Pour le clopidogrel …

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CONFLIT D'INTERET

Journal of Thrombosis and Haemostasis, 5: 1–7 DOI: 10.1111/j.1538-7836.2007.02609.x

ORIGINAL ARTICLE

Vasodilator-stimulated phosphoprotein phosphorylation analysis prior to percutaneous coronary intervention for exclusion of postprocedural major adverse cardiovascular events

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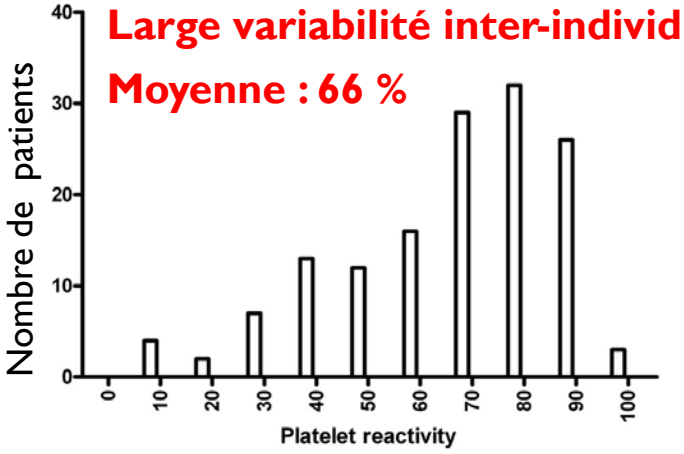
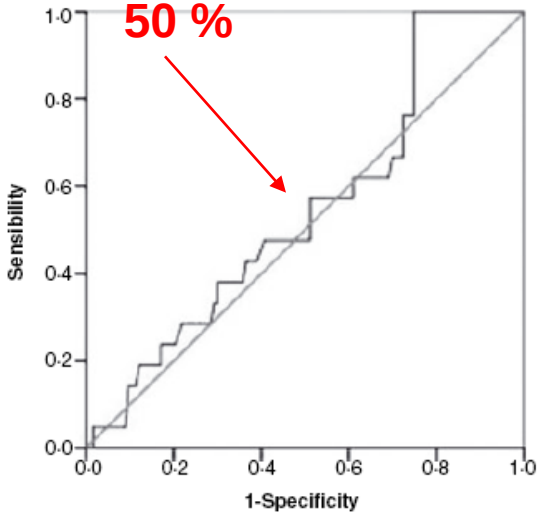
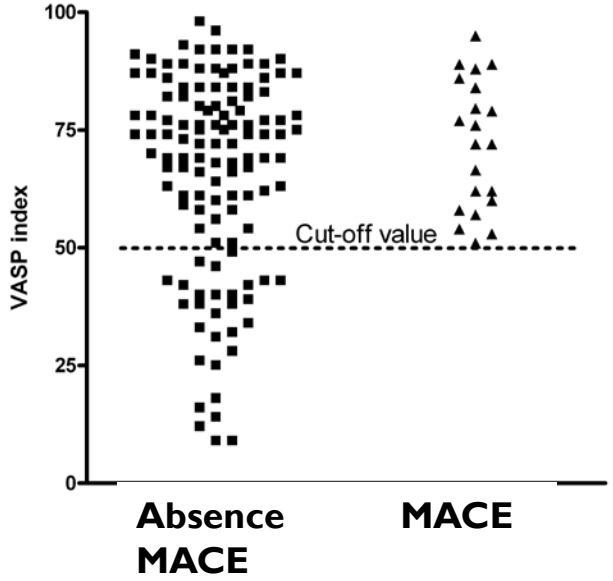
CONFLIT D'INTERET







- Résistance biologique au clopidogrel si index de phosphorylation > 50 %
- Survenue de complications thrombo-emboliques si index de phosphorylation de VASP >50 %

Bonello et al, J Thromb Haemost 2007

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doi:10.1016/j.jacc.2007.12.044

EXPEDITED PUBLICATION: LATE-BREAKING CLINICAL TRIAL

Adjusted Clopidogrel Loading Doses According to Vasodilator-Stimulated Phosphoprotein Phosphorylation Index Decrease Rate of Major Adverse Cardiovascular Events in Patients With Clopidogrel Resistance

A Multicenter Randomized Prospective Study

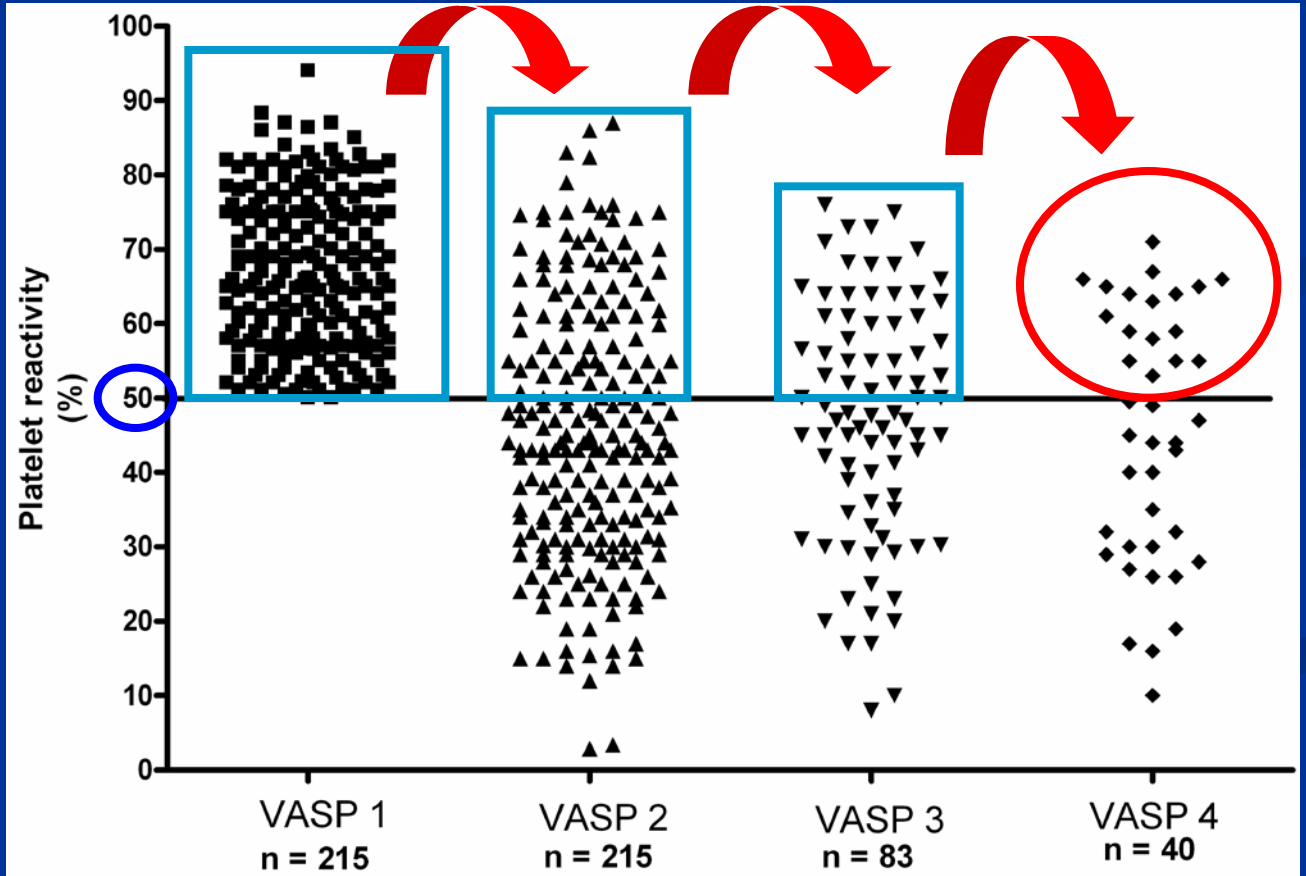
Laurent Bonello, MD,* Laurence Camoin-Jau, MD, PHD,† Stéphane Arques, MD,‡ Christian Boyer, MD,§ Dimitri Panagides, MD, PHD,‖ Olivier Wittenberg, MD,¶ Marie-Claude Simeoni, MD,# Paul Barragan, MD,** Françoise Dignat-George, MD, PHD,† Franck Paganelli, MD, PHD*

Marseille, Aubagne, and Ollioules, France

Conflit d'intérêt

VASP after first LD	66 ± 11	67 ± 10
VASP after sensitization	–	37 ± 12†

† p <0.01



17 patients (8%)

Les Thiénopyridines

- Le clopidogrel
- Le prasugrel
- Le ticagrelor (pas AMM)

Physiopathologie

Sem Vasc Med 3:113, 2003

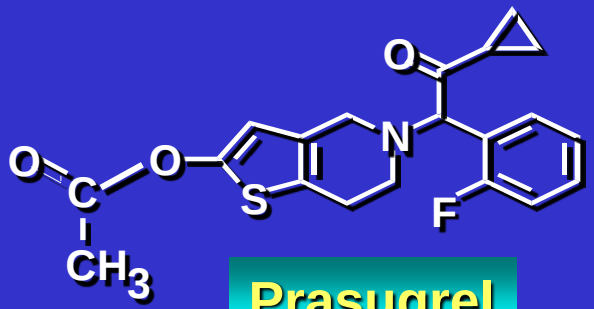
Sankyo Ann Report 51:1,1999

Clopidogrel

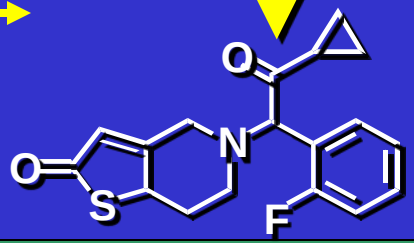
Pro-drug

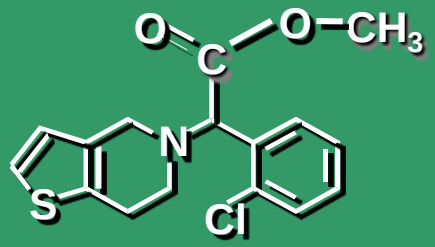
Hydrolysis
(Esterases)

85% Inactive Metabolites
(*Esterases*)



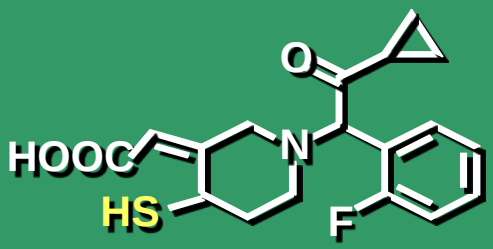
Prasugrel



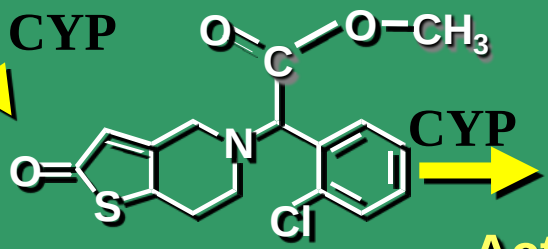


Oxidation
(Cytochrome P450)

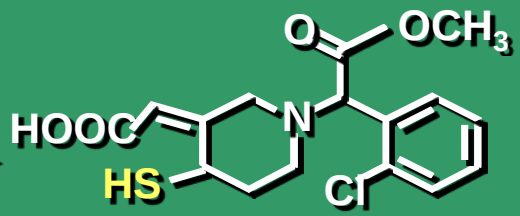
CYP



CYP



CYP



Active Metabolite

Active Metabolite

Pharmacogénétique

Absorption, mediated by intestinal efflux pump (ABCB1)

Hepatic metabolization of prodrug by P450 (CYP3A5, CYP2C19)

ADP receptor (P2RY12)

GPIIb/IIIa receptor involved in platelet aggregation (ITGB3)

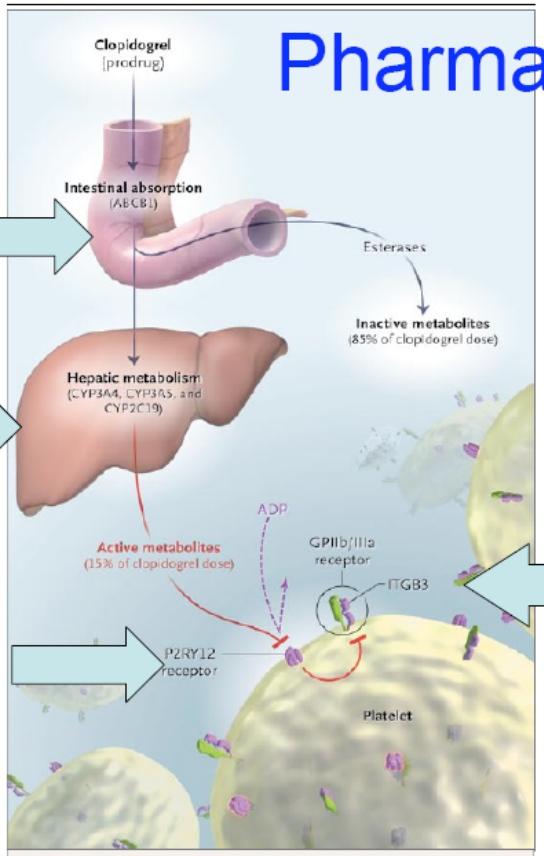


Figure 1. Roles in Clopidogrel Activity of Proteins with Known Genetic Polymorphisms.

Intestinal absorption of the prodrug clopidogrel is limited by an intestinal efflux pump P-glycoprotein coded by the *ABCB1* gene. The majority of the prodrug is metabolized into inactive metabolites by ubiquitous esterases. The minority is bioactivated by various cytochrome P450 (CYP) isoforms into active metabolites. These metabolites irreversibly antagonize the adenosine diphosphate (ADP) receptor (coded by the *P2RY12* gene), which in turn inactivates the fibrinogen receptor (the glycoprotein [GP] IIb/IIIa receptor coded by the *ITGB3* gene) involved in platelet aggregation.

N Engl J Med.
2009 Jan 22;360(4):363-75

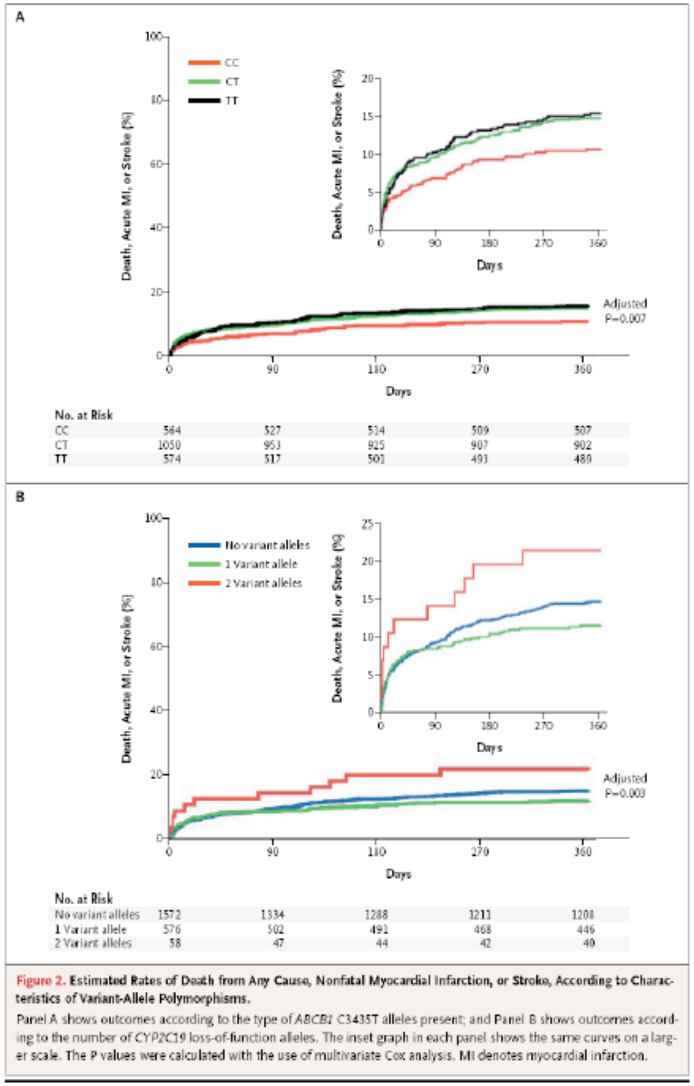


Figure 2. Estimated Rates of Death from Any Cause, Nonfatal Myocardial Infarction, or Stroke, According to Characteristics of Variant-Allele Polymorphisms.

Panel A shows outcomes according to the type of *ABCB1* C3435T alleles present; and Panel B shows outcomes according to the number of *CYP2C19* loss-of-function alleles. The inset graph in each panel shows the same curves on a larger scale. The P values were calculated with the use of multivariate Cox analysis. MI denotes myocardial infarction.

Déterminants génétiques de la réponse au clopidogrel et évènements cardiovasculaires

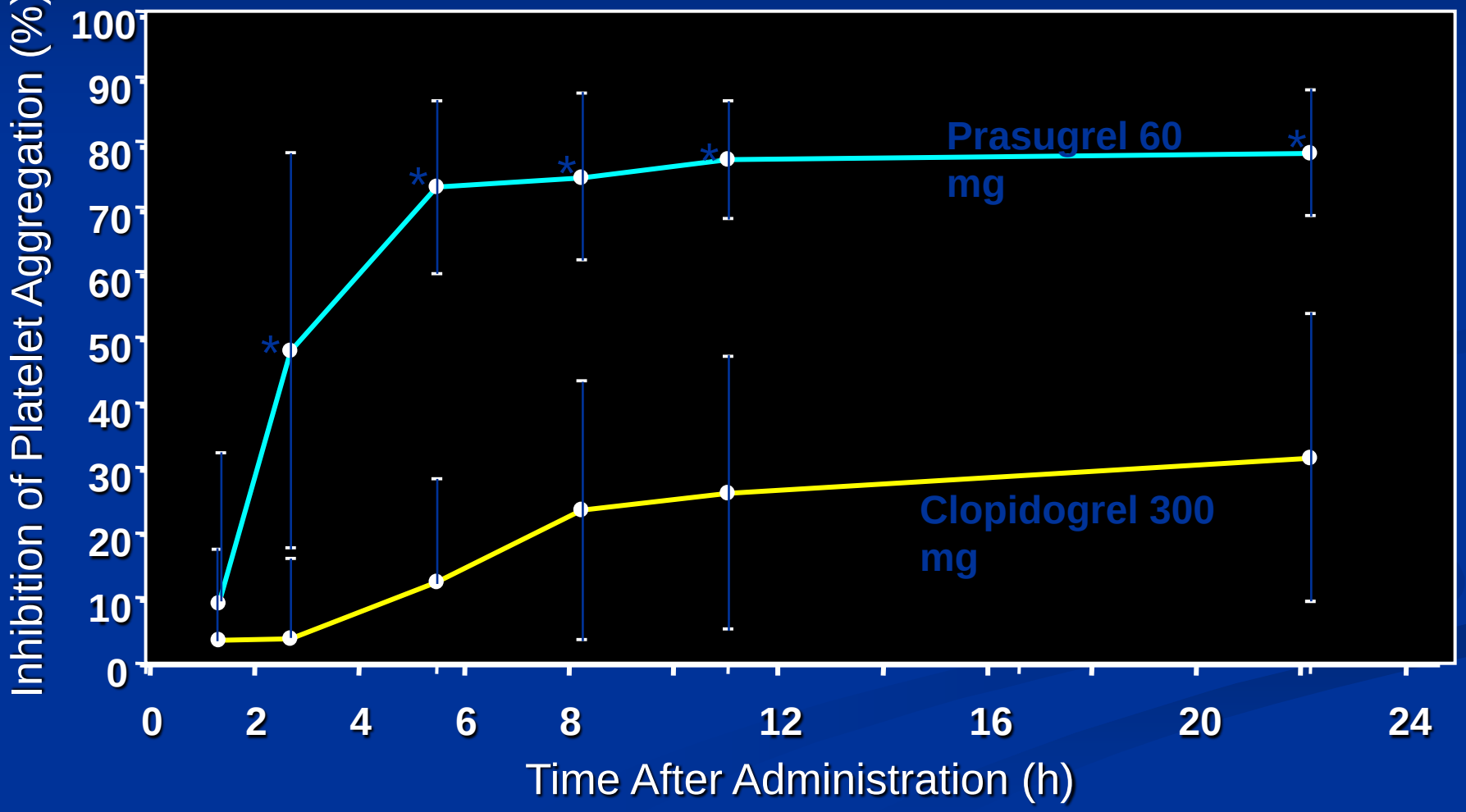
Les sujets porteurs des alllèles de perte de fonction de CYP2C19 ont un taux plus élevé de nouvel évènement cardiovasculaire que les non porteurs de ces allèles.

N Engl J Med.
2009 Jan 22;360(4):363-75

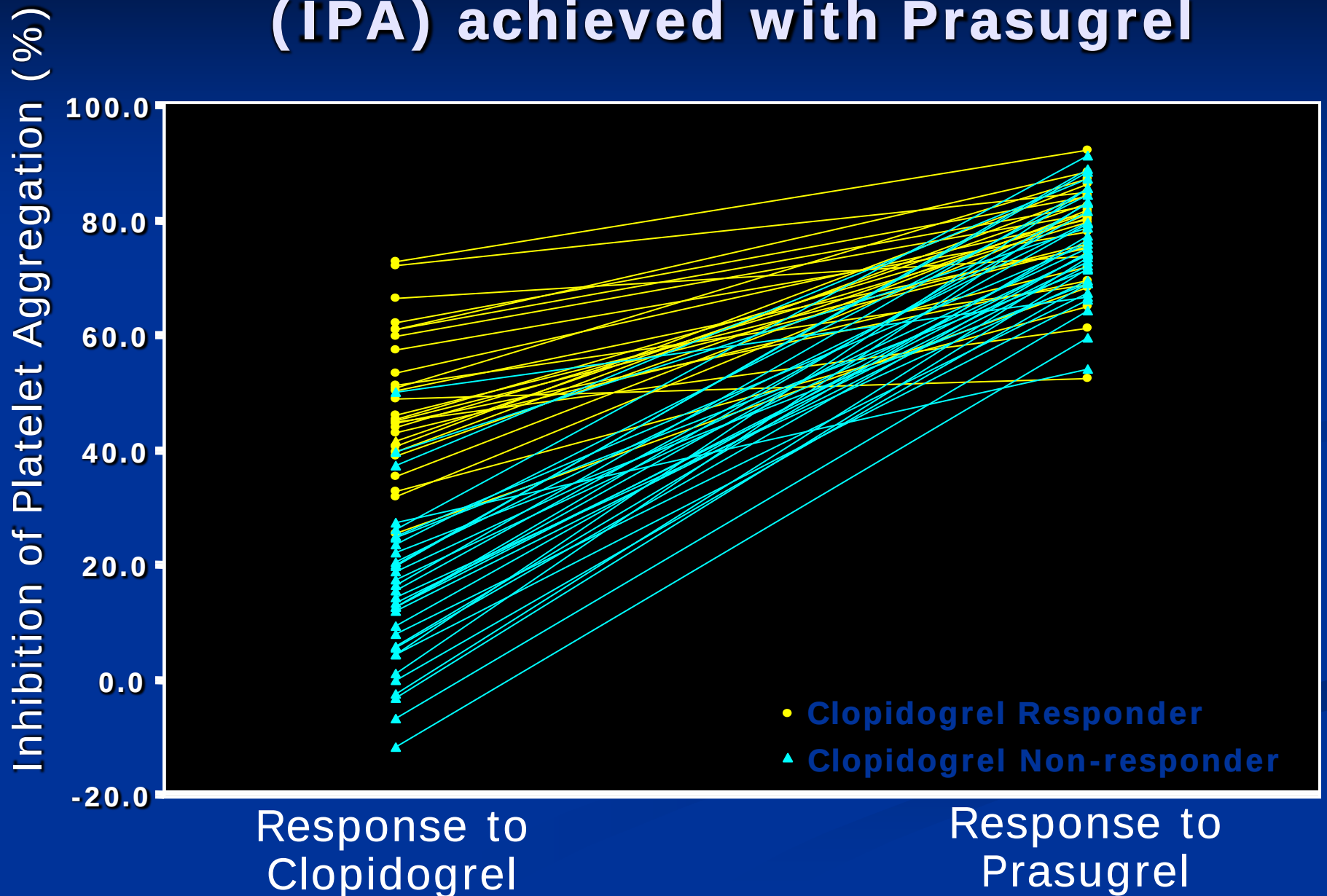
On ne soigne pas des chromozomes…

On soigne des patients…

Superior Inhibition of Platelet Aggregation (IPA) achieved with Prasugrel



Reliable Inhibition of Platelet Aggregation (IPA) achieved with Prasugrel



On ne soigne pas des tests biologiques…

On soigne des patients…

Les études cliniques

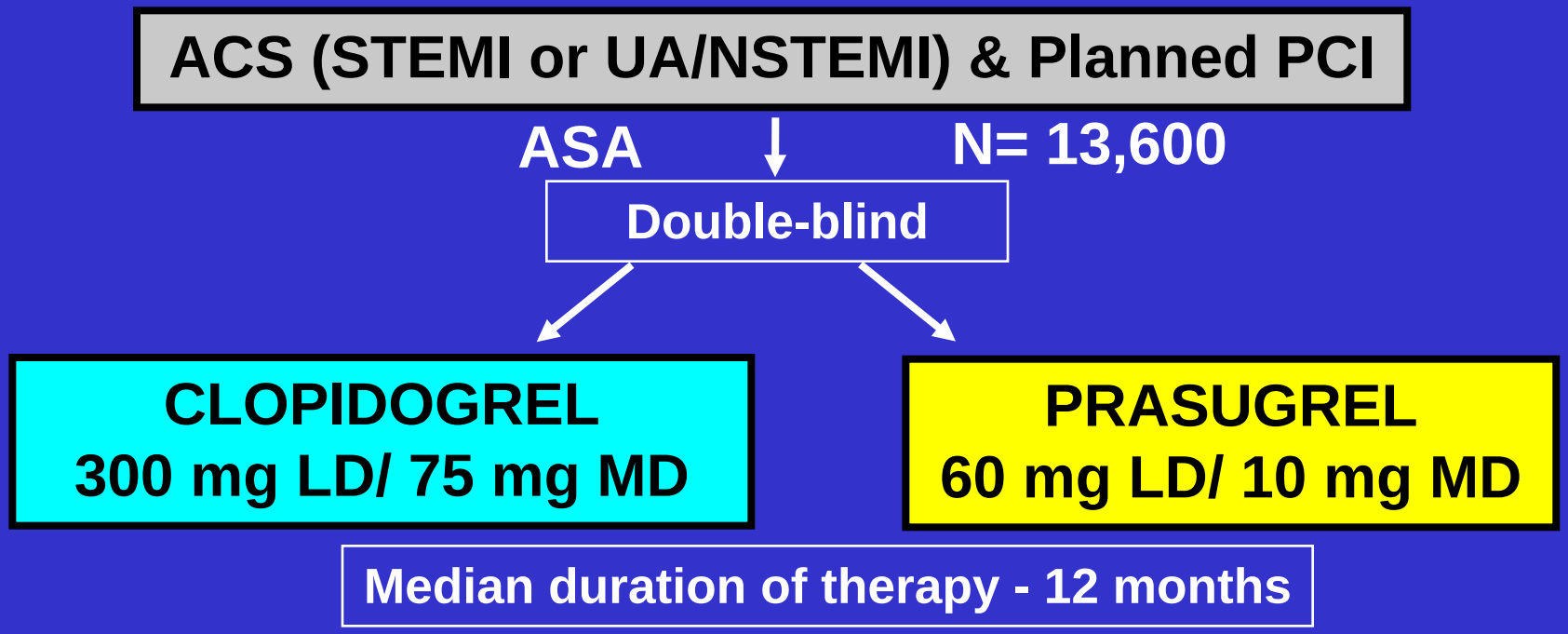
Les patients

The NEW ENGLAND JOURNAL of MEDICINE

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

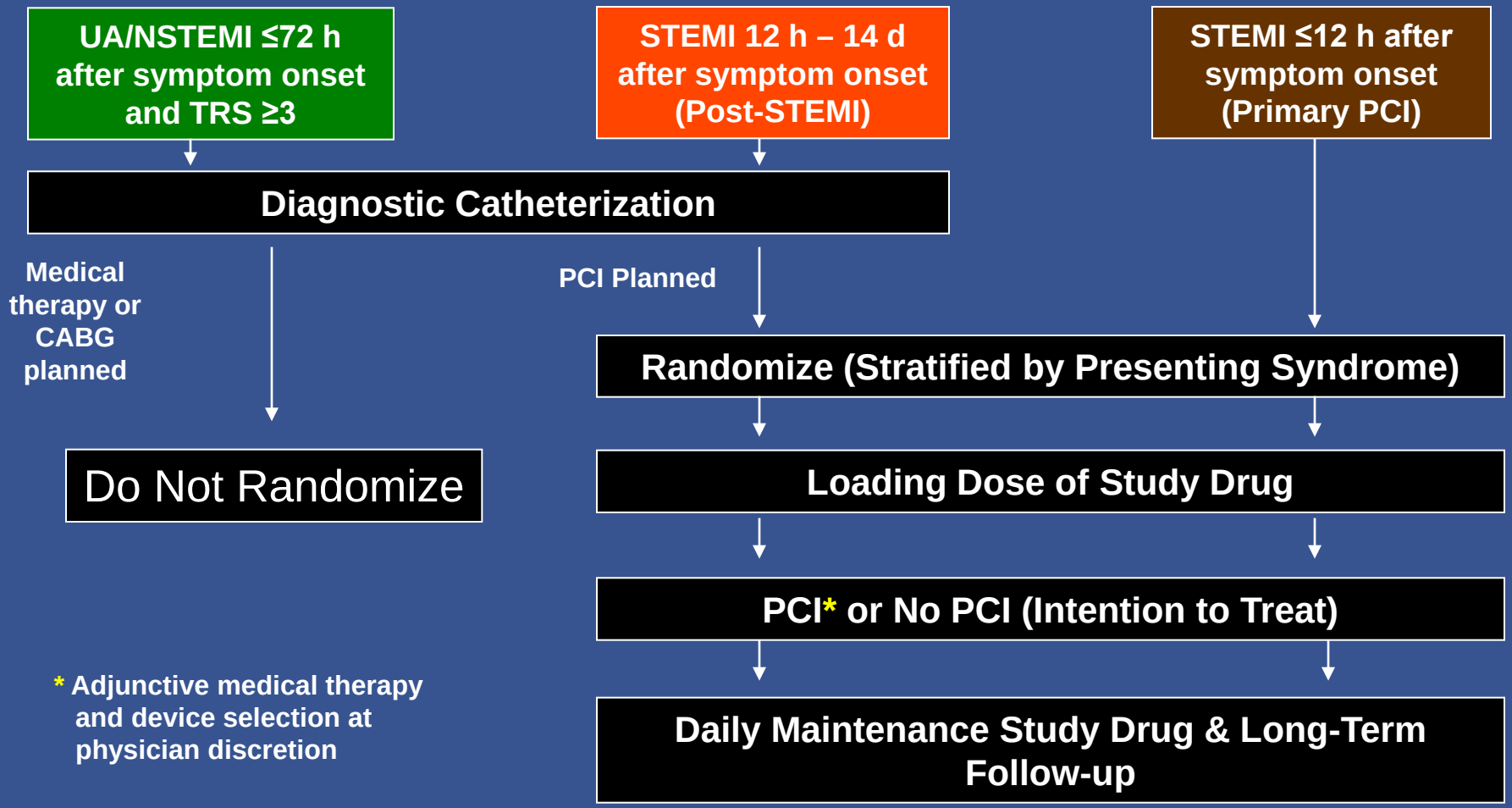
Schéma de l'étude



1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch
	CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

Pas les bonnes doses

TRITON-TIMI 38: Enrollment Evaluation



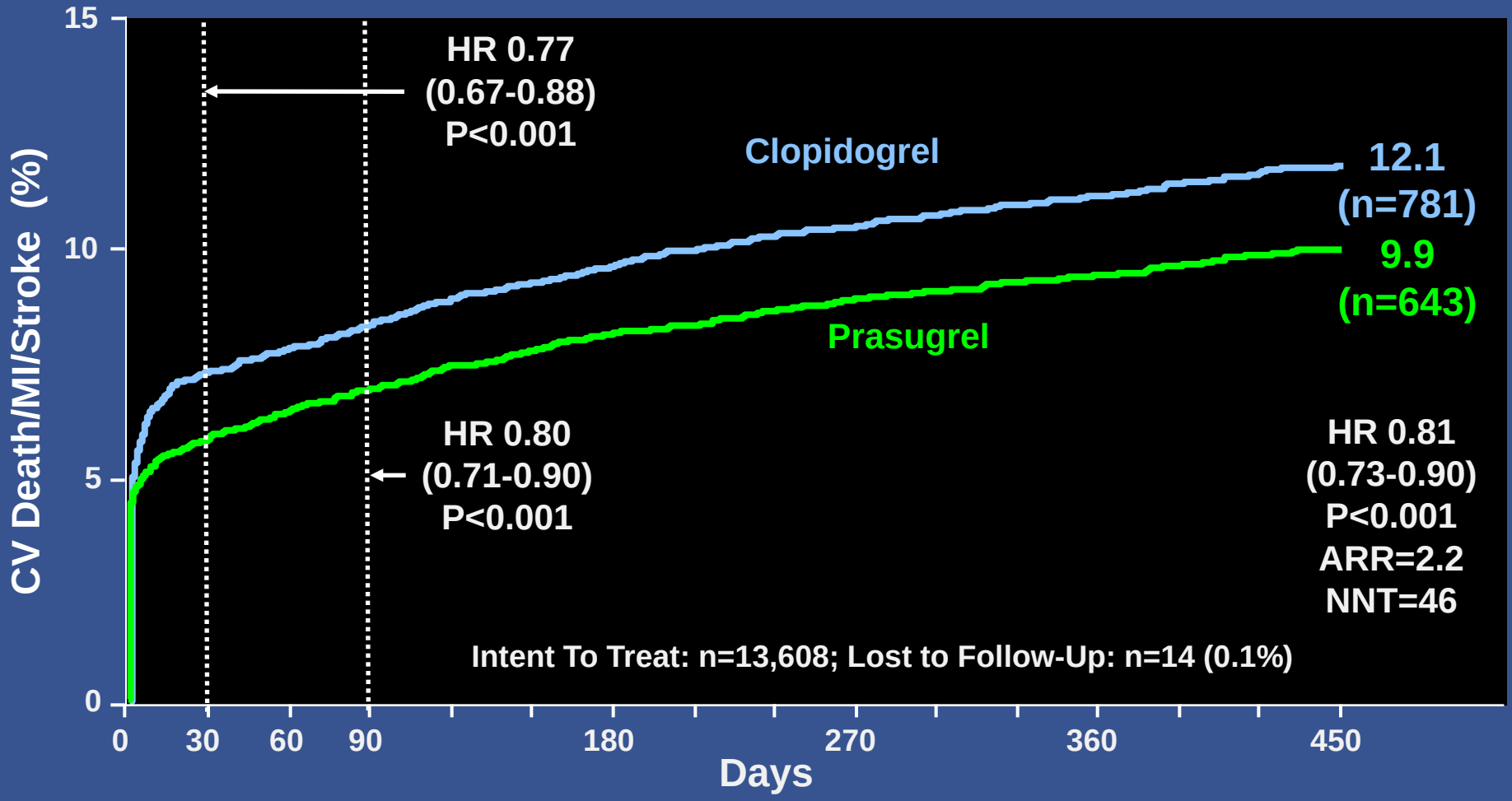
CABG=Coronary Artery Bypass Graft surgery; NSTEMI=Non–ST-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; STEMI=ST-Elevation Myocardial Infarction; TRS=TIMI Risk Score; UA=Unstable Angina

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

Clopidogrel
Médicament pour une maladie

Prasugrel
Médicament pour une technique de revascularisation

TRITON-TIMI 38: Primary End Point All ACS Population

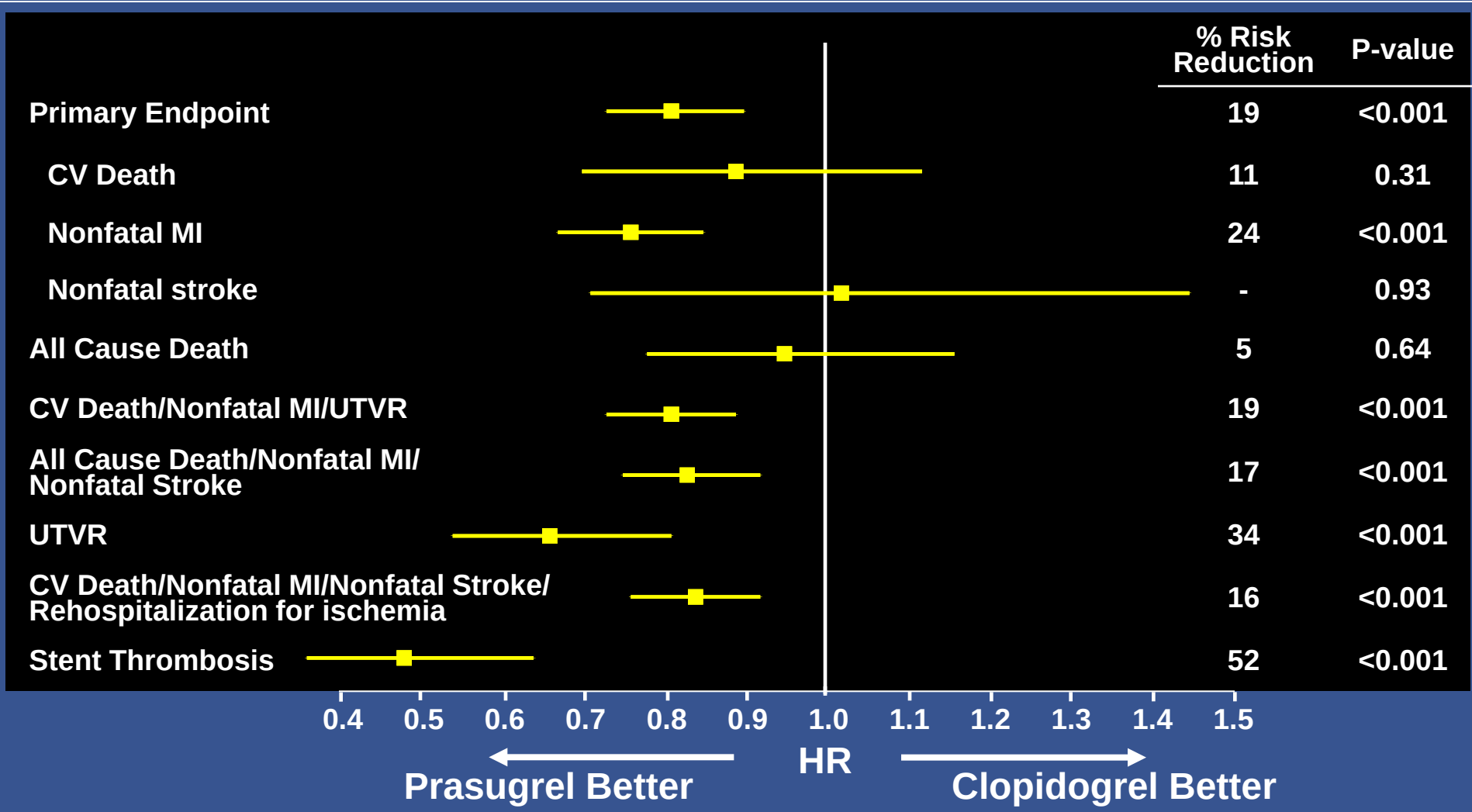


ACS=Acute Coronary Syndrome; ARR=Absolute Risk Reduction; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT=Number Needed to Treat

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

Bénéfice clinique??

TRITON-TIMI 38: Follow-up Duration for Major Efficacy End Points (All ACS)

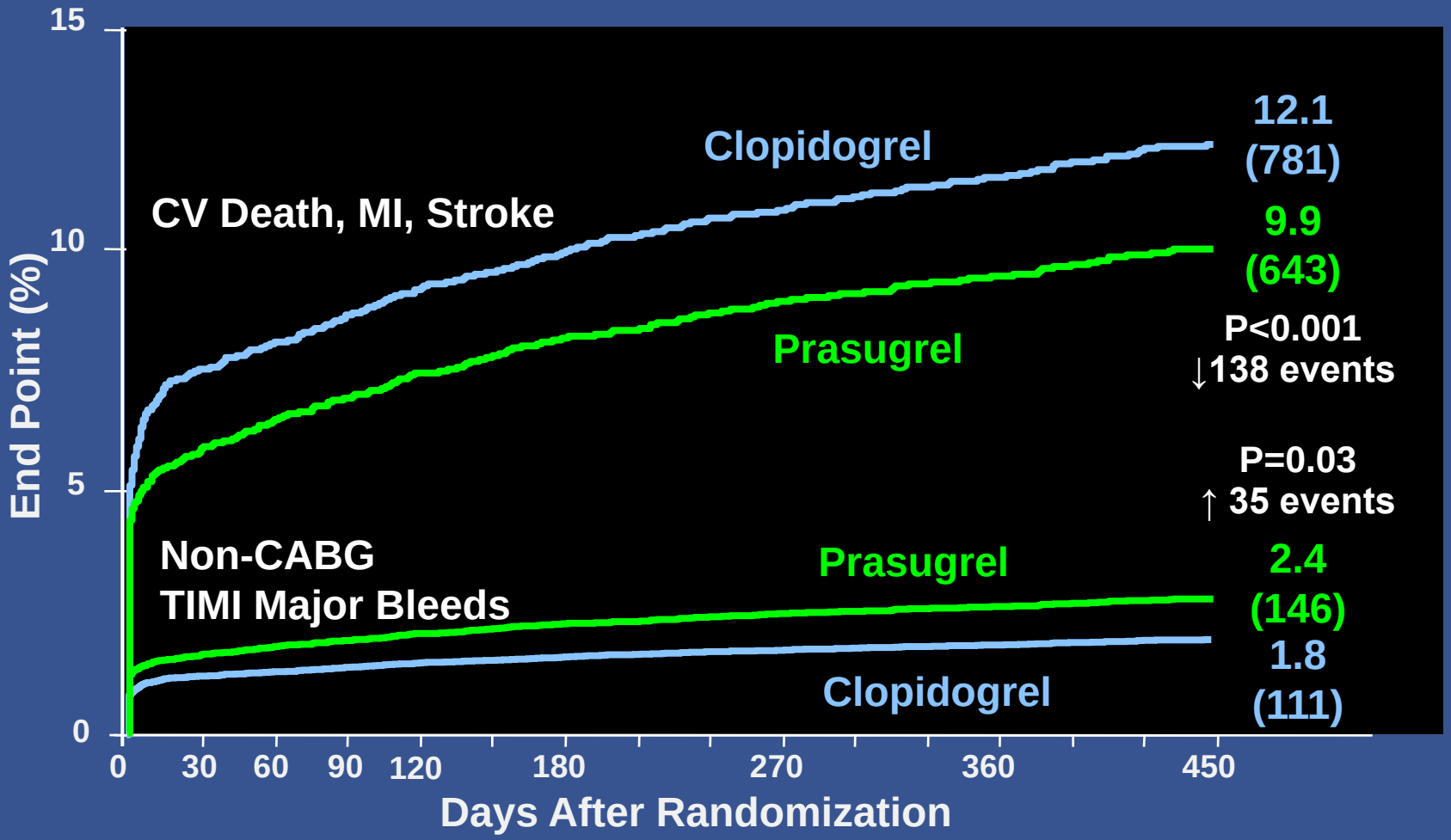


ACS=Acute Coronary Syndrome; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; UTVR=Urgent Target Vessel Revascularization

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

Bénéfice-risque??

TRITON-TIMI 38: Rates of Key Study End Points (All ACS)



CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; MI=Myocardial Infarction; TIMI=Thrombolysis In Myocardial Infarction

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

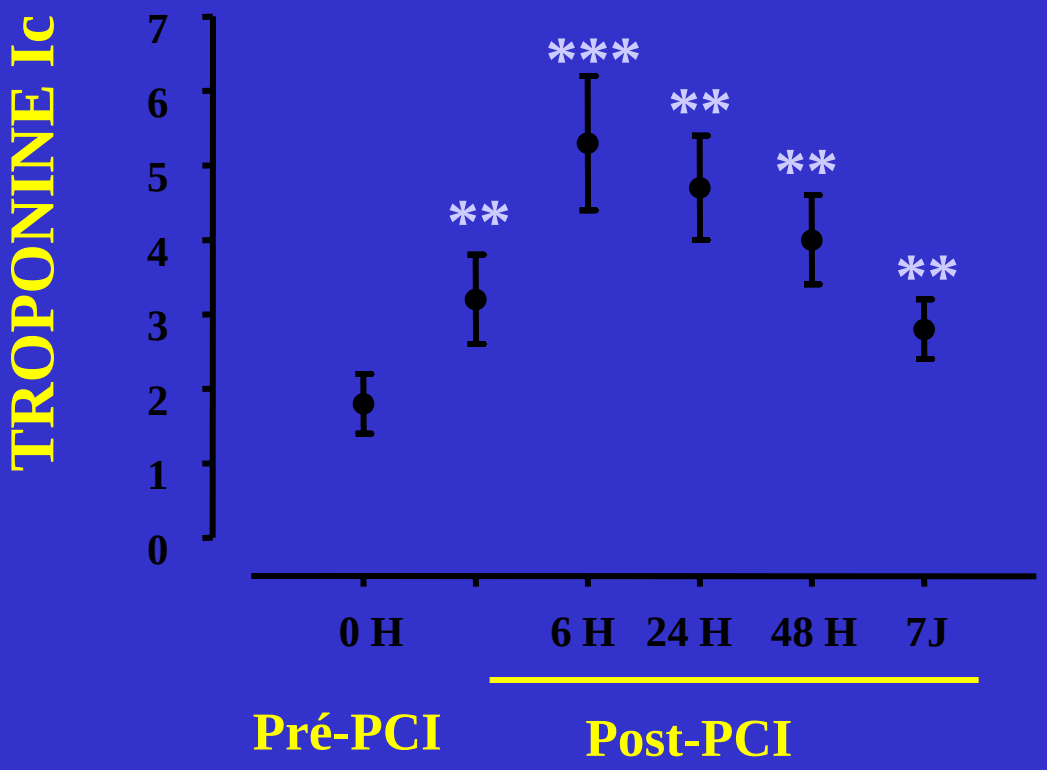
TRITON-TIMI 38: Definitions of Nonfatal Myocardial Infarction

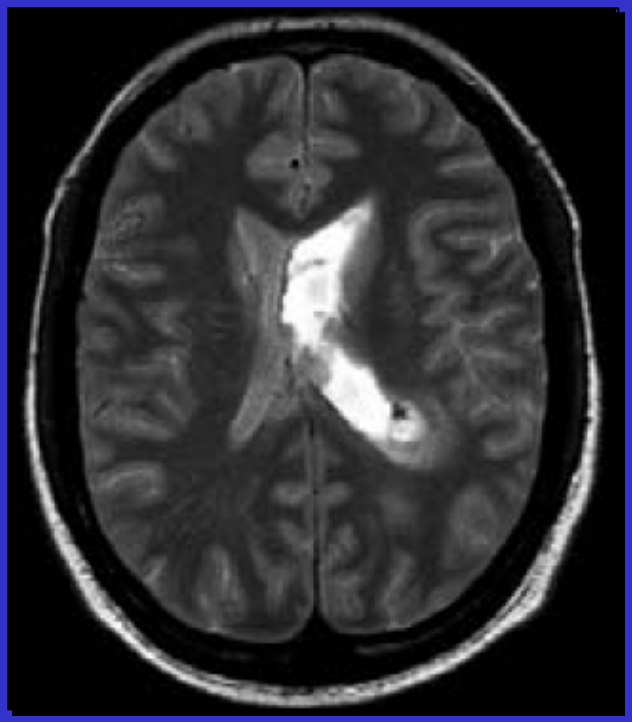
ST	♦ Re-elevation of ST-segment and one of the following: • Ischemic chest pain or equivalent >20 minutes • Hemodynamic decompensation
Spontaneous	♦ CK-MB or troponin > ULN and one of the following: • Ischemic chest pain (or anginal equivalent) >20 minutes • ST-segment deviation 1 mm or more in one or more leads
PCI	♦ CK-MB >3 times ULN on 2 samples post-PCI, or 5 times ULN on 1 sample if it is the final sample and more than 12 h post-PCI
CABG	♦ CK-MB is >10 times ULN on 1 sample after CABG
New Q Waves	♦ 0.04 seconds or longer, or pathology distinct from prior MI

CK-MB=Creatine Kinase-Myocardial Band; CABG=Coronary Artery Bypass Graft surgery; MI=Myocardial Infarction; PCI=Percutaneous Coronary Intervention; ULN=Upper Limit of Normal

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

Que voulez-vous ?





Mauvaise dose

mais aussi mauvais Timing

Mais que faire après un an??

Articles

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

*CAPRIE Steering Committee**

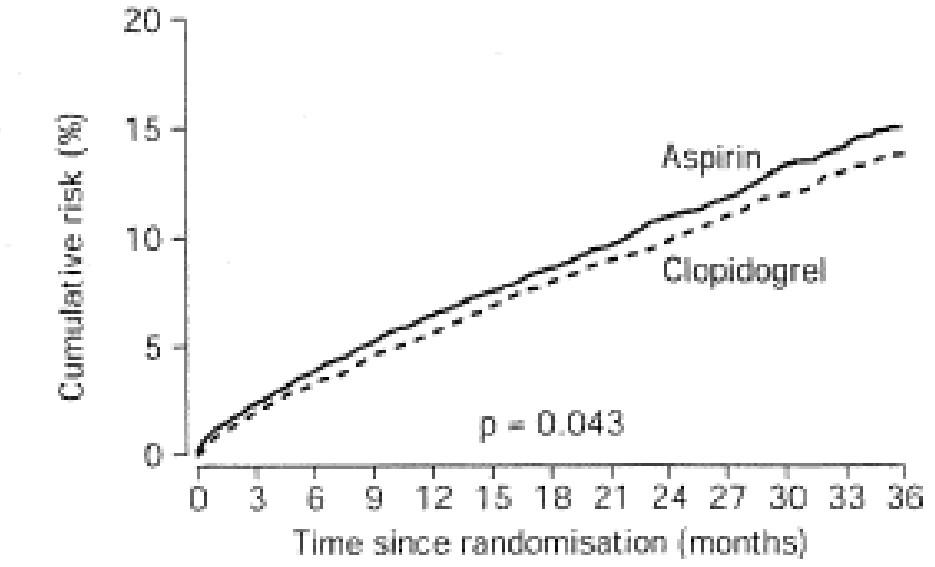
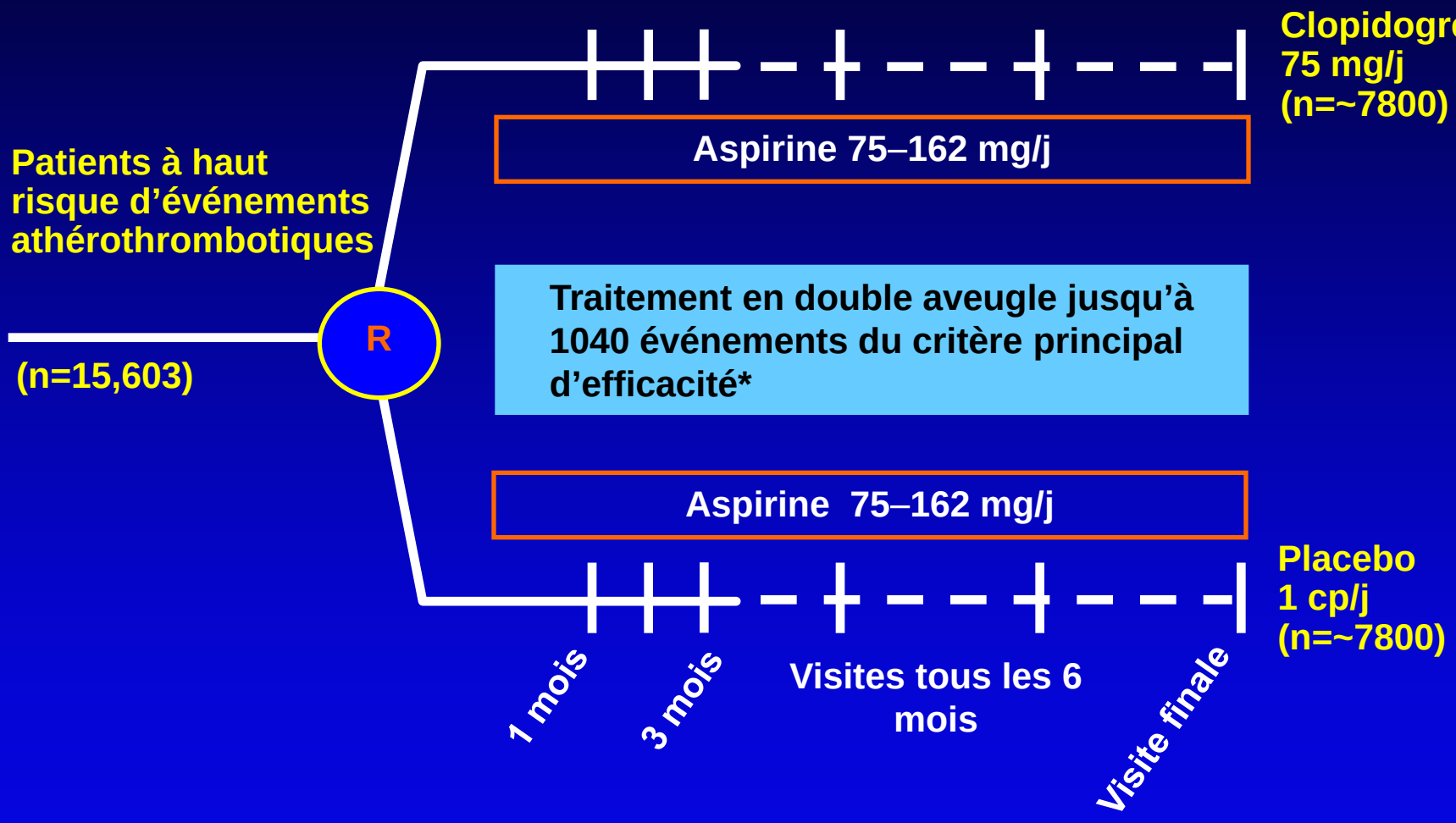


Figure 3: **Cumulative risk of ischaemic stroke, myocardial infarction, or vascular death**
A=aspirin; C=clopidogrel.

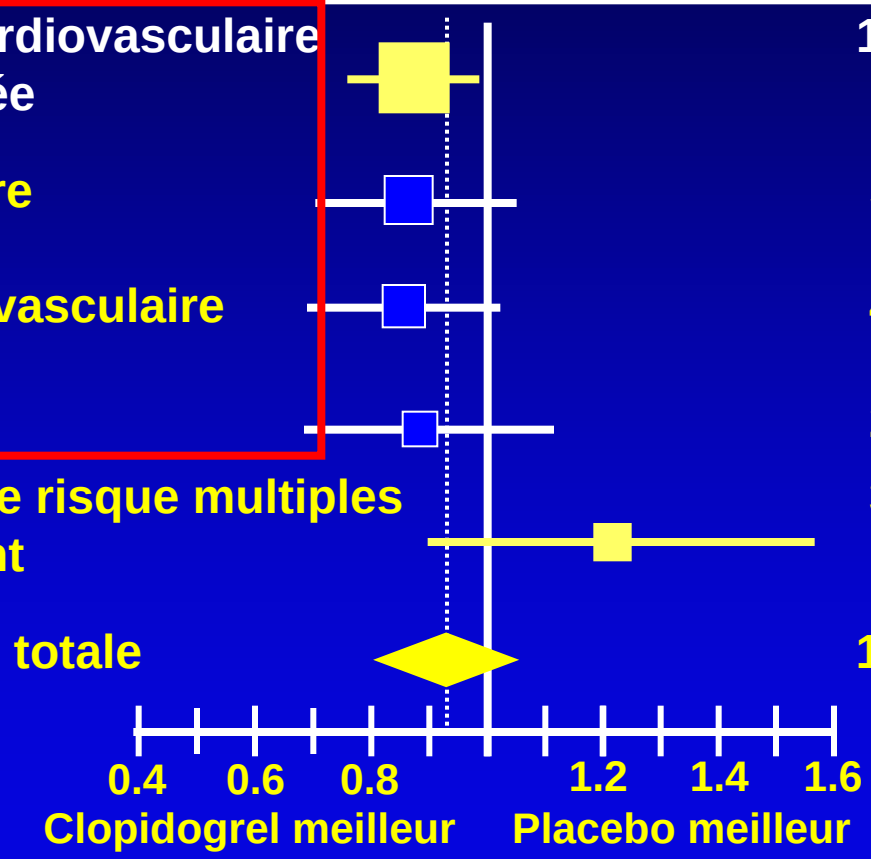
Schéma de l'étude

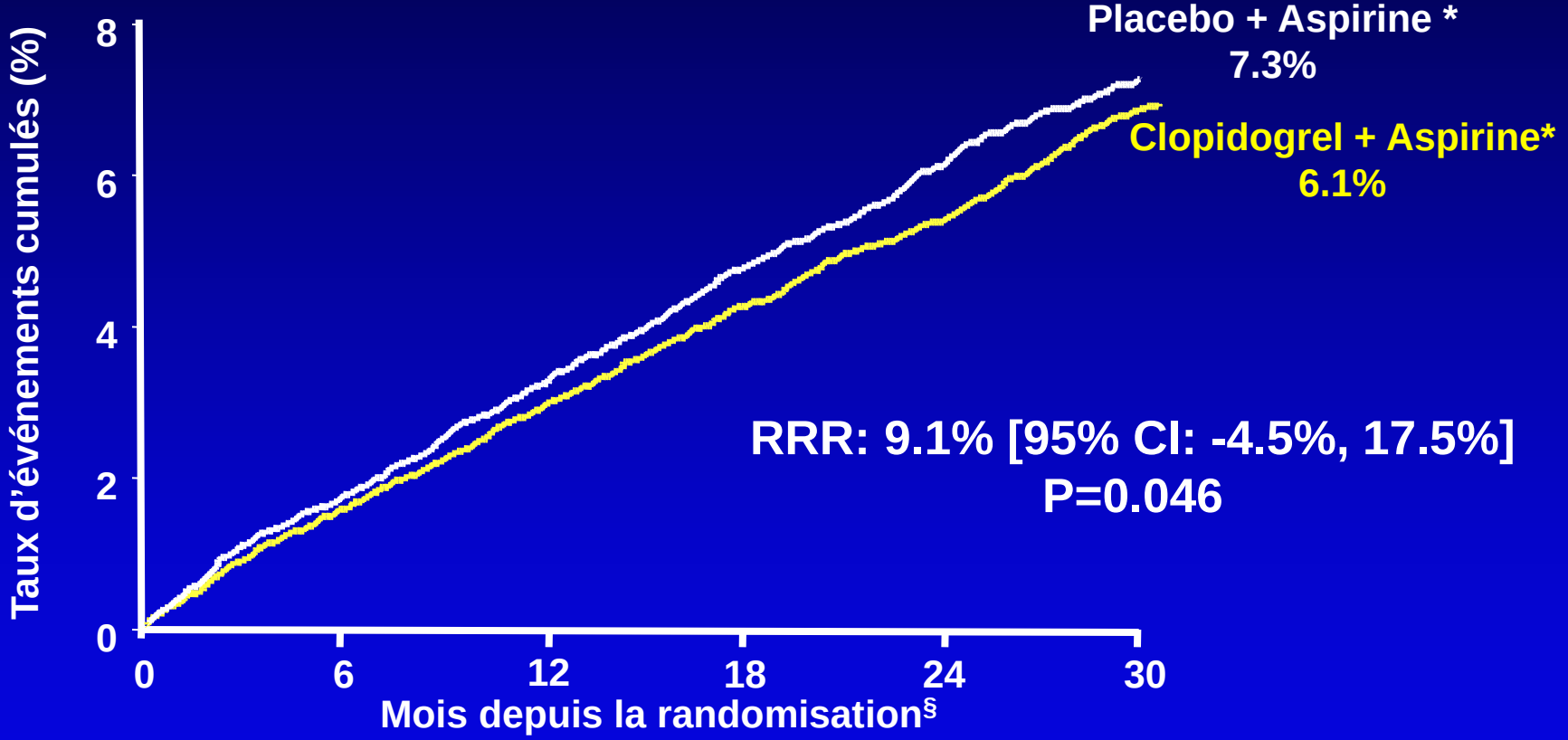


*décès cardiovasculaire,IDM non-fatal ou AVC non-fatal;
event-driven trial; R=randomization

Critère principal (IDM/AVC/Décès CV) selon les sous-groupes d'inclusion

Population	N	RR (IC 95%)	p
Maladie cardiovasculaire documentée	12,153	0.88 (0.77, 0.998)	0.046
Coronaire	5,835	0.86 (0.71, 1.05)	0.13
Cérébrovasculaire	4,320	0.84 (0.69, 1.03)	0.09
AOMI	2,838	0.87 (0.67, 1.13)	0.29
Facteurs de risque multiples uniquement	3,284	1.20 (0.91, 1.59)	0.20
Population totale	15,603	0.93 (0.83, 1.05)	0.22





† Première survenue d'événement: IDM (fatal ou non fatal), AVC (fatal or non fatal), ou décès CV
*Tous les patients ont reçu de l'aspirine à la dose de 75-162 mg/j

Mais que faire après un an??

- Clopidogrel au moins 3 ans (CAPRIE, CHARISMA….)

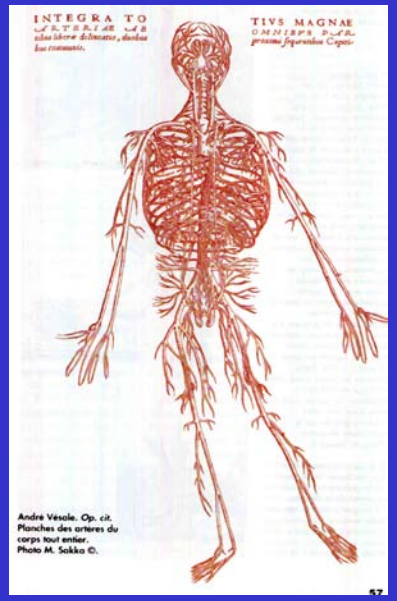
- Prasugrel ?????????

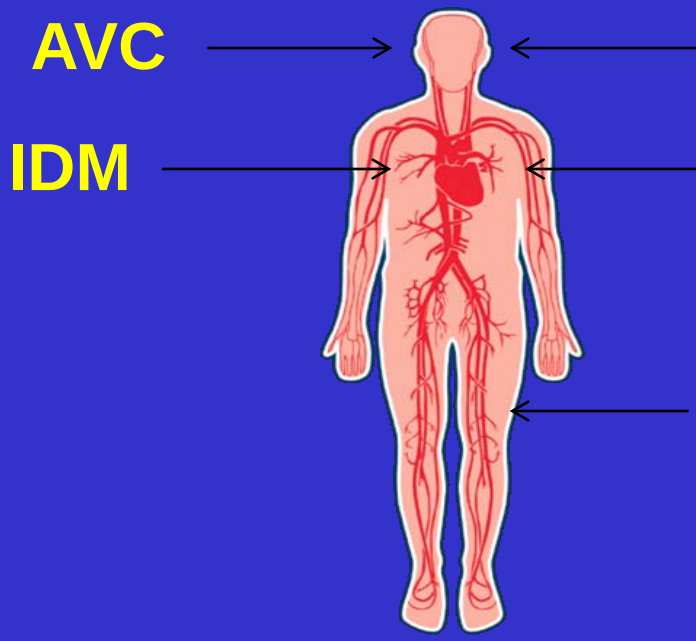
Nous sommes tous diplômés ….

En pathologie cardio-VASCULAIRE …….

VASCULAIRE !!!!!!!!!

4 000 km de long





Angor:
- Stable
- Instable

AOMI:
- Claudication
- Douleurs de repos
- Gangrène
- Necrose

Nous sommes des spécialistes de la pathologie cardio-vaculaire

- Pas des généticiens
- Pas des hématologues
- Pas des coronarographistes
- Pas des neurologues

Et donc nous prescrivons du clopidogrel

ASMR prasugrel 5

ASMR clopidogrel 2