PEUT-ON LUTTER CONTRE LES EVENEMENTS ISCHEMIQUES ET HEMORRAGIQUES LORS D'UN SCA ?

La Gestion pharmacologique du thrombus

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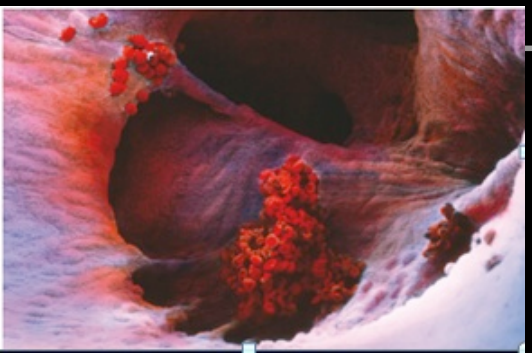
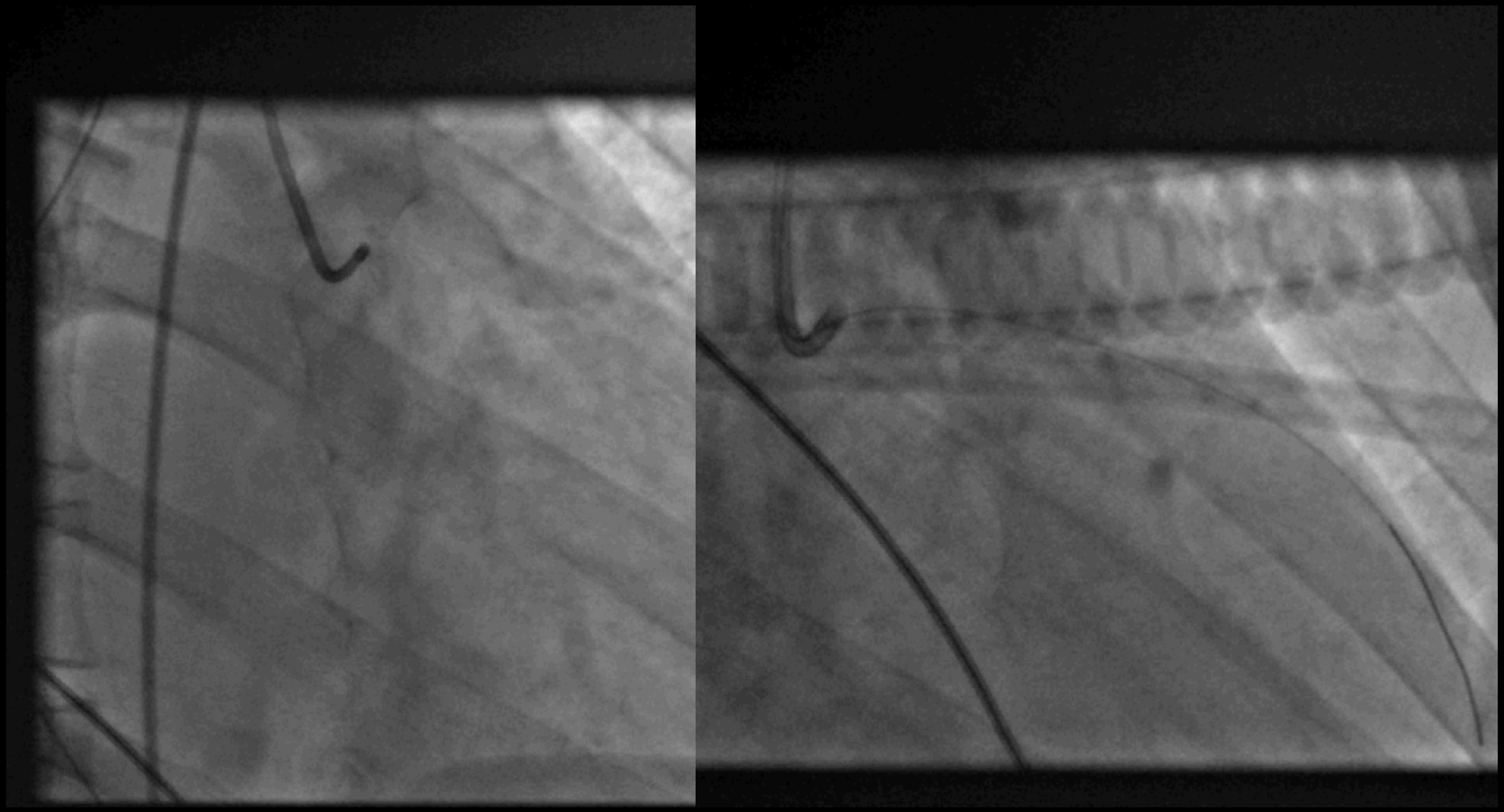
Professeur agrégé de Cardiologie
Service de cardiologie
HU A. Mami-Ariana-Tunisie



Cas clinique

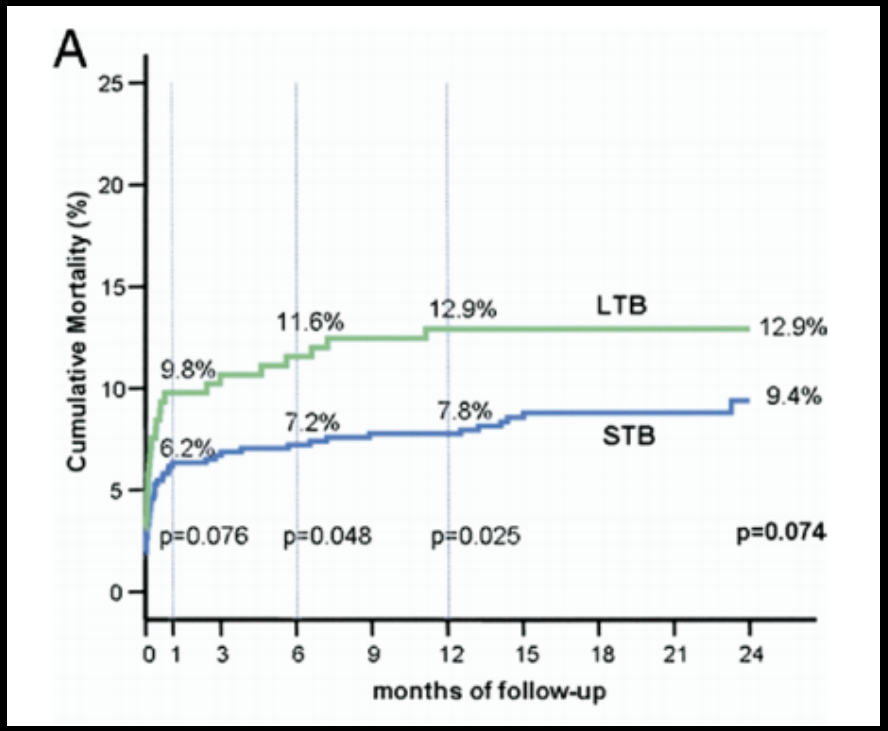
- Patient âgé de 36 ans
- Tabagique 20 paquets/années
- Douleur thoracique évoluant depuis 2heures
- ECG: sus décalage de ST en antérieur étendu
- Transporté par le SAMU
- Arrivée au Cath Lab après 80 min
- Door Cardio to balloon=25 min

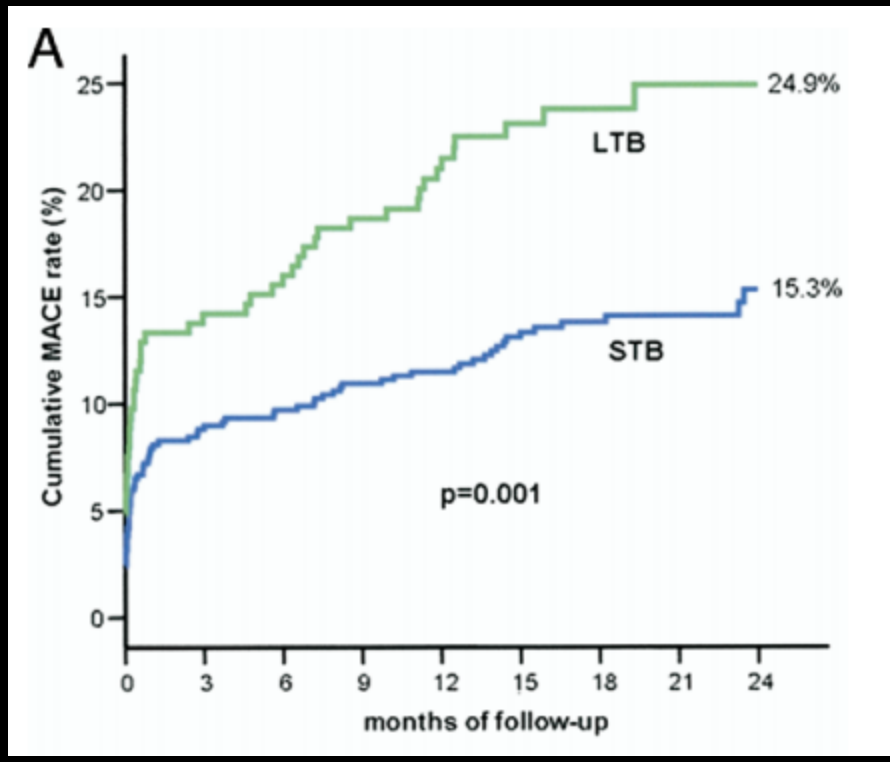


CLINICAL RESEARCH Interventional Cardiology

Angiographic Stent Thrombosis After Routine Use of Drug-Eluting Stents in ST-Segment Elevation Myocardial Infarction

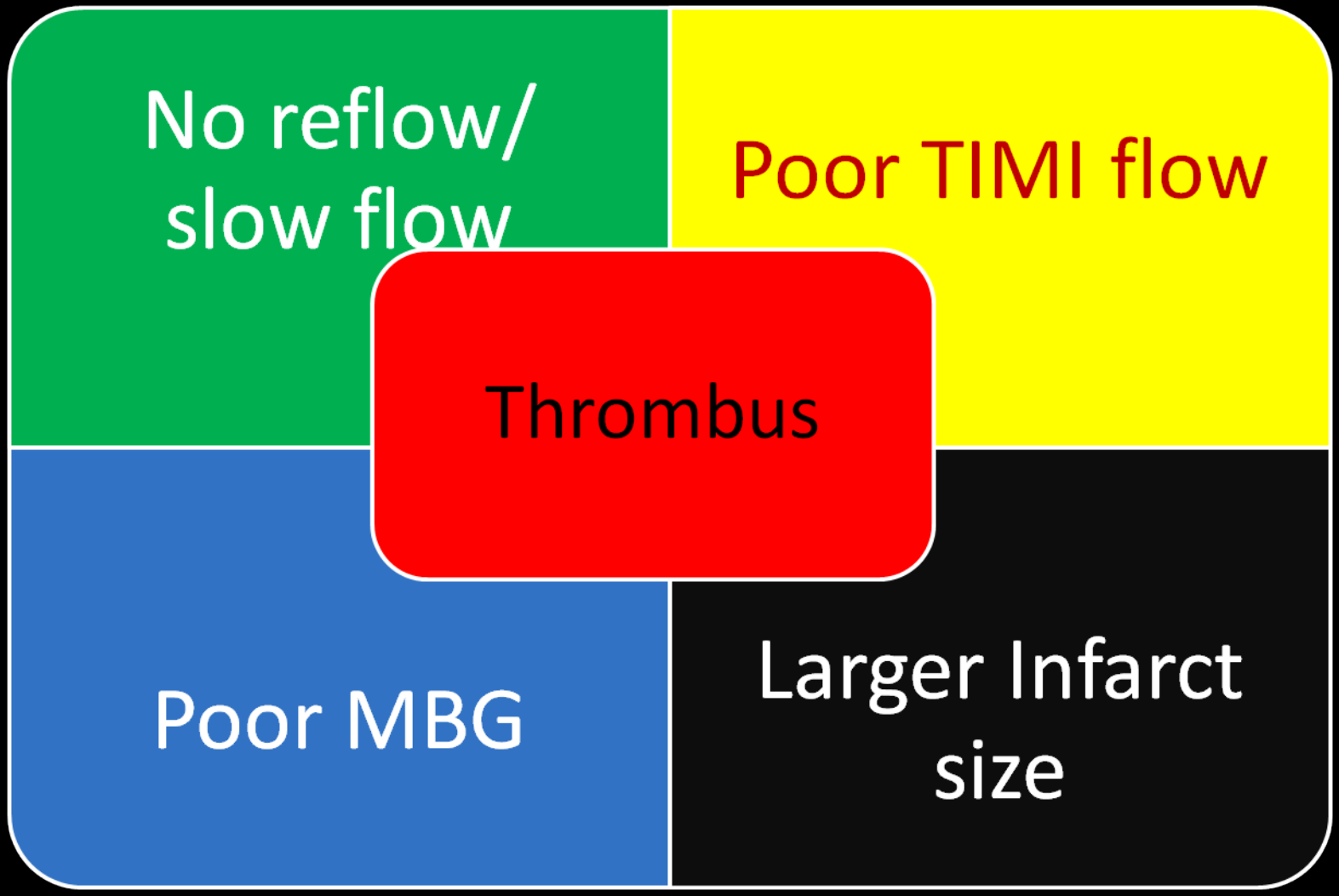
The Importance of Thrombus Burden



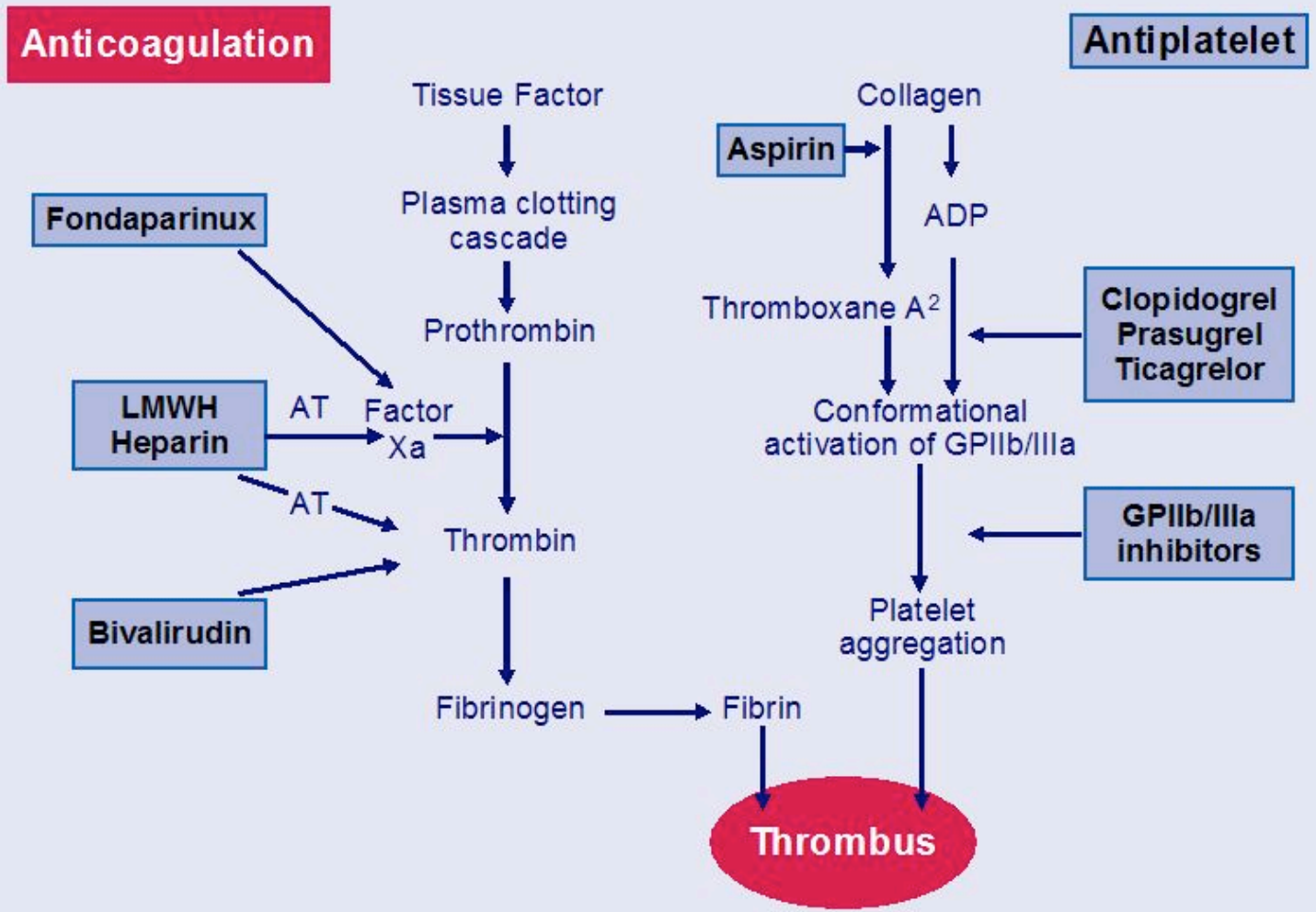


LTB was an independant predictor factor of mortality at 2 years

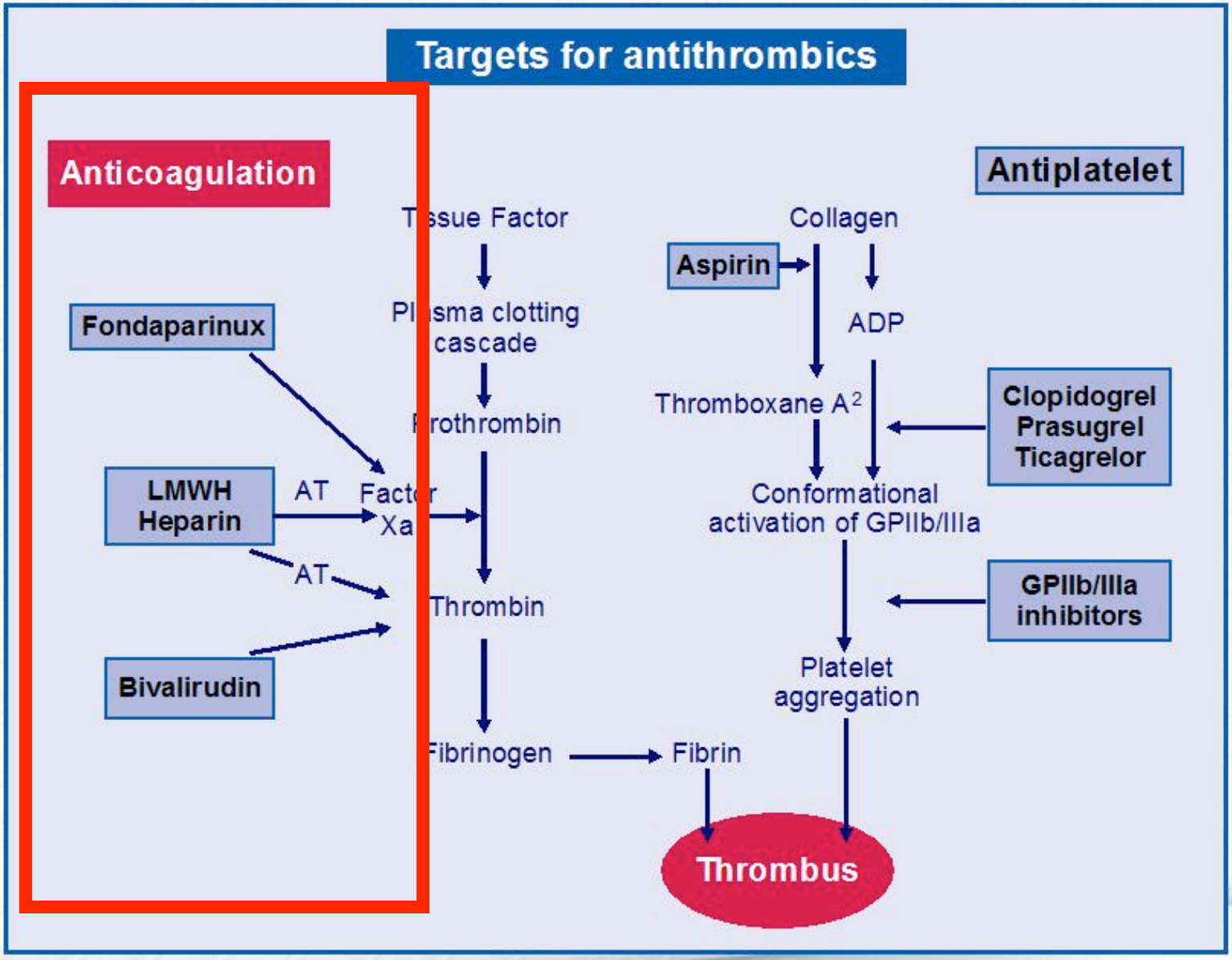
Sianos G et al. J Am Coll Cardiol 2007;50:573–83


No reflow/
slow flow
Poor TIMI flow
Thrombus
Poor MBG
Larger Infarct
size

Targets for antithrombics



European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236



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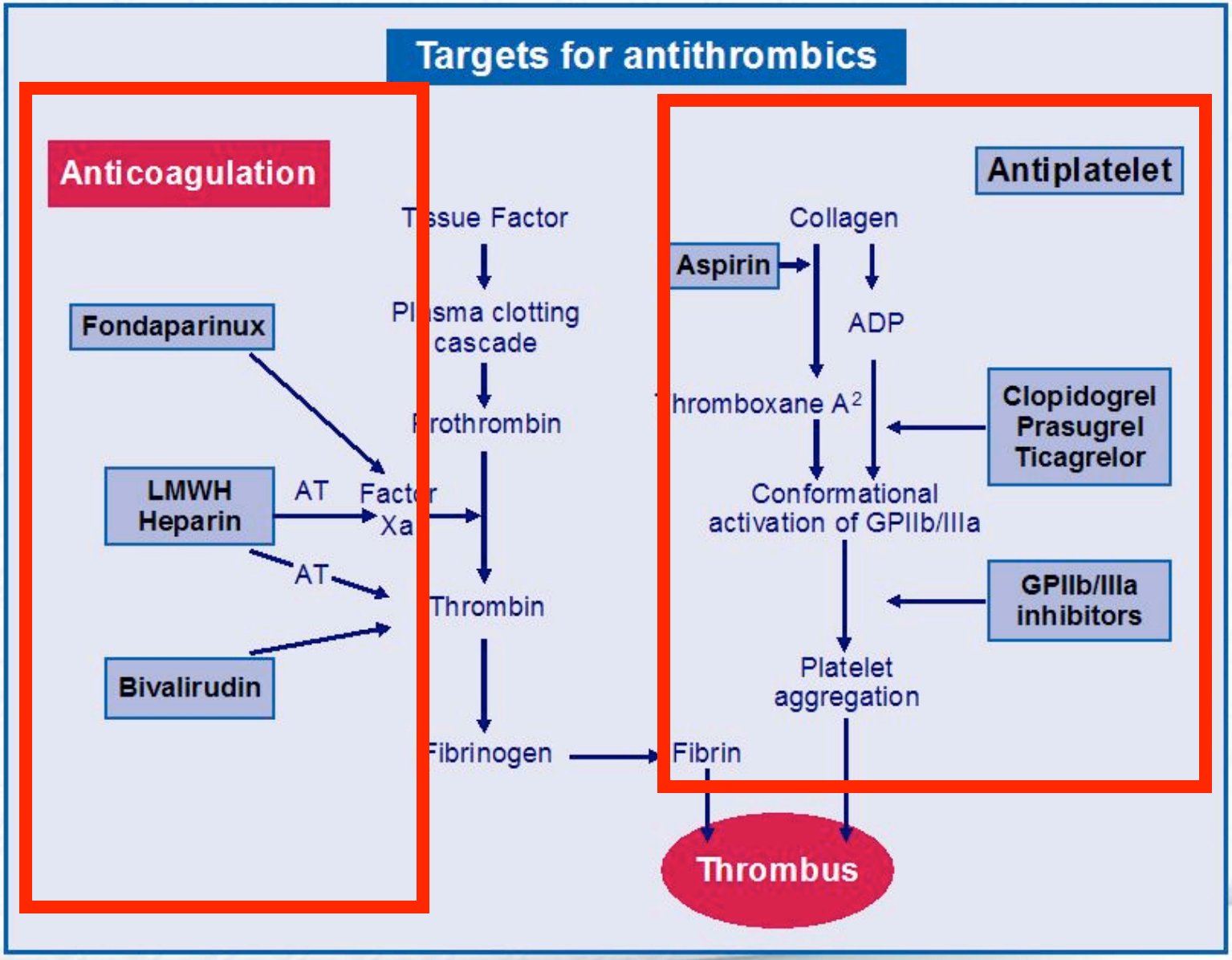
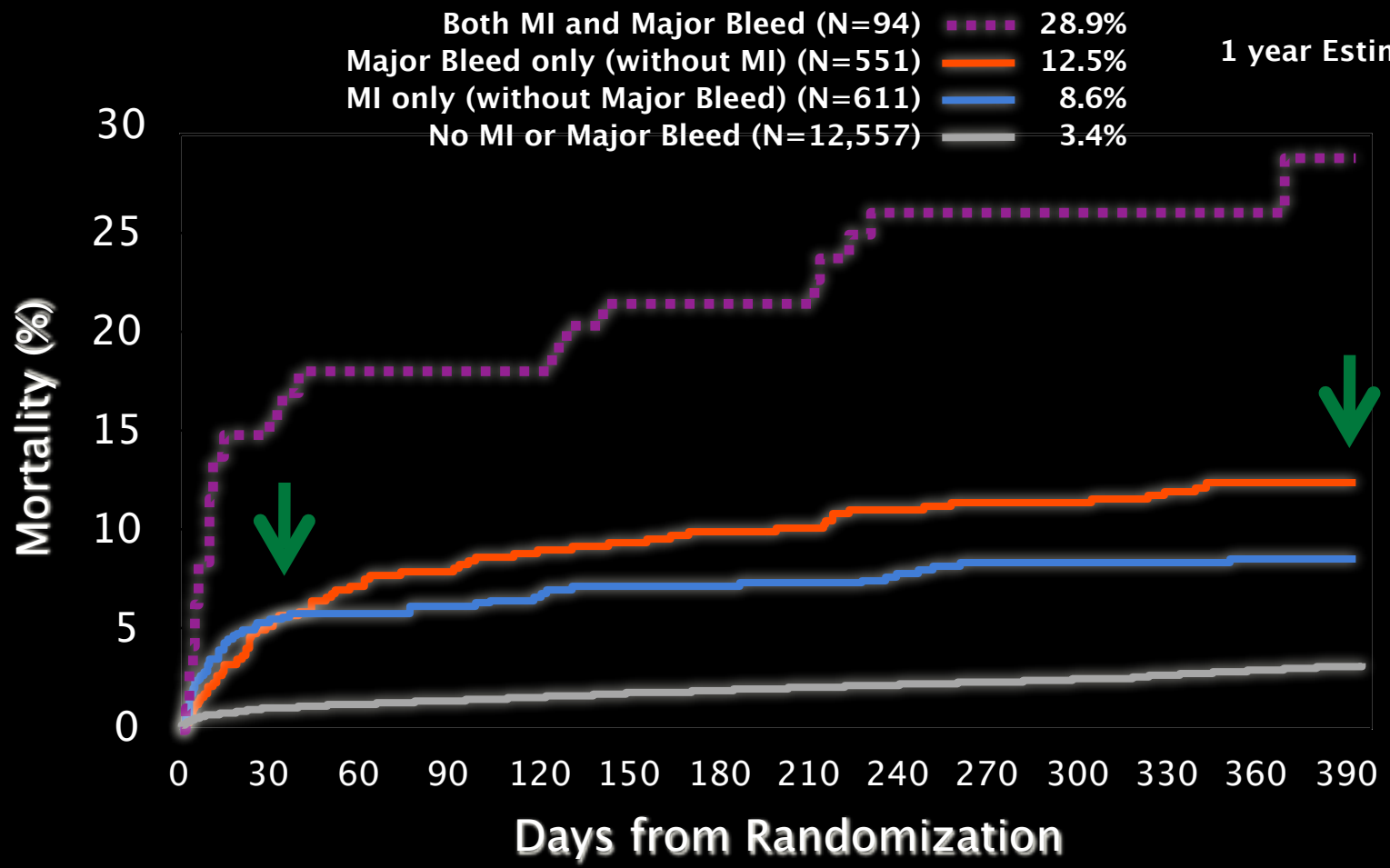
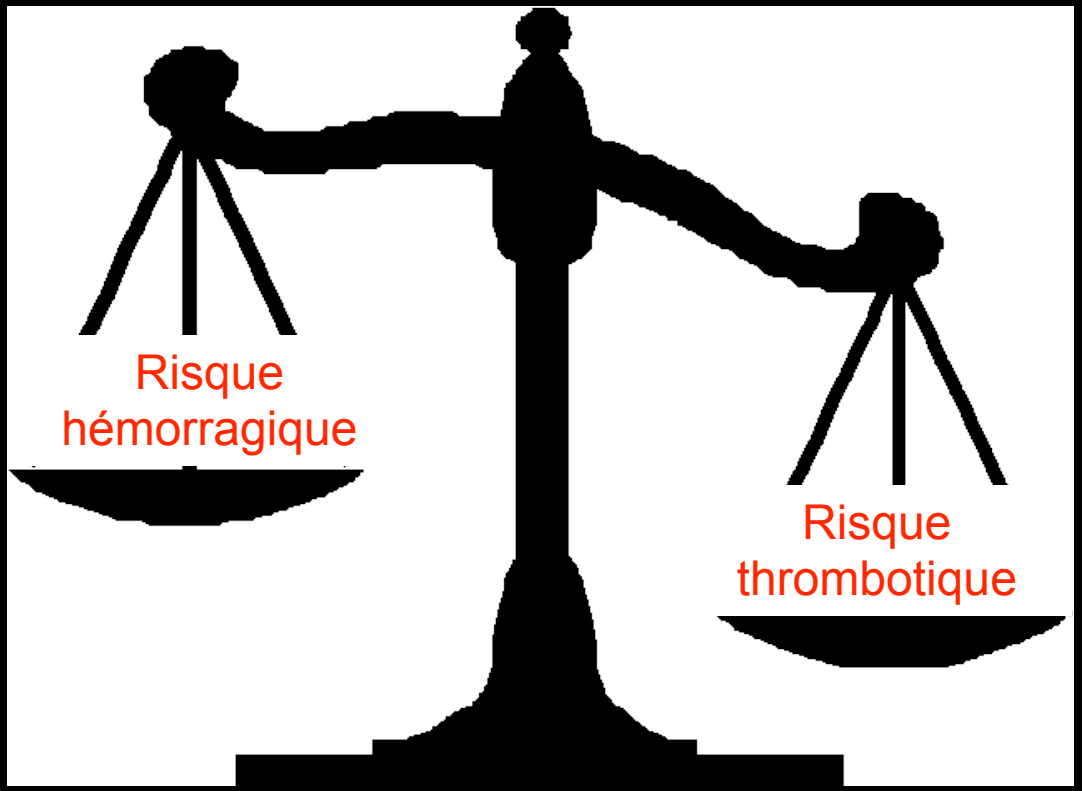


European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

ACUITY Trial: Impact of MI and Major Bleeding (non-CABG) in the First 30 Days on Risk of Death Over 1 Year



Stone GW, et al. JAMA 2007; 298:2497-2506.



1.PLACE DES ANTI GP 2B3A DANS LE STEMI?

European Heart Journal
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

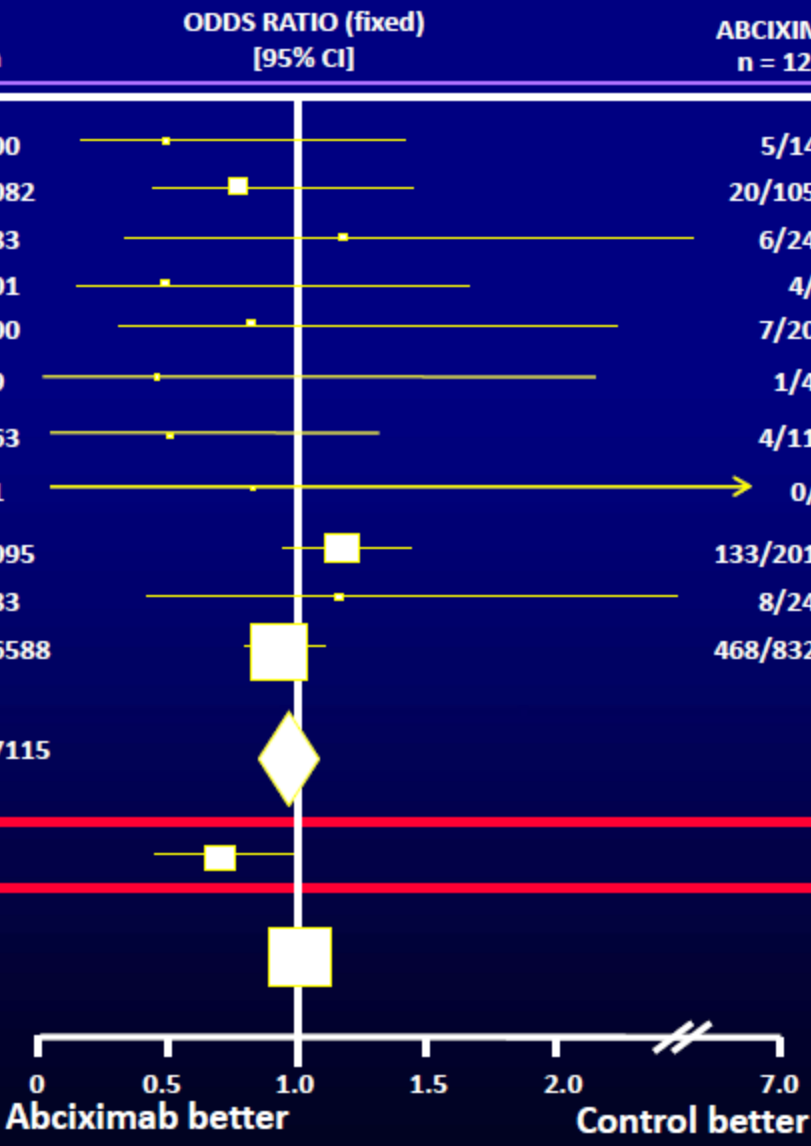
Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel[d]	I	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B

ESC 2010

30-DAY MORTALITY



	n	ABCIXIMAB n = 12602	CONTROL n = 14513	p
ADMIRAL[10]	300	5/149 (3.4%)	10/151 (6.6%)	0.19
CADILLAC [2]	2082	20/1052 (1.9%)	24/1030 (2.3%)	0.49
RAPPORT [4]	483	6/241 (2.5%)	5/242 (2.1%)	0.75
ISAR-2 [8]	401	4/201 (2.0)	8/200 (4.0%)	0.24
ACE [18]	400	7/200 (3.5%)	8/200 (4.0%)	0.79
Petronio et al [14]	89	1/44 (2.3%)	4/45 (8.9%)	0.36
Zorman et al [16]	163	4/112 (3.6%)	5/51 (9.8%)	0.1
Petronio et al [15]	31	0/17 (0%)	0/14 (0%)	1.0
ASSENT III [11]	6095	133/2017 (6.6%)	231/4078 (5.7%)	0.15
ENTIRE-TIMI 23 [13]	483	8/241 (3.3%)	7/242 (2.9%)	0.79
GUSTO V [12]	16588	468/8328 (5.6%)	488/8260 (5.9%)	0.43
OVERALL	27115	5.2%	5.5%	0.61
Primary PCI	3949	2.4%	3.4%	0.047
Fibrinolysis	23166	5.8%	5.8%	0.95

De Luca G et al. JAMA 2005; 293: 1759-65

Anti-GPIIbIIIa et STEMI

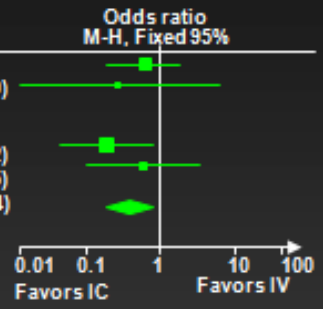
2.QUELLE MODALITÉ D'ADMINISTRATION DANS LE CATH LAB?

Abciximab IC versus IV

30-day Mortality

Study or Subgroup	Intracoronary abciximab Events	Total	Intravenous abciximab Events	Total	Weight	Odds ratio M-H, Fixed 95%
CICERO 2010	5	271	7	263	33.7%	0.69
CRYSTAL AMI 2010	0	25	1	23	7.4%	0.29 (0.01;7.59)
Dominguez-Rodriguez 2009	0	25	0	25		Not estimable
EASY-MI 2010	0	53	0	52		Not estimable
Iversen 2011	2	185	9	170	44.8%	0.20 (0.04;0.92)
Thiele 2008	2	77	3	77	14.1%	0.66 (0.11;4.05)
Total (95%)		636		610	100.0%	0.43 (0.20;0.94)
Total events	9		20			

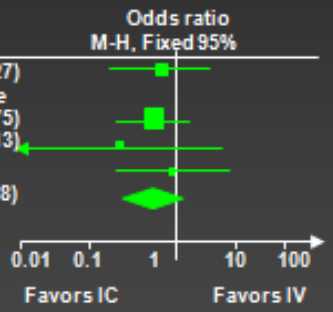
Heterogeneity: Chi² =1.88, df=3 (P=0.60); I²=0%
Test for overall effect: Z=2.11 (P=0.03)



30-day Myocardial Infarction

Study or Subgroup	Intracoronary abciximab Events	Total	Intravenous abciximab Events	Total	Weight	Odds ratio M-H, Fixed 95%
CICERO 2010	3	271	4	263	27.5%	0.72 (0.16;3.27)
EASY-MI 2010	0	53	0	52		Not estimable
Iversen 2011	5	185	8	170	55.5%	0.56 (0.18;1.75)
Thiele 2008	0	77	2	77	17.0%	0.19 (0.01;4.13)
Total (95%)		586		562	100.0%	0.54 (0.23;1.28)
Total events	8		14			

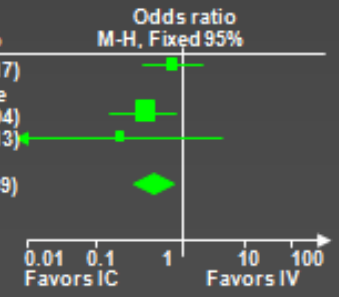
Heterogeneity: Chi² =0.58, df=2 (P=0.75); I²=0%
Test for overall effect: Z=1.39 (P=0.17)



30-day Target Vessel Revascularization

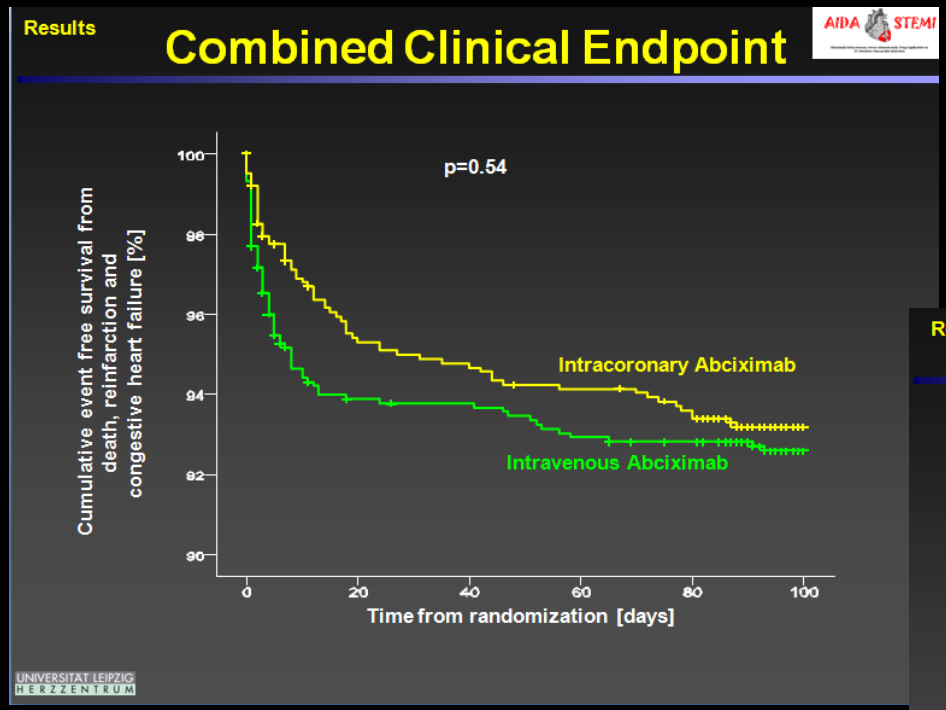
Study or Subgroup	Intracoronary abciximab Events	Total	Intravenous abciximab Events	Total	Weight	Odds ratio M-H, Fixed 95%
CICERO 2010	9	271	10	263	27.5%	0.87 (0.35;2.17)
EASY-MI 2010	0	53	0	52		Not estimable
Iversen 2011	7	185	16	170	55.5%	0.38 (0.15;0.94)
Thiele 2008	0	77	2	77	17.0%	0.19 (0.01;4.13)
Total (95%)		586		562	100.0%	0.53 (0.29;0.99)
Total events	16		28			

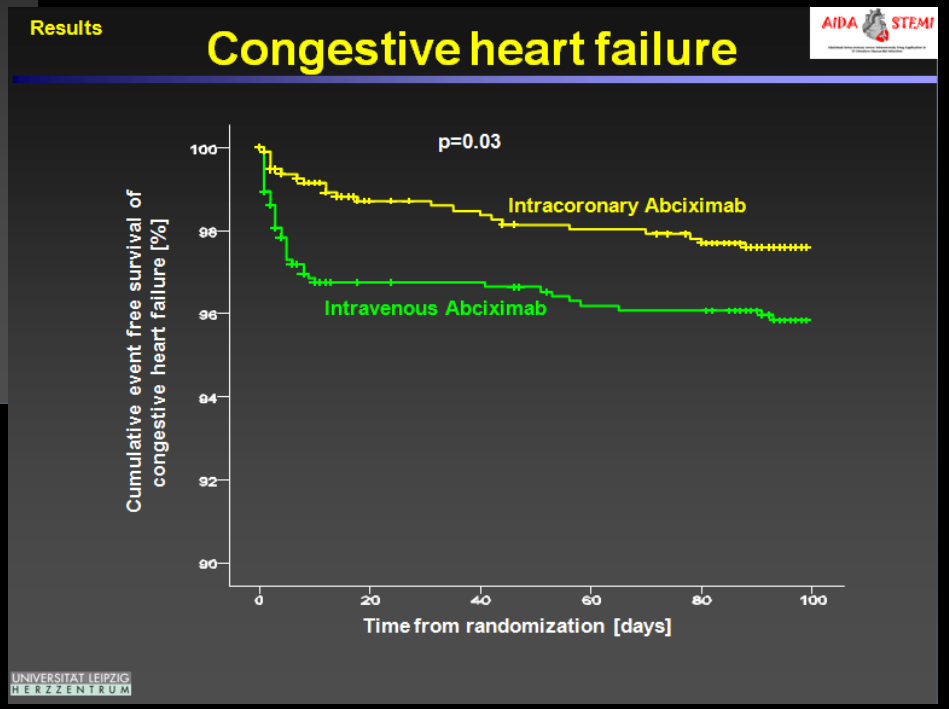
Heterogeneity: Chi² =2.58, df=2 (P=0.36); I²=2%
Test for overall effect: Z=2.00 (P=0.05)



UNIVERSITÄT LEIPZIG
HERZZENTRUM

Navarese et al. Platelets 2011;1-8





Administration d'un antiGp2b3a par voie intra-coronaire ou IV? **Pas de bénéfice claire !!!**

Thiele L et al. Lancet 2012 10;379:923-3

Anti-GPIIbIIIa et STEMI

3.QUAND? ANTI-GPIIBIIIA EN PRÉHOSPITALIER?

Anti-GPIIbIIIa et STEMI

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel[d]	I	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb–IIIa antagonists	III	B

3.QUAND? ANTI-GPIIBIIIA EN PRÉHOSPITALIER?

ESC 2010

Anti-GPIIbIIIa et STEMI

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
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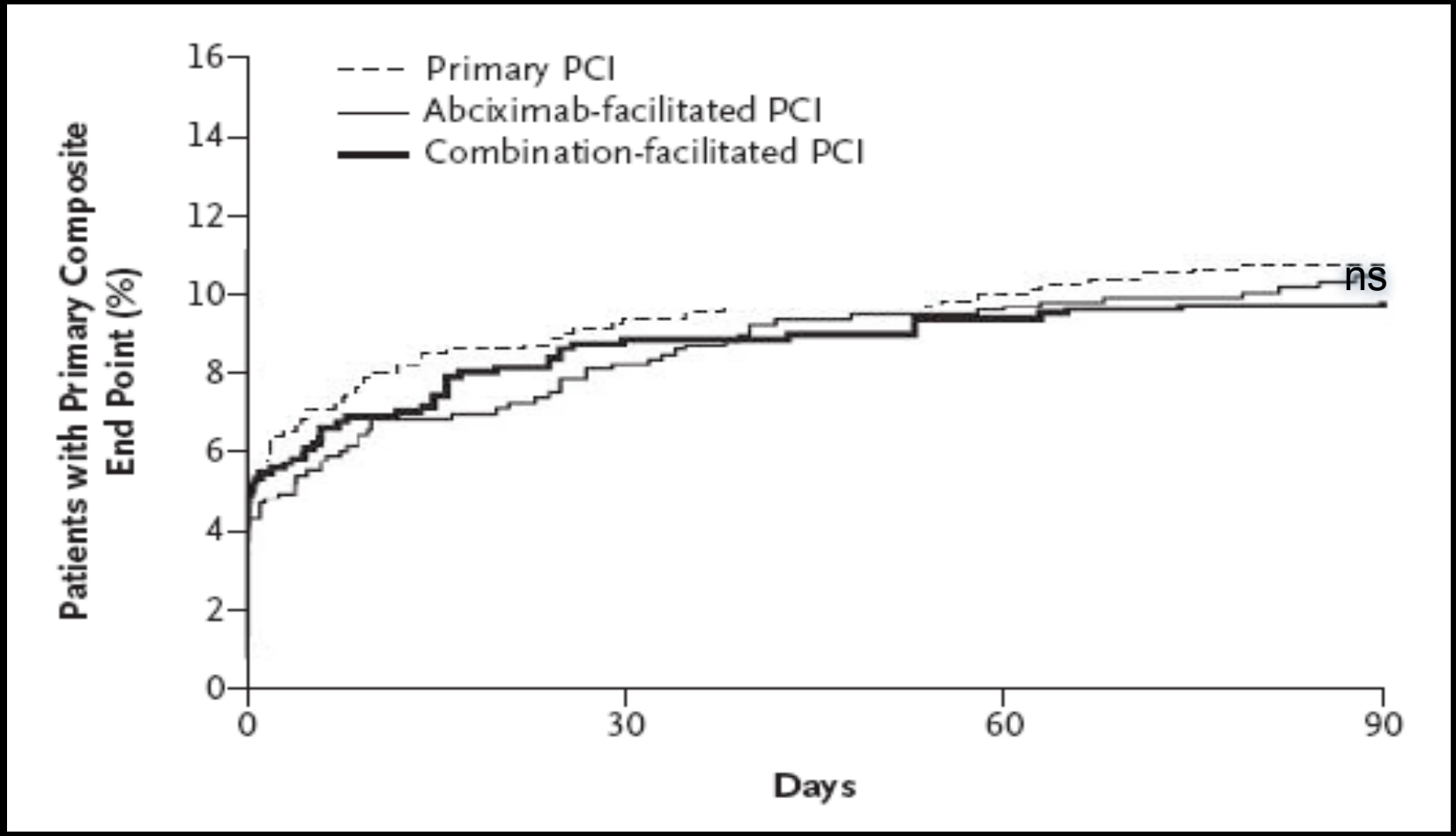
	Upstream GPIIb–IIIa antagonists	III	B

3.QUAND? ANTI-GPIIBIIIA EN PRÉHOSPITALIER?

ESC 2010

Anti-GPIIbIIIa en préhospitalier FINESSE

Médiane: début symptômes-administration antiGPIIbIIIa = 165 min



Ellis, NEJM 2008

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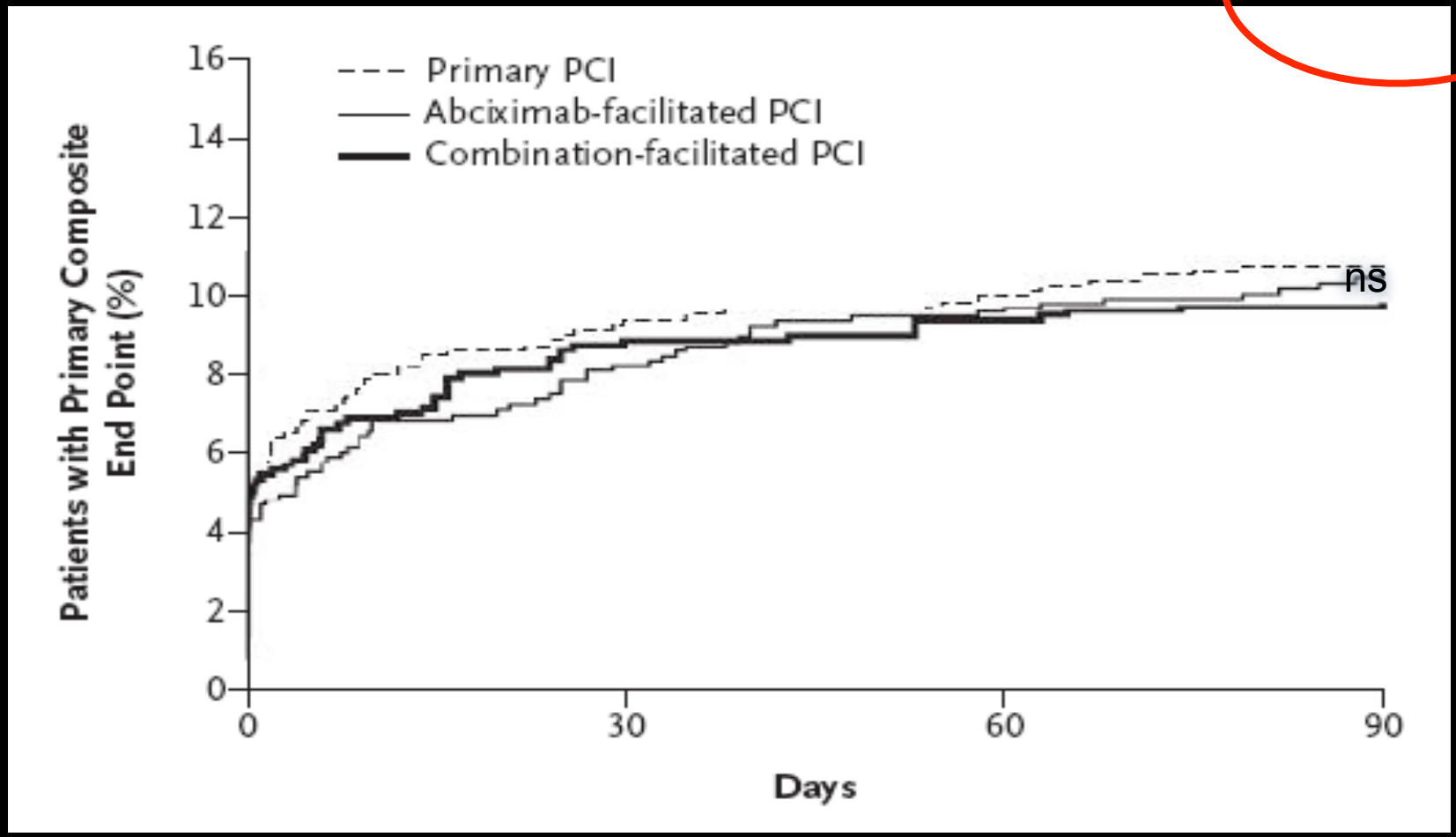

Ellis, NEJM 2008

BRAVE 3

STEMI < 24 heures: Clopidogrel 600 mg +/- Abciximab
Délai moyen = 200 minutes

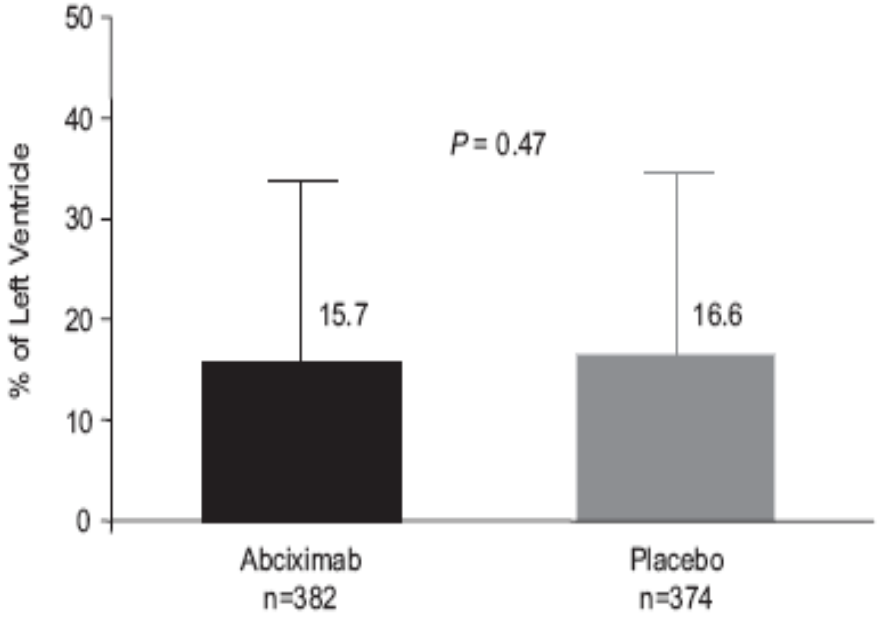

Figure 2. Graphs showing the primary end point of infarct size in both groups (mean±SD).

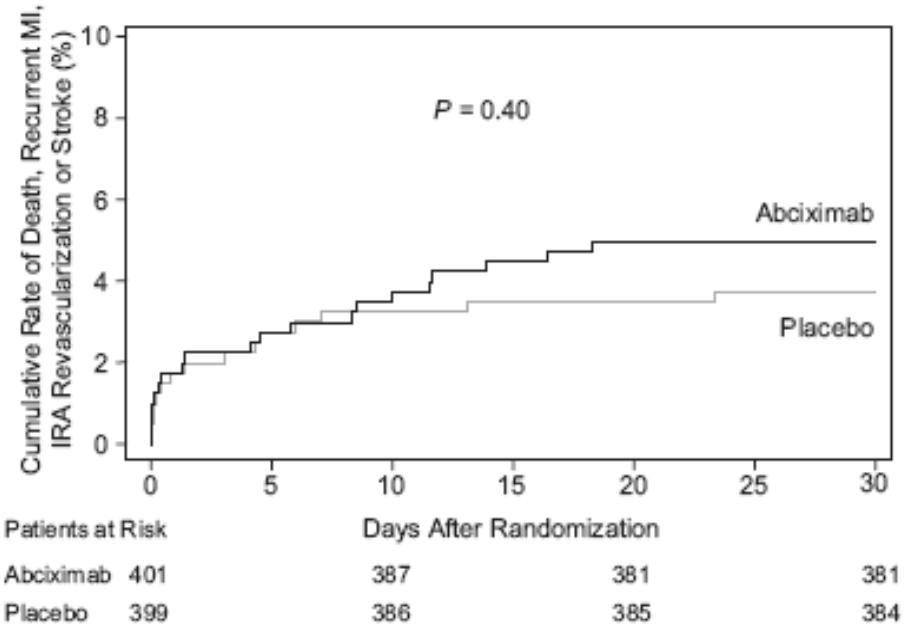

Figure 4. The 30-day cumulative rate of death, recurrent MI, IRA revascularization, and stroke in both groups.

Mehili, Circulation 2009)

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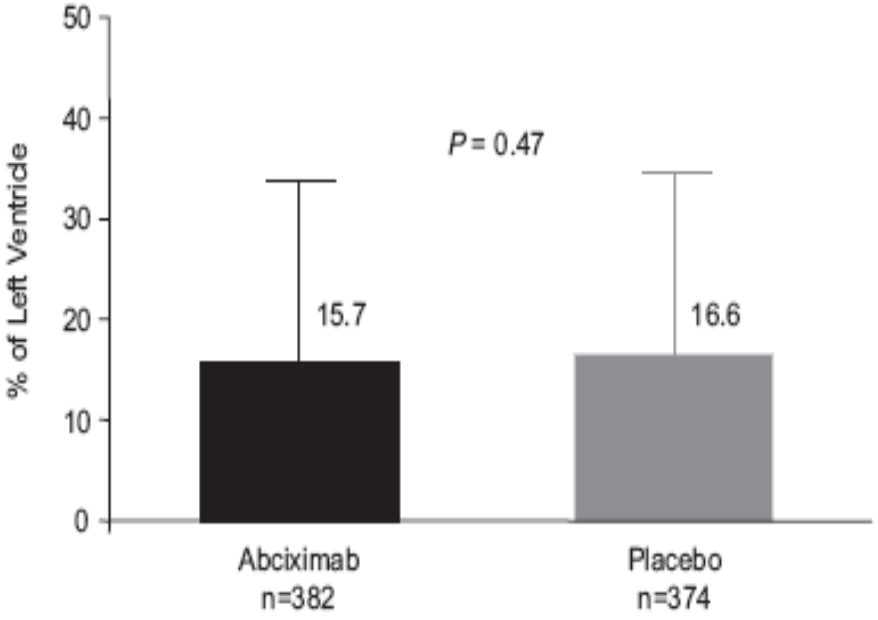

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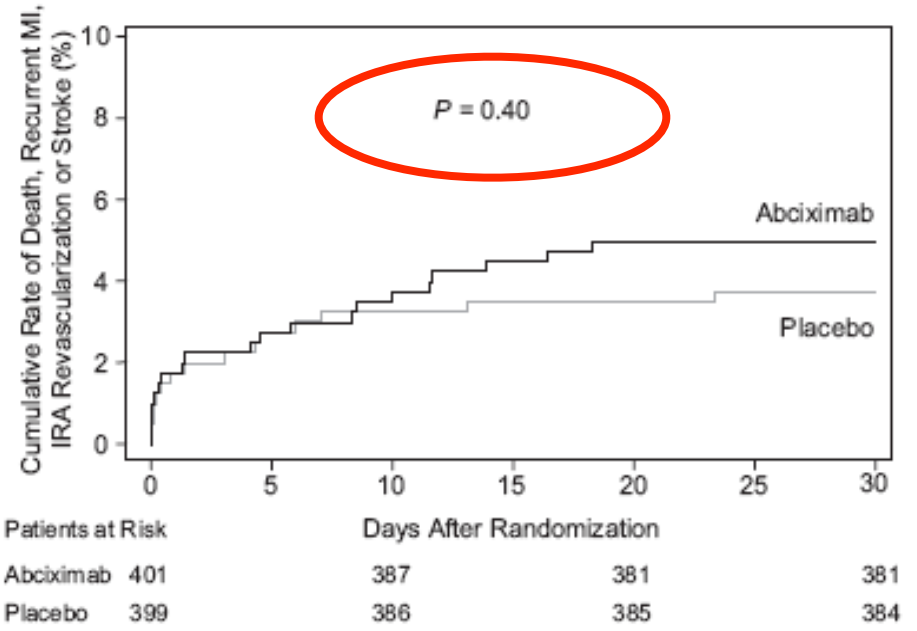

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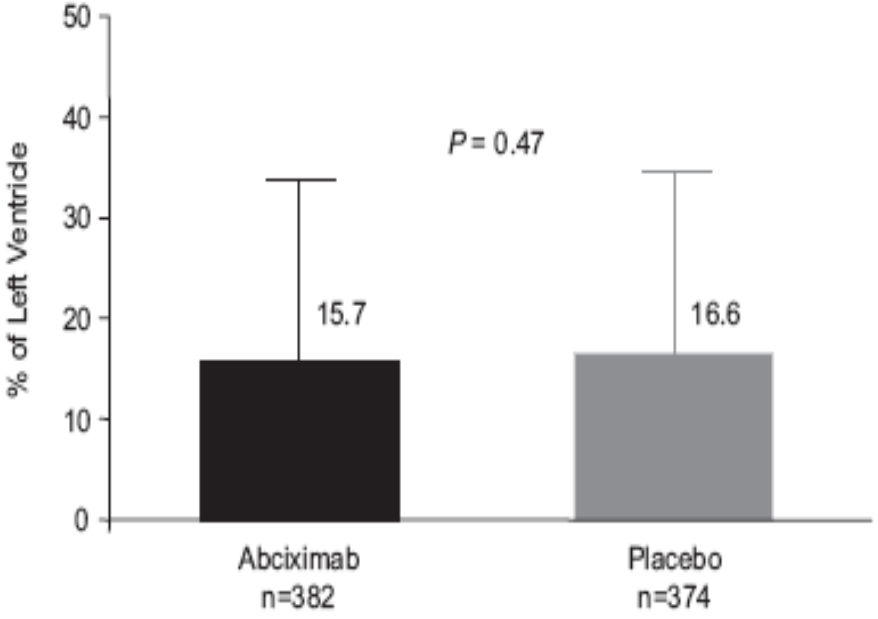

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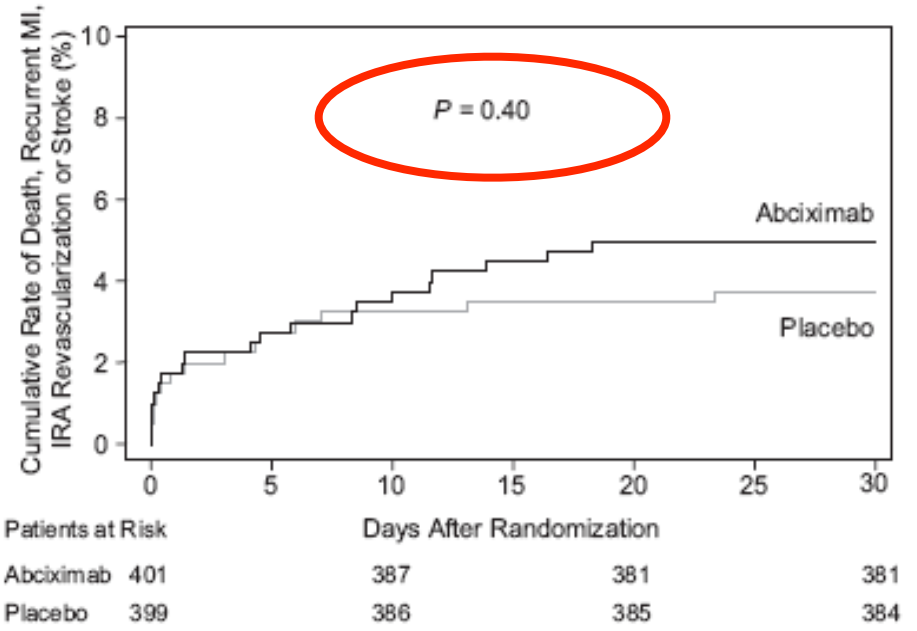

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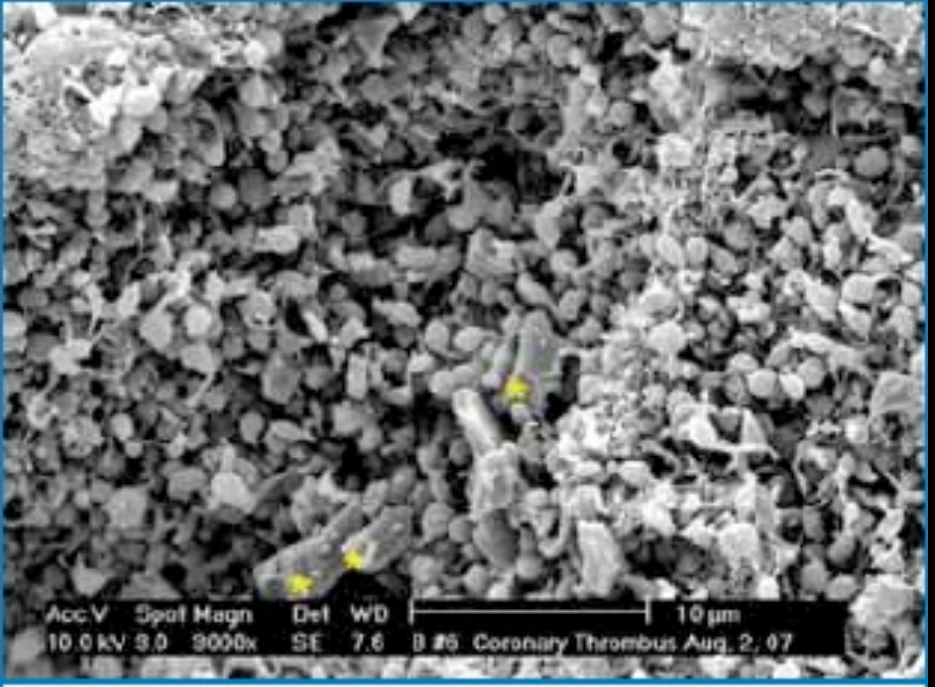
Mehili, Circulation 2009)

Le contenu en fibrine du thrombus double toutes les 2 heures.

C'est le concept des golden hours qui s'applique à la thrombolyse mais aussi aux inhibiteurs de la GPIIb/IIIa qui bloquent la voie finale commune de l'agrégation plaquettaire

AntiGp2b3a en pré-hospitalier: oui si administration précoce<2-3h

Silvain et al. J Am Coll Cardiol 2011



Deuxième heure

Le contenu en fibrine du thrombus double toutes les 2 heures.

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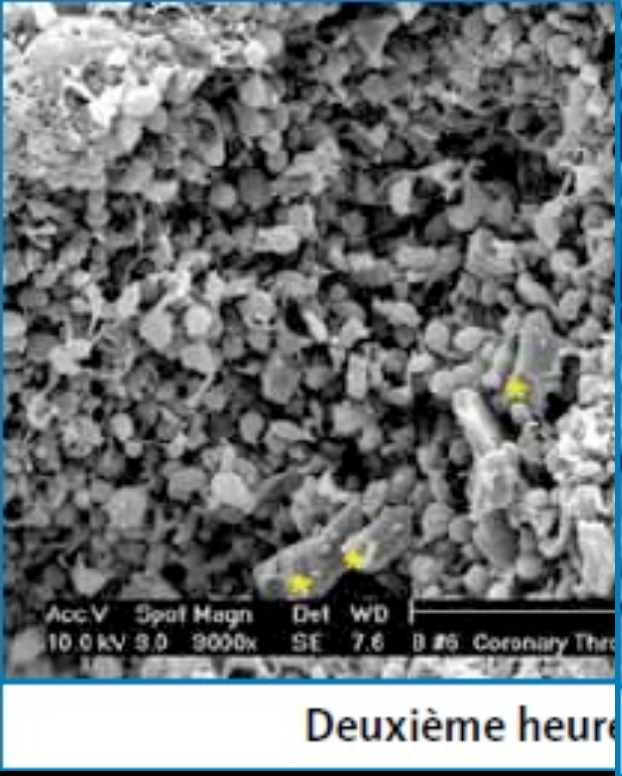

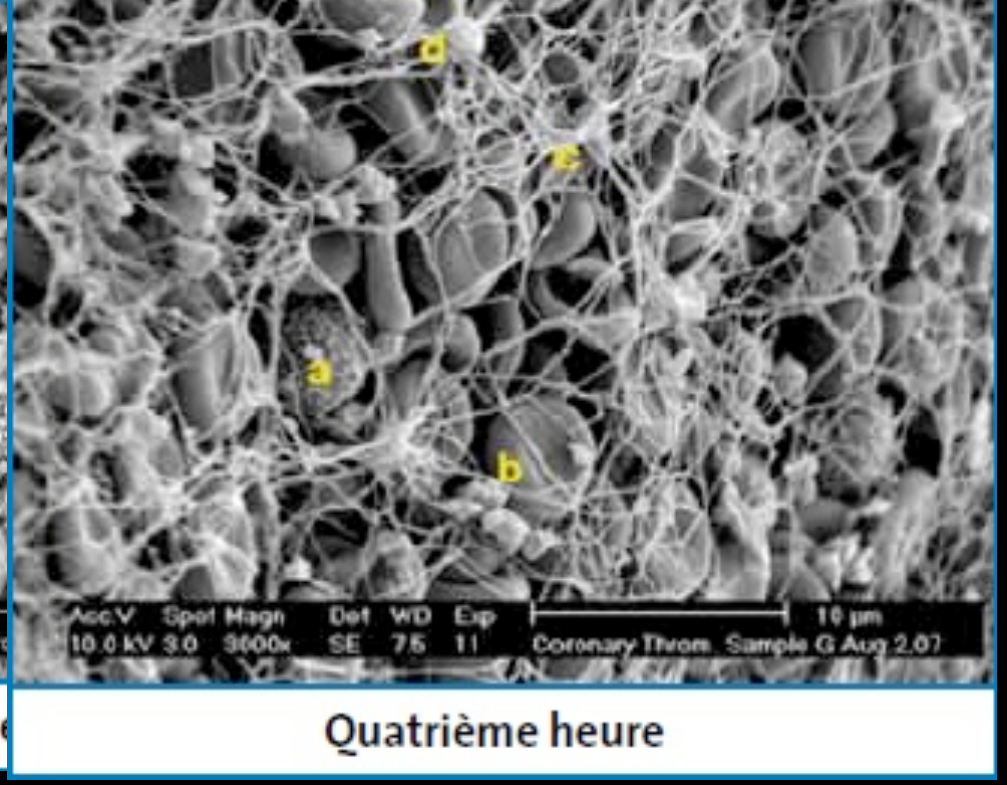

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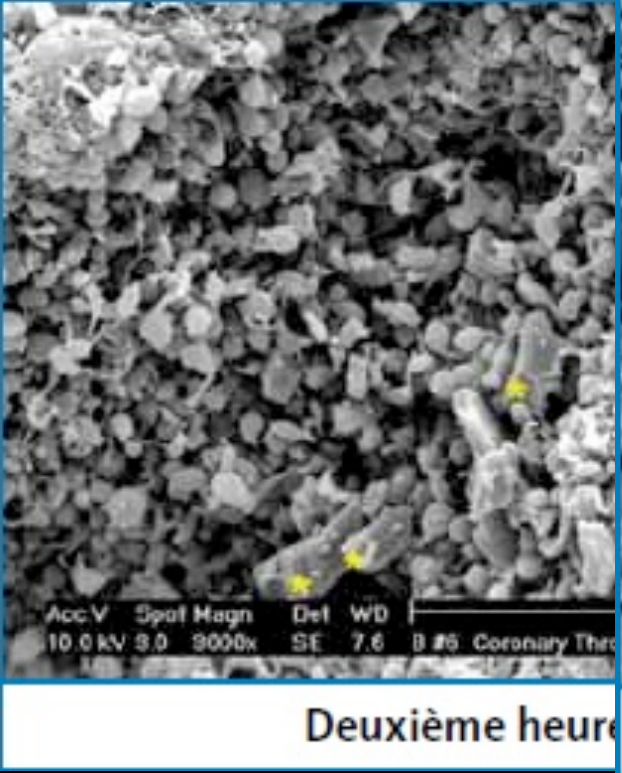

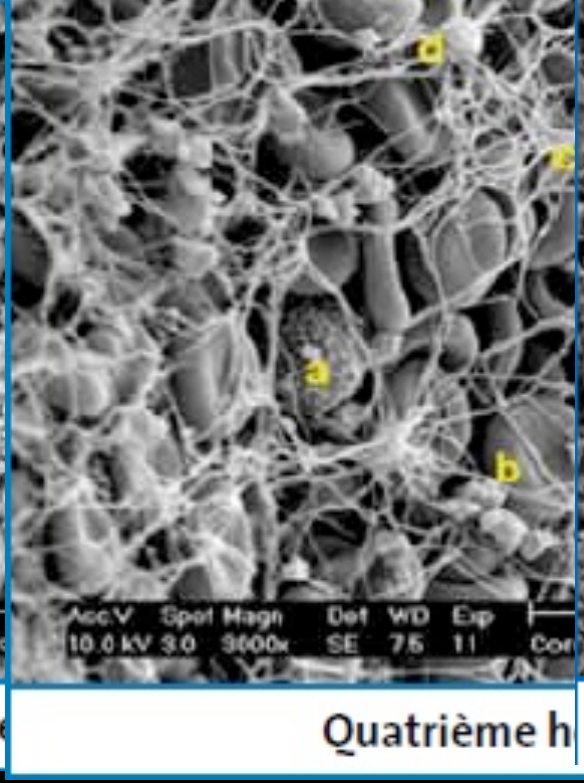

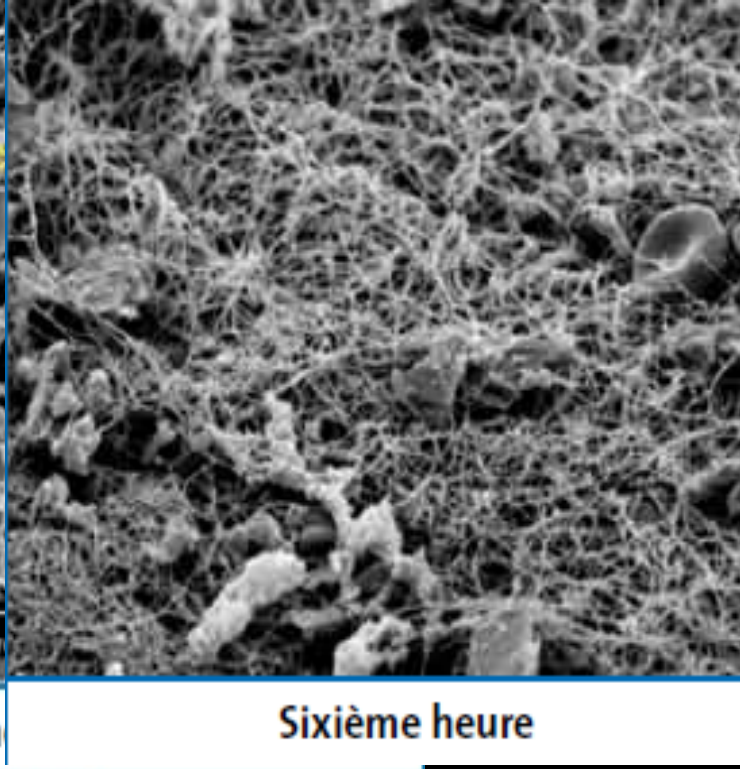

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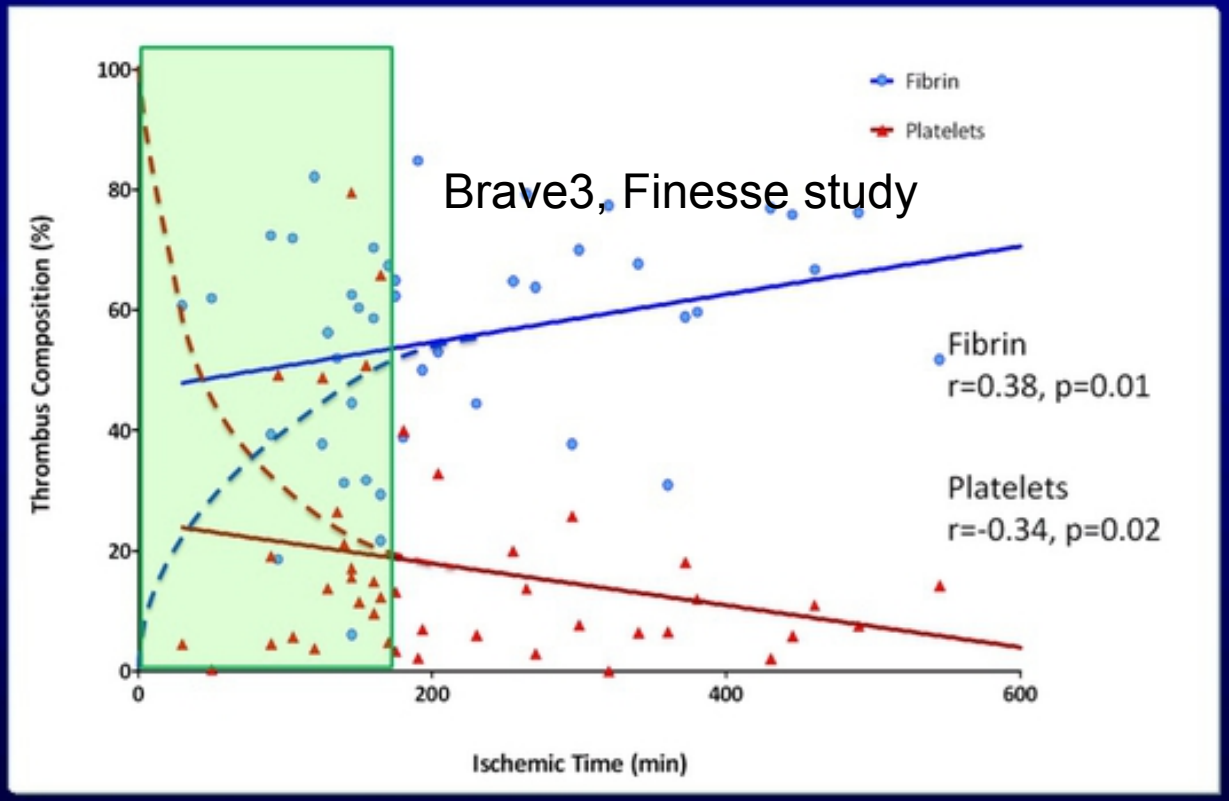
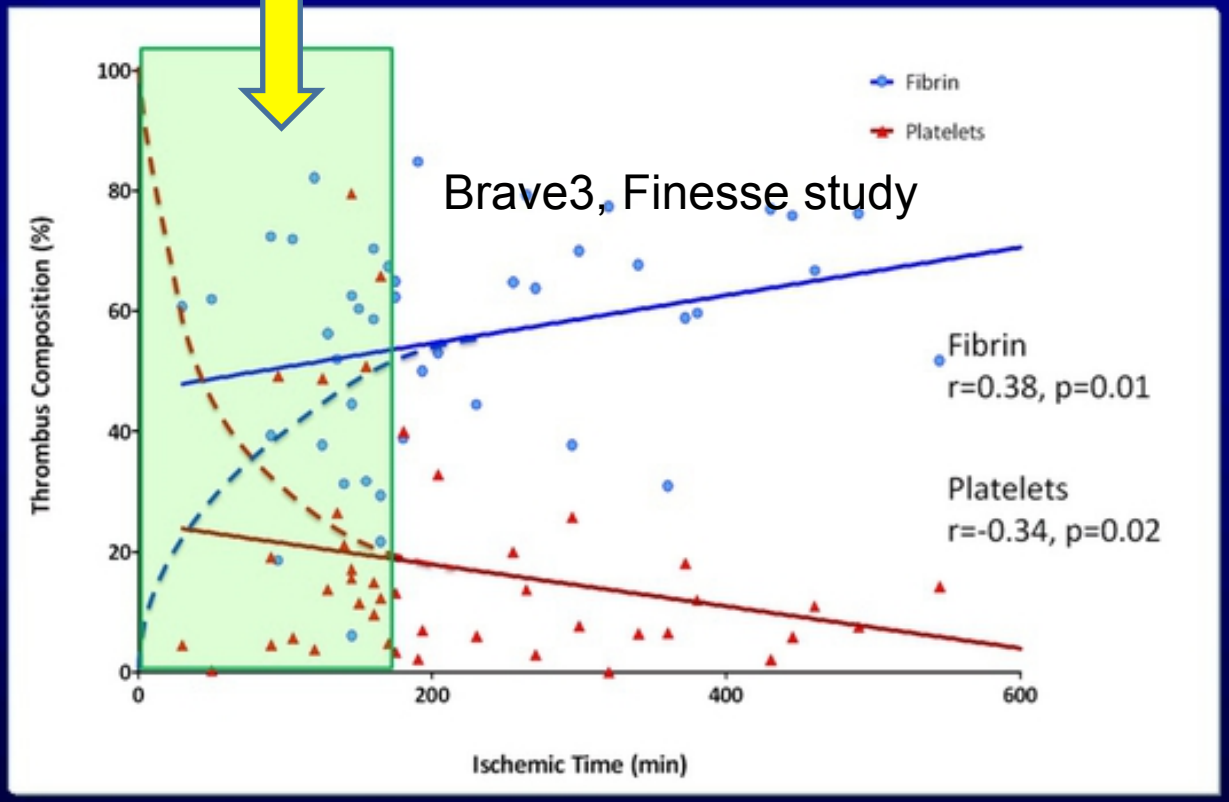


Every additional hour of Ischemic time

- X2 rate of fibrin rich thrombus — adjOR 2 [1.03-3.7], p=0.001
- 50% reduction in platelet content — adjOR 0.5 [0.27-0.94], p=0.001

Silvain et al. J Am Coll Cardiol 2011

AntiGpIIbIIIa+++



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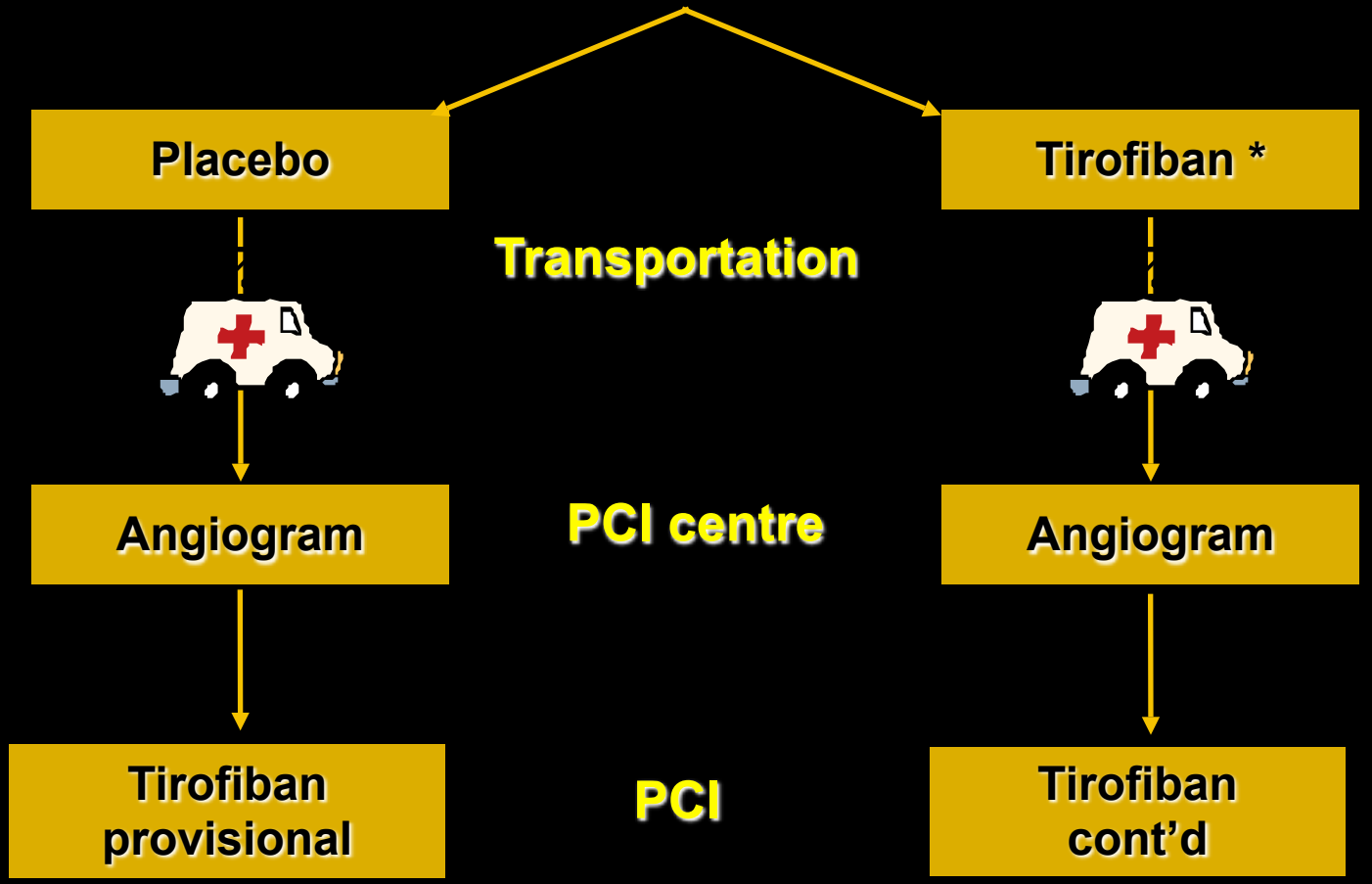
Silvain et al. J Am Coll Cardiol 2011

OnTIME 2: Study design

Acute myocardial infarction diagnosed in ambulance or referral center ASA+600 mg Clopidogrel



van't Hof et al. Lancet 2008;372:537-46


Articles

Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial

Arnoud W J van't Hof, Jurriën ten Berg, Tan Heestermans, Thorsten Dill, Reinhard C Funck, Wouter van Werkum, Jan-Henk E Dambrink, Hamy Suryapranata, Gert van Houwelingen, Jan Paul Ottervanger, Pieter Stella, Evangelos Giannitsis, Christian Hamm, on behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group*

OnTIME 2: Study design

Acute myocardial infarction diagnosed in ambulance or referral center ASA+600 mg Clopidogrel

STEMI: Tirofiban versus placebo Prétraitement par 600 mg clopidogrel

Délai administration OnTIME 2 = 90 min

BRAVE 3: 200 min, FINESSE: 165 min)

Angiogram → **Tirofiban provisional**

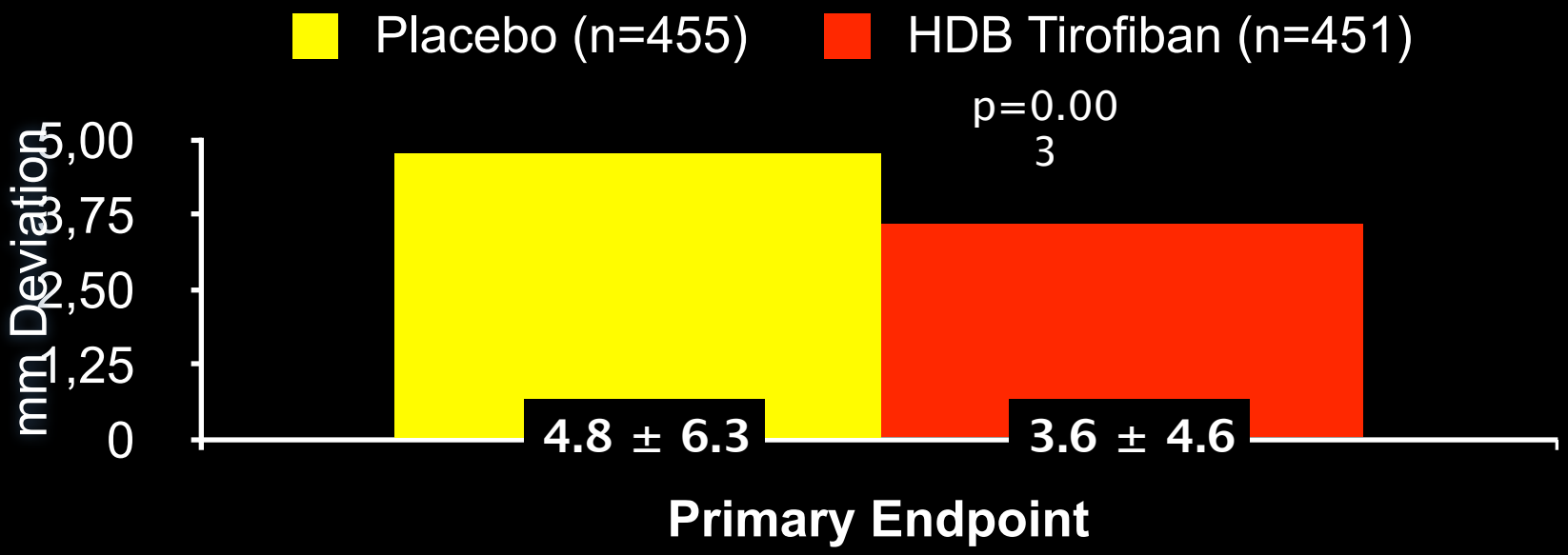
PCI centre → **PCI**

Angiogram → **Tirofiban cont'd**

van't Hof et al. Lancet 2008;372:537-46

On-TIME 2

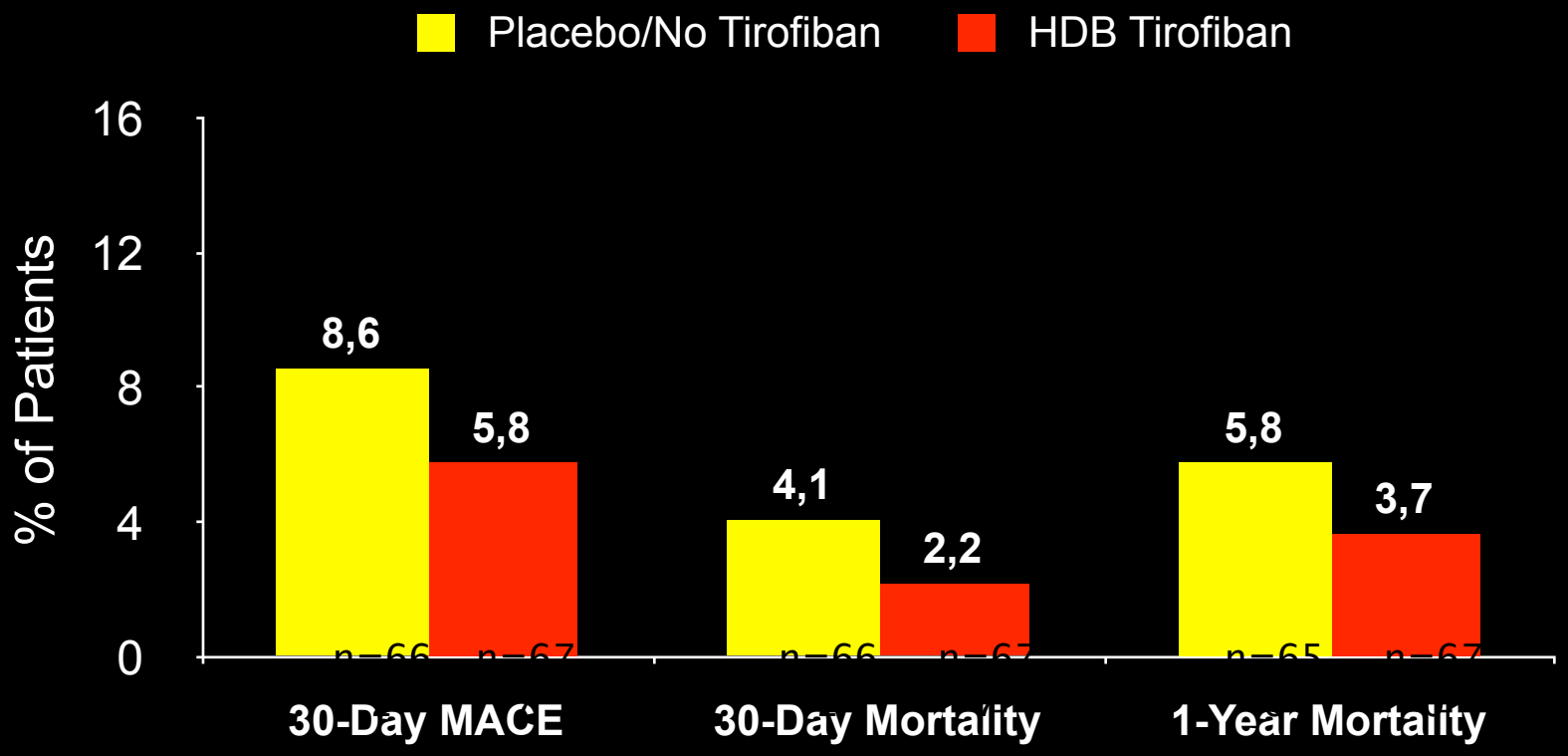
Primary Endpoint: Cumulated ST-Segment Deviation at 1 Hour Post-



van 't Hof AWJ, et al. Lancet 2008;372(9638):537-46.

Results of the pooled analysis confirm

On-TIME 2 Pooled

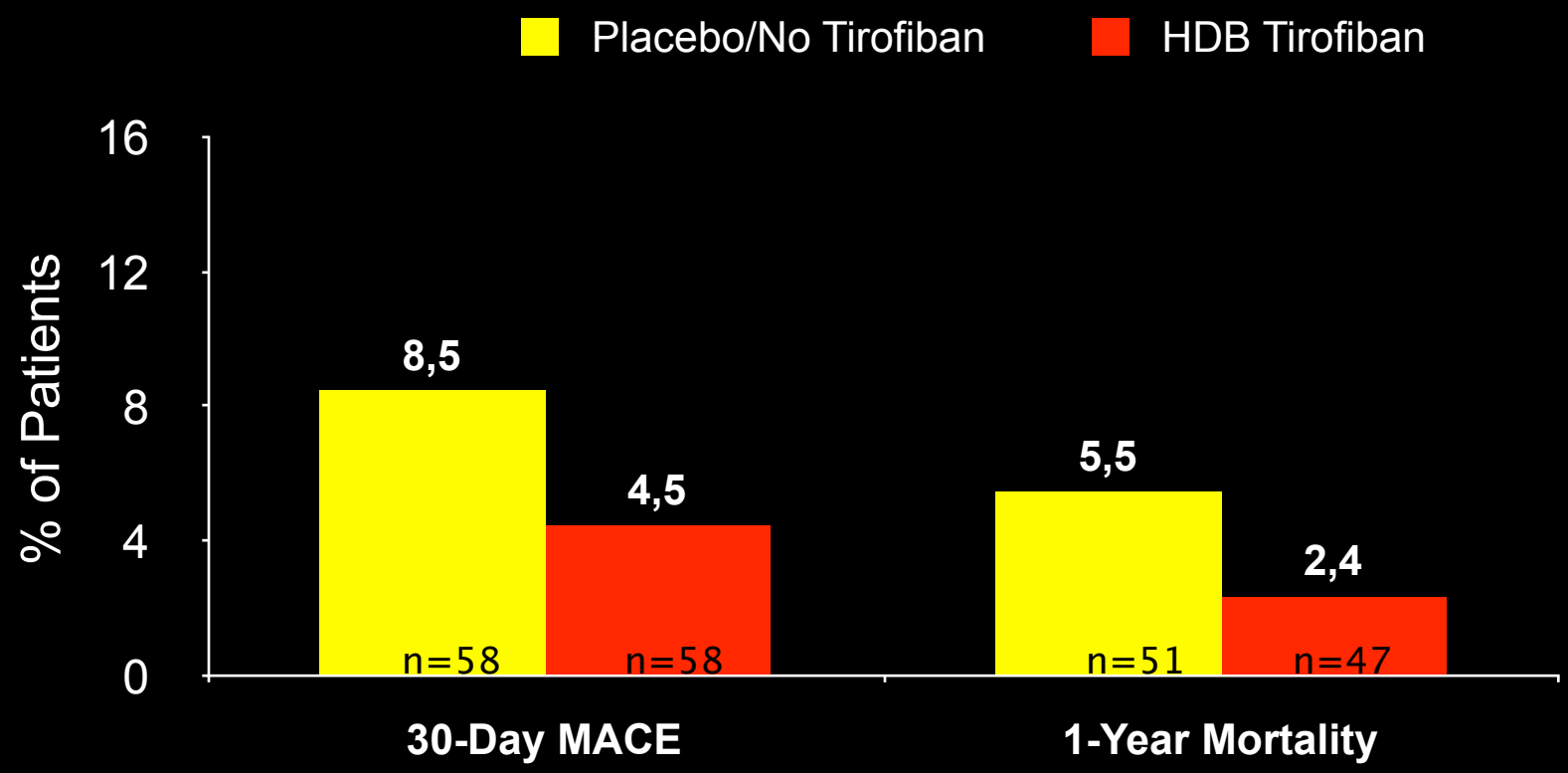


Ten Berg, et al. J Am Coll Cardiol. 2010;55(22):2446-55.

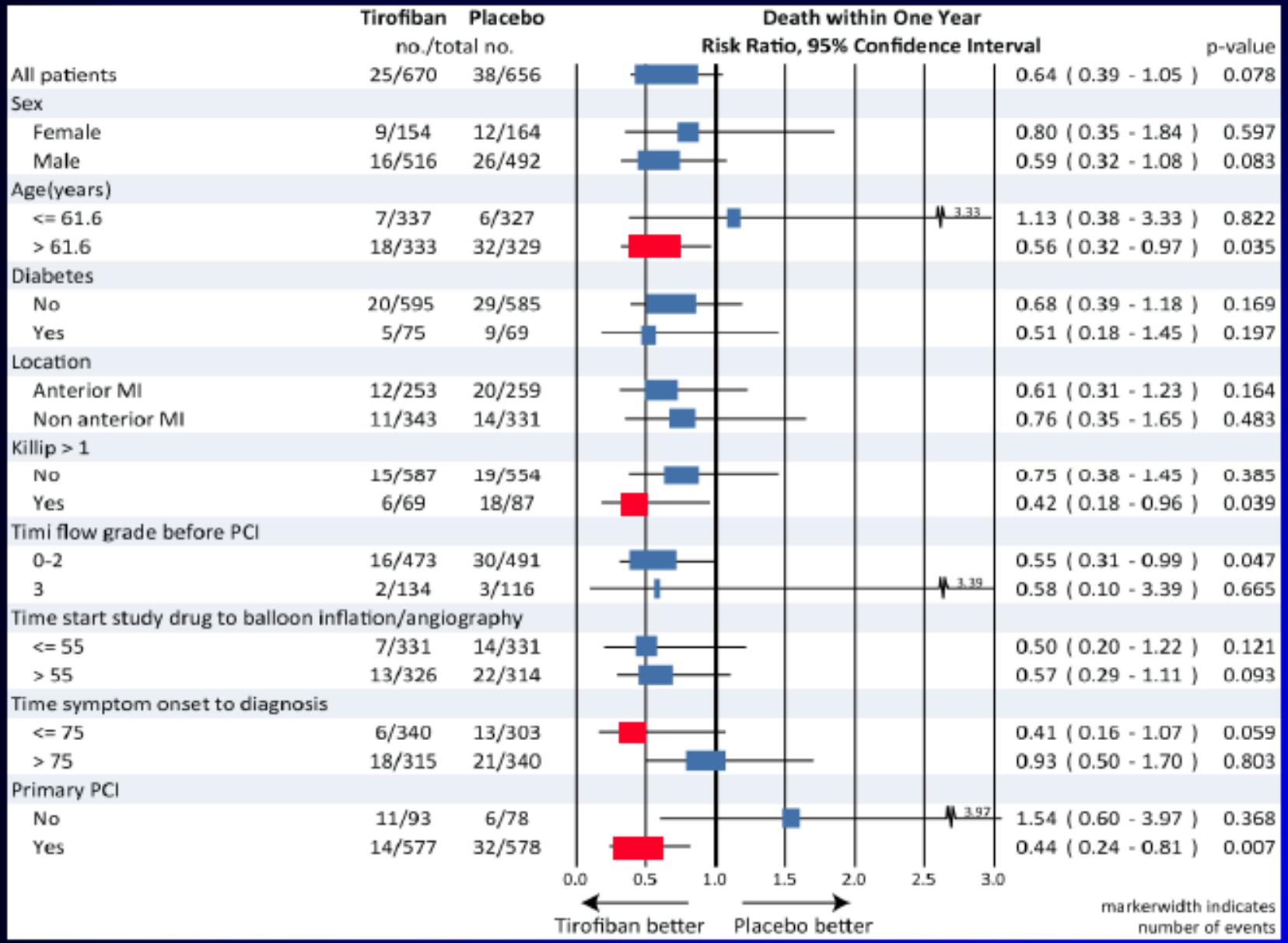
30 Day-MACE and 1 Year-Mortal in

On-TIME 2 Pooled

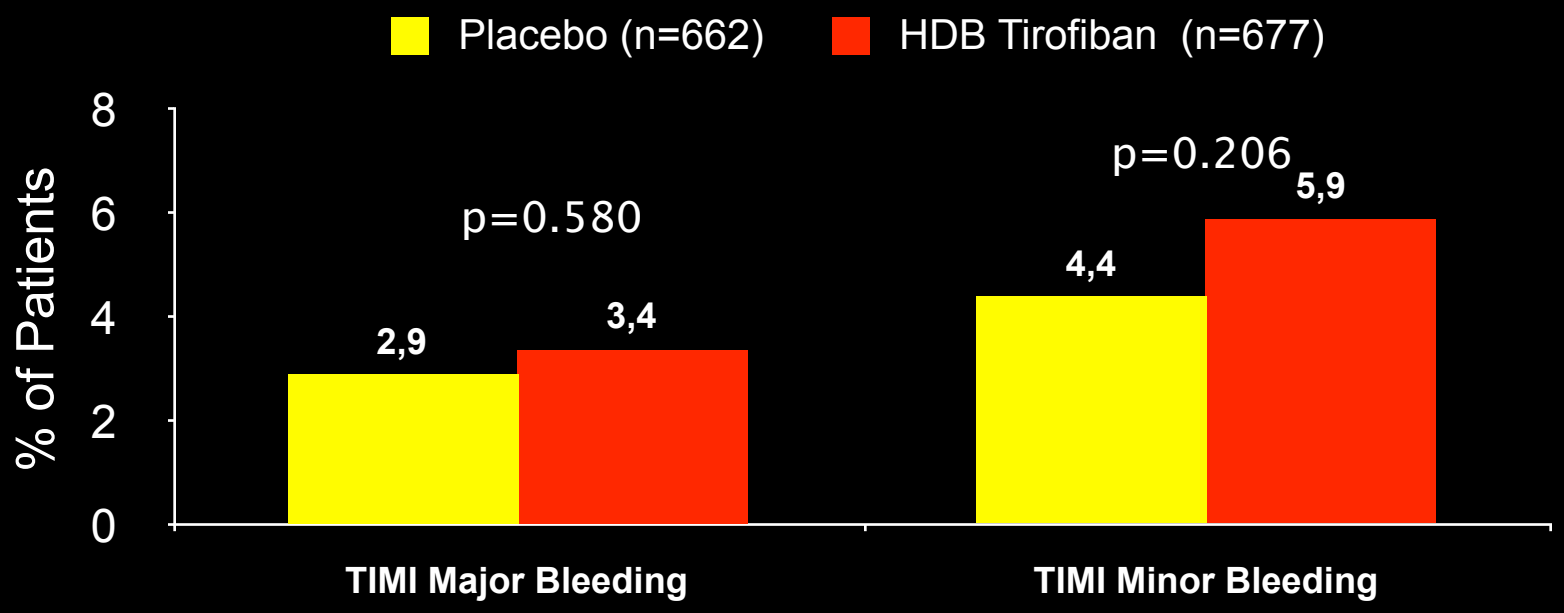
On average, patients underwent pPCI within 2.5 hours of symptom onset



Ten Berg, et al. J Am Coll Cardiol. 2010;55(22):2446-55.


Tirofiban
Placebo
no./total no.
Death within One Year
Risk Ratio, 95% Confidence Interval
p-value
All patients 25/670 38/656 0.64 (0.39 - 1.05) 0.078
Sex
Female 9/154 12/164 0.80 (0.35 - 1.84) 0.597
Male 16/516 26/492 0.59 (0.32 - 1.08) 0.083
Age(years)
<= 61.6 7/337 6/327 1.13 (0.38 - 3.33) 0.822
> 61.6 18/333 32/329 0.56 (0.32 - 0.97) 0.035
Diabetes
No 20/595 29/585 0.68 (0.39 - 1.18) 0.169
Yes 5/75 9/69 0.51 (0.18 - 1.45) 0.197
Location
Anterior MI 12/253 20/259 0.61 (0.31 - 1.23) 0.164
Non anterior MI 11/343 14/331 0.76 (0.35 - 1.65) 0.483
Killip > 1
No 15/587 19/554 0.75 (0.38 - 1.45) 0.385
Yes 6/69 18/87 0.42 (0.18 - 0.96) 0.039
Timi flow grade before PCI
0-2 16/473 30/491 0.55 (0.31 - 0.99) 0.047
3 2/134 3/116 0.58 (0.10 - 3.39) 0.665
Time start study drug to balloon inflation/angiography
<= 55 7/331 14/331 0.50 (0.20 - 1.22) 0.121
> 55 13/326 22/314 0.57 (0.29 - 1.11) 0.093
Time symptom onset to diagnosis
<= 75 6/340 13/303 0.41 (0.16 - 1.07) 0.059
> 75 18/315 21/340 0.93 (0.50 - 1.70) 0.803
Primary PCI
No 11/93 6/78 1.54 (0.60 - 3.97) 0.368
Yes 14/577 32/578 0.44 (0.24 - 0.81) 0.007
3.33
3.39
3.97
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Tirofiban better
Placebo better
markerwidth indicates number of events

On-TIME 2
Pooled



Ten Berg, et al. J Am Coll Cardiol. 2010;55(22):2446-55

Anti-GPIIbIIIa et STEMI

4.QUELLE MOLÉCULE?

Méta analyses d'études randomisées récentes Comparaison Abciximab,Integrilin,Tirofiban

-5 études randomisées (*n=2138 patients*)

-Evaluation:

Décès, RVC, ré infarctus, et saignements à J30 et 8 mois

-Pas de différences à J30 sur :

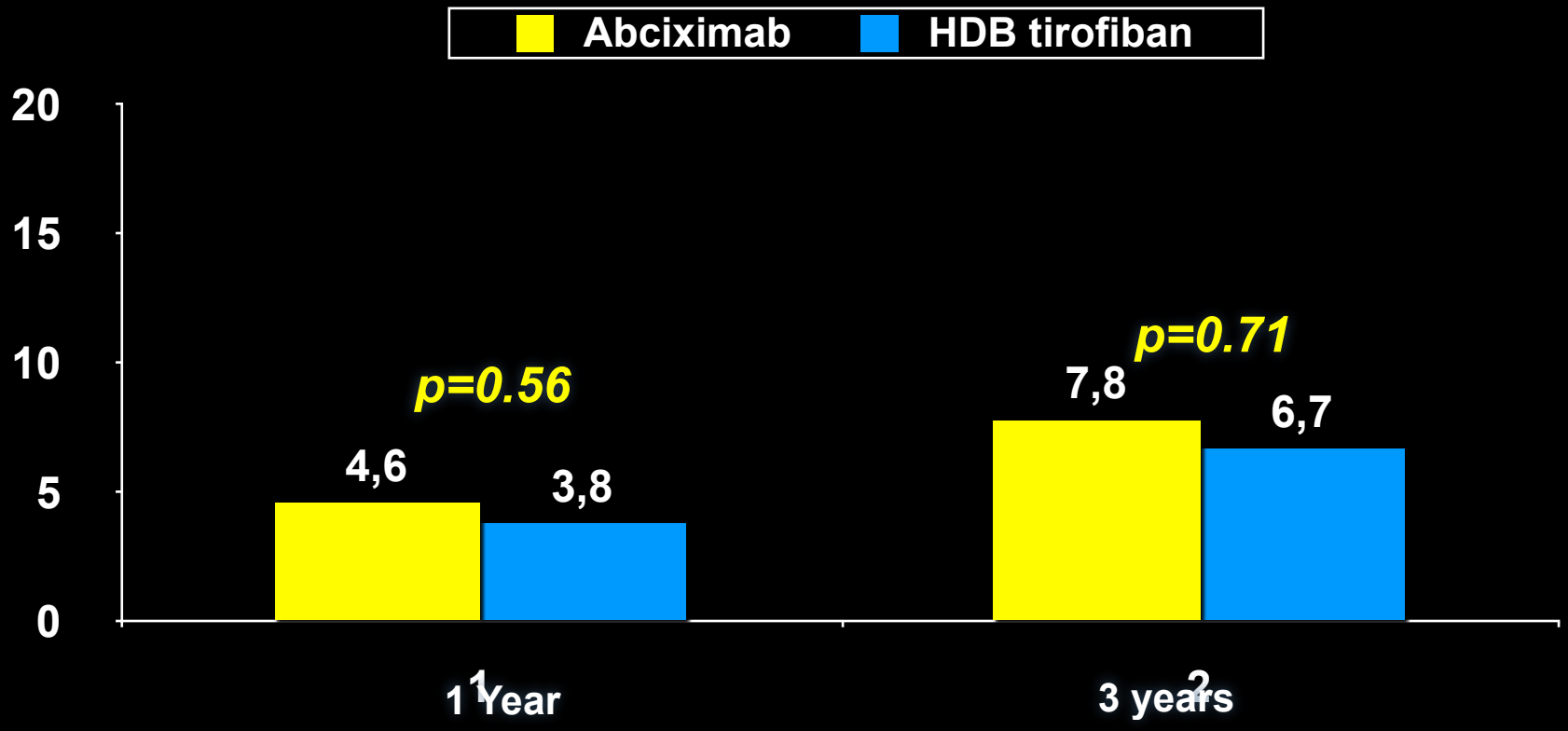
Décès , ré infarctus et saignements majeurs

-Pas de différences à 8 mois sur:

Décès et ré infarctus.

Gurm et al. 2009 Circ Cardiovasc Intervent. 108.847996cv

MULTISTRATEGY: Long Term Results



JACC;2010:55:10A 1100-277

Oral presentation; ESC Stockholm 2010

Anti-GPIIbIIIa et STEMI

5.L'UTILISATION DU PRASUGREL VA-T-ELLE

Point-of-Care Measured Platelet Inhibition Correlates With a Reduced Risk of an Adverse Cardiac Event After Percutaneous Coronary Intervention

Results of the GOLD (AU-Assessing Ultegra) Multicenter Study

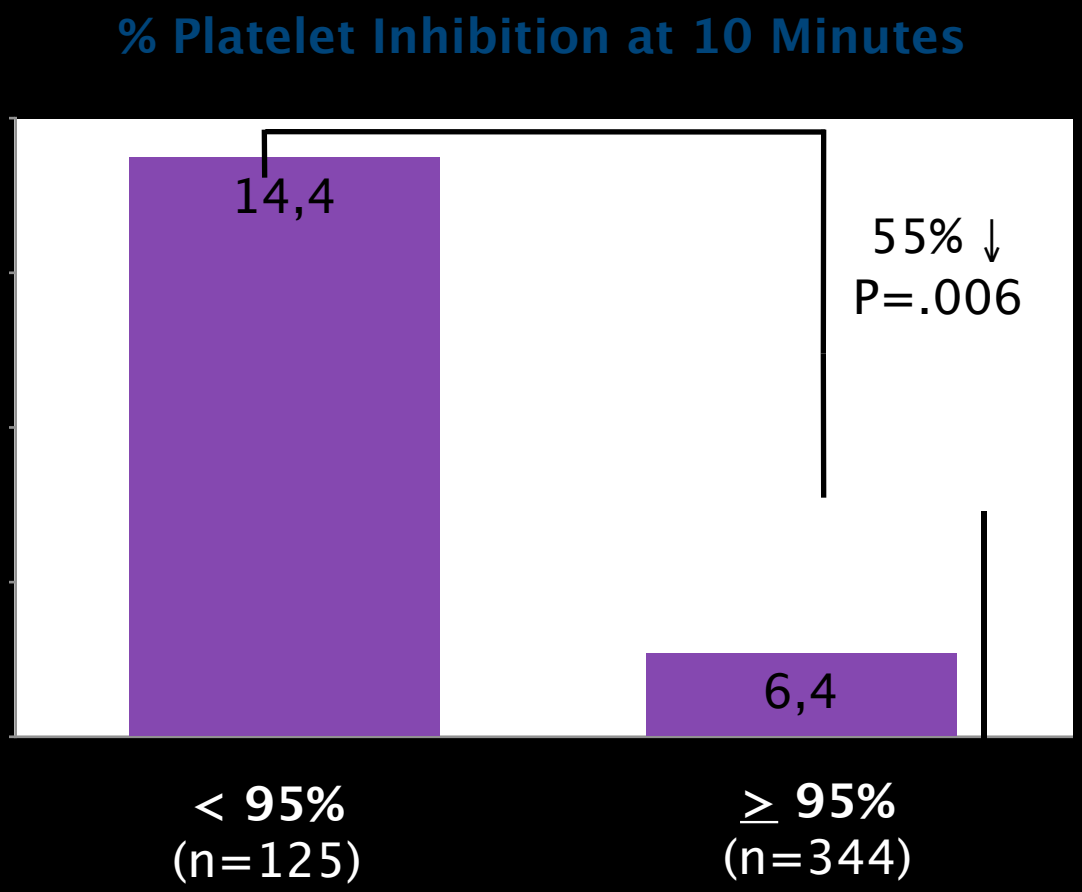
Steven R. Steinhubl, MD; J. David Talley, MD; Gregory A. Braden, MD; James E. Tcheng, MD; Peter J. Casterella, MD; David J. Moliterno, MD; Frank I. Navetta, MD; Peter B. Berger, MD; Jeffrey J. Popma, MD; George Dangas, MD; Richard Gallo, MD; David C. Sane, MD; Jorge F. Saucedo, MD; Gang Jia, MA; A. Michael Lincoff, MD; Pierre Theroux, MD; David R. Holmes, MD; Paul S. Teirstein, MD; Dean J. Kereiakes, MD

Background—The optimal level of platelet inhibition with a glycoprotein (GP) IIb/IIIa antagonist necessary to minimize thrombotic complications in patients undergoing a percutaneous coronary intervention (PCI) is currently unknown.

Methods and Results—Five hundred patients undergoing a PCI with the planned use of a GP IIb/IIIa inhibitor had platelet inhibition measured at 10 minutes, 1 hour, 8 hours, and 24 hours after the initiation of therapy with the Ultegra Rapid Platelet Function Assay (Accumetrics). Major adverse cardiac events (MACEs: composite of death, myocardial infarction, and urgent target vessel revascularization) were prospectively monitored, and the incidence correlated with the measured level of platelet function inhibition at all time points. One quarter of all patients did not achieve ≥95% inhibition 10 minutes after the bolus and experienced a significantly higher incidence of MACEs (14.4% versus 6.4%, $P=0.006$). Patients whose platelet function was <70% inhibited at 8 hours after the start of therapy had a MACE rate of 25% versus 8.1% for those ≥70% inhibited ($P=0.009$). By multivariate analysis, platelet function inhibition ≥95% at 10 minutes after the start of therapy was associated with a significant decrease in the incidence of a MACE (odds ratio 0.46, 95% CI 0.22 to 0.96, $P=0.04$).

Conclusions—Substantial variability in the level of platelet function inhibition is achieved with GP IIb/IIIa antagonist therapy among patients undergoing PCI. The level of platelet function inhibition as measured by a point-of-care assay is an independent predictor for the risk of MACEs after PCI. (*Circulation*. 2001;103:2572-2578.)

Platelet Inhibition (Measured by RPFA) and Clinical Events



Steinhubl et al Circulation 2001: 103

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Prasugrel Versus Tirofiban Bolus With or Without Short Post-Bolus Infusion With or Without Concomitant Prasugrel Administration in Patients With Myocardial Infarction Undergoing Coronary Stenting

The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial

Marco Valgimigli, MD, PHD,* Matteo Tebaldi, MD,* Gianluca Campo, MD,* Stefania Gambetti, BSC,† Laura Bristot, BSC,* Monia Monti, BSC,* Giovanni Parrinello, PHD,‡ Roberto Ferrari, MD, PHD,*§ on behalf of the FABOLUS PRO Investigators

Ferrara and Brescia, Italy

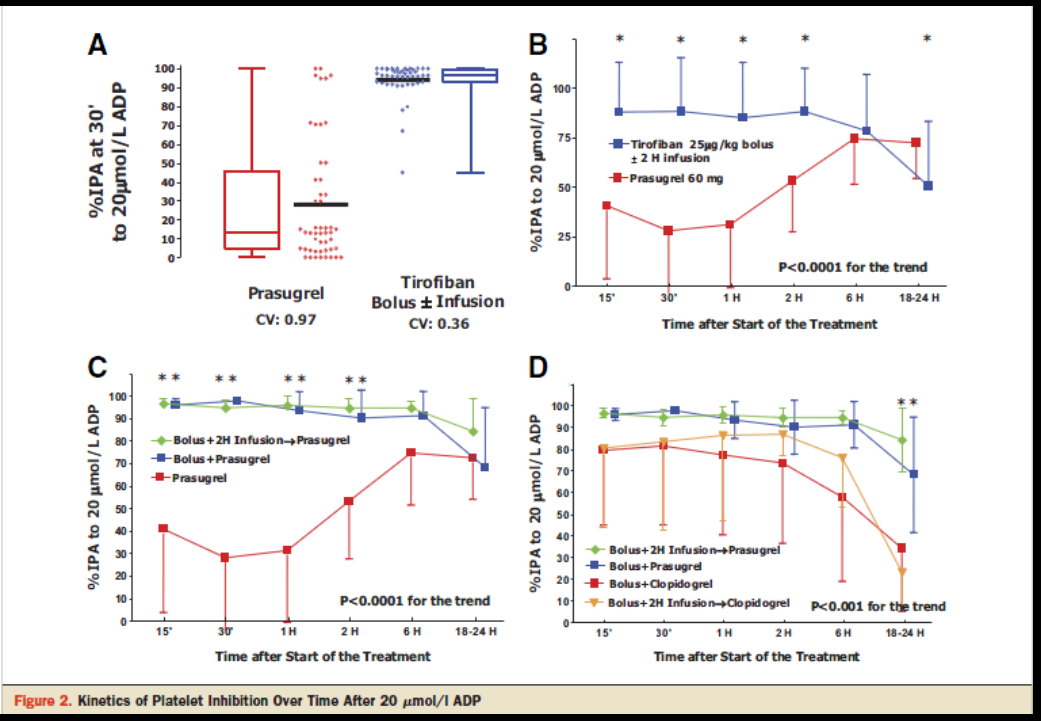


Figure 2. Kinetics of Platelet Inhibition Over Time After 20 µmol/l ADP

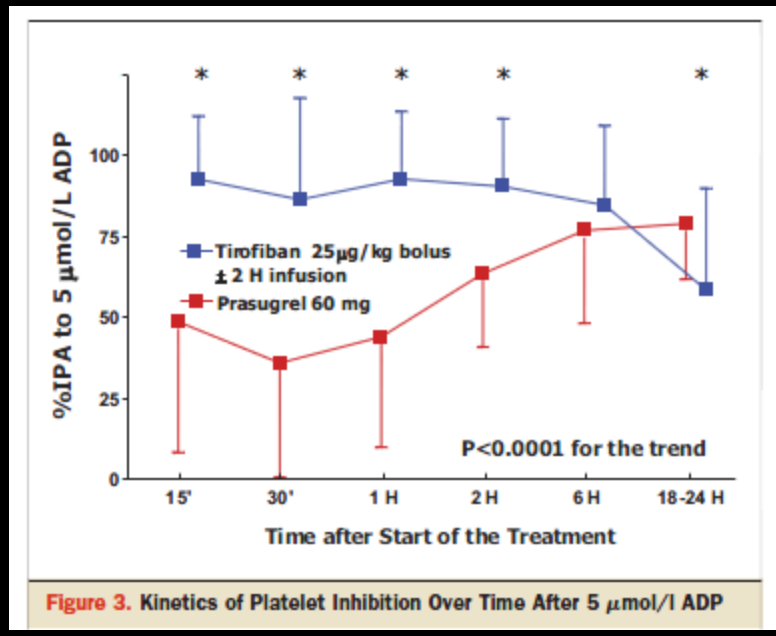
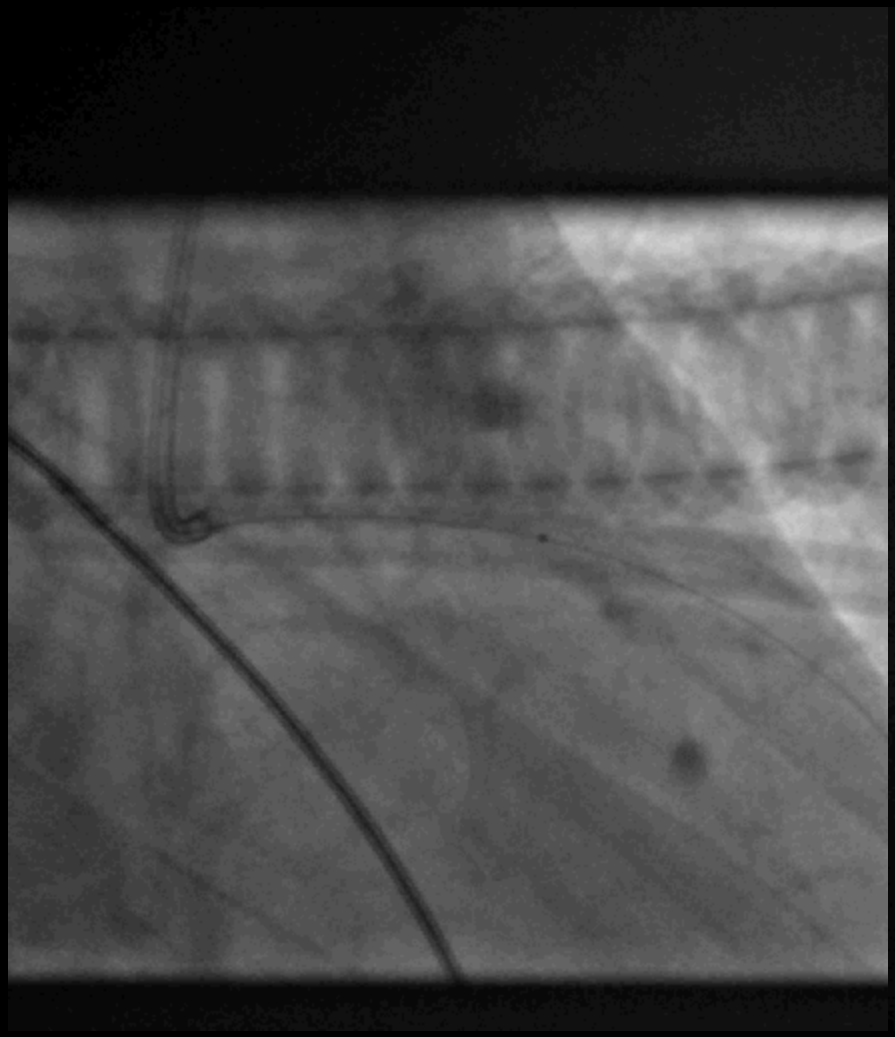
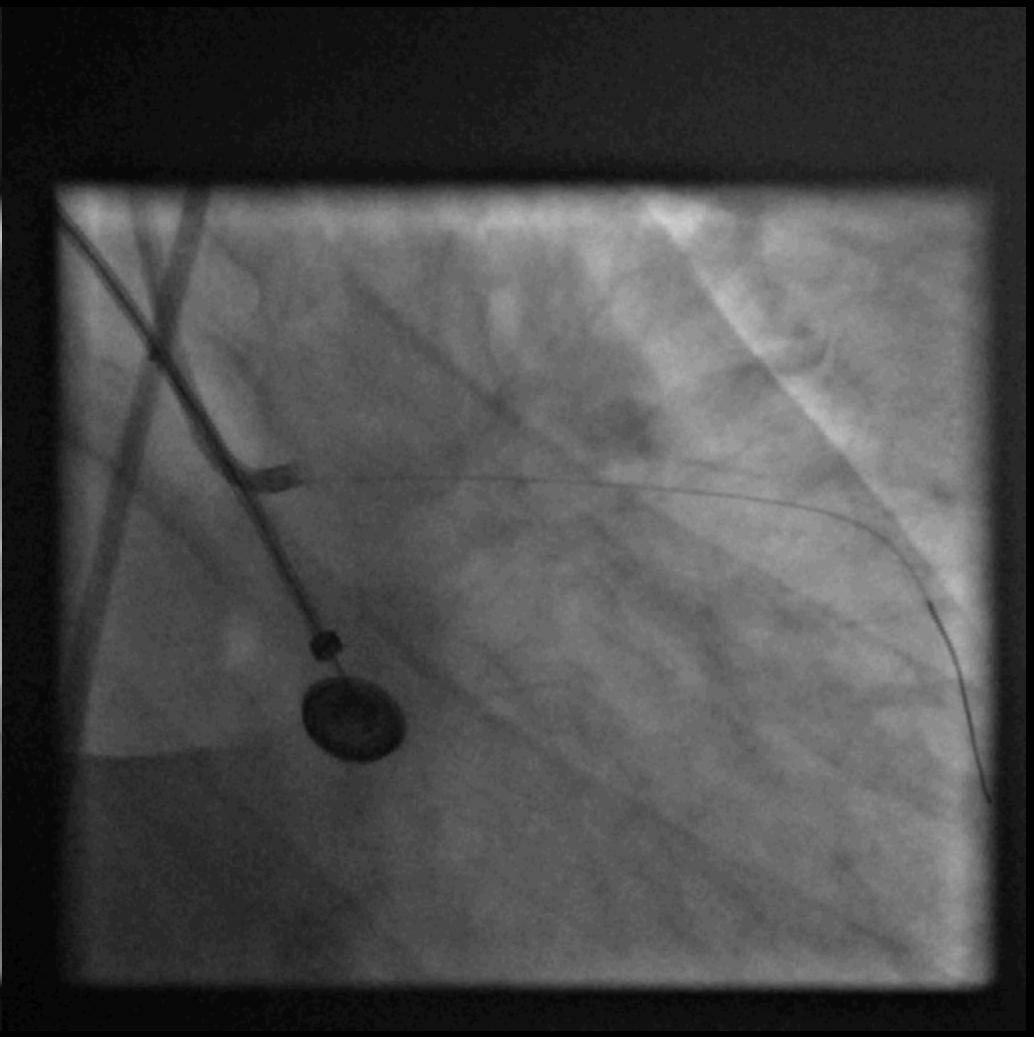
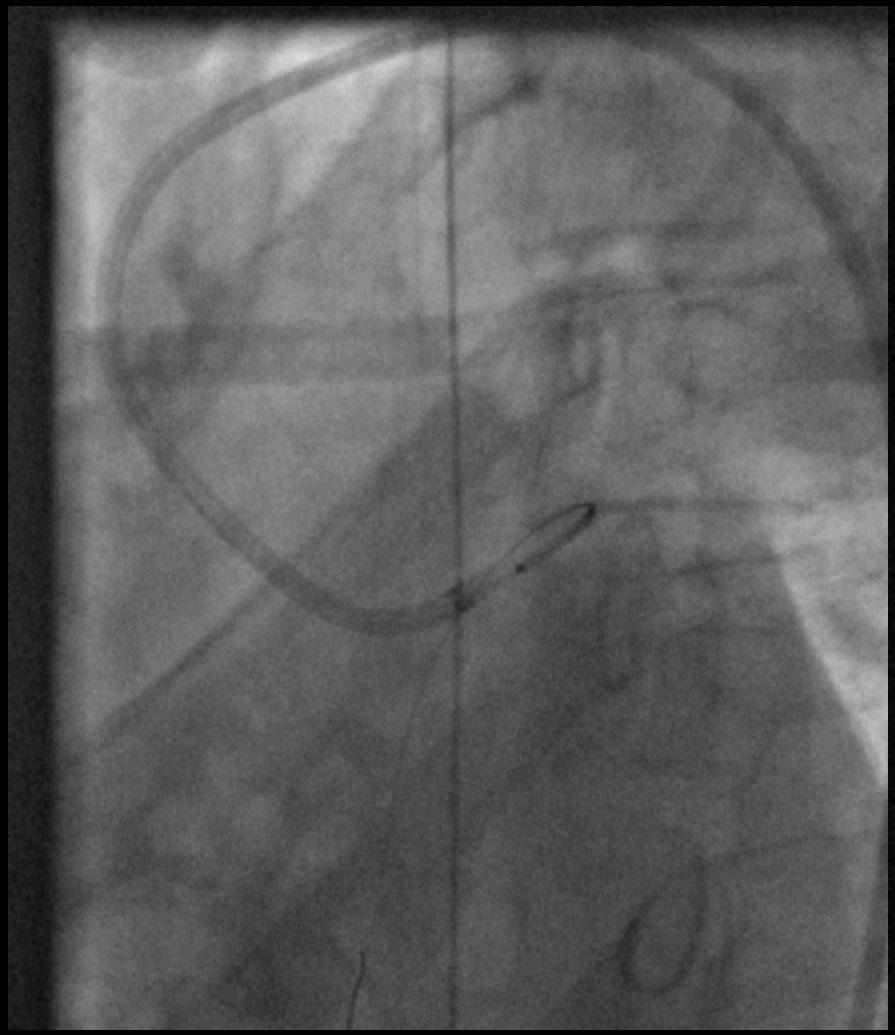
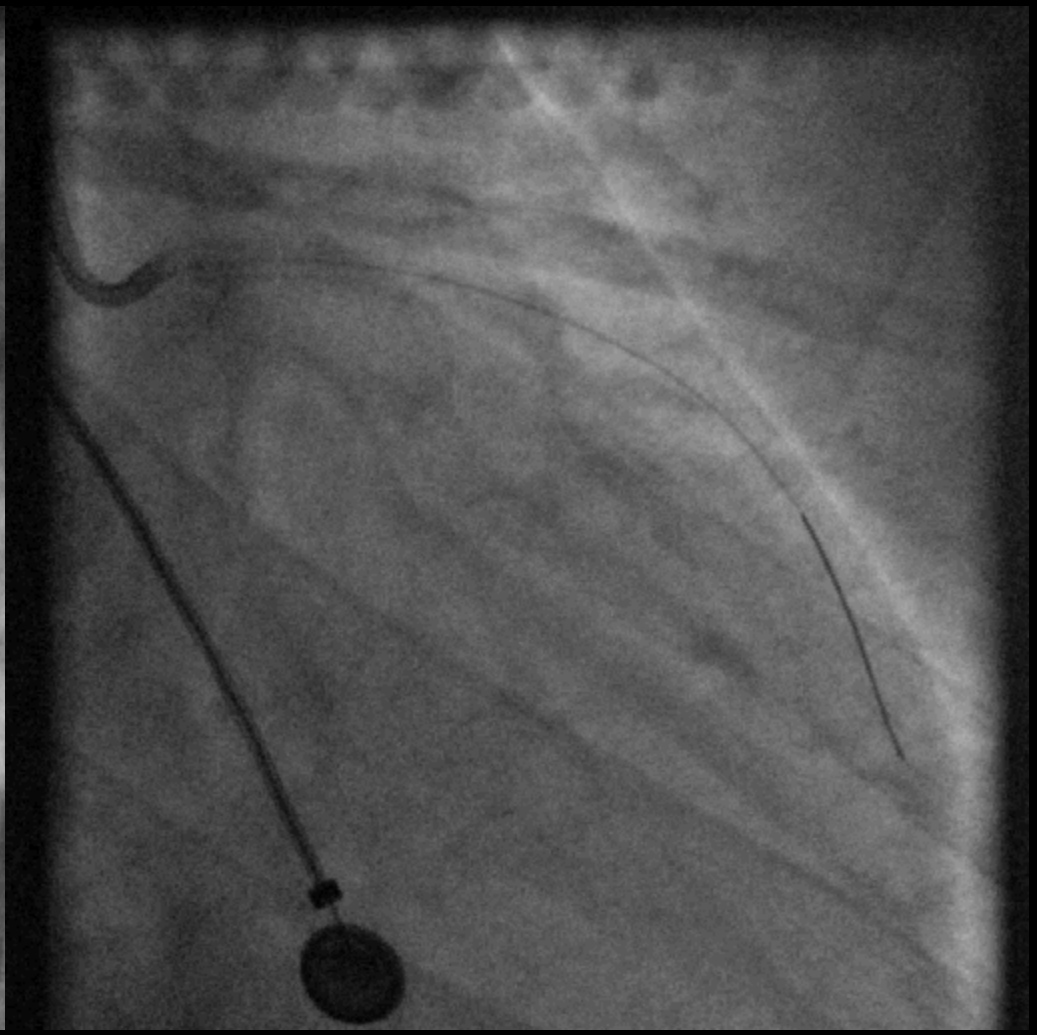


Figure 3. Kinetics of Platelet Inhibition Over Time After 5 µmol/l ADP









conclusions

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- L'inhibition antiplaquettaire puissante et rapide par antiGpIIbIIIa comme environnement pharmacologique d'une angioplastie primaire est clairement établie.

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- Le bénéfice d'une « déthrombose antiplaquettaire » par un anti-GPIIbIIIa administré dès la phase pré-hospitalière pourrait se justifier:

conclusions

- L'inhibition antiplaquettaire puissante et rapide par antiGpIIbIIIa comme environnement pharmacologique d'une angioplastie primaire est clairement établie.
- Le bénéfice d'une « déthrombose antiplaquettaire » par un anti-GPIIbIIIa administré dès la phase pré-hospitalière pourrait se justifier:
- Chez les patients vu précocement (<3h), à haut risque thrombotique (antérieur, diabétique, killip>1…) et à risque hémorragique faible à modérée

Merci de votre attention