ACTUALITES
Insuffisance coronaire et traitement anti-thrombotique

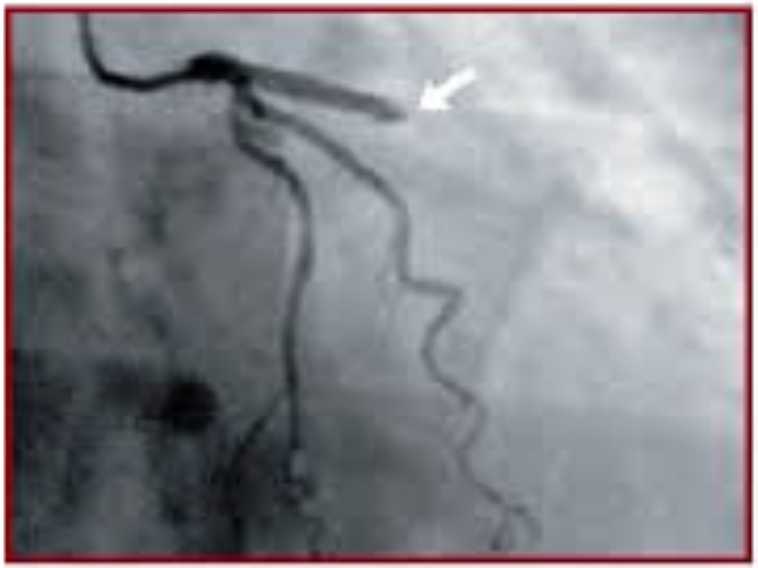
15 minutes

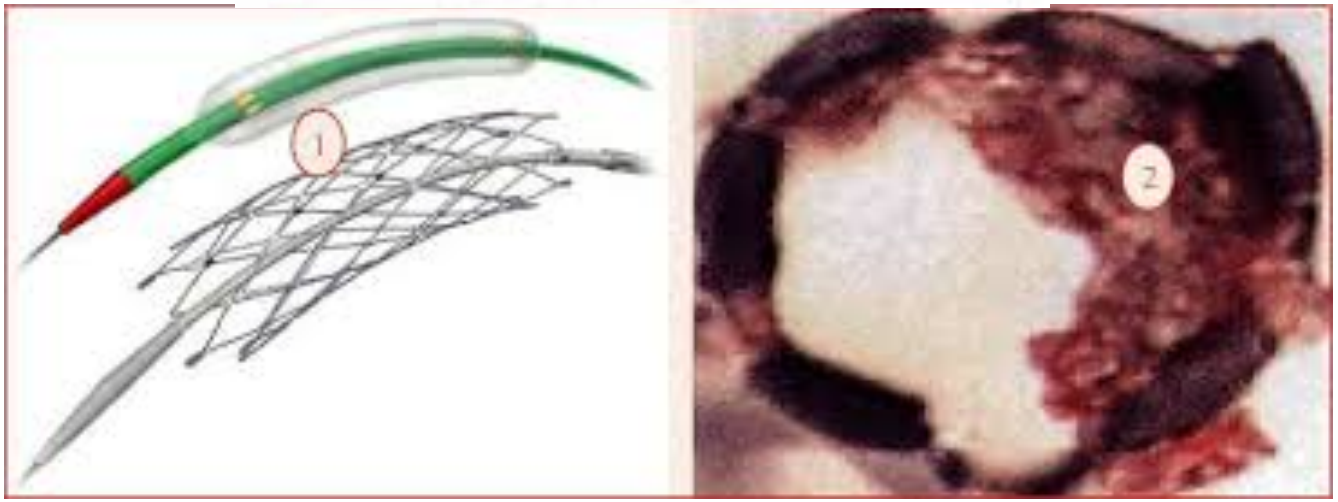
E. FERRARI

Deux leçons du passé à retenir

Pas de traitement anti-thrombotique universel

Thrombose de stent

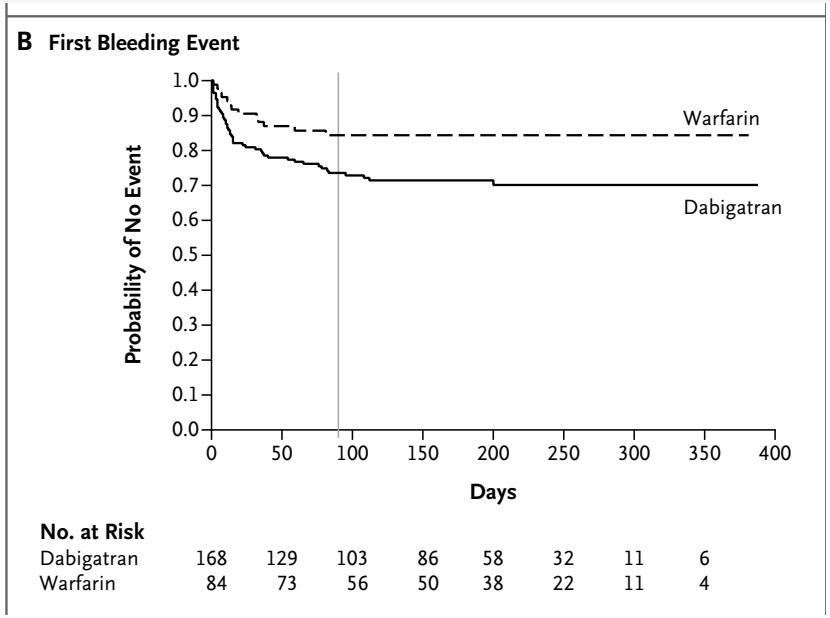




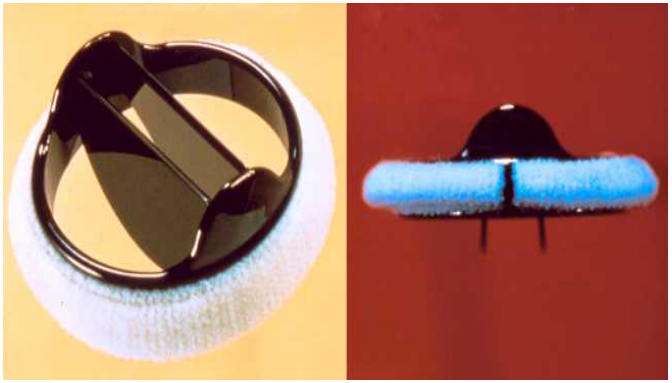
Qu’à t’on appris avec la Thrombose de stent ?

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*



Prothèse mécanique



Diplôme Universitaire

Faculté de Médecine de Nice

DU de Thrombose clinique

Responsable scientifique : **Pr E. Ferrari**

Renseignements

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Conditions d'admissions

Examen du dossier

Objectifs

Familiariser les praticiens aux nouvelles données épidémiologiques, cliniques, thérapeutiques sur la thrombose artérielle et veineuse.

Transmettre les connaissances indispensables à la compréhension et la prise en charge des pathologies thrombo-emboliques.

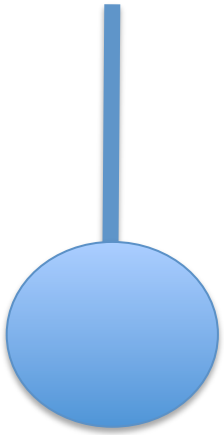
Public concerné

- Docteur en Médecine : cardiologue, hématologiste, pneumologues, anesthésiste réanimateur…
- Interne en Médecine et/ou en spécialité
- Médecin de l'industrie et industriels

1

Durée de la bithérapie AAP
Comment y voir clair ?

Durée DAPT après stenting



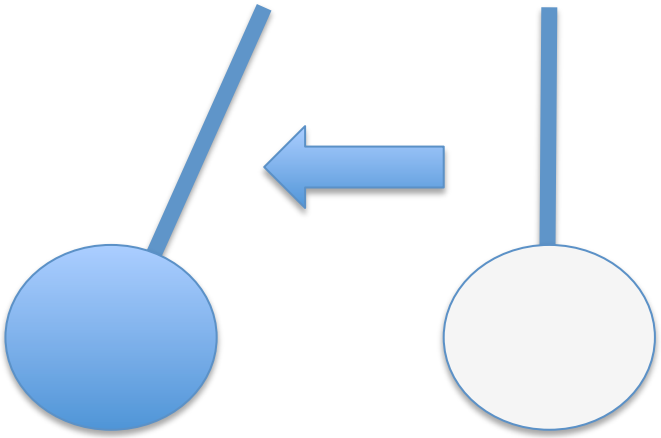
12 mois

CURE

PCI-CURE

CREDO

Durée DAPT après stenting



3 mois

REAL/ZEST NEJM 2010

EXCELLENT Circulation 2012

PRODIGY Circulation 2012

RESET JACC 2012

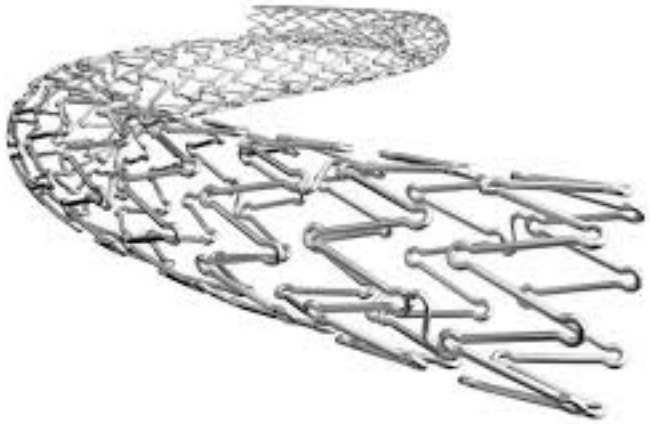
12 mois

CURE

PCI-CURE

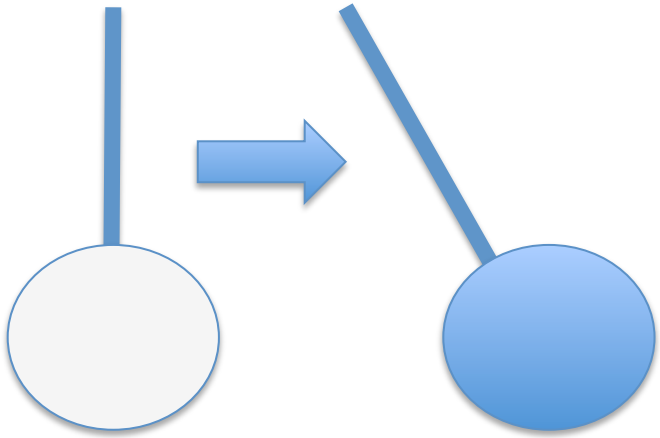
CREDO

D’où la publicité de certaines firmes de stents.



Avec “le notre” la bithérapie peut être raccourcie..

Durée DAPT après stenting



3 mois

12 mois

CURE

PCI-CURE

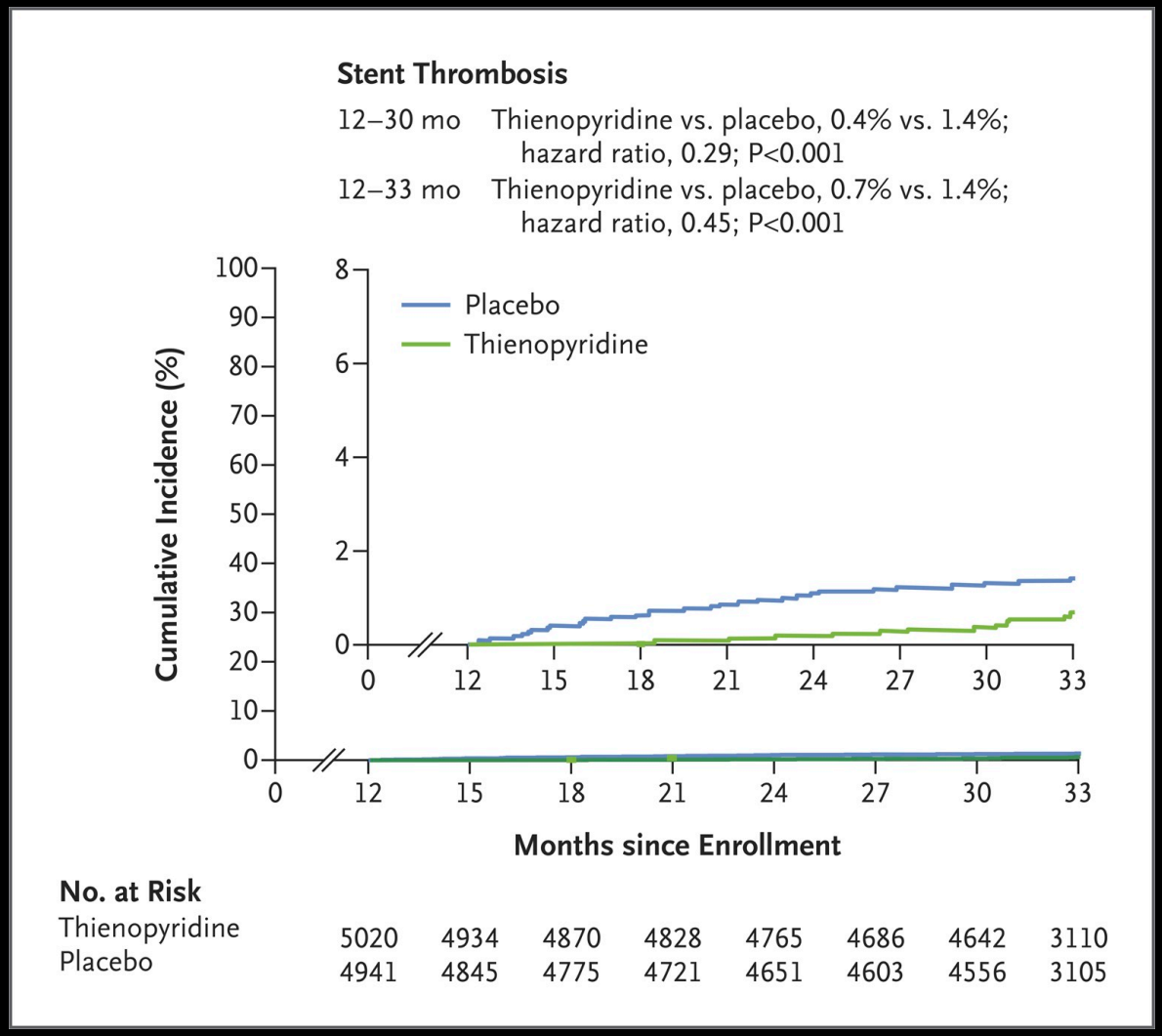
CREDO

24 mois

DAPT NEJM 2014

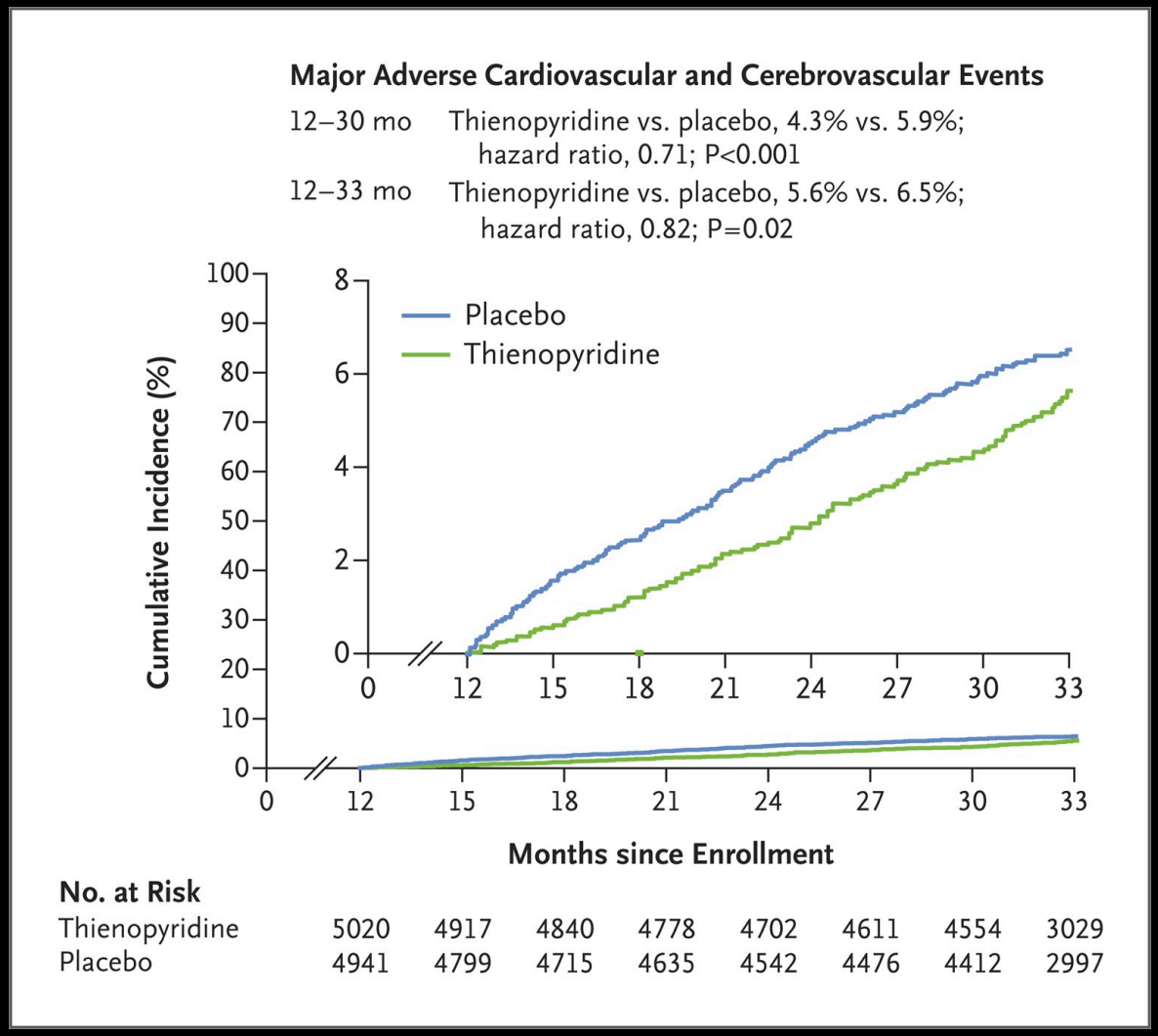
PEGASUS NEJM 2014

Cumulative Incidence of Stent Thrombosis, According to Study Group.



Mauri L et al. N Engl J Med 2014;371:2155-2166

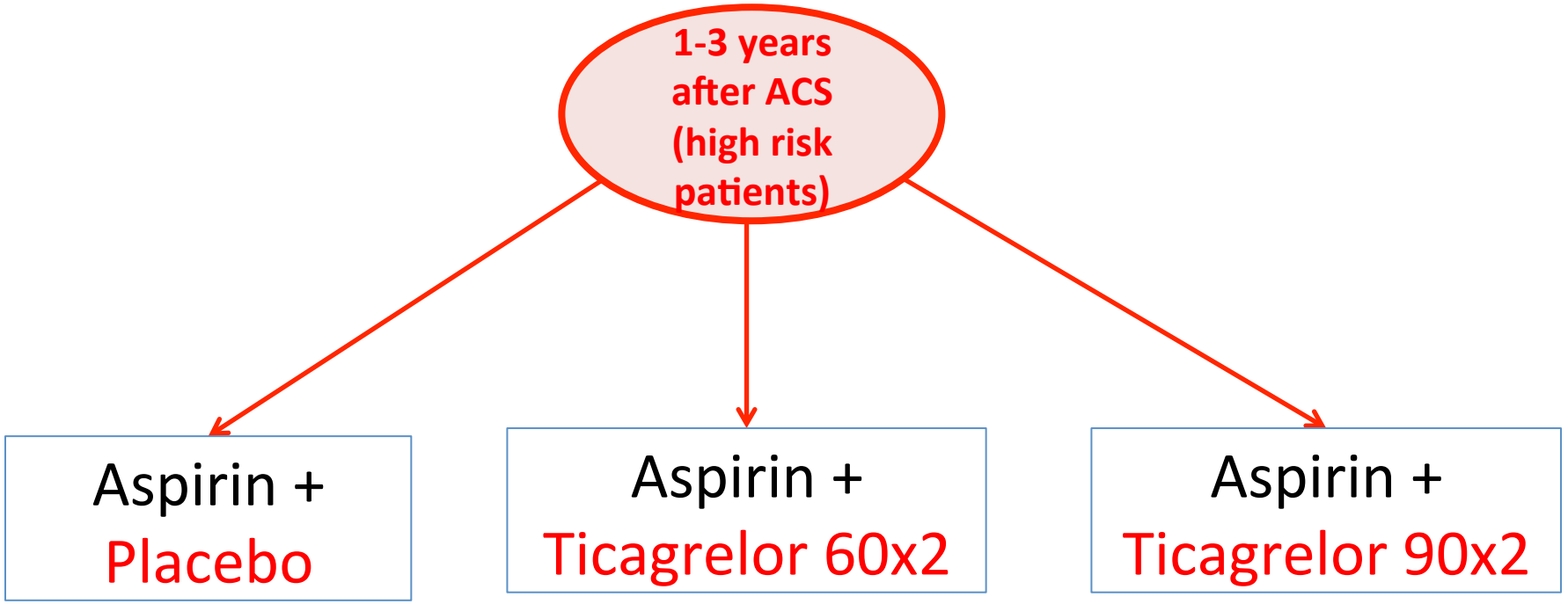
Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events, According to Study Group.



Mauri L et al. N Engl J Med 2014;371:2155-2166

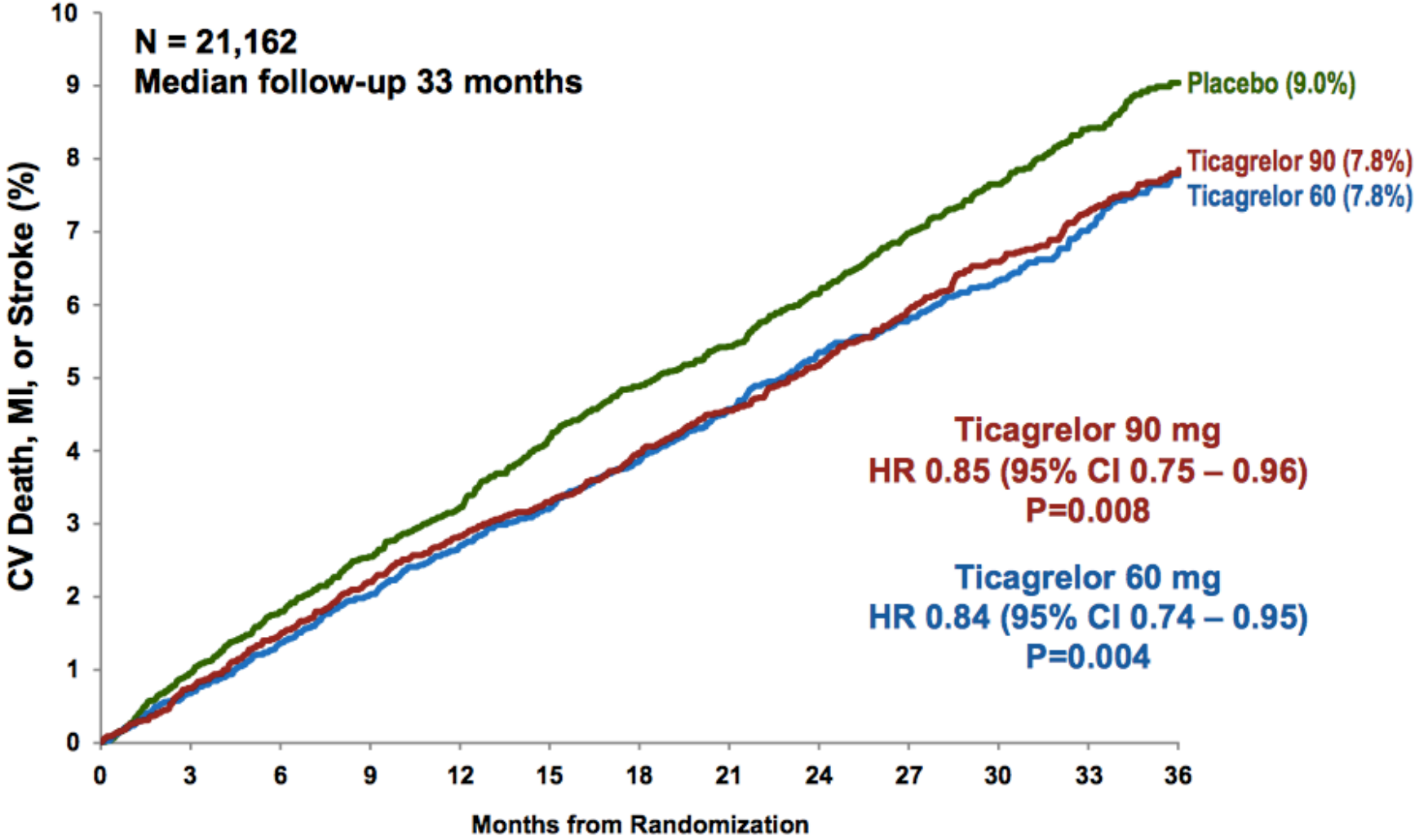
Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

for the PEGASUS-TIMI 54 Steering Committee and Investigators*

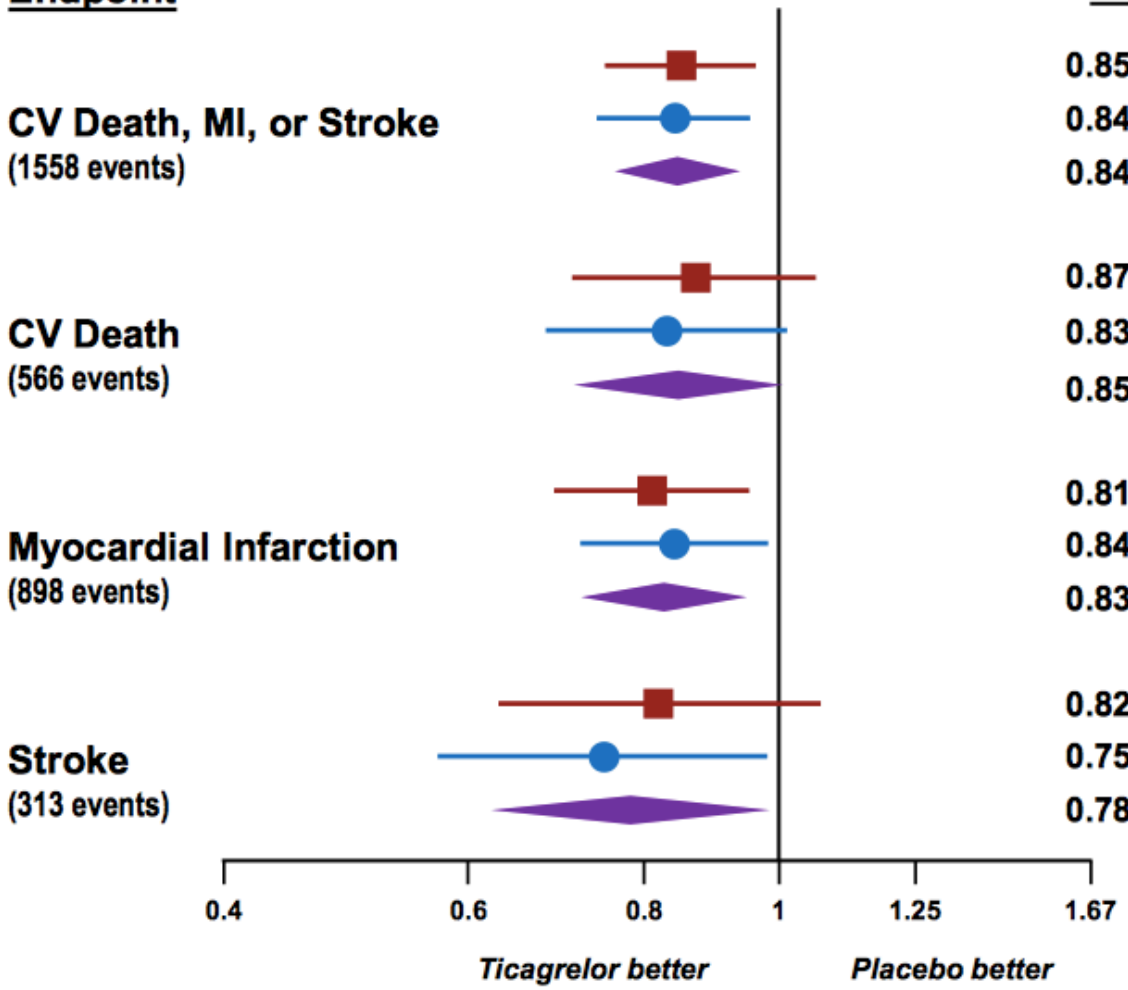


PEGASUS TIMI 54

Primary Endpoint

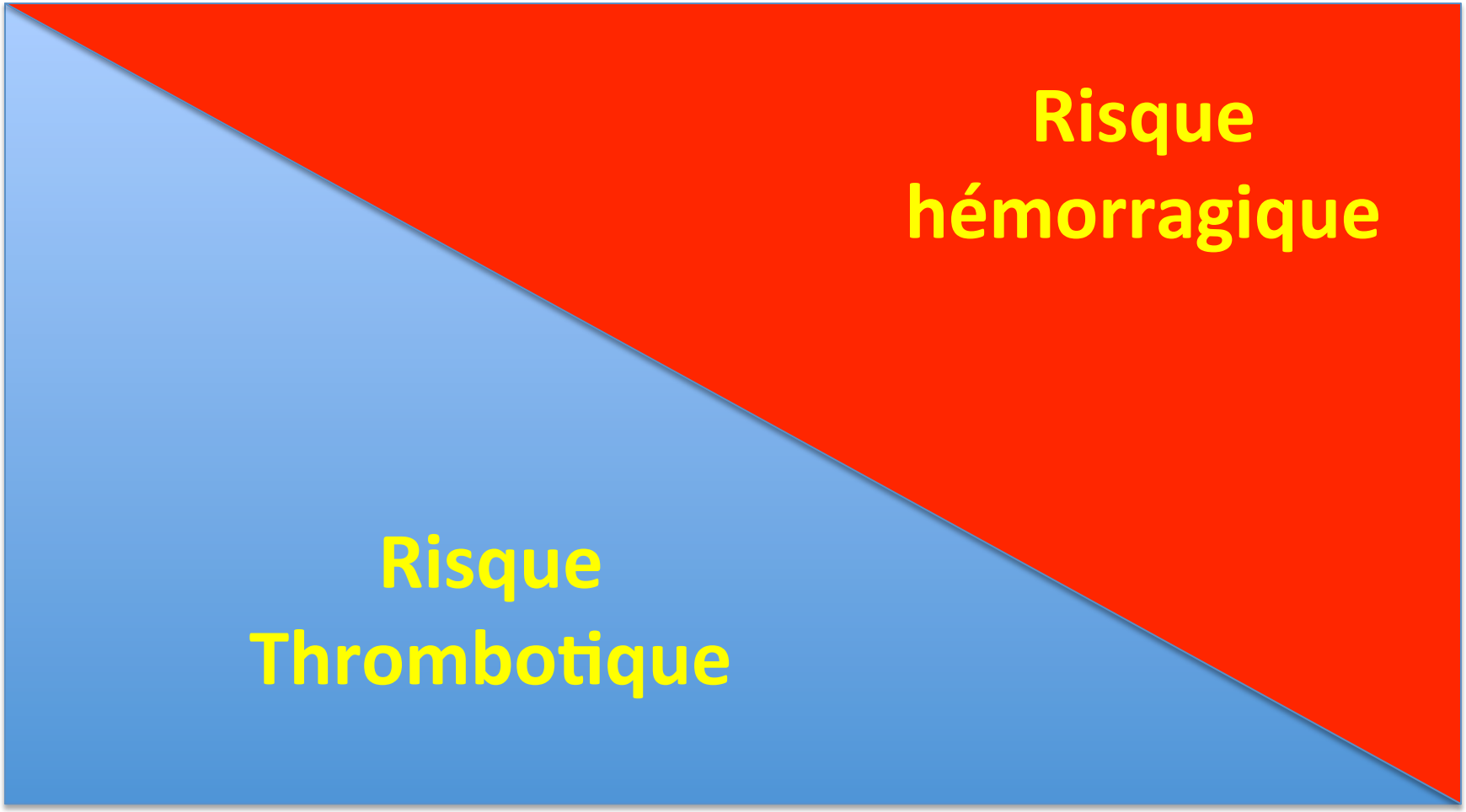


Components of Primary Endpoint

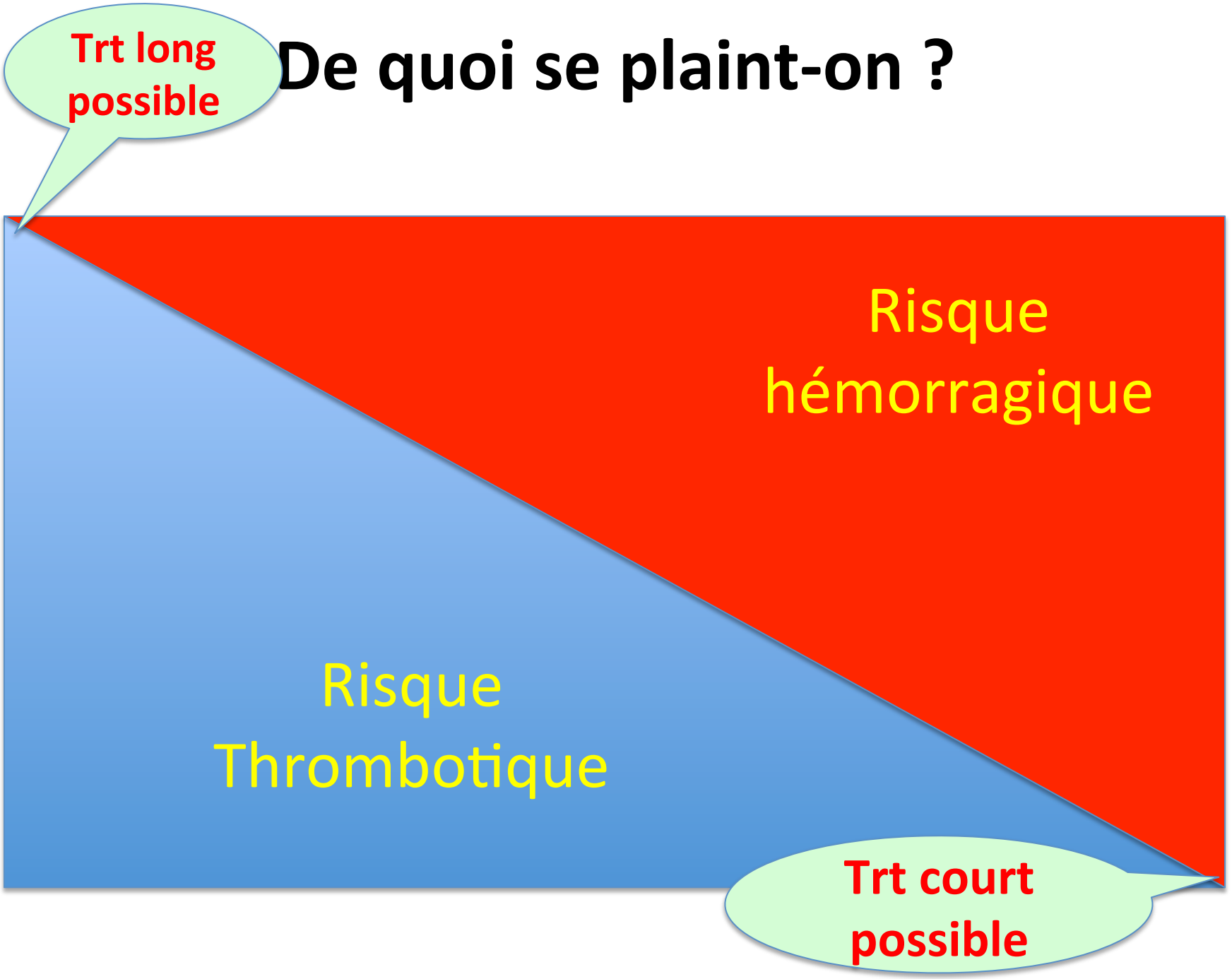


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

De quoi se plaint-on ?



De quoi se plaint-on ?



2

…….Depuis le temps que l'on demandait un inh des P2Y12 IV

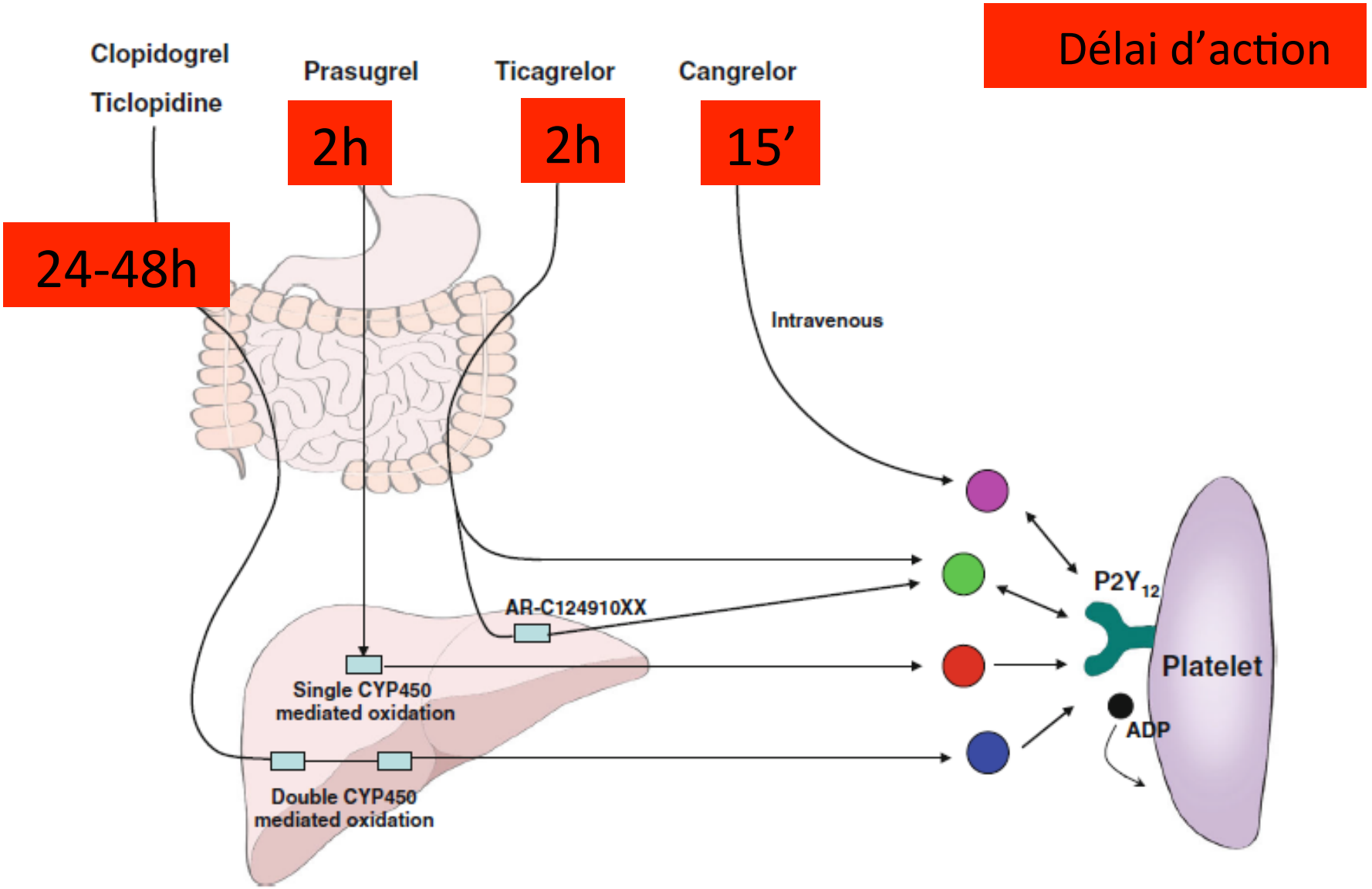
CANGRELOR

inhibiteur des P2Y12 par voie IV

(Kengreal ® the medicine company)

Cangrelor (AR-C69931MX)

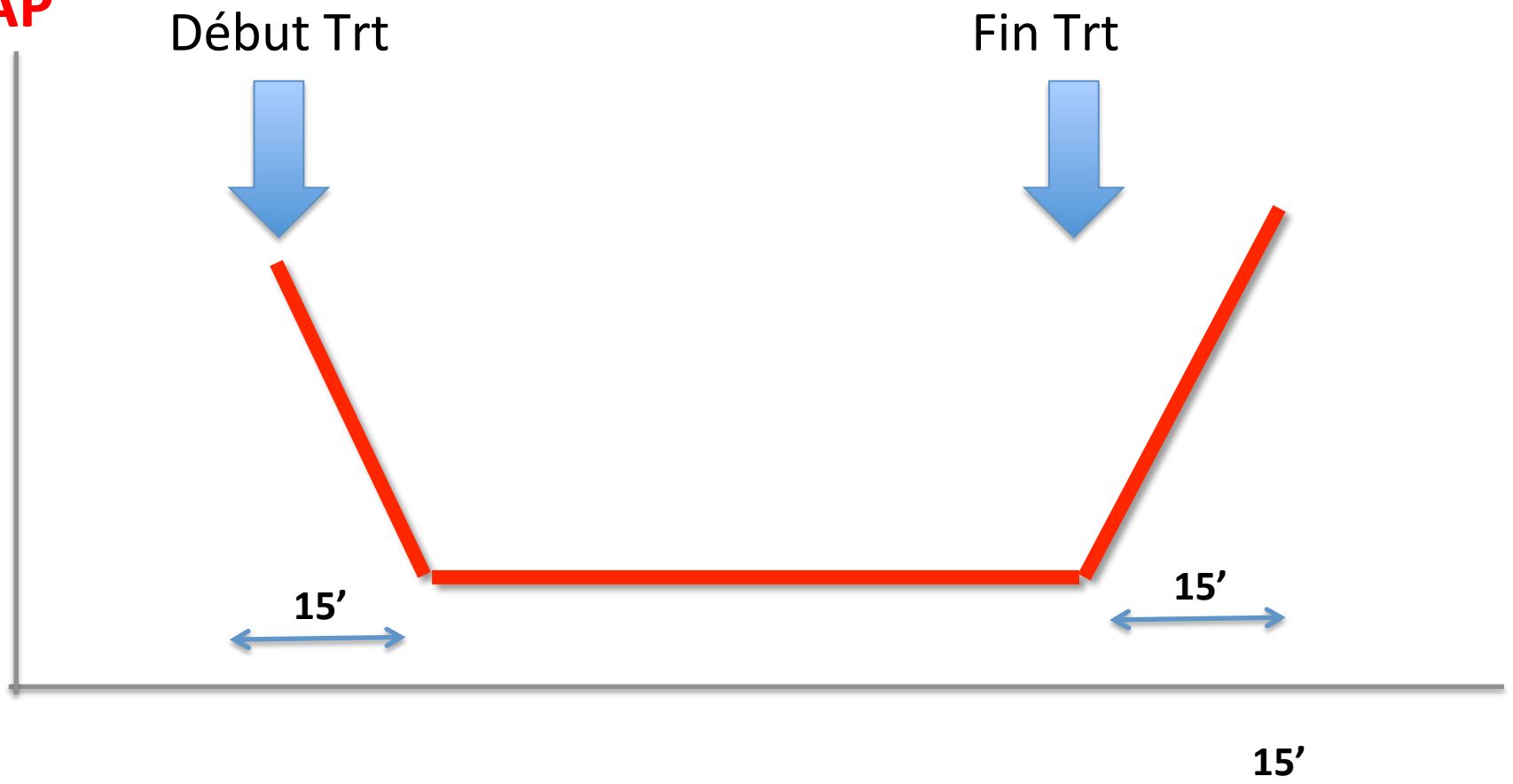
Parenteral direct acting (not a prodrug).



Cangrelor (AR-C69931MX)

“ the minute you turn it on, it works, and the minute you turn it off, it stops”

Effet AAP



Comment intégrer le Cangrelor dans la pratique ?

- **Dans le ST-**
  - Si la prémédication du ST- n'est plus d'actualité (ACCOAST) en revanche une fois "sur l'artère" il y a besoin d'une AAP efficace.

- **Dans le ST+**
  - Effet plus rapide que le Prasu ou le Tica (Atlantic)
  - Eviter Interférences avec d'autres trt (Morphine?)

- **Dans tous les cas** certains patients ne peuvent pas avaler les cp

- **En Bridge** pour un acte à risque hémorragique: **NON**

3

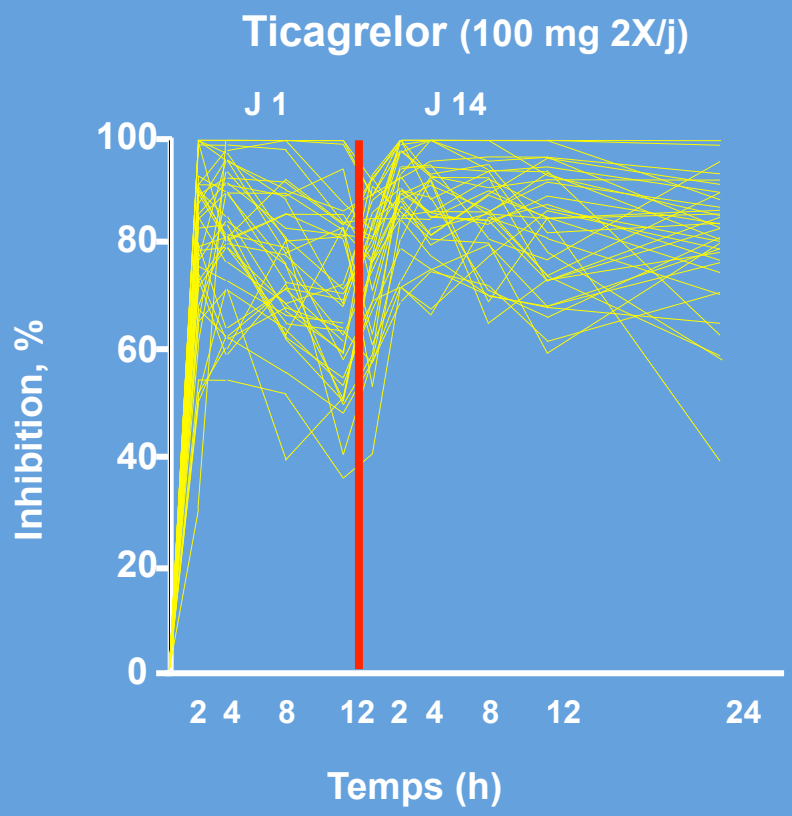
Utilisons nous “trop” de Clopidogrel en France en post SCA ?

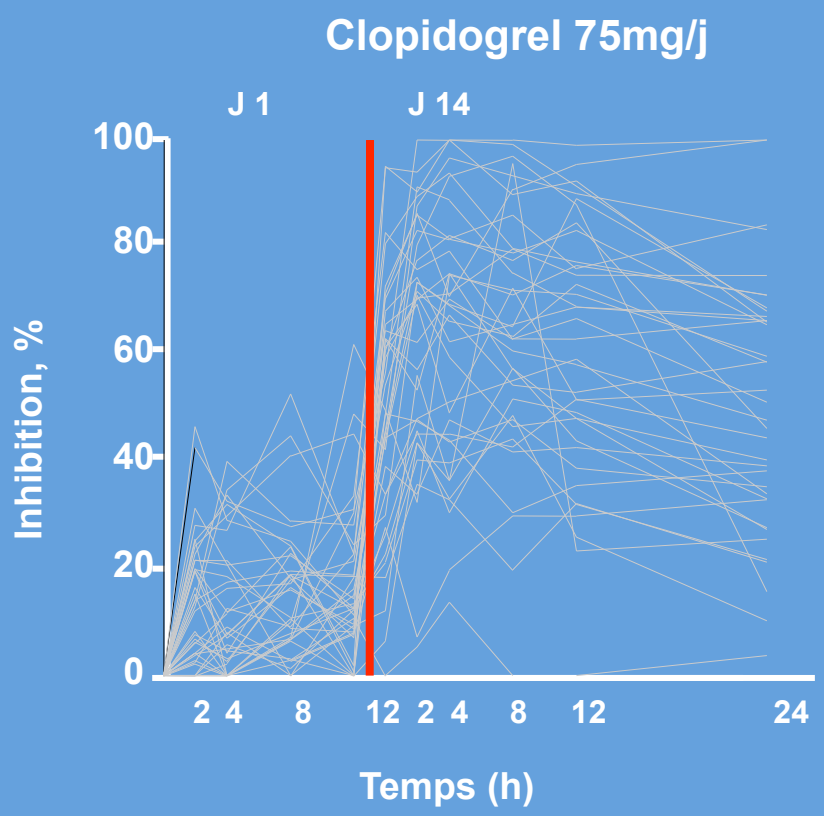
Les 3 AAP per os actuels en sus de l'aspirine

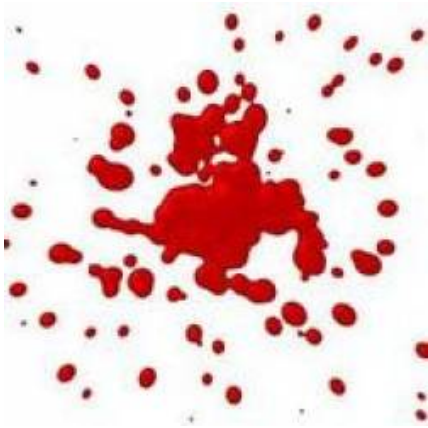
Clopidogrel	Prasugrel	Ticagrelor
Trt Facile **40% d'inh plaq** 25% de resistance Forte variabilité	**60% d'inh Plaq** Dose: 6 cp Puis **1 cp/j** **CI si ATCD AVC**	**60% d'inh Plaq** LD: 2 cp **puis 2 cp/j** **EI: DYSPNEE**
CURE PCI-CURE CREDO	TRITON ACCOAST TRILOGY	PLATO ATLANTIC PEGASUS

Hypocrisie de la prescription du Clopidogrel

Ticagrelor : IAP rapide, puissante, homogène et maintenue







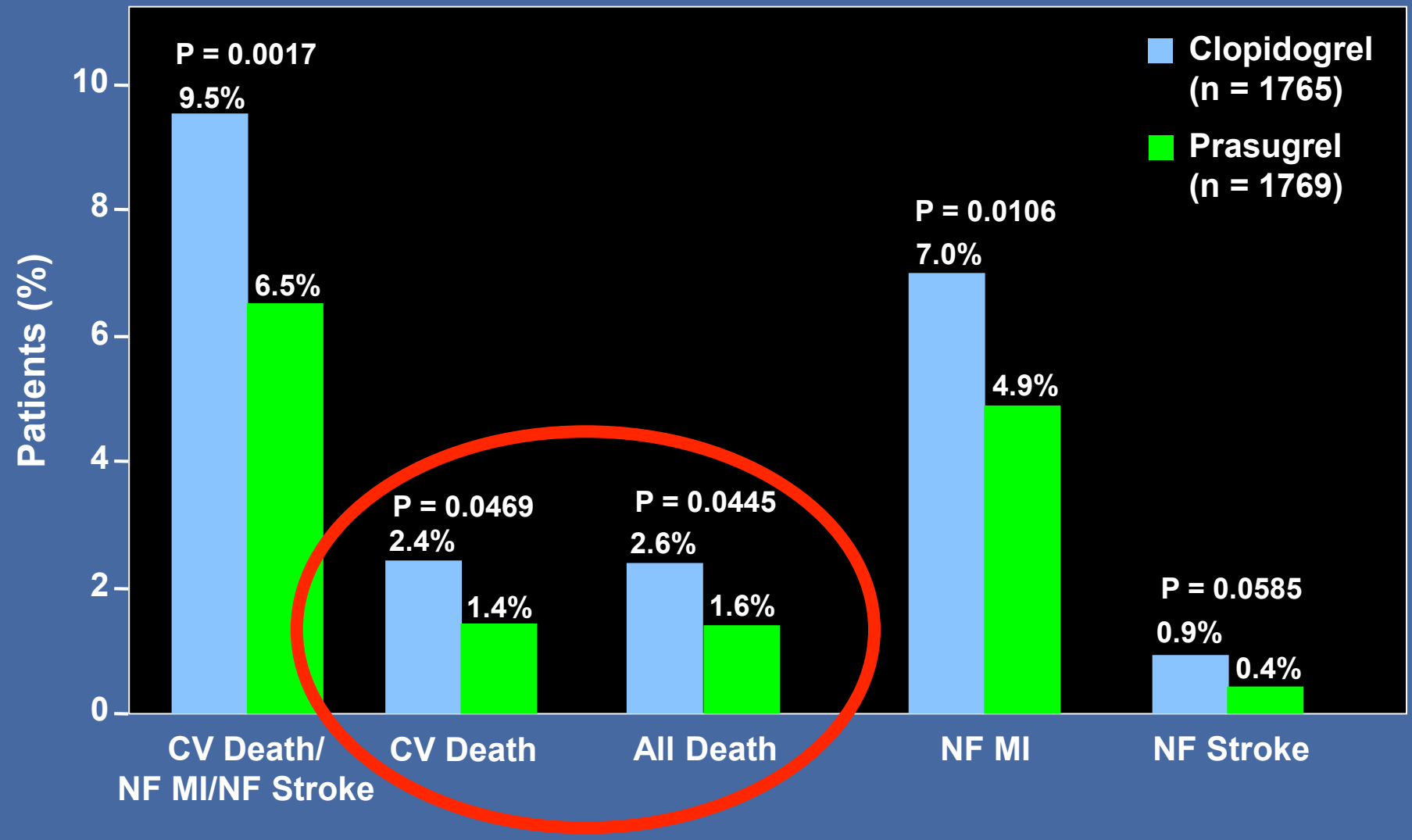
Valeur (très) péjorative du

saignement

chez le patient qui présente un SCA

STEMI Cohort: Components and Secondary Efficacy End Points at 30 Days (part 1 of 2)

TRITON
TIMI 38



Montalescot G et al. *Lancet* 2009 Feb 28;373(9665):723-731

CV=Cardiovascular; NF=Nonfatal; MI=Myocardial Infarction; STEMI=ST Segment Elevation Myocardial Infarction

PLATO: Bénéfice sur le critère primaire obtenu sur les IDM et la mortalité CV

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR (95% CI)	p
Critère laire, n (%) Mortalité CV+ IDM + AVC	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Critères llaires, n (%) Mortalité totale+ IDM + AVC	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
Mortalité CV+ IDM + AVC +ischémie + AIT + Athéro-Thrombotique	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
IDM	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
Mortalité CV	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
AVC	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Mortalité totale	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

L. Wallentin. N Engl J Med 2009;361:1045-57

Recommendations for antithrombotic treatment in patients with NSTE-ACS undergoing PCI

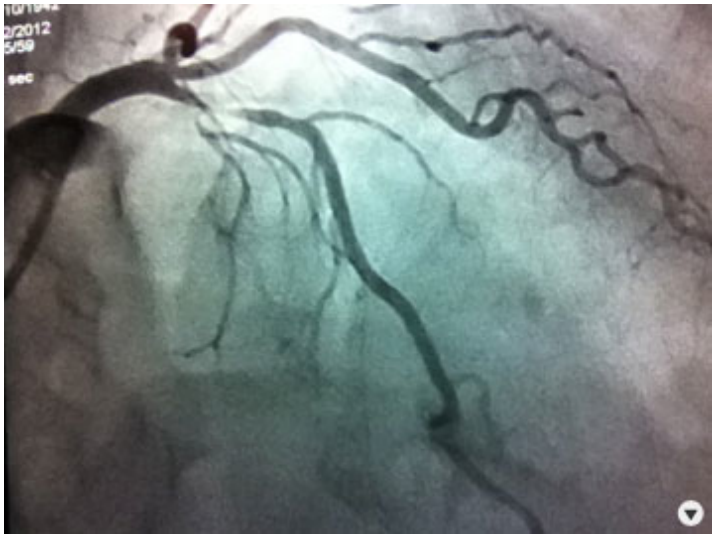
Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin.	I	C
In patients on fondaparinux (2.5 mg daily s.c.), a single bolus UFH (85 IU/kg, or 60 IU/kg in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated during PCI.	I	B
Enoxaparin should be considered as anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin.	IIa	B
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C
Crossover of UFH and LMWH is not recommended.	III	B

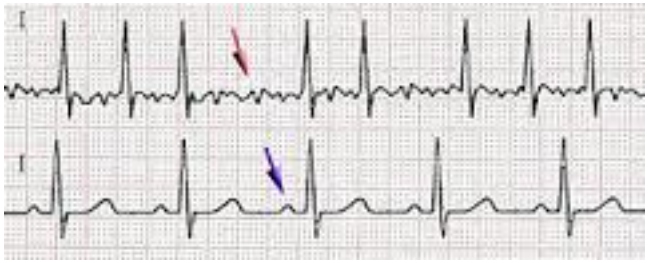
Clopidogrel **seulement** quand Prasugrel ou Ticagrelor contre indiqués

4

L'important problème du traitement Anti-thrombotique chez le coronarien en FA

Coronaropathie et FA





- 25% des FA
- 5% des SCA
- Trithérapie = Triple risque hémorragique

Coronaropathie et FA

Des principes simples à garder à l'esprit

les AVK n'évitent pas la thrombose de stent

La nécessité d'une trithérapie n'est pas aussi évidente que certains l'ont déclaré pendant longtemps.

ISAR

Schomig et al: N Engl J Med 1996

517 Stenting
Randomisation

Héparine Aspirine & Ticlopidine		Héparine Aspirine AVK
1.6%	End points	6.2%
0	Stent thrombosis	5%

Coronaropathie et FA

Des principes simples à garder à l'esprit

les AVK n'évitent pas la thrombose de stent

La nécessité d'une trithérapie n'est pas aussi évidente que certains l'ont déclaré pendant longtemps.

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

Evolution des idées

WOEST

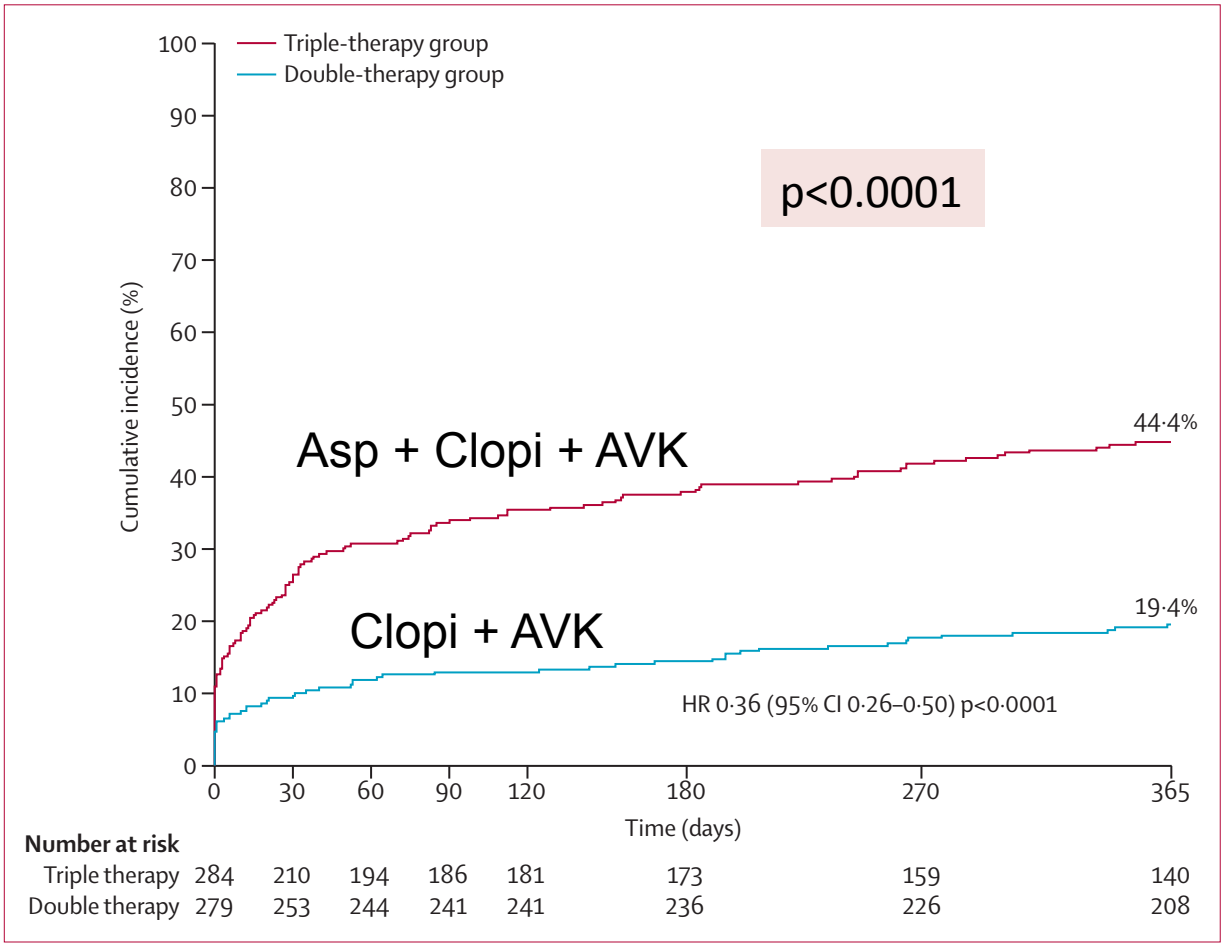


Figure 2: **Incidence of the primary endpoint (any bleeding)**
HR=hazard ratio.

Coronaropathie et FA

Ce qu'on ne sait pas

Quel AAP en 1ère intention ?

Faut-il un 2nd AAP ?

Si oui quand l'arrêter

……

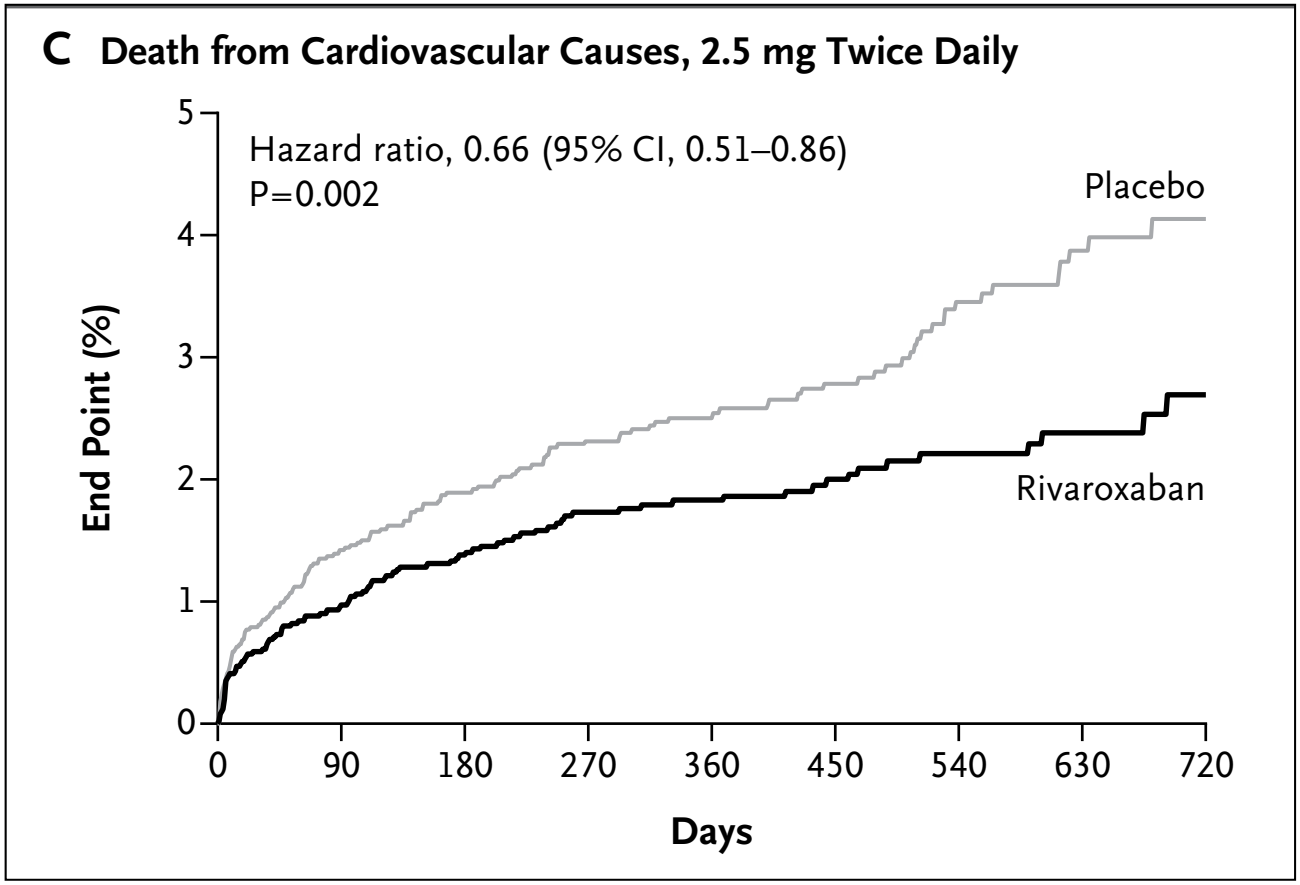
……

Peut-on remplacer un AVK par un AOD dans cette situation ?

Etudes “spécifiques” coronaires & NACO

ETUDES	Phase	n	DC/IdM/AVC NACO vs standard	Saignements NACO vs standard
RE-DEEM (Dabigatran)	II	1861	**4.6% vs 3.8%**	**7.8% vs 2.2%**
APPRAISE (Apixaban)	III	7392	**7.5% vs 7.9%**	**1.3% vs 0.5%**
ATLAS TIMI 51 (Rivaroxaban)	III	15526	**8.9% vs 10.7%**	**2.1% vs 0.6%**

Rivaroxaban + Aspirine + Clopi dans TIMI-51



ESC 2014 Revascularisation myocardique

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

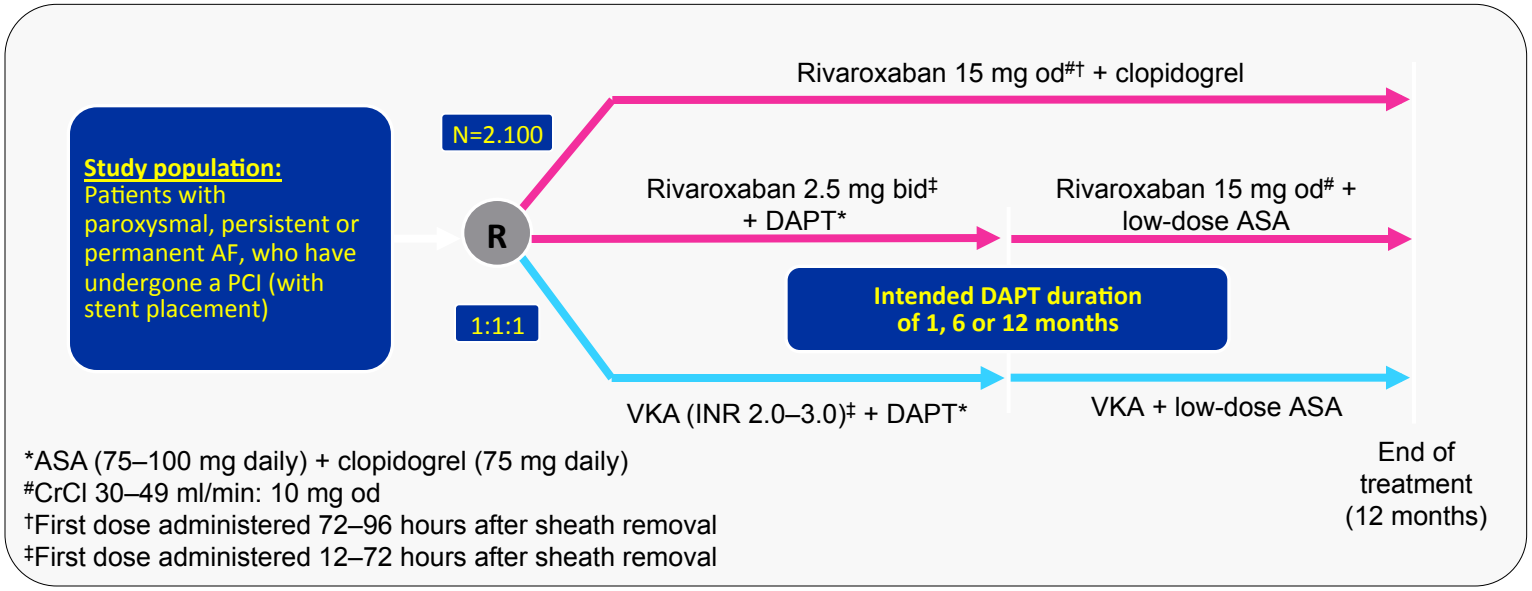
Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day considered for a duration of at least one month after BMS or new-generation DES with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day)	IIa	C	
DAPT should be considered as alternative to initial triple therapy with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk, triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel for a duration of 6 months irrespective of stent type followed by (N)OAC 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) should be considered for a duration of one month followed by (N)OAC and clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or new-generation DES).	IIa	C	
ASA and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
Use of ticagrelor and prasugrel as part of initial triple therapy is not recommended	III	C	
Anticoagulation therapy after PCI in ACS patient			
In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk.	IIb	B	855
Anticoagulation during PCI in patients on oral anticoagulation			
It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC.	I	C	
Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI.	IIa	C	

La plupart des Reco AOD à la place de l'AVK
Sont de grade II a ou II b C

Clinical study: rivaroxaban and PCI in AF (PIONEER AF-PCI) – study design

Randomized, open-label, multicentre study

Objective: To assess the safety of two rivaroxaban treatment strategies and a dose-adjusted vitamin K antagonist (VKA) treatment strategy after percutaneous coronary intervenion (PCI) (with stent placement) in subjects with non-valvular atrial fibrillation (AF)



*ASA (75–100 mg daily) + clopidogrel (75 mg daily)
#CrCl 30–49 ml/min: 10 mg od
†First dose administered 72–96 hours after sheath removal
‡First dose administered 12–72 hours after sheath removal

Primary endpoint:
Safety: Composite of TIMI major bleeding, minor bleeding and bleeding requiring medical attention (known collectively as clinically significant bleeding) events

Study milestones:
FPFV: May 1st 2013
LPLV: 30 Aug 2015
CSR: 30 Dec 2015

Participating countries:
Argentina, Belgium, Canada, Chile, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, Sweden, UK, USA

www.clinicaltrials.gov/

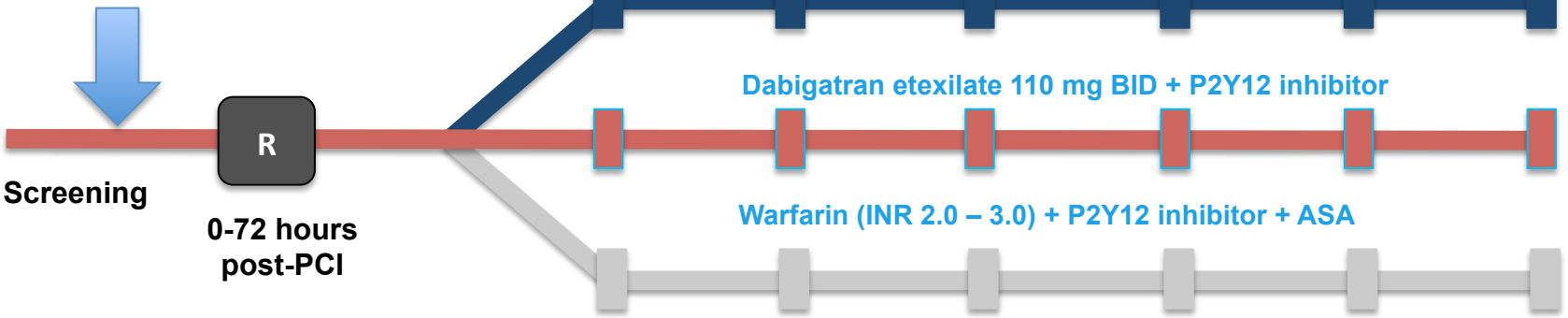
DUAL PCI

Trial design

1° End Point

Time to death or first thrombotic event (all death, MI, stroke/SE)
plus
Time to first major bleeding event (ISTH Major)

Paroxysmal, persistent or permanent AF, PCI with stenting [BMS or DES] elective or ACS



n = approximately 2840 patients per arm (Total = approximately 8520 patients)

DE arms: ASA (≤100 mg) discontinuation immediately after PCI

Warfarin arm: ASA discontinuation after 1 month (BMS) or 3 months (DES)

P2Y12 inhibitor (clopidogrel 75 mg qd or ticagrelor 90 mg bid) can be discontinued after 12 months of follow up at the discretion of the investigator

✔ BIVALIRUDINE (ANGIOX® OU ANGIOMAX®):

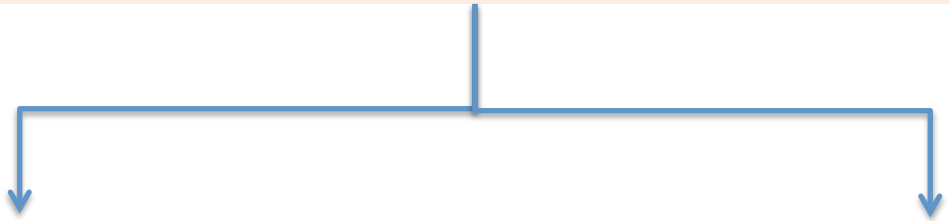
5

La Bivalirudine

L'exemple d'un succès fugace monté de toutes pièces par des études bizarrement ficelées

Principe d'une étude

Evaluation d'1 nouveau Trt x
par rapport au Trt de référence



Trt Référence vs Idem + Trt X

Trt Référence vs Trt X

Meta-analyse: Bivalirudine vs héparine
Saignements graves bénéfice vs GPIIB-IIa + HNF

IIBIIIa Programmé
Seult ds le bras Crontrôle

IIBIIIa prévisionnel dans
les 2 bras

IIBIIIa programmé dans
les 2 bras

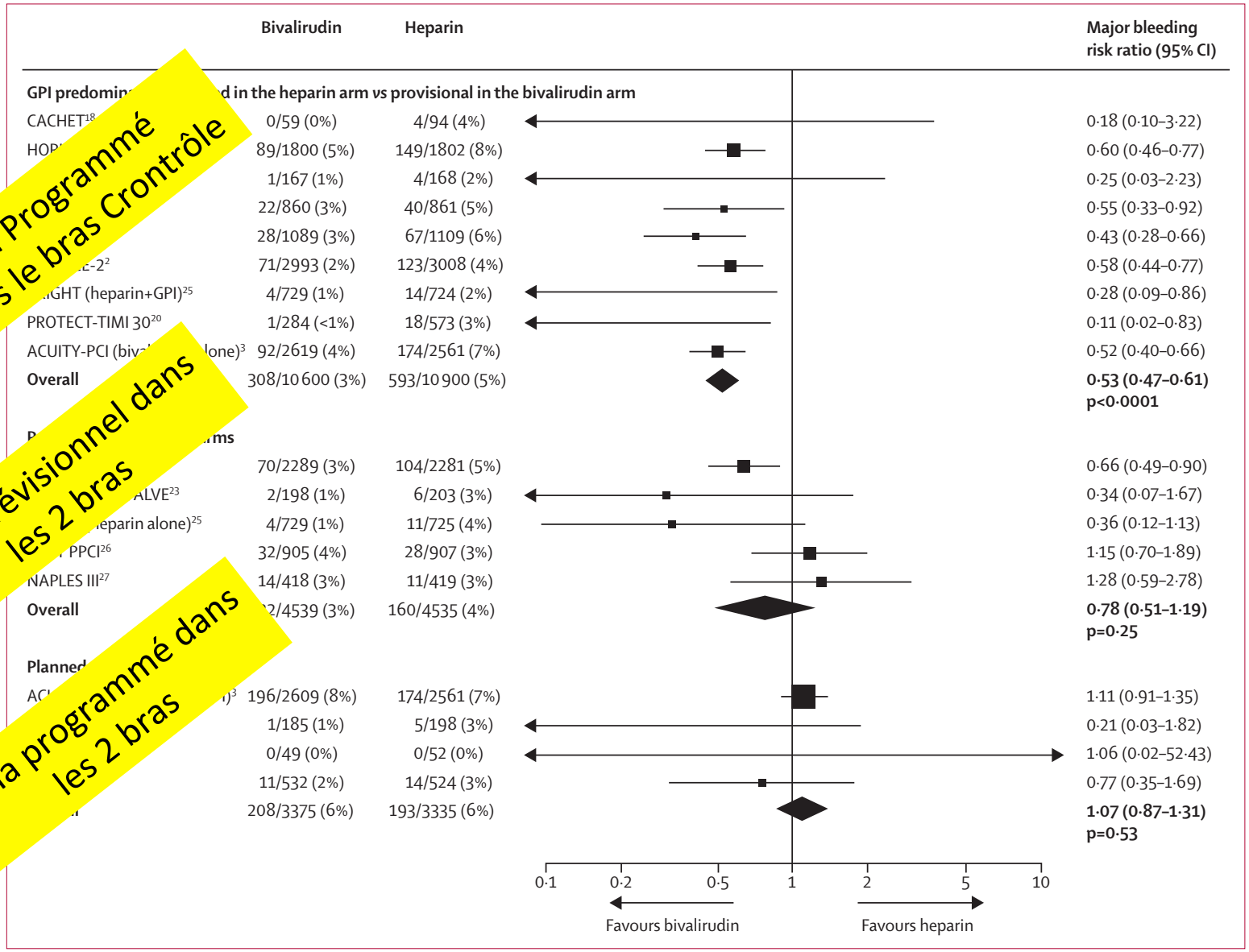
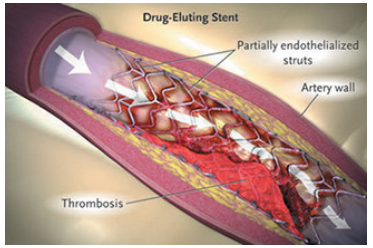


Figure 4: Major bleeding, stratified by use of glycoprotein IIb/IIIa inhibitors

Meta-analyse: Bivalirudine vs héparine. MACE



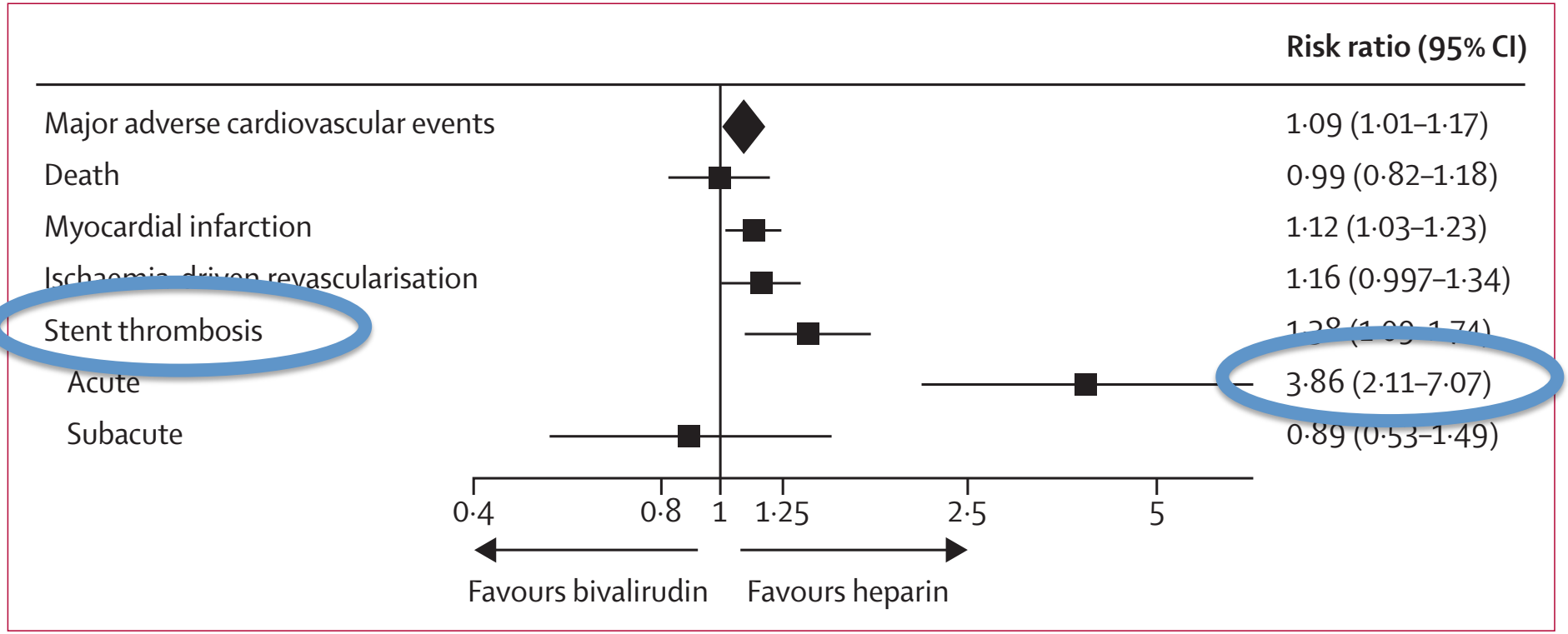


Figure 2: **Major adverse cardiovascular events and individual cardiovascular events**

Lorsque la coronaropathie n’a pas tué le malade….
le traitement peut encore le faire

Dans la prise en charge initiale d'un SCA qu'est ce qui peut tuer le malade?

Registre CRUSADE

30 136 SCA

Valeur (très) péjorative du saignement chez le patient qui présente un SCA

11.5%

Saignements majeurs

Surdosage en antithrombotiques

=

Mortalité x 5.8 à 12.4

Surdosage en HNF = Mortalité **x 5.8**

Surdosage en HBPM = Mortalité **x 3.4**

Surdosage en IIbIIIa = Mortalité **x 12.4**