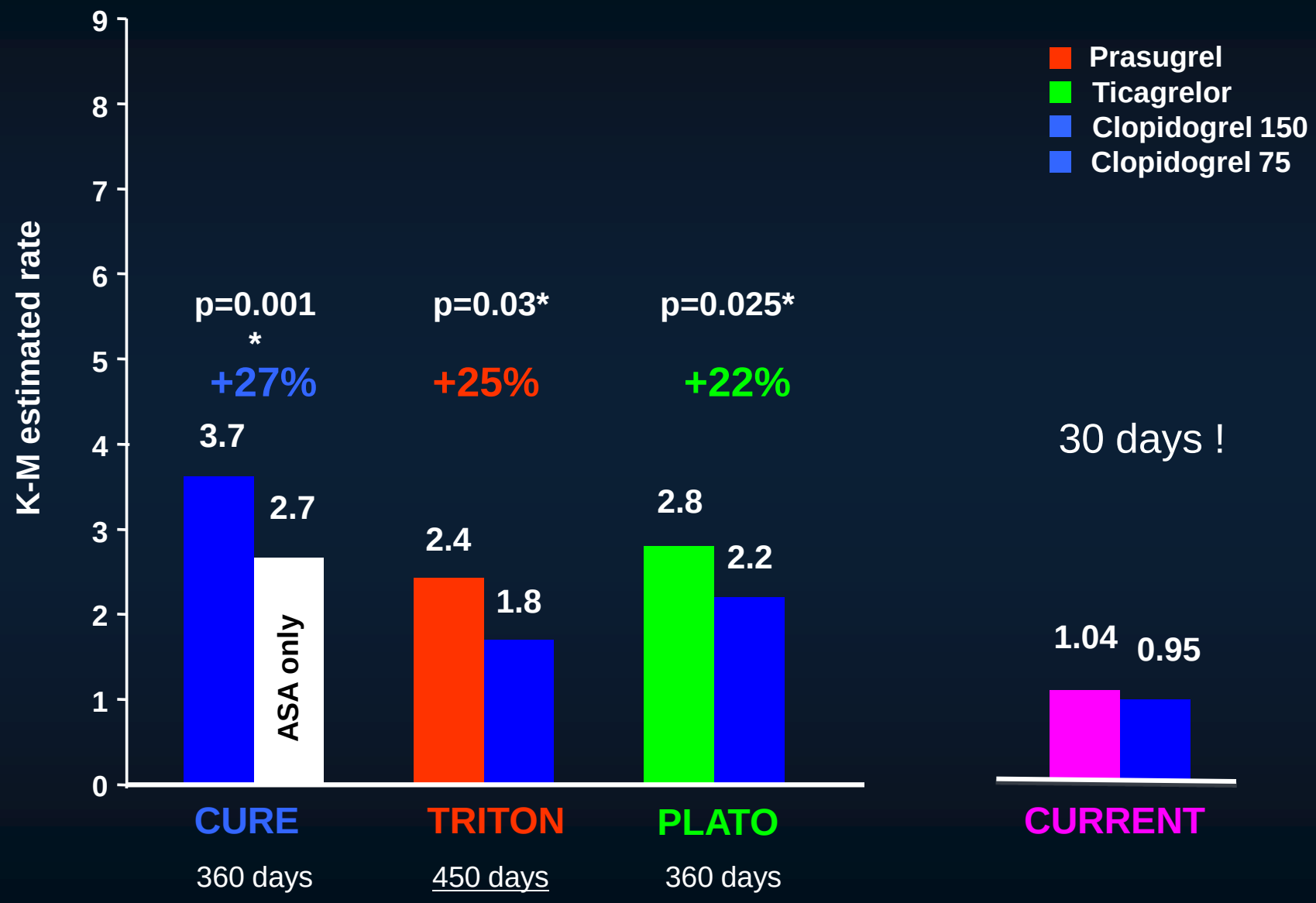
Par contre–indication



Caractéristiques	Groupe Ticagrelor	Groupe Clopidogrel
Âge médian (années)	62,0	62,0
Âge ≥ 75 ans : nombre/nombre total (%)	1396/9333 (15,0)	1482/9291 (16,0)
Femmes : nombre/nombre total (%)	2633/9333 (28,4)	2633/9291 (28,3)
Poids médian : kg (intervalle)	80,0 (28–174)	80,0 (29–180)
Poids < 60 kg : nombre/nombre total (%)	652/9333 (7,0)	660/9291 (7,1)
IMC : médiane (intervalle)	27 (13–68)	27 (13–70)
Origine ethnique : nombre/nombre total (%)‡		
Blanc	8566/9332 (91,8)	8511/9291 (91,6)
Noir	115/9332 (1,2)	114/9291 (1,2)
Asiatique	542/9332 (5,8)	554/9291 (6,0)
Autre	109/9332 (1,2)	112/9291 (1,2)
Facteur de risque cardiovasculaire : nombre/nombre total (%)		
Tabagisme	3360/9333 (36,0)	3318/9291 (35,7)
Hypertension	6139/9333 (65,8)	6044/9291 (65,1)
Dyslipidémie	4347/9333 (46,6)	4342/9291 (46,7)
Diabète sucré	2326/9333 (24,9)	2336/9291 (25,1)
Autres antécédents médicaux : nombre/nombre total (%)		
IM	1900/9333 (20,4)	1924/9291 (20,7)
Intervention coronaire percutanée	1272/9333 (13,6)	1220/9291 (13,1)
Pontage coronarien	532/9333 (5,7)	574/9291 (6,2)
Insuffisance cardiaque congestive	513/9333 (5,5)	537/9291 (5,8)
AVC non hémorragique	353/9333 (3,8)	369/9291 (4,0)
Artériopathie périphérique	566/9333 (6,1)	578/9291 (6,2)
Insuffisance rénale chronique	379/9333 (4,1)	406/9291 (4,4)
Antécédents de dyspnée	1412/9333 (15,1)	1358/9291 (14,6)
Bronchopneumopathie chronique obstructive	555/9333 (5,9)	530/9291 (5,7)
Asthme	267/9333 (2,9)	265/9291 (2,9)
Goutte	272/9333 (2,9)	262/9291 (2,8)

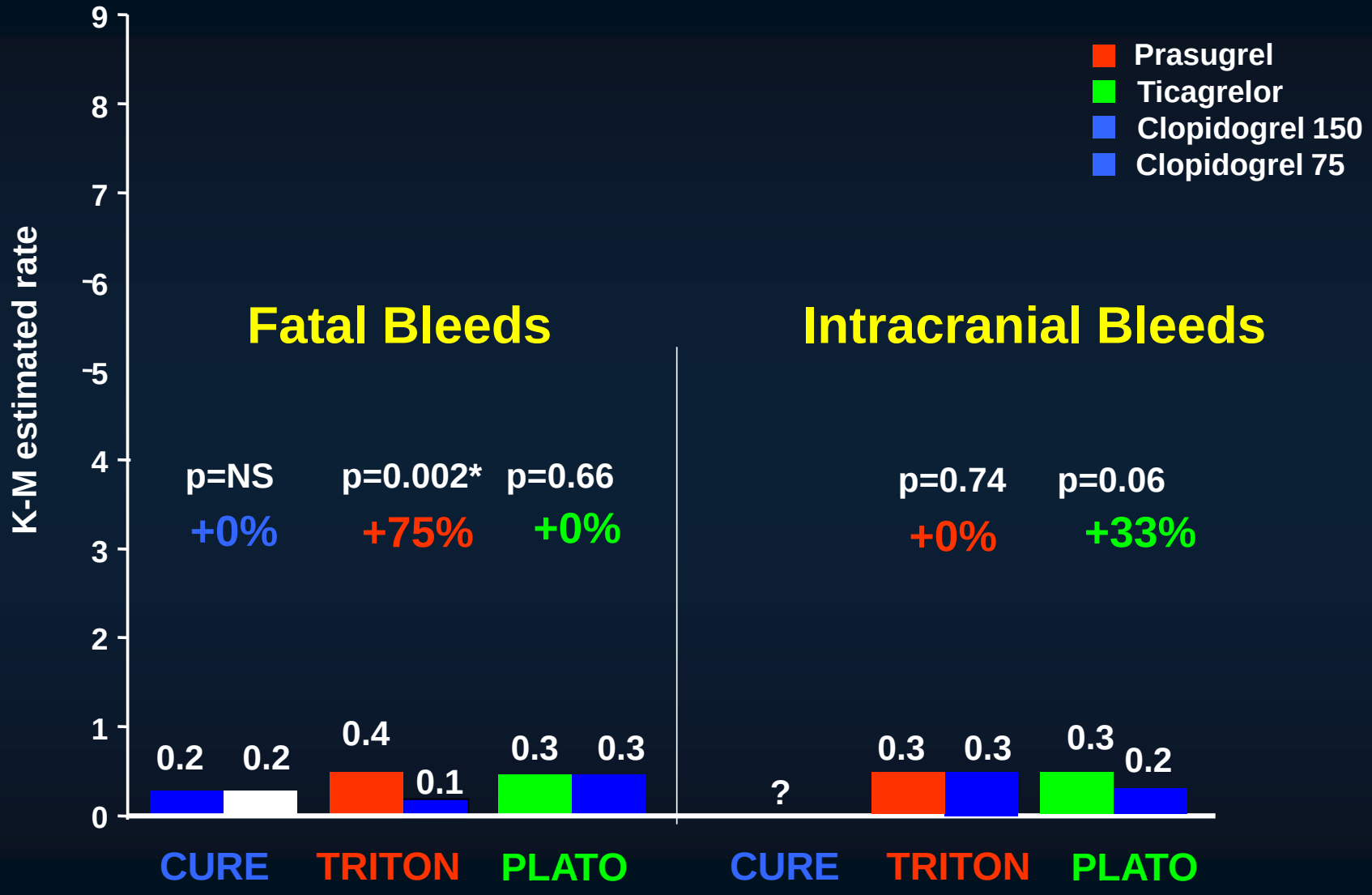
Par risque hémorragique

Safety = TIMI Major Non-CABG Bleeds (12-15 months)



Par type d’hémorragique

Safety = (12-15 months)



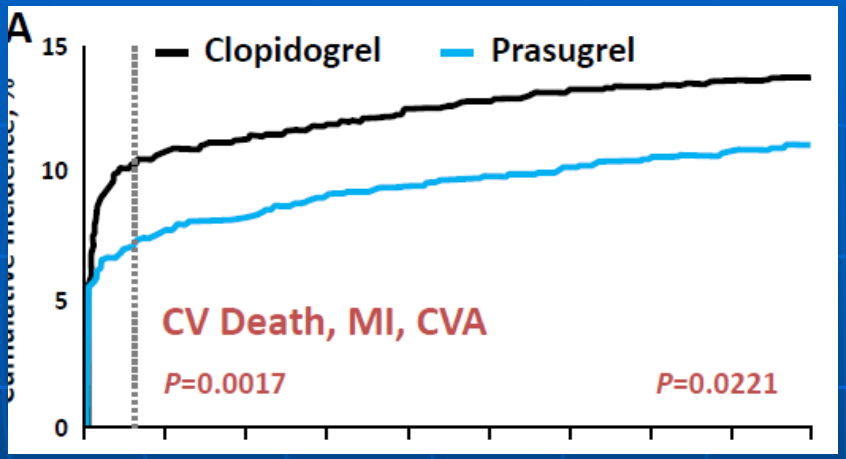
450 days

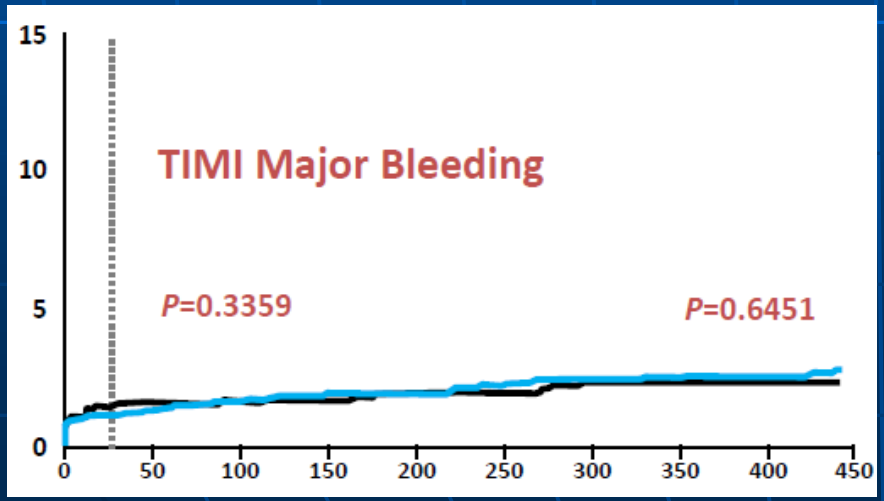
Par efficacité clinique

	Prasugrel (N = 6813)	Clopidogrel (N = 6795)	HR	P
Critères	**Nombre de patients (%)**			
Décès de causes cardiovasculaires IDM non fatal ou AVC non fatal	643 (9.9)	781 (12.1)	0.81	<0.001
Décès de causes cardiovasculaires	133 (2.1)	150 (2.4)	0.89	0.31
Thrombose de stent	68 (1.1)	142 (2.4)	0.48	<0.001

	Ticagrelor (n=9 333)	Clopidogrel (n=9 291)	HR	p
Mortalité CV + IDM + AVC	864 (9.8)	1,014 (11.7)	0.84	<0.001
Mortalité totale + IDM + AVC	901 (10.2)	1,065 (12.3)	0.84	<0.001
IDM	504 (5.8)	593 (6.9)	0.84	0.005
Mortalité CV	353 (4.0)	442 (5.1)	0.79	0.001

Par sous-groupe
ex: Prasugrel = AAP du ST+





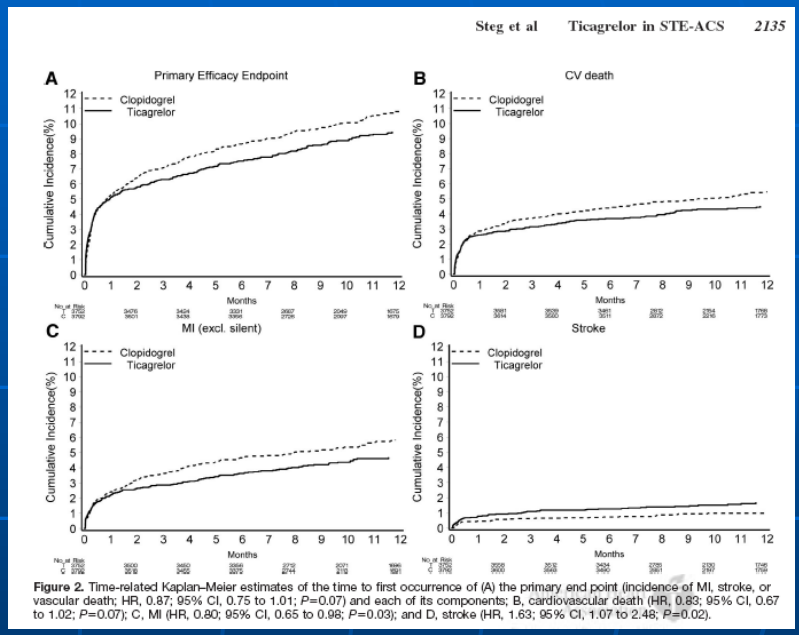


Table 3. Kaplan–Meier Estimates of Event Rates for Efficacy End Points

	Ticagrelor (n=3752), n (%)	Clopidogrel (n=3,792), n (%)	HR (95% CI)	P
Primary end point				
CV death/MI/stroke	331 (9.4)	384 (10.8)	0.87 (0.75–1.01)	0.07
Secondary end points				

Efficacy endpoints					
Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)					
All STEMI cohort	166 (9·5%)	115 (6·5%)	0·68 (0·54–0·87)	0·0017	35 (24–84)
Primary PCI	101 (8·2%)	79 (6·6%)	0·80 (0·60–1·08)	0·1440	..
Secondary PCI	65 (12·3%)	36 (6·4%)	0·50 (0·34–0·76)	0·0008	17 (12–35)

STEMI 12 h – 14 d after symptom onset (Post-STEMI)

STEMI ≤12 h after symptom onset (Primary PCI)

PRASUGREL spécifique du SCA ST+

HORS DELAI ….

Par les recommandations

Recommendations	Class [a]	Level [b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B

Dans les sous groupes spécifiés …

Par le prix

Molécules	Prix (mois)	SMR	ASMR
Kargégic	2.95	important	
Gé clopidogrel	26.09		
Clopidogrel	37.11	important	II (importante) -> III (modérée) (selon indication)
Duoplavin°	31.04	important	V (aucune)
Prasugrel	55.41	important	V (aucune)
Ticagrelor	75.78	important	IV (minime)

Prasugrel:

1) **Médicament de ACTP**
    1) **Médical =0**
    2) **Chrirgical ??**

2) Critères d'exclusion

>75 ans, <60 kg, antcdt AVC ou AIT

3) EI = 0

4) Mortalité CV=0

5) Une seule prise

Ticagrelor

1) **Médicament de**
    1) **ACTP**
    2) **TT médical**
    3) **+chirurgie**

2) Critères d'exclusion =0

3) EI= Dyspnée (10%)

4) Effet sur mortalité CV

5) 2 prises observance?

Ticagrelor:
Baisse de mortalité CV ?

Chance ?
Effet Pléiotrope ?

Effet pléiotropes du ticagrelor

- Inhibiteur réversible des PY12 donc cette molécule agit par sa concentration plasmatique et non par affinité sur le recepteur (parsugrel ou clopidogrel)
- Si la concentration est plus élevé, le ticagrelor va agir sur récepteur PY12 en dehors de la PS et donc par exemple
  - sur la paroi artérielle,
  - sur la paroi des GR.

Effet pléiotropes du ticagrelor

- Action annexe du ticagrelor= inhibition de la capture de adénosine donc [adénosine] circulant augmente
  - Action directe anti agrégante plaquettaire
  - Action directe sur vasodilatation
  - Action sur la cellule endothéliale (vasculogénèse)

Résumé

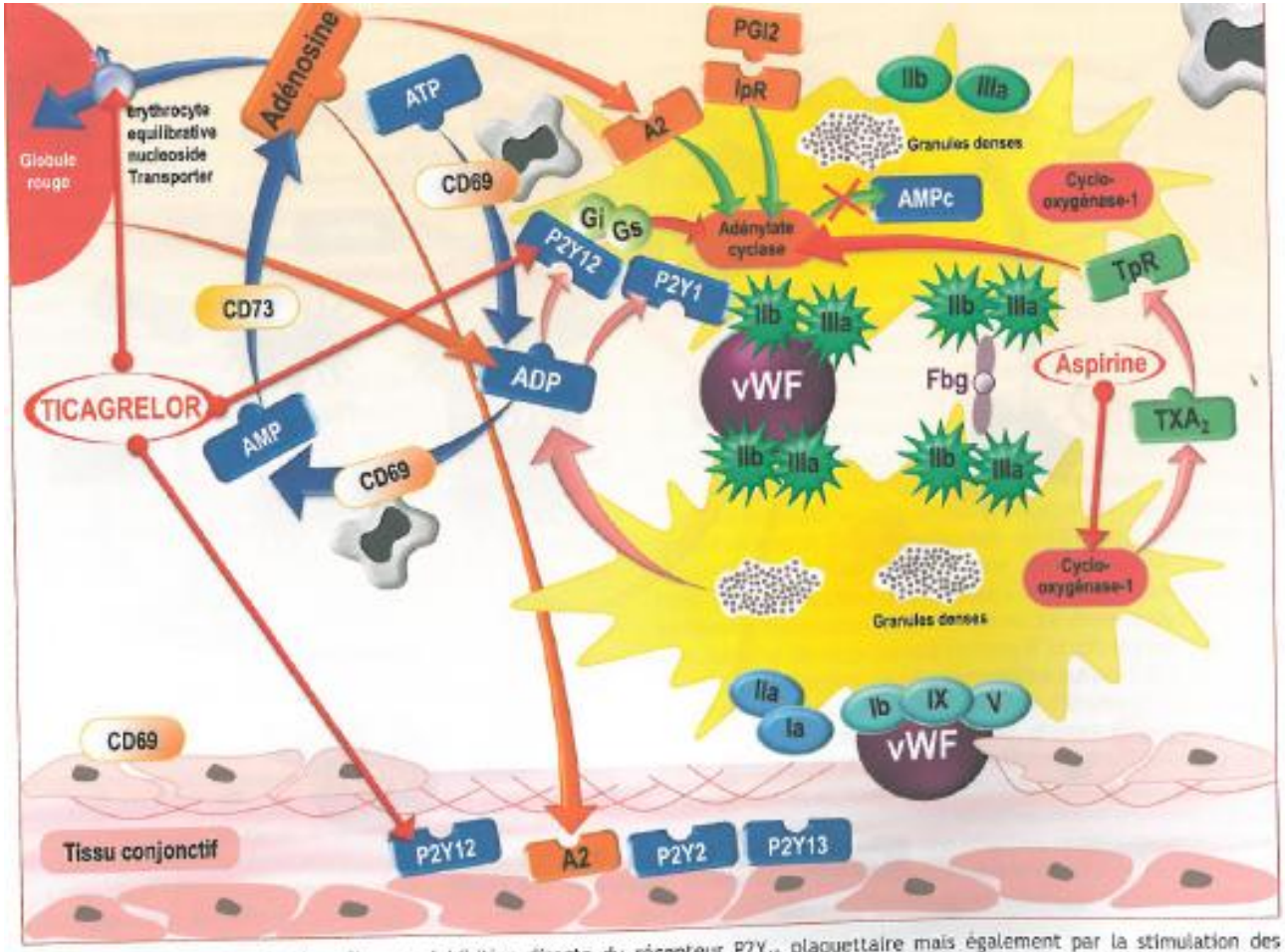


Figure 2. Mode d'action du ticagrélor par inhibition directe du récepteur $P2Y_{12}$ plaquettaire mais également par la stimulation des récepteurs plaquettaires A_{2A} et A_{2B}.

PAGANELLI et adenosine ???

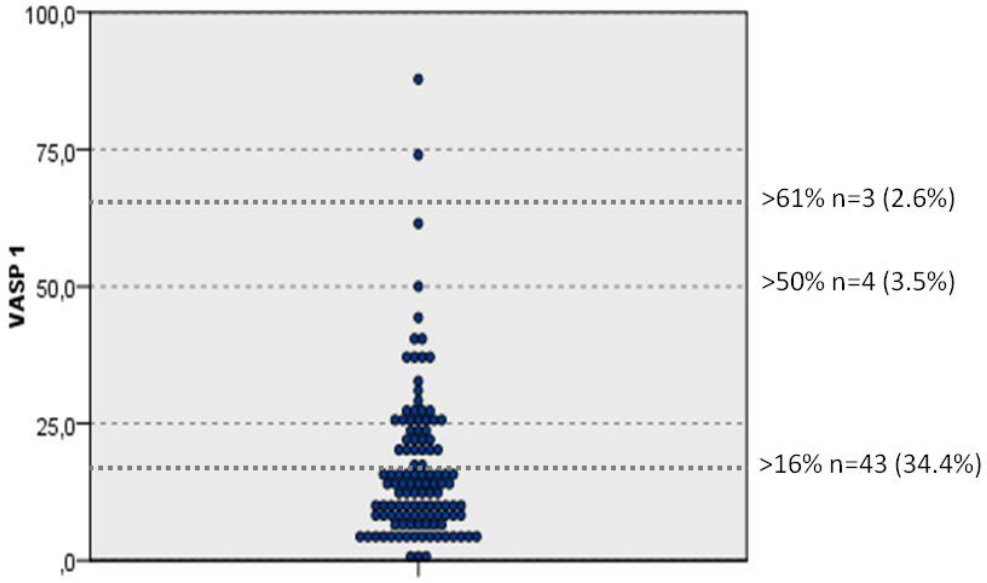
European Journal of Clinical Investigation (2000) **30**, 105–110

Effects of percutaneous transluminal coronary angioplasty on coronary adenosine concentrations in humans

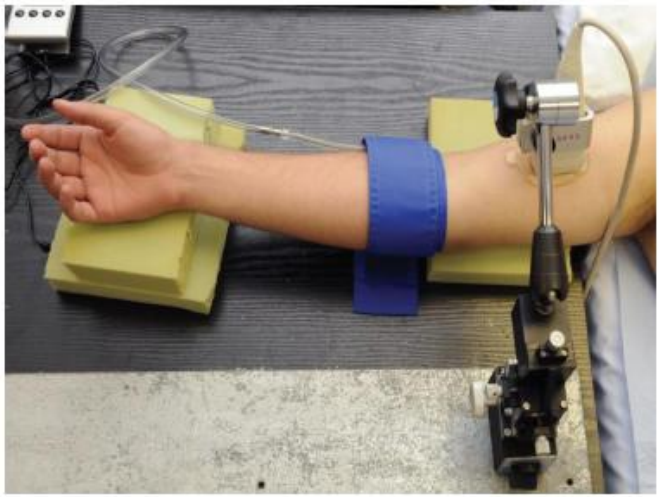
F. Paganelli[*], A. Saadjian[*], J. J. Sampol[‡], J.-M. Maixent[*], S. Levy[†‡] and R. Guieu[*]

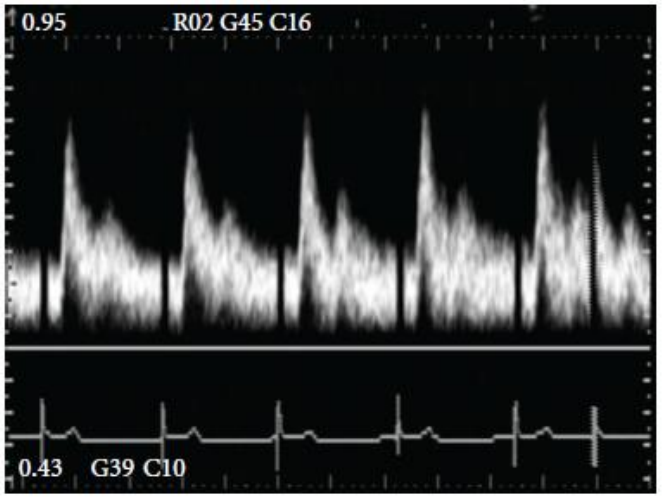
[*]Hôpital Nord, [†]UMR, CNRS 6560, Faculté de Médecine Secteur Nord, [‡]CIC Hôpital, Marseille, France

Action AAP de adénosine

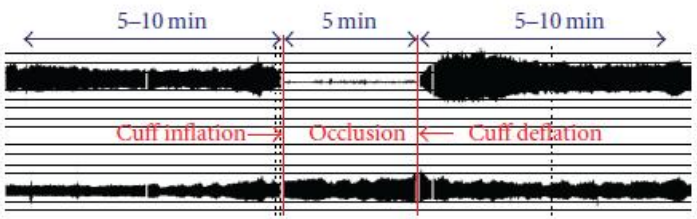


Activité vasodilatatrice de adénosine





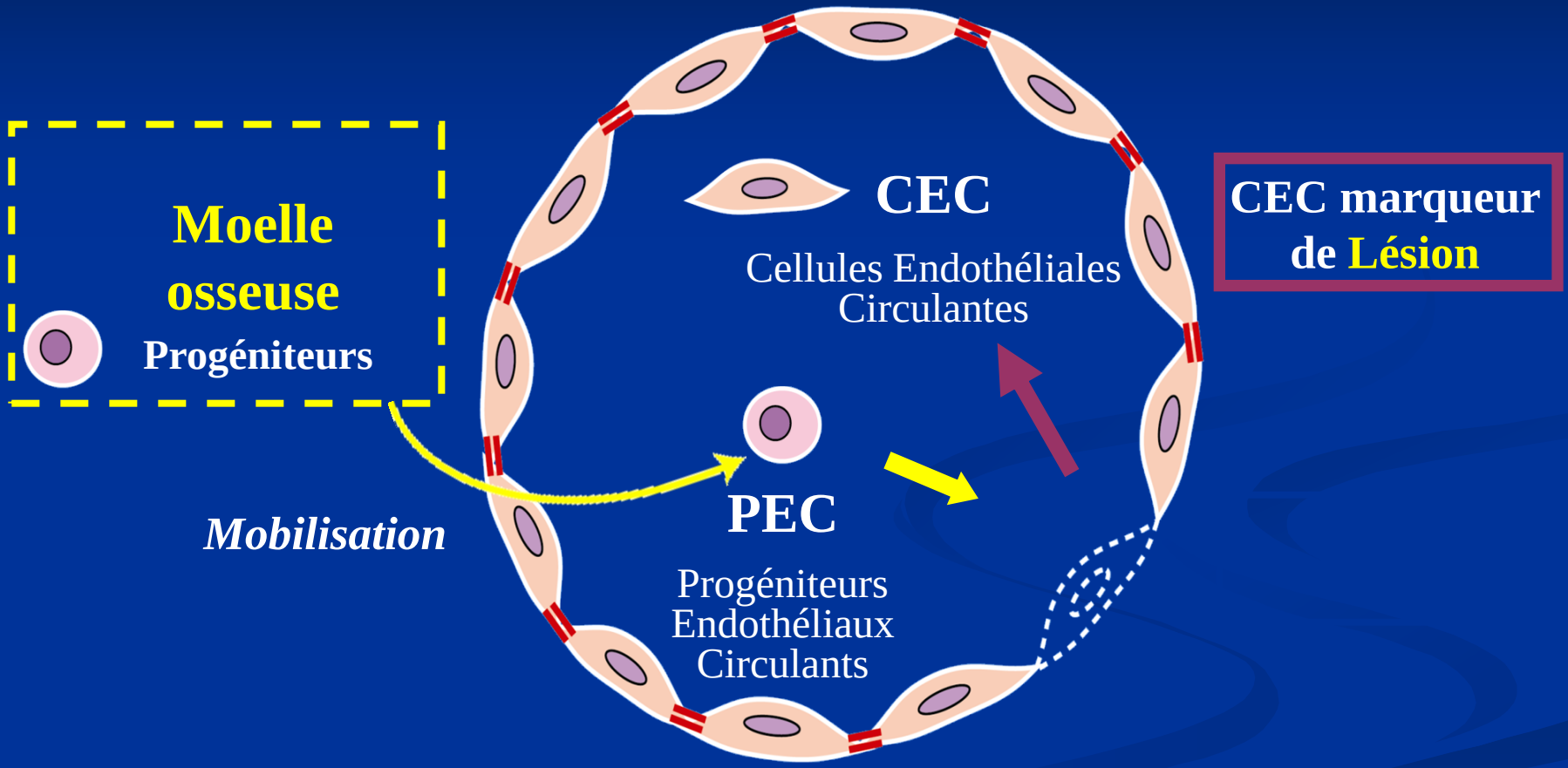
(a)



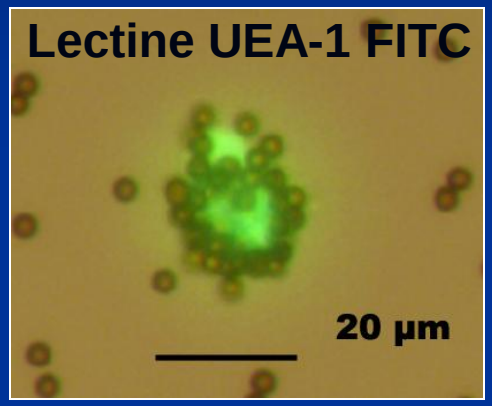
(b)

Action sur la vasculogénèse de adenosine

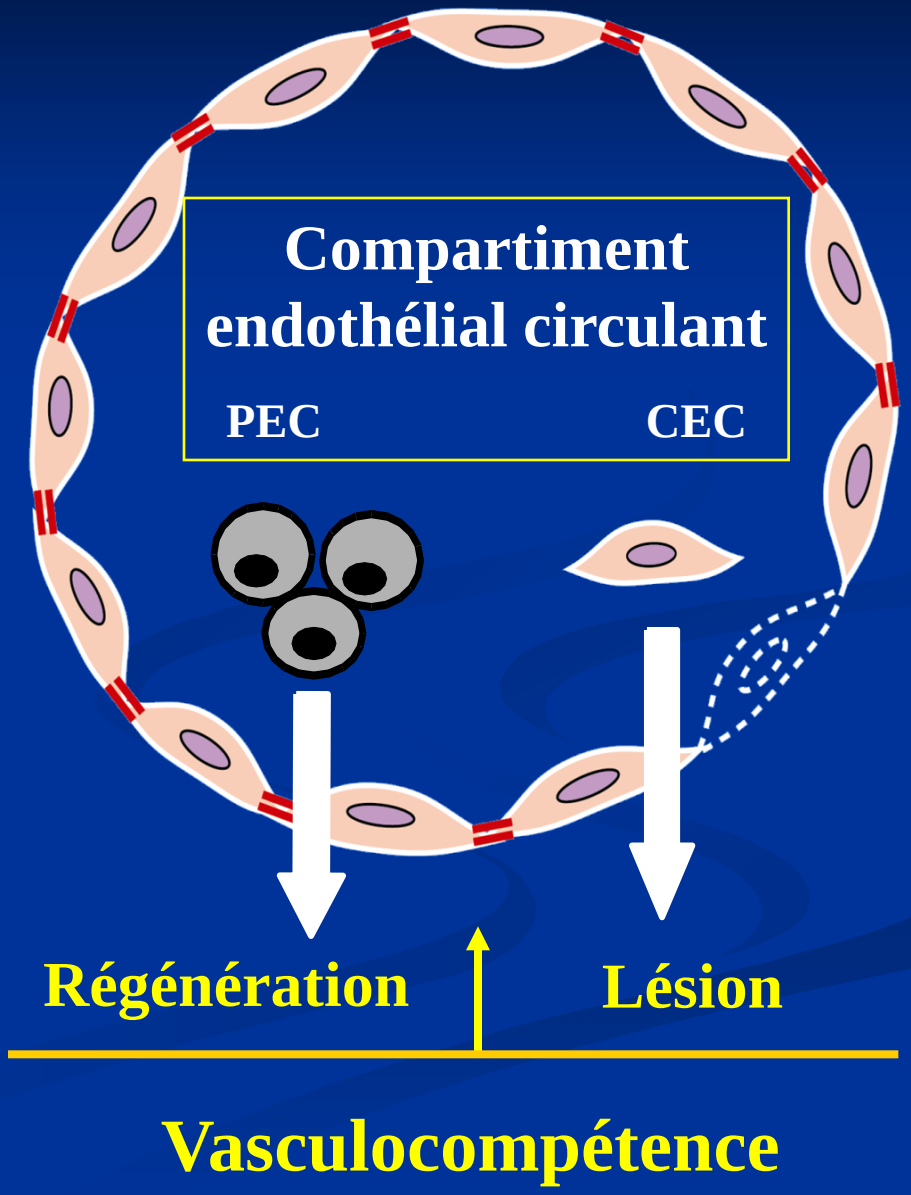
La vasculogénèse



ADENOSINE active vasculo-compétence



Cellules CD146+
isolées par IMS



Resultats 2014

SI vous m’invitez

ENCORE…