QUE FAUT-IL SAVOIR DU TRAITEMENT PRE-HOSPITALIER DU SCA?

NAIT-SAIDI Lyassine
Cardiologie interventionnelle
CHI Toulon la Seyne sur Mer

Conflits d'intérêt

- Astra-Zeneca, Boehringer Ingelheim, MDS, Pfizer, Novartis Lilly, Daïchi Sankyo, Sanofi aventis

- Hexacath, Boston Scientific, B.Braun, Abbot Vascular, Biotronik, Medtronic, Bolton, Medecine Compagny, St jude Medical, Teleflexe.

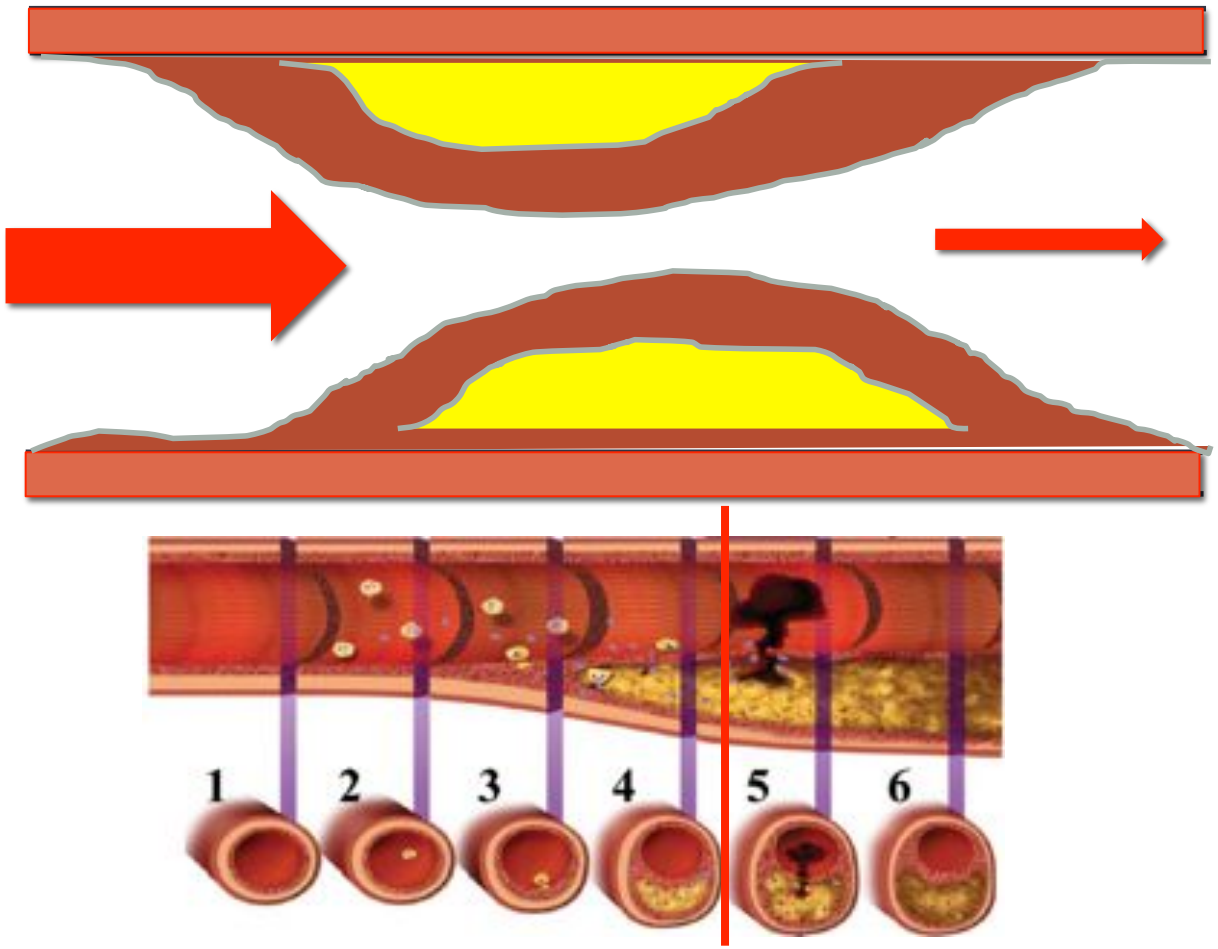
Savoir de quoi on parle

Différencier un syndrome coronaire aigu d'une douleur thoracique.

- Toute douleur thoracique n'est pas une douleur angineuse
- Toute douleur angineuse n'est pas un syndrome coronaire aigu.

- Le syndrome coronaire aigu est un continuum allant du SCA non ST+ au SCA ST+

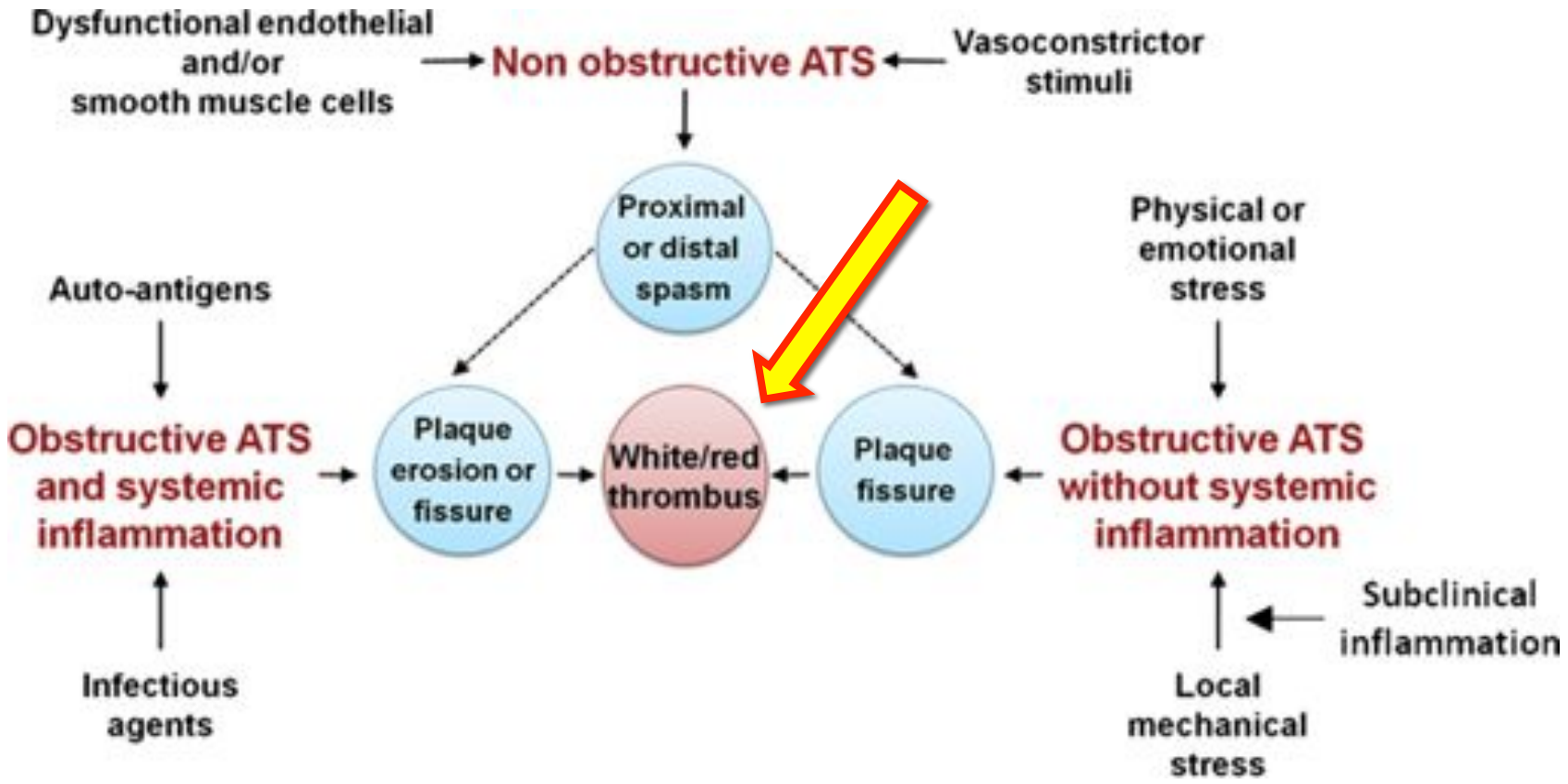
Angor stable



Peter Libby Circulation 2001; 104:365

- La chape fibreuse est épaisse
- Pas de rupture de plaque
- Pas d'activation de la coagulation
- Pas d'activation de l'agrégation plaquettaire

A new pathogenetic classification of ACS



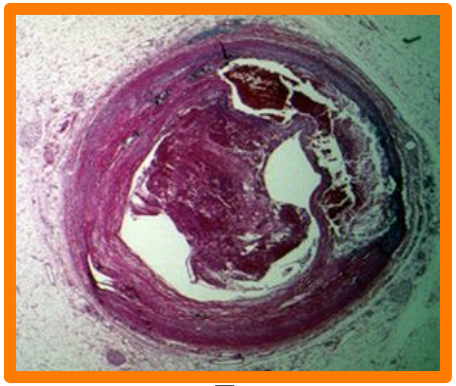
The Year in Acute Coronary Syndrome

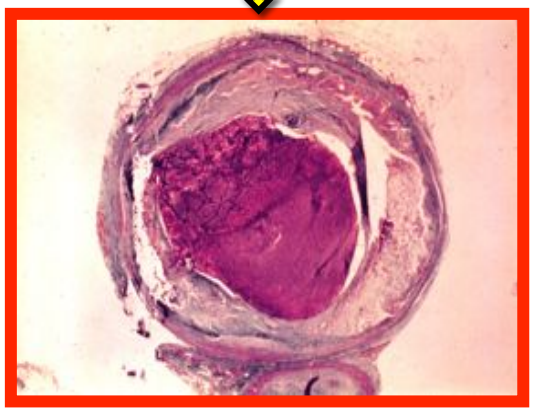
Robert P. Giugliano, MD, SM, Eugene Braunwald, MD
Boston, Massachusetts

Journal of the American College of Cardiology Vol. 63, No. 3, 2014

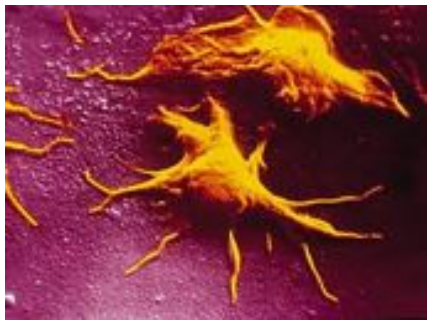
Syndrome coronaire aigu

Accident coronaire aigu	Physiopathologie	Base du traitement





- Des plaquettes



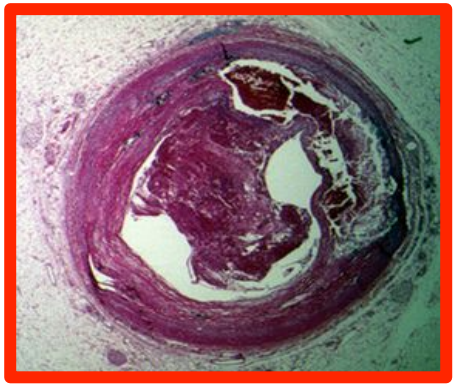
- De la fibrine :

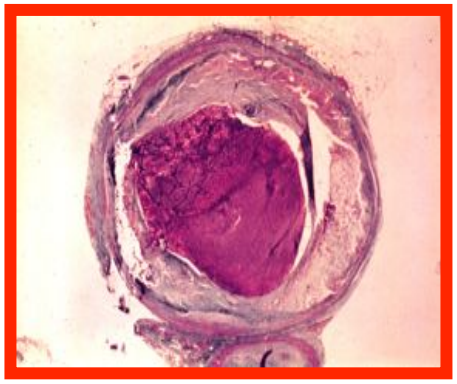
hémostase primaire avec activation de la coagulation.

AAP → IV / PO

Anticoagulants → Héparines? /Bivaluridine?

Ne faut-il pas éteindre le feu rapidement?.





Syndrome coronaire aigu sans sus décalage de ST

Prétraitement: Etudes négatives?

Clopidogrel pre-treatment in stable angina: for all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8

Petr Widimský[1]*, Zuzana Motovská[1], Stanislav Šimek[2], Petr Kala[4], Radek Pudil[3], František Holm[5], Robert Petr[1], Dana Bílková[1], Hana Skalická[2], Petr Kuchynka[2], Martin Poloczek[4], Roman Miklík[4], Marek Malý[6], and Michael Aschermann[2] on behalf of the PRAGUE-8 trial Investigators

European Heart Journal (2008) **29**, 1495–1503
doi:10.1093/eurheartj/ehn169

PRAGUE-8.

- 1028 patients avec un **ANGOR Stable**

- Critère Primaire composite dans les 7 jours:
  - Mortalité,
  - IDM per procédure,
  - AVC,
  - Revascularisation.

- Critère secondaire:
  - Elévation de la troponine
  - Complications hémorragiques.

PRAGUE-8.

- Pas de différence sur le critère primaire:
  - 0.8% vs 1% (p=0.749)
- Augmentation du taux de complications hémorragiques (mineurs+++) dans le groupe pré-traitement.
  - 3.1% vs 1.2% (p=0.033)

Conclusion High (600 mg) loading dose of clopidogrel before elective CAG increased the risk of minor bleeding complications, while the benefit on periprocedural infarction was not significant. Clopidogrel can be given safely in the catheterization laboratory between CAG and PCI in chronic stable angina patients.

Les conclusions d'une étude sur l'angor stable ne peuvent s'extrapoler ni s'appliquer aux syndromes coronaires aigus!!!!

ARMYDA-5 PRELOAD

Effectiveness of In-Laboratory High-Dose Clopidogrel Loading Versus Routine Pre-Load in Patients Undergoing Percutaneous Coronary Intervention

Results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) Randomized Trial

Germano Di Sciascio, MD,* Giuseppe Patti, MD,* Vincenzo Pasceri, MD,† Laura Gatto, MD,* Giuseppe Colonna, MD,‡ Antonio Montinaro, MD,‡ on behalf of the ARMYDA-5

Journal of the American College of Cardiology Vol. 56, No. 7, 2010

ARMYDA-5 PRELOAD

- 409 patients (39 % de syndrome coronaire aigu)

  6 h de prétraitement au moins / 600mg de Clopidogrel.

- 204 patients : bras pré-traitement:
- 205 patients: Cath lab

- Critère primaire à J30
  - Mortalité CV, IDM, revascularisation

- Critères secondaires
  - Elévation de la troponine ou des CPKMB x 3N
  - Hémorragies majeurs et mineurs selon TIMI

ARMYDA-5 PRELOAD

- Critère primaire:
  - Pas de différence: 8,8% vs 10,3% **(p=0,72)**

- <u>Pas de sur-risque hémorragique.</u>

Si le prétraitement n'apporte pas de bénéfice, il n' entraine pas de saignement majeur plus important.
Mais il n'y a que 39% de SCA!!!!!!!

Prétraitement: Etudes positives

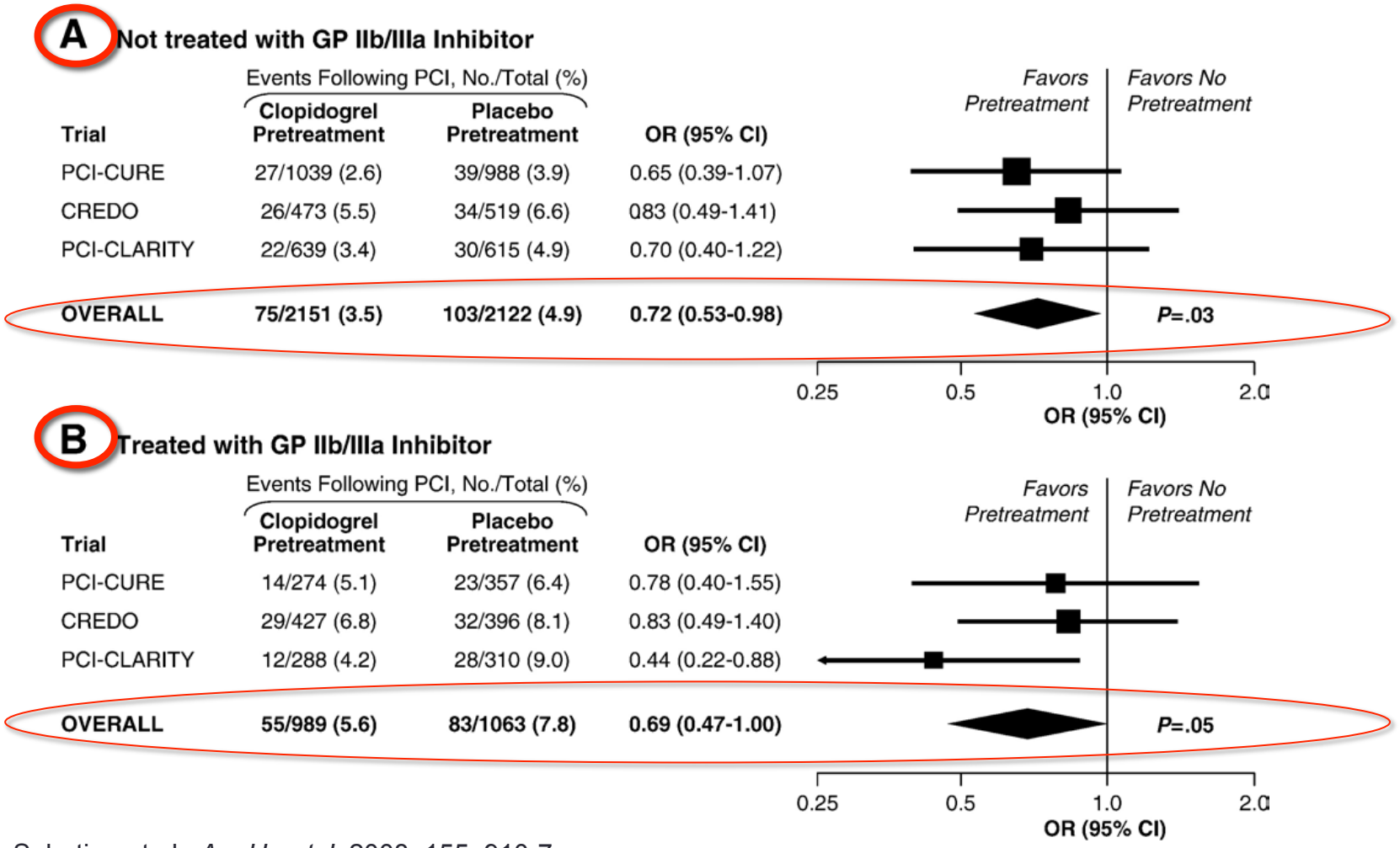
Efficacy and safety of clopidogrel pretreatment before percutaneous coronary intervention with and without glycoprotein IIb/IIIa inhibitor use

Marc S. Sabatine et al , *Am Heart J*. 2008; 155: 910-7

- Méta-analyse de PCI-CURE, CREDO, PCI-CLARITY:
  - 6325 patients inclus
  - 32% ont reçu des anti-GP2B3A
  - Pré-traitement par Clopidogrel 300mg
- Critère primaire:
  - Mortalité CV, IDM et AVC.
- Critère de sécurité:
  - Saignements majeurs et mineurs selon TIMI

Résultats

Figure 1



Marc S. Sabatine et al , *Am Heart J*. 2008; 155: 910-7

Méta-analyse… en faveur

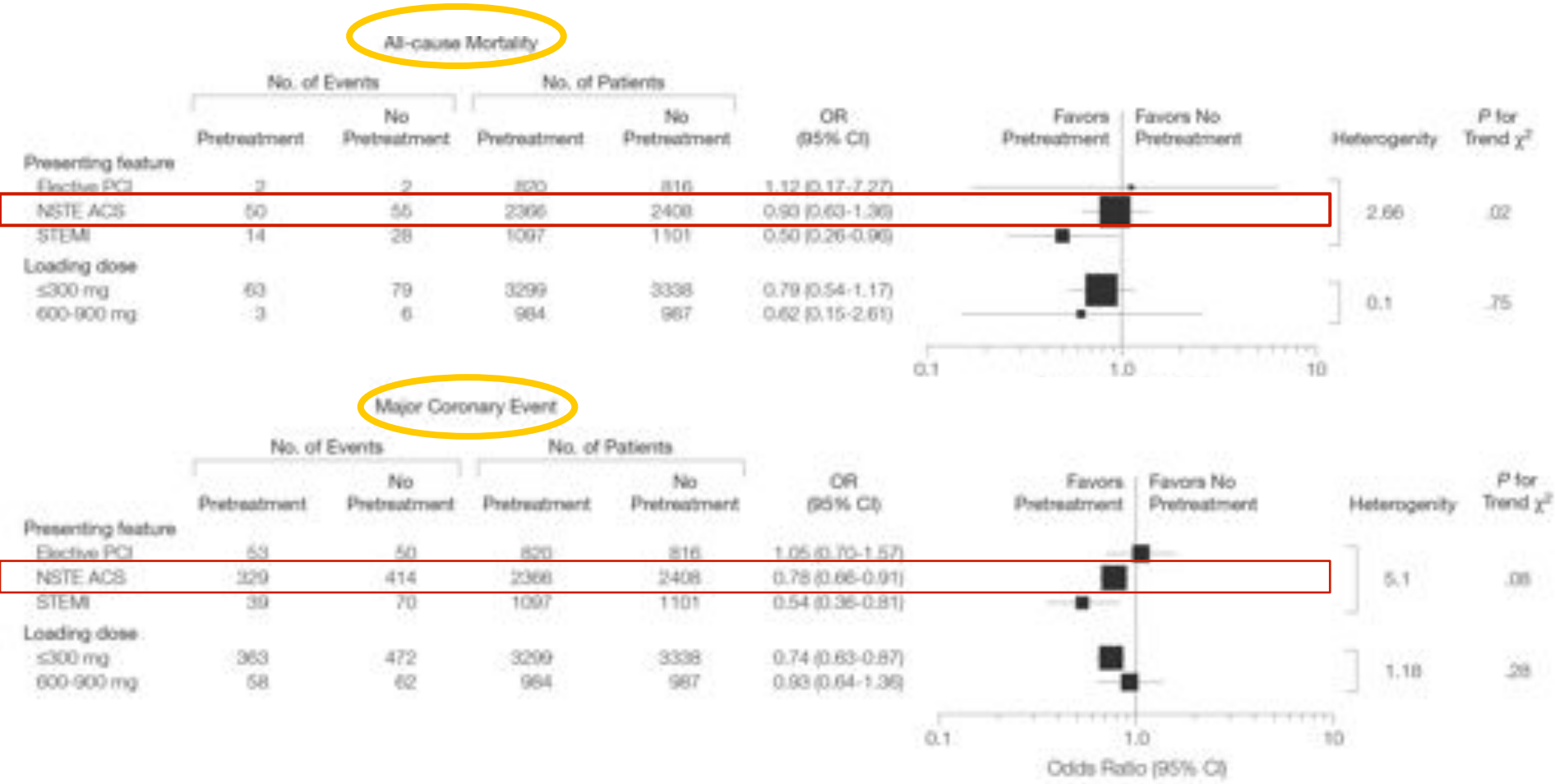
Association of Clopidogrel Pretreatment With Mortality, Cardiovascular Events, and Major Bleeding Among Patients Undergoing Percutaneous Coronary Intervention

A Systematic Review and Meta-analysis

REVIEW Anne Bellemain-Appaix, MD *JAMA. 2012;308(23):2507-2516*

6 Registres
9 études randomisées

Méta-analyse: bénéfice du pré-traitement par le Clopidogrel surtout chez les patients à haut risque cardiovasculaire



Bellemain-Appaix A, et al. ***JAMA***. 2012;308:2507-16.

ACCOAST: remise en question?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 12, 2013 VOL. 369 NO. 11

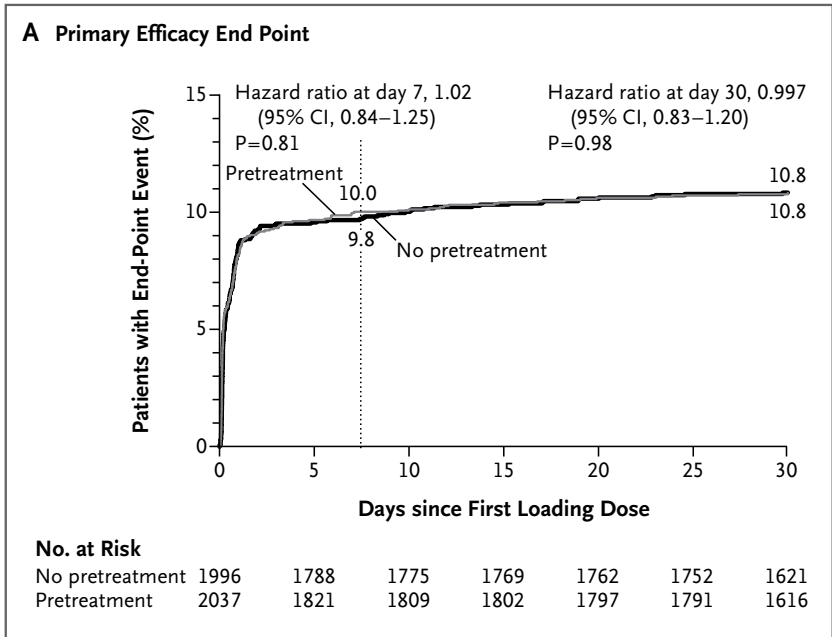
Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes

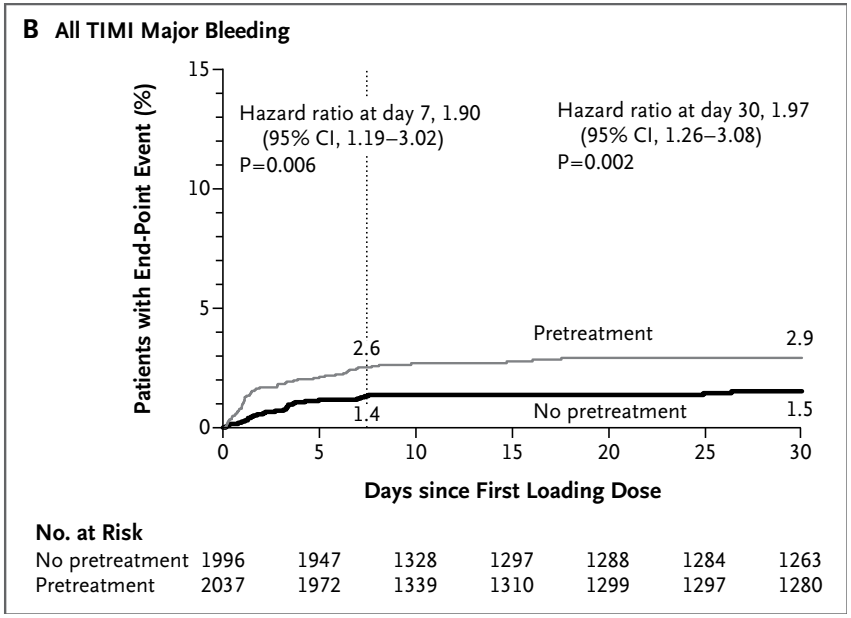
Gilles Montalescot, M.D., Ph.D., Leonardo Bolognese, M.D., Dariusz Dudek, M.D., Ph.D., Patrick Goldstein, M.D., Christian Hamm, M.D., Jean-Francois Tanguay, M.D., Jurrien M. ten Berg, M.D., Ph.D., Debra L. Miller, R.N., Timothy M. Costigan, Ph.D., Jochen Goedicke, M.D., Johanne Silvain, M.D., Ph.D., Paolo Angioli, M.D., Jacek Legutko, M.D., Ph.D., Margit Niethammer, M.D., Zuzana Motovska, M.D., Ph.D., Joseph A. Jakubowski, Ph.D., Guillaume Cayla, M.D., Ph.D., Luigi Oltrona Visconti, M.D., Eric Vicaut, M.D., Ph.D., and Petr Widimsky, M.D., D.Sc., for the ACCOAST Investigators*

ACCOAST

- 4033 NSTEMI à troponine positive
- Critère primaire (au 7ième jour):
  - Mortalité CV,IDM,AVC, Revascularisation urgente; utilisation de GP2b3a en sauvetage.
- Critères secondaires :
  - Critère combiné de mortalité CV, IDM, AVC
  - Mortalité toute cause
  - Thrombose de stent
- Critères de sécurité:
  - Saignements majeurs non liés au pontage augmenté avec le prétraitement.

ACCOAST





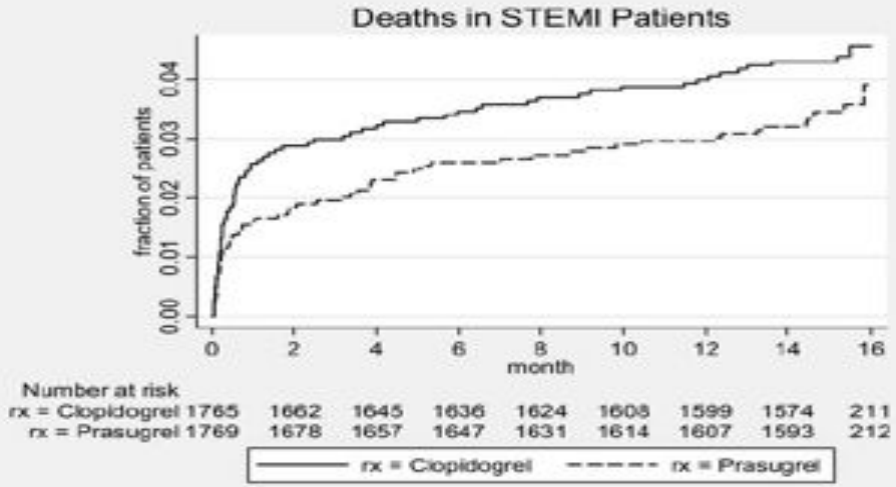
ACCOAST est une étude négative sur les évènements ischémiques
Mais plus de saignements dans le bras pré traitement.

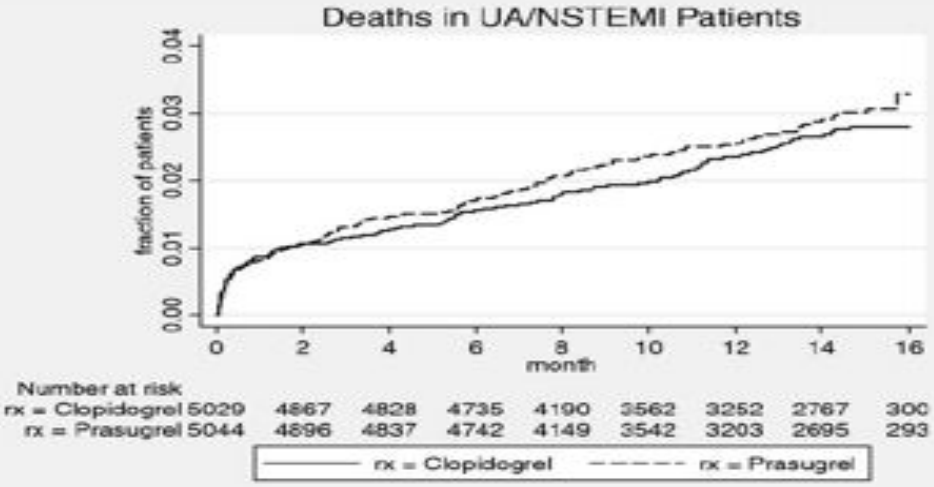
Montalescot et al:, NEJM

SEPTEMBER 12, 2013 VOL. 369 NO. 11

Des résultats homogènes ?

TRITON STEMI





Site-reported first event types in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition (TRITON)

Event	UA or NSTEMI			STEMI			All		
	Clopidogrel	Prasugrel	Δ	Clopidogrel	Prasugrel	Δ	Clopidogrel	Prasugrel	Δ
MI	235	175	60	62	48	14	297	223	74
Stroke	43	43	0	24	22	2	67	65	2
Death	83	113	−30	58	49	9	141	162	−21

US Food and Drug Administration. Drug approval package: Effient (prasugrel) tablets. Available at: *http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022307s000TOC.cfm*. Accessed on January 16, 2010.

Recommandations ESC

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

Au vue des résultats d'ACCOAST peut-on généraliser le non pré-traitement des SCA a tous les bloqueurs du P2Y12?
Probablement que NON

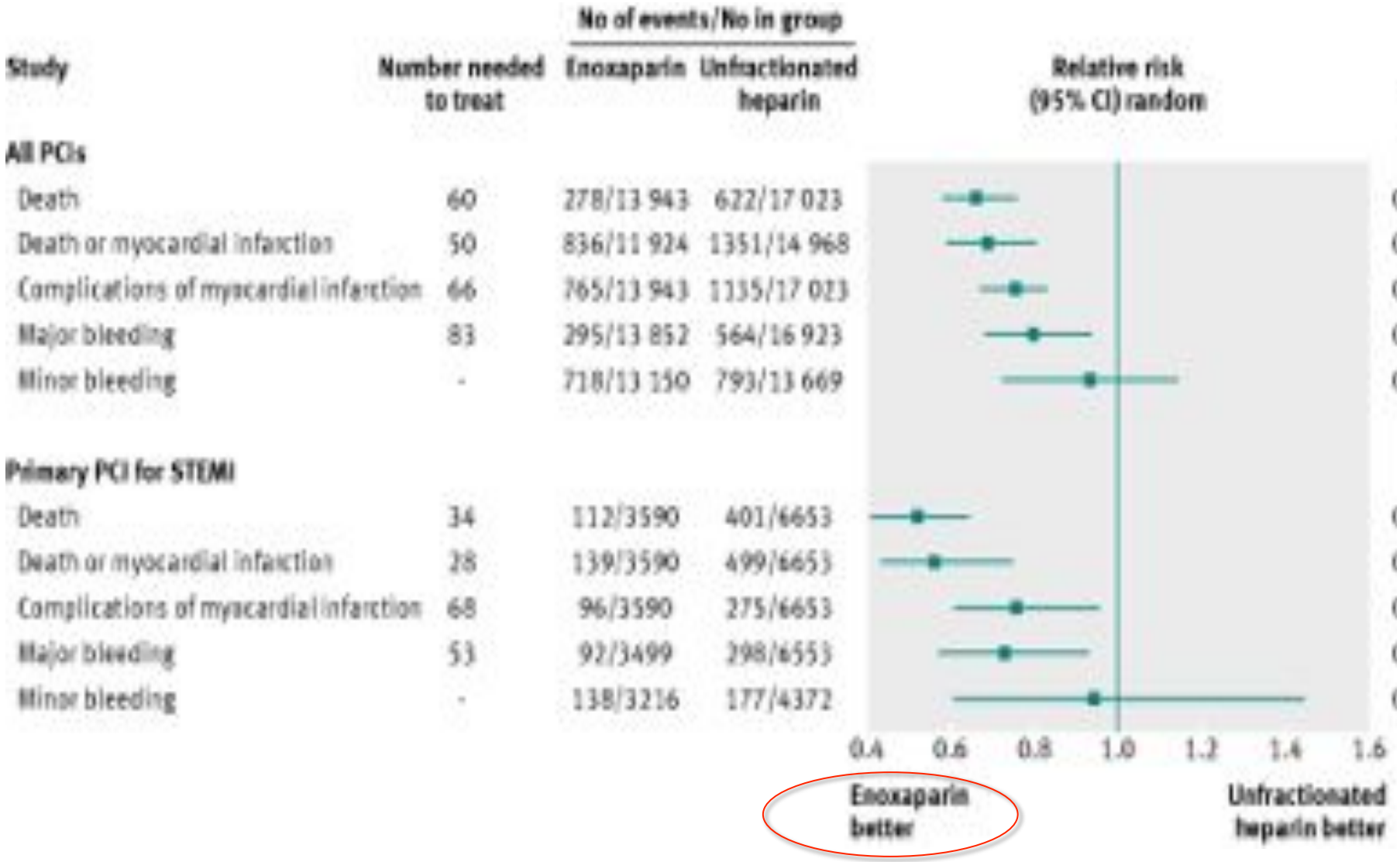
STEMI?

Les anticoagulants: HBPM ou HNF?

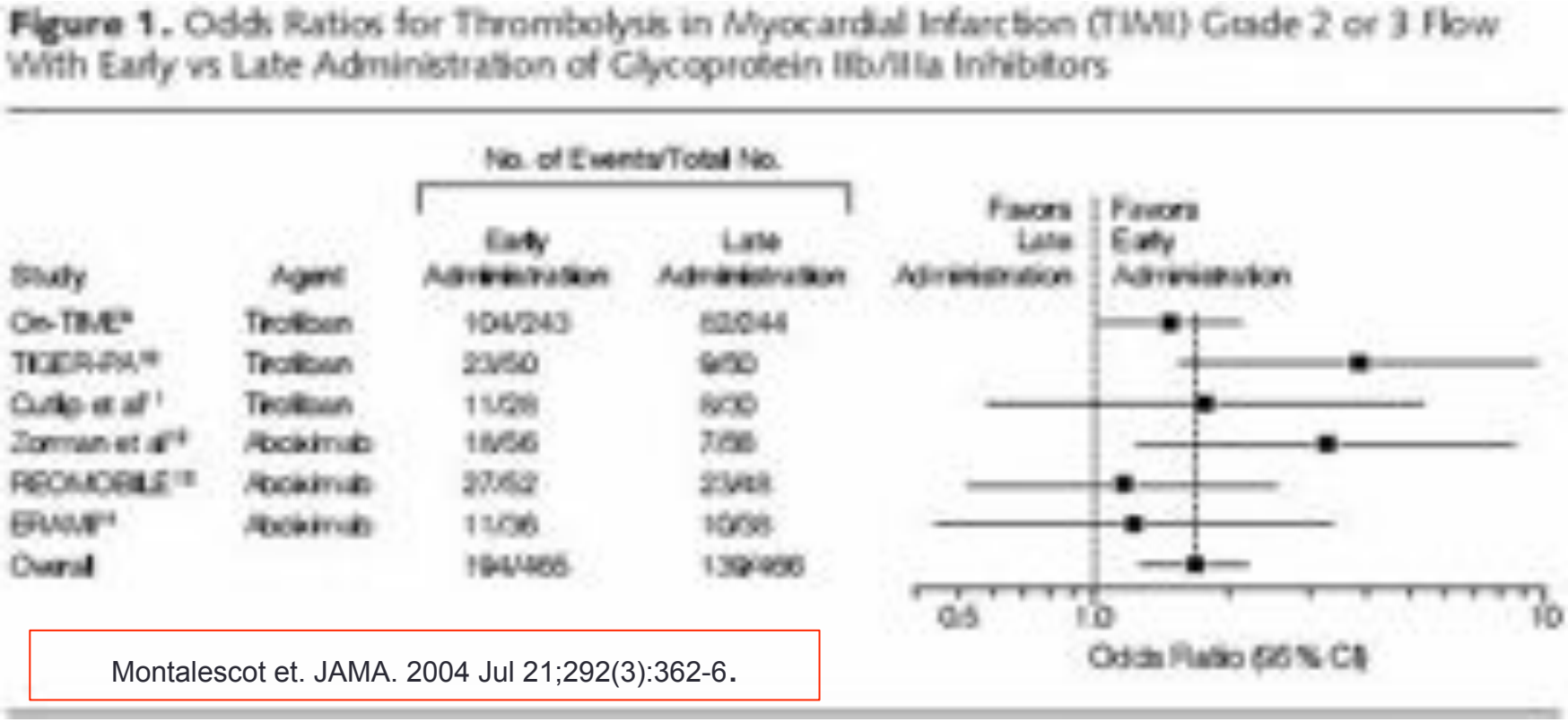
Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis

BMJ

J Silvain et al, BMJ 2012;344:e 553



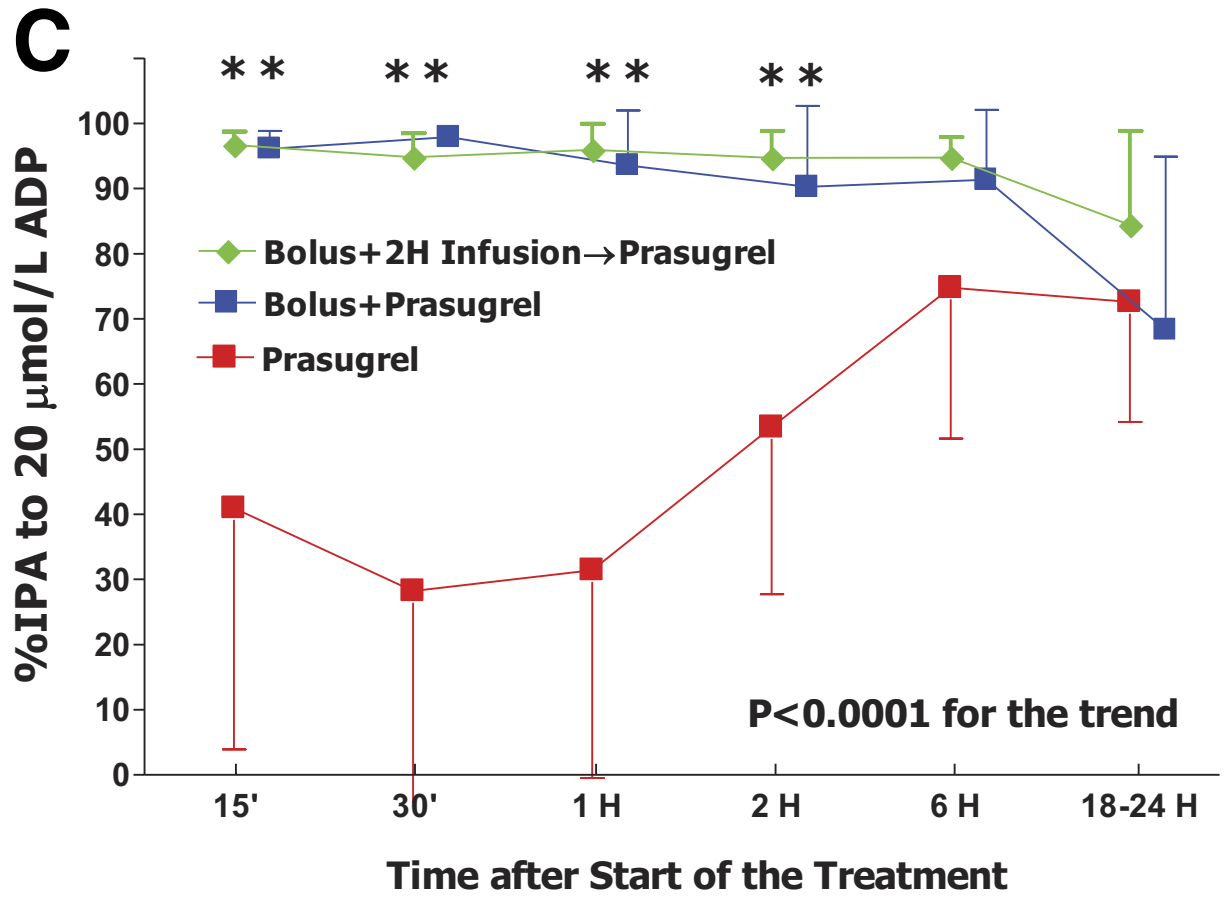
Anti-GP2B3A



Montalescot et. JAMA. 2004 Jul 21;292(3):362-6.

On TIME-2: Amélioration du Flux TIMI3, et de la résolution du segment ST.

FABOLUS



M Valgimigli et al, J Am Coll Cardiol Intv 2012;5:268-77

Quid des antiagrégants plaquettaires per os dans le pré-traitement?

CIPAMI: Pas de bénéfice au pré-traitement par Clopidogrel

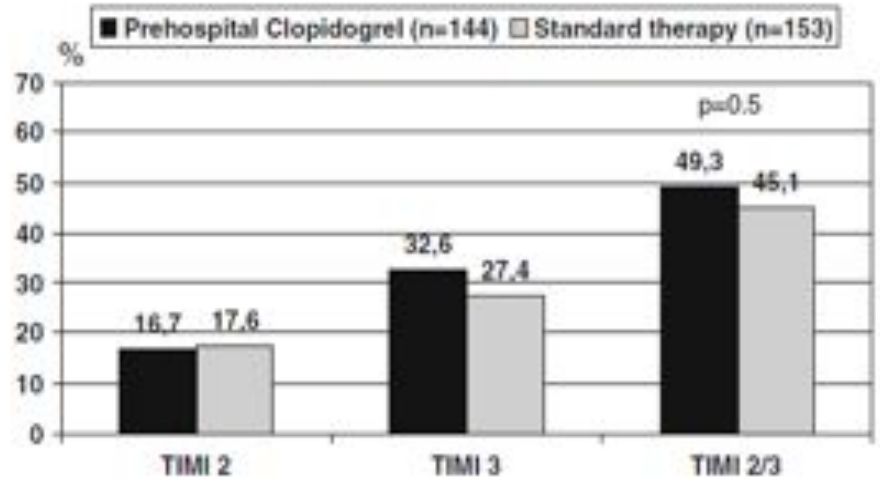


Fig. 2 TIMI patency of the infarct related artery before PCI as assessed by the angiographic core laboratory

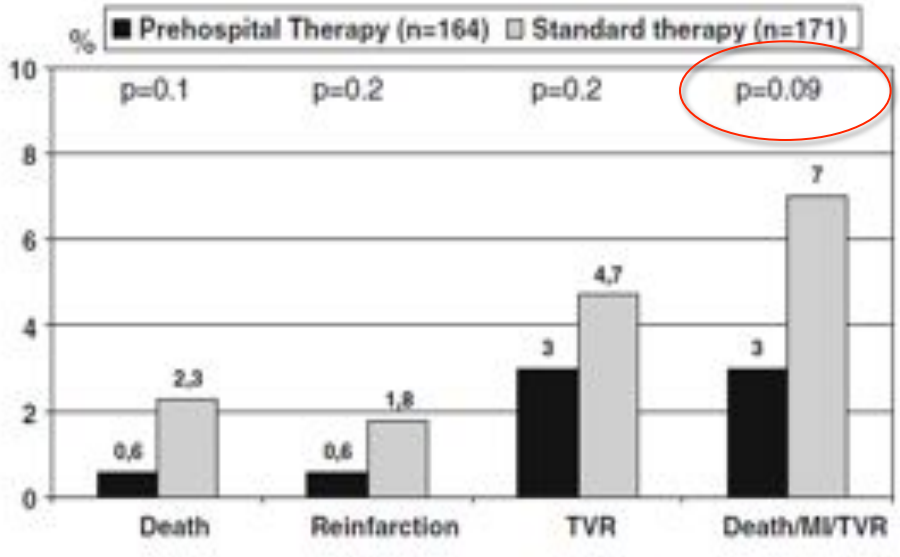
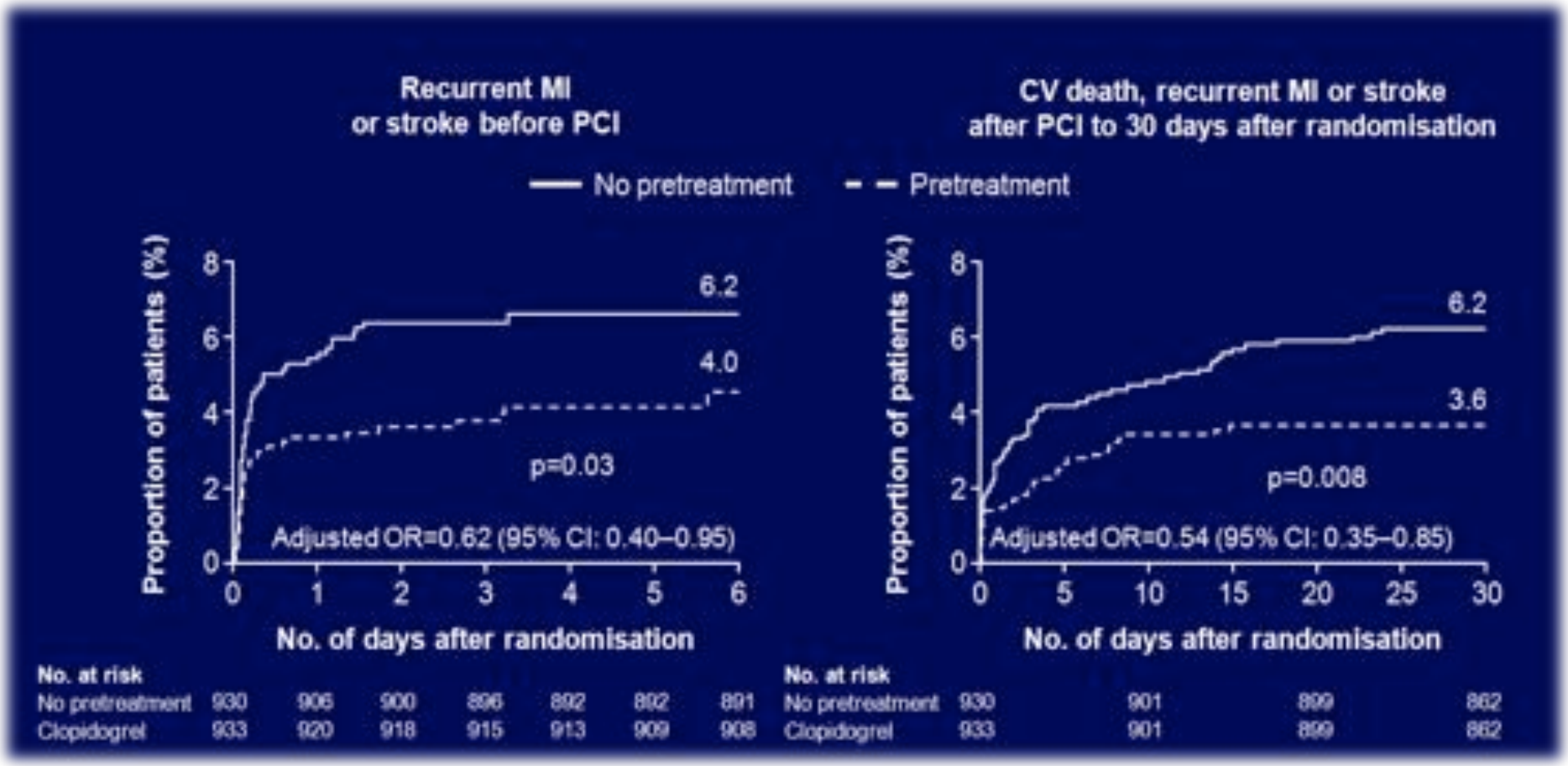


Fig. 3 Clinical events until day 7 or hospital discharge

Zeymer U, et al. *Clin Res Cardiol* 2012;101:305–312.

PCI-CLARITY: Primary efficacy endpoint at 30 days post-PCI



CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STE-ACS, ST-segment elevation acute coronary syndromes.

Sabatine MS, et al. *JAMA* 2005;294:1224–1232.

PCI-CLARITY: Bleeding at 30 days post-PCI

Bleeding definition	No pretreatment (n=923)	Clopidogrel pretreatment (n=918)	p value
Major or minor	2.0%	1.9%	>0.99
Major	0.5%	1.1%	0.21
Minor	1.4%	0.8%	0.26

Bénéfice d'une administration précoce de Clopidogrel, sans excès de saignements chez les patients bénéficiant d'une angioplastie après une fibrinolyse intra-veineuse

PCI, percutaneous coronary intervention; STE-ACS, ST-segment elevation acute coronary syndromes.

Sabatine MS, et al. *JAMA* 2005;294:1224–1232.

Méta-analyse en faveur

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Impact of Pretreatment With Clopidogrel on Initial Patency and Outcome in Patients Treated With Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: A Systematic Review

Pieter J. Vlaar, Tone Svilaas, Kevin Damman, Bart J.G.L. de Smet, Jan G.P. Tijssen, Hans L. Hillege and Felix Zijlstra

Circulation. 2008;118:1828-1836; originally published online October 13, 2008;

Méta-analyse

- 26 études randomisées.
- 8429 patients dont 4114 patients pré-traités

Table 3. Effect of Pretreatment With Clopidogrel on Early Reperfusion and Adverse Event Rates in Univariate-Weighted Logistic Regression Analysis

	Unadjusted Treatment Effect		
	OR	95% CI	*P*
TIMI grade 2/3 flow	1.53	1.39–1.68	<0.0001
Mortality	0.52	0.41–0.67	<0.0001
Death/reinfarction	0.50	0.40–0.62	<0.0001

OR is for the occurrence of TIMI grade 2/3 flow, mortality, and death/reinfarction for pretreatment with clopidogrel.

Pieter J Vlaar et al. Circulation. 2008:118: 1836-1836

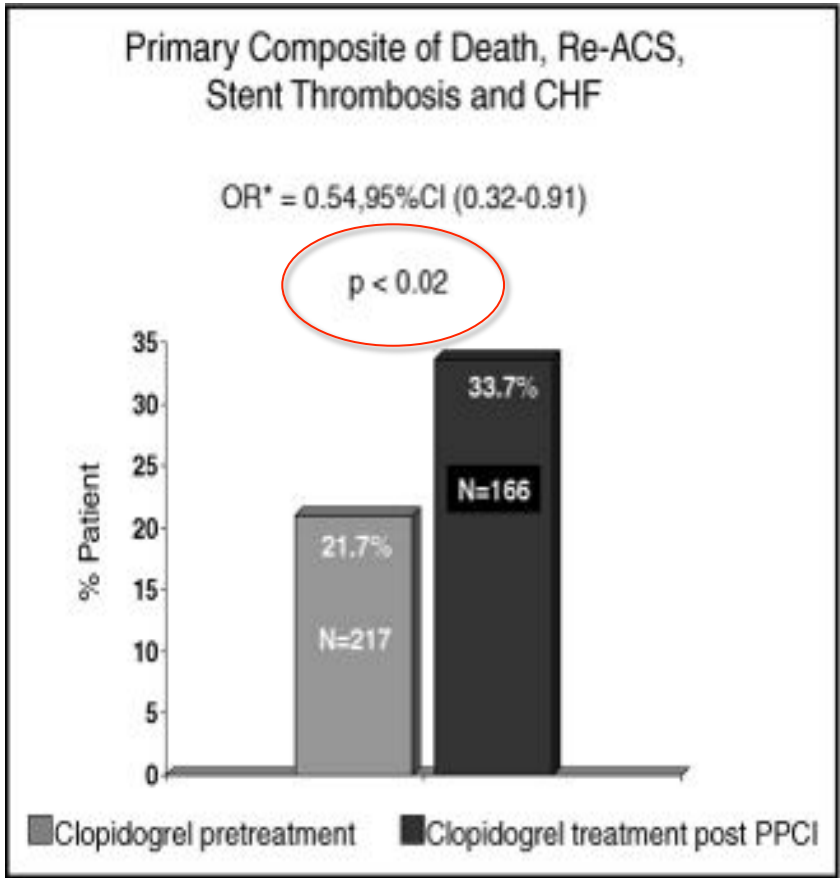
Usefulness of Pretreatment With High-Dose Clopidogrel in Patients Undergoing Primary Angioplasty for ST-Elevation Myocardial Infarction

Paul Fefer, MD[a,*], Hanoch Hod, MD[b], Haim Hammerman, MD[c], Amit Segev, MD[b], Roy Beinart, MD[b], Valentina Boyko, MSc[d], Shlomo Behar, MD[d], and Shlomi Matetzky, MD[b]

(Am J Cardiol 2009;104:514–518)

Table 1
Baseline characteristics

Variable	Clopidogrel Loading		p Value
	Before PPCI (n = 217)	After PPCI (n = 166)	
Age (years)	59 ± 13	62 ± 13	0.06
Women	29 (13%)	37 (22%)	0.02
Diabetes mellitus	49 (22%)	39 (23%)	0.8
Hypertension	101 (46%)	68 (41%)	0.3
Dyslipidemia	115 (53%)	90 (54%)	0.8
Smokers	99 (46%)	85 (52%)	0.2
Body mass index (kg/m^2)	27 ± 5	28 ± 4	0.6
Previous myocardial infarction	28 (13%)	31 (19%)	0.12
Previous PCI/CABG	39 (18%)	28 (17%)	0.8
Previous TIA/CVA	11 (5%)	11 (7%)	0.5
Long-term medical therapy			
Previous aspirin	72 (34%)	56 (34%)	0.8
Previous ACE/ARB	57 (26%)	34 (21%)	0.2
Previous β blockers	49 (23%)	28 (17%)	0.2
Previous statins	57 (26%)	50 (30%)	0.4



PRETREATMENT IN STEMI

Clopidogrel pre-treatment is associated with reduced in-hospital mortality in primary percutaneous coronary intervention for acute ST-elevation myocardial infarction

Registre autrichien de 2005 a 2009
5955 patients
Prétraitement: 1635 patients

Jakob Dörler[1], Michael Edlinger[2], Hannes F. Alber[1], Johann Altenberger[3], Werner Benzer[4], Georg Grimm[5], Kurt Huber[6], Otmar Pachinger[1], Herwig Schuchlenz[7], Peter Siostrzonek[8], Gerald Zenker[9], and Franz Weidinger[10]*, for the Austrian Acute PCI Investigators

European Heart Journal (2011) **32**, 2954–2961

Table 3 **In-hospital outcome in primary percutaneous coronary intervention according to clopidogrel treatment timing**

	Clopidogrel			P_{trend}
	Pre-treatment, *n* = 1635	**Intermediate, *n* = 3244**	**Late, *n* = 1076**	
Mortality	3.4% (*n* = 55)	4.7% (*n* = 154)	10.2% (*n* = 110)	<0.01
Re-infarction	0.6% (*n* = 10)	1.2% (*n* = 39)	2.1% (*n* = 22)	<0.01
Major bleeding	1.0% (*n* = 16)	0.8% (*n* = 26)	1.5% (*n* = 15)	0.39
Second revascularization	4.4% (*n* = 72)	4.7% (*n* = 150)	4.2% (*n* = 41)	0.89
Stroke	0.7% (*n* = 12)	1.1% (*n* = 35)	2.4% (*n* = 25)	<0.01

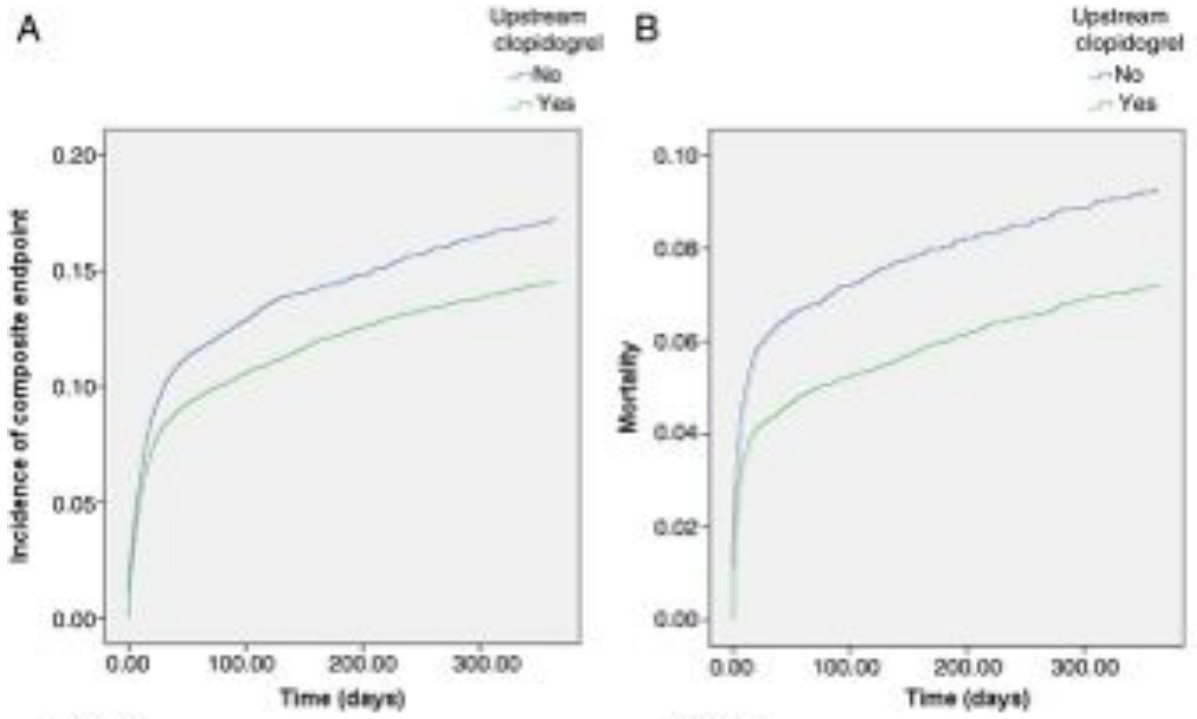
Data are presented as percentages with corresponding numbers in brackets.

SCAAR

Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

Sasha Koul[1], J. Gustav Smith[1,2], Fredrik Scherstén[1], Stefan James[3], Bo Lagerqvist[3], and David Erlinge[1]*

European Heart Journal (2011) **32**, 2989–2997



Prétraitement par Clopidogrel

- Les études randomisées, les registres, les méta-analyses

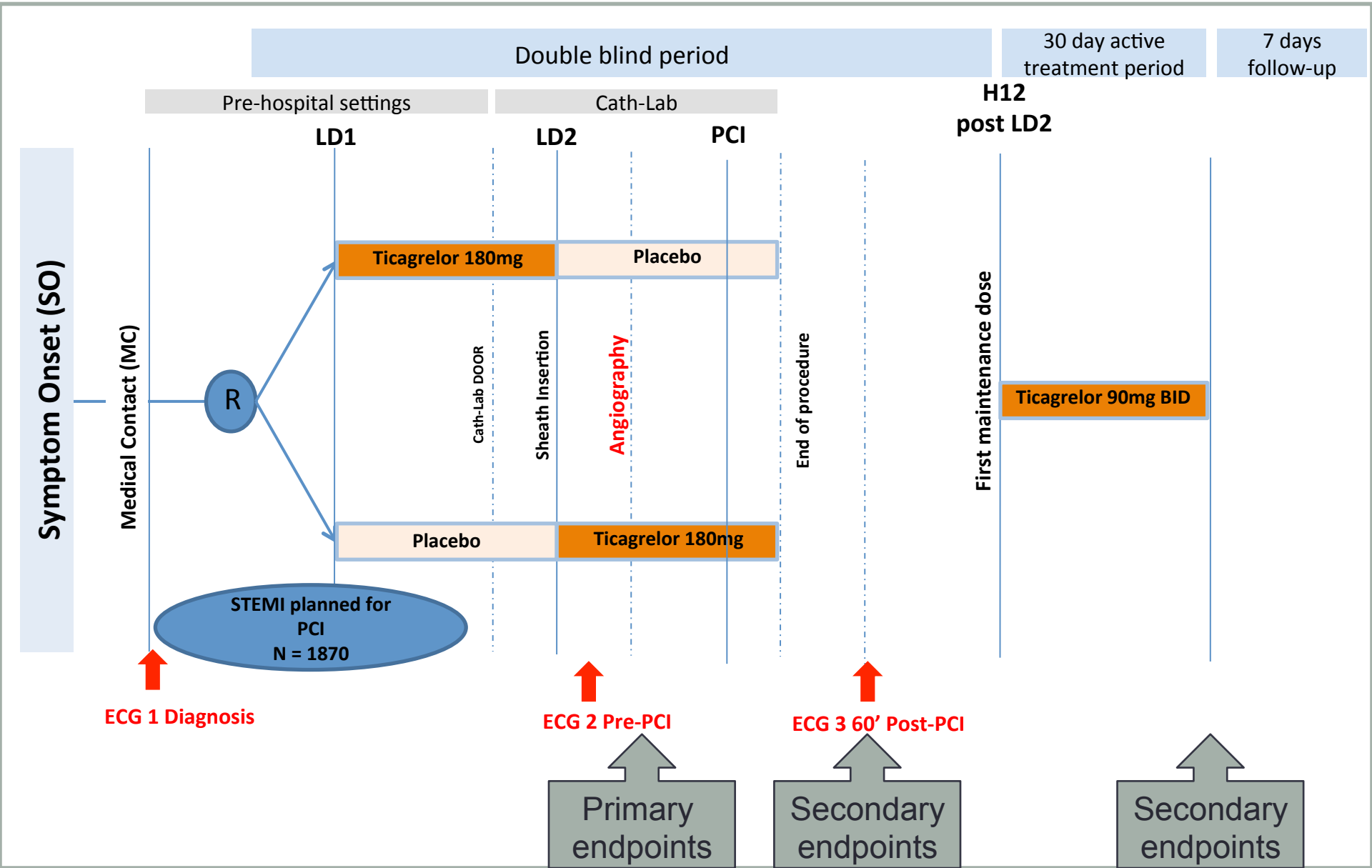
→ en faveur du Clopidogrel dans le prétraitement dans l'IDM

- Peut-on extrapoler ces données aux autres antiagrégants plaquettaires?

NON pour le PRASUGREL

OUI jusqu'à preuve du contraire pour le TICAGRELOR

Study Flow Chart: ATLANTIC



Conclusion.

- Les études de prétraitement sont plus en faveur qu'en défaveur
- Il y a un bénéfice sur les évènements ischémiques, d'autant plus que les patients présentent un SCA a haut risque.
- Il est difficile à ce jour de parler d'effet de classe sur le pré-traitement par les AAP.

- Il faut attendre les résultats des études en cours pour peut-être se prononcer plus clairement…

Merci …