COMBATTRE LA MORTALITE DANS L'IDM ST+

Réduire la mortalité

Didier Carrié

CHU Toulouse Rangueil

APPAC 10 Juin 2010

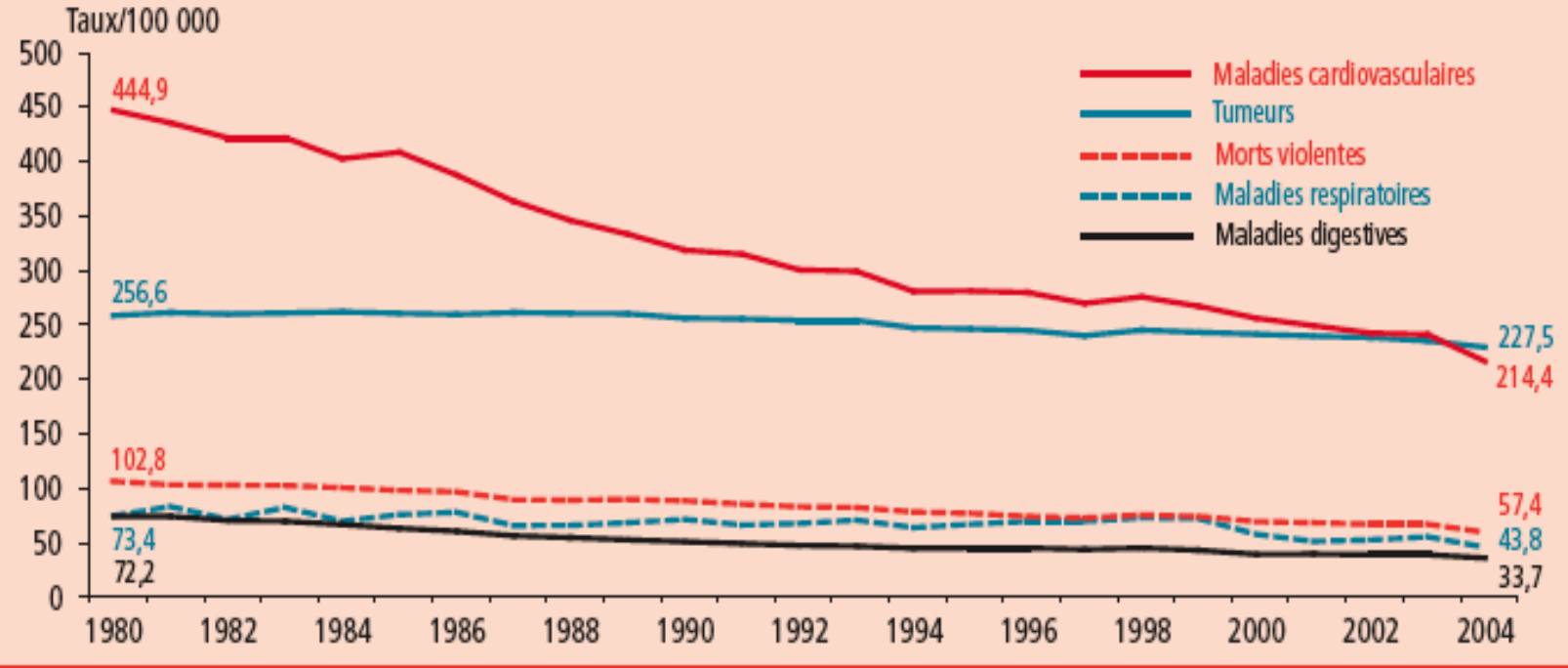
Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

Quelle est actuellement la mortalité dans les SCA ?

Evolution de la mortalité en France

Figure 2 Evolution des taux* de décès par grande catégorie de causes de décès, 1980-2004, France métropolitaine, deux sexes / *Figure 2 Trends in death rates by main category of causes of death, 1980-2004, Metropolitan France, both sexes*

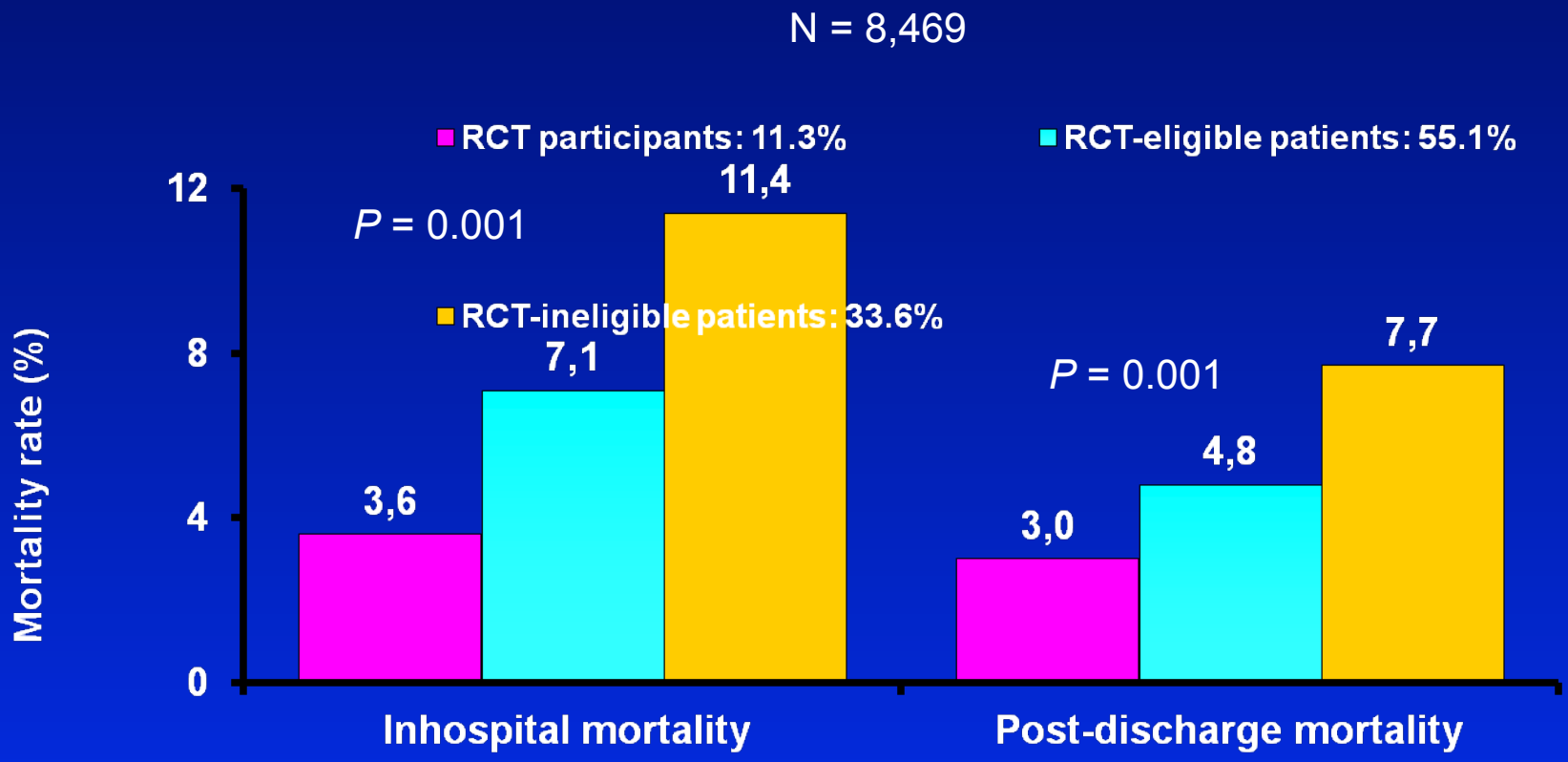


* Taux de décès standardisés pour 100 000.

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

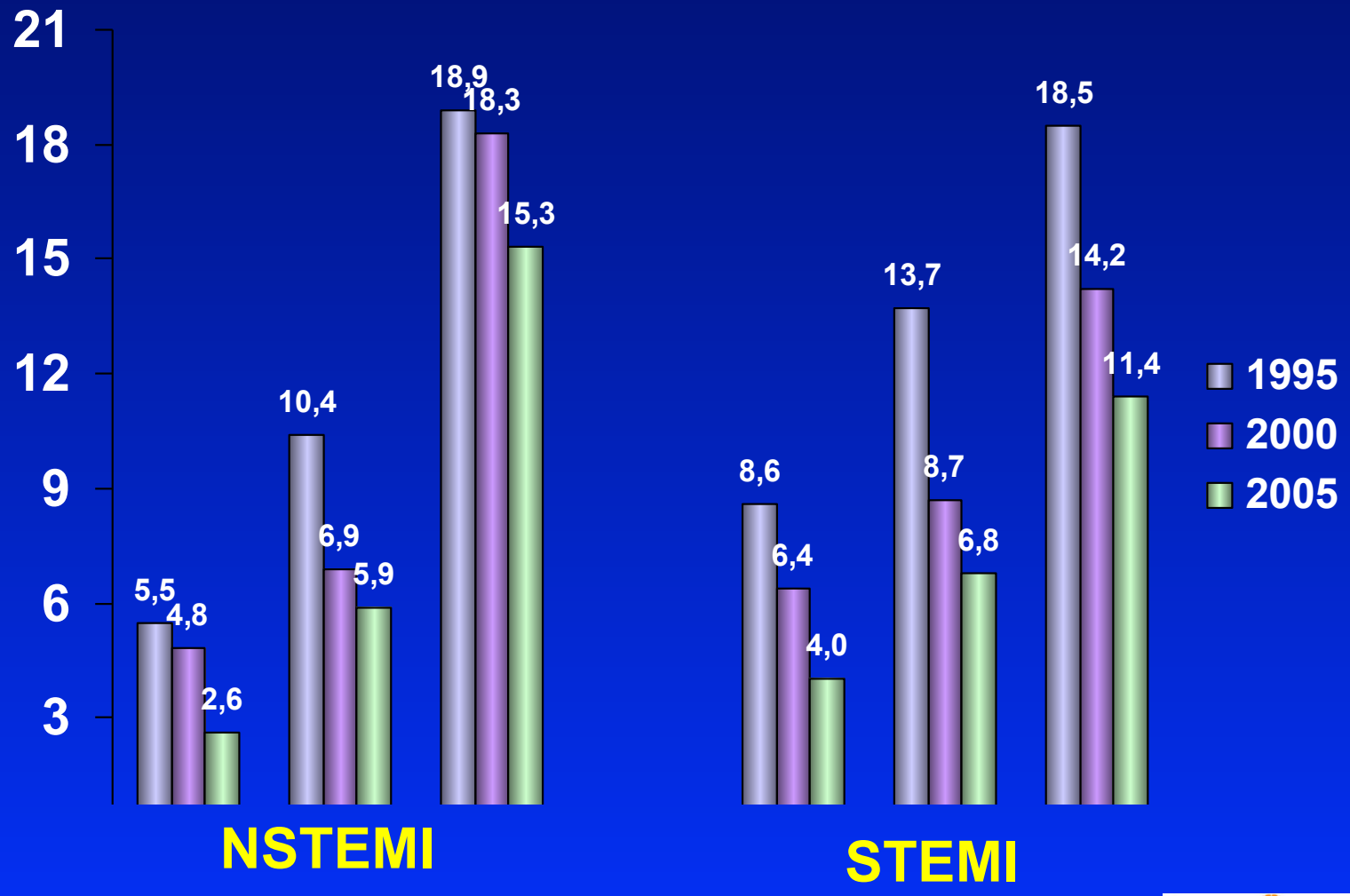
Validité externe des études randomisées ?



Steg PG, et al. *Arch Int Med*. 2007

Evolution de la mortalité dans les SCA en France :

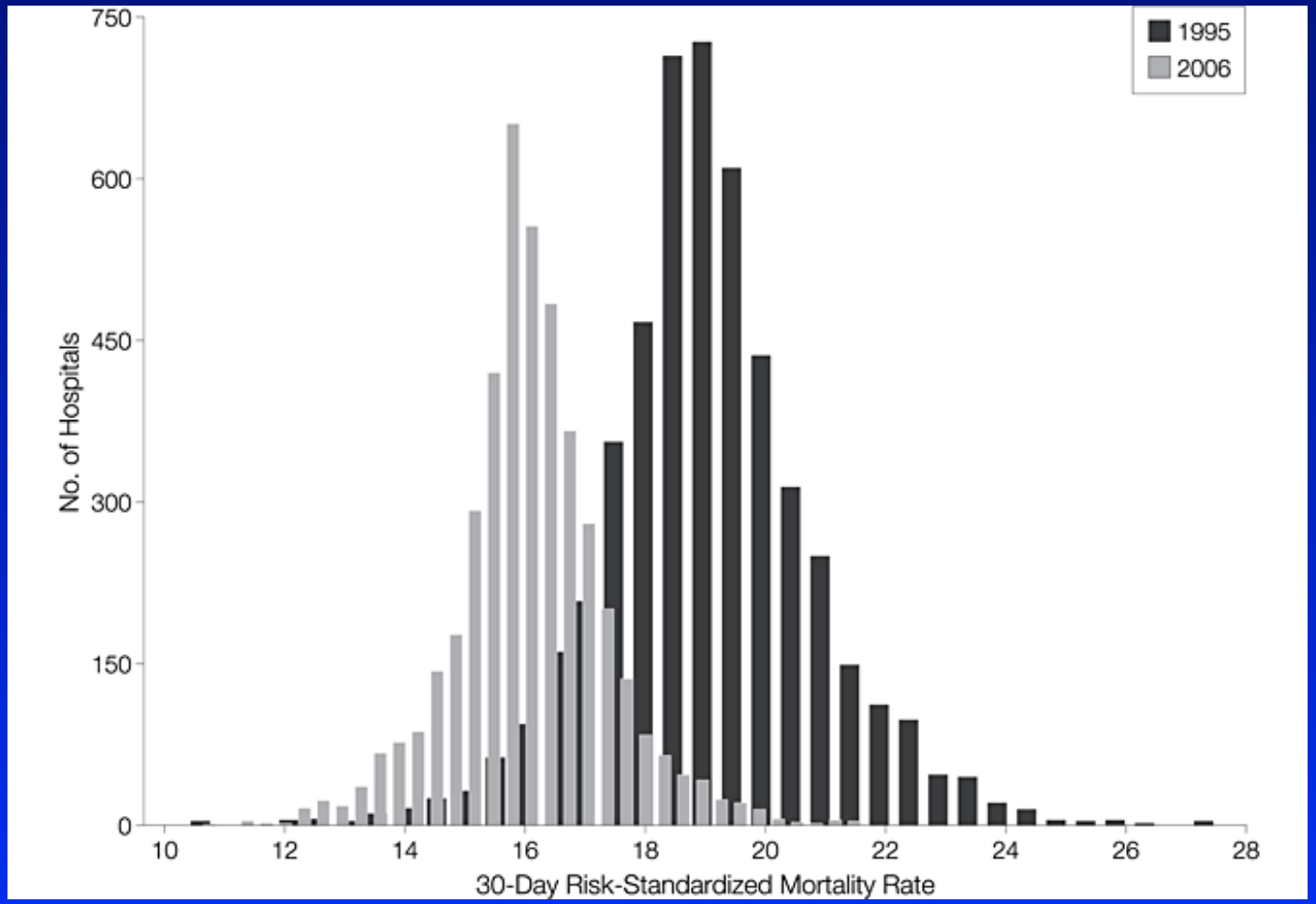
Registres USIK 1995, USIC 2000 et FAST-MI 2005



Cambou, Ann Cardiol Angeiol 2004
Cambou, Arch Mal Coeur Vaiss 2007

Hôpitaux de Toulouse
Pôle Cardiovasculaire et Métabolique

Mortalité à 30 jours dans l'infarctus (Registre MEDICARE)



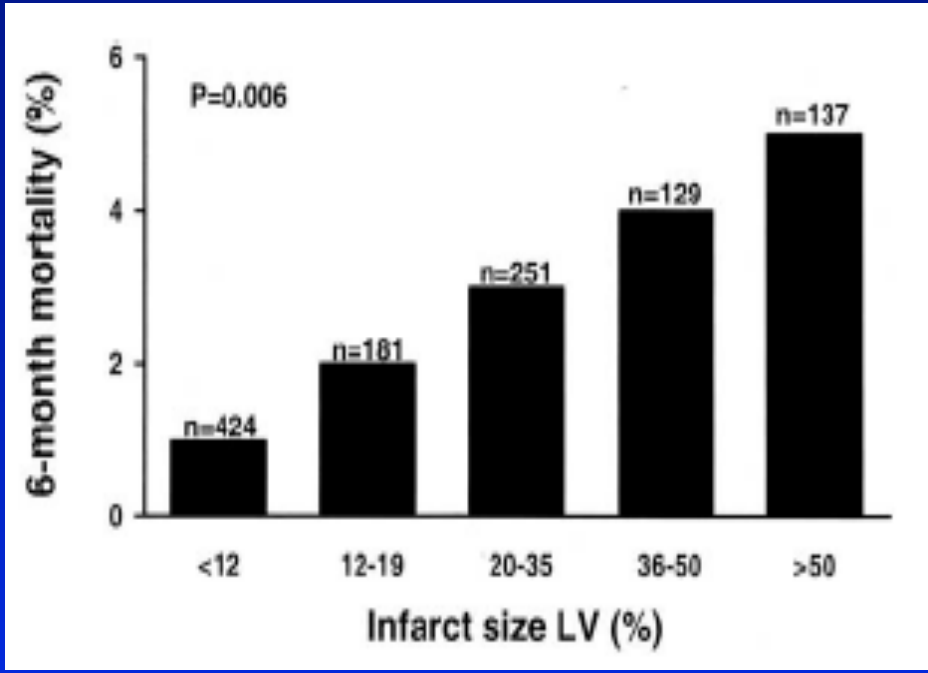
Krumholz MD et al, JAMA 2009

Quels sont

les déterminants

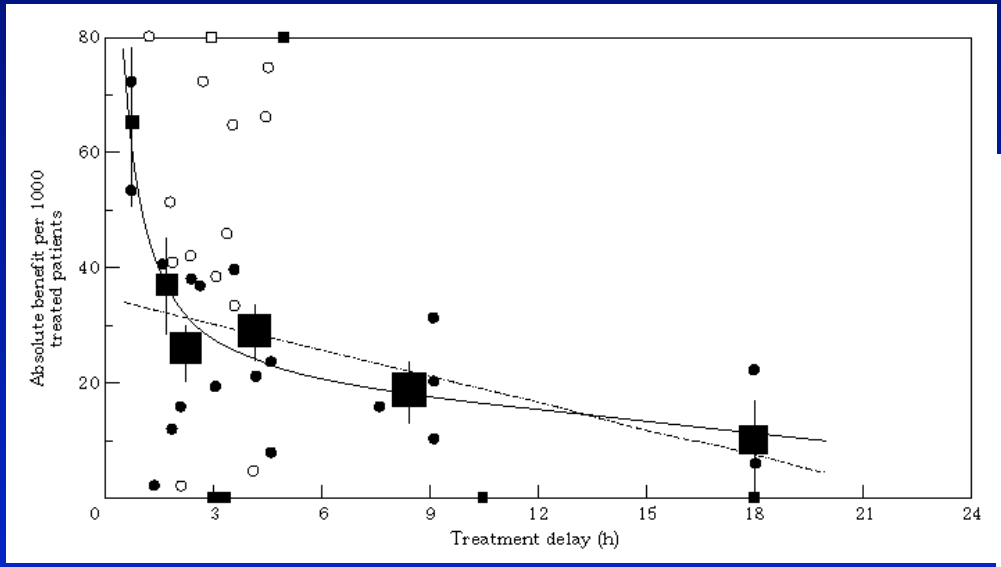
de la mortalité dans le SCA ?

STEMI : taille de l'infarctus

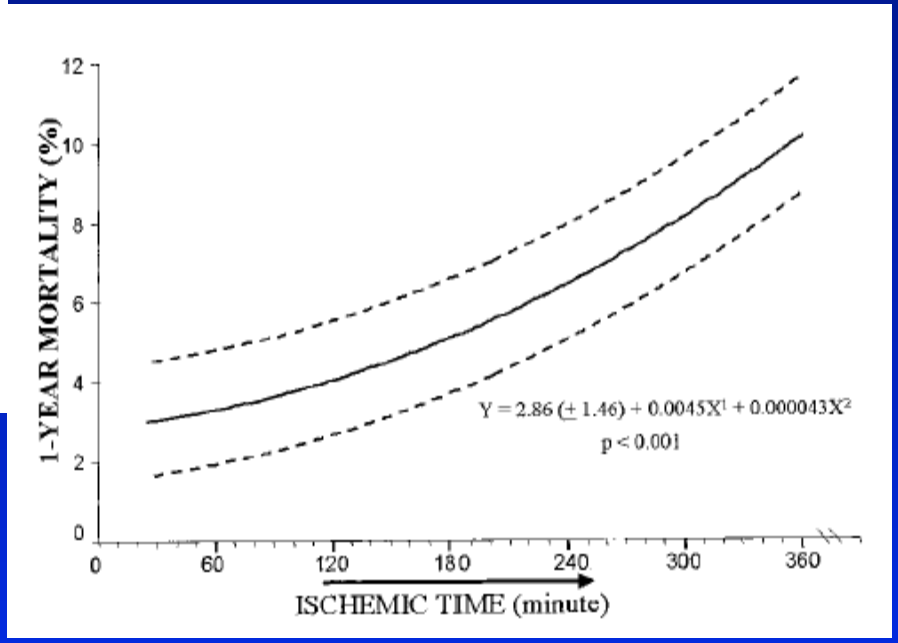


Gibbons et al. JACC 2004

STEMI : Délais de reperfusion



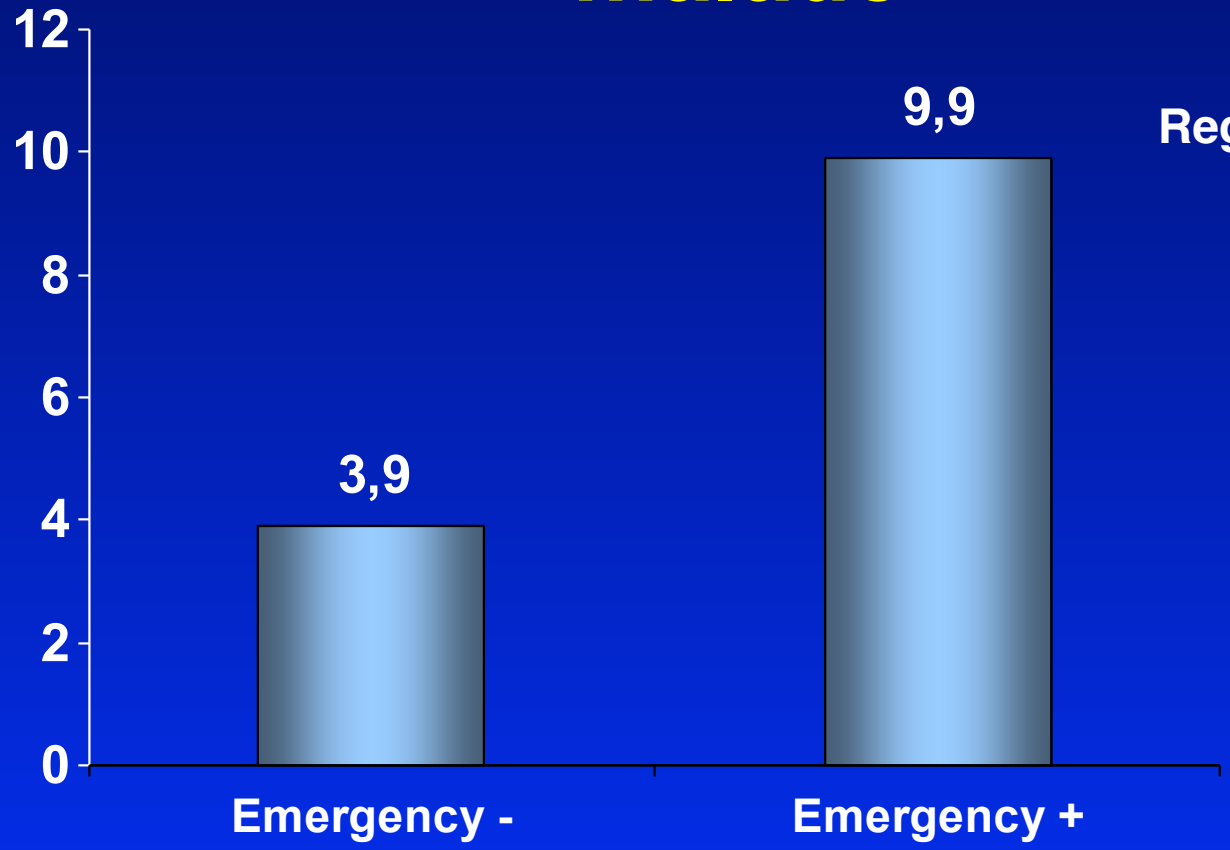
Thrombolyse
Boersma E Lancet 1996



Angioplastie primaire
De Luca circ 2004

Comment avons nous diminué la mortalité ?

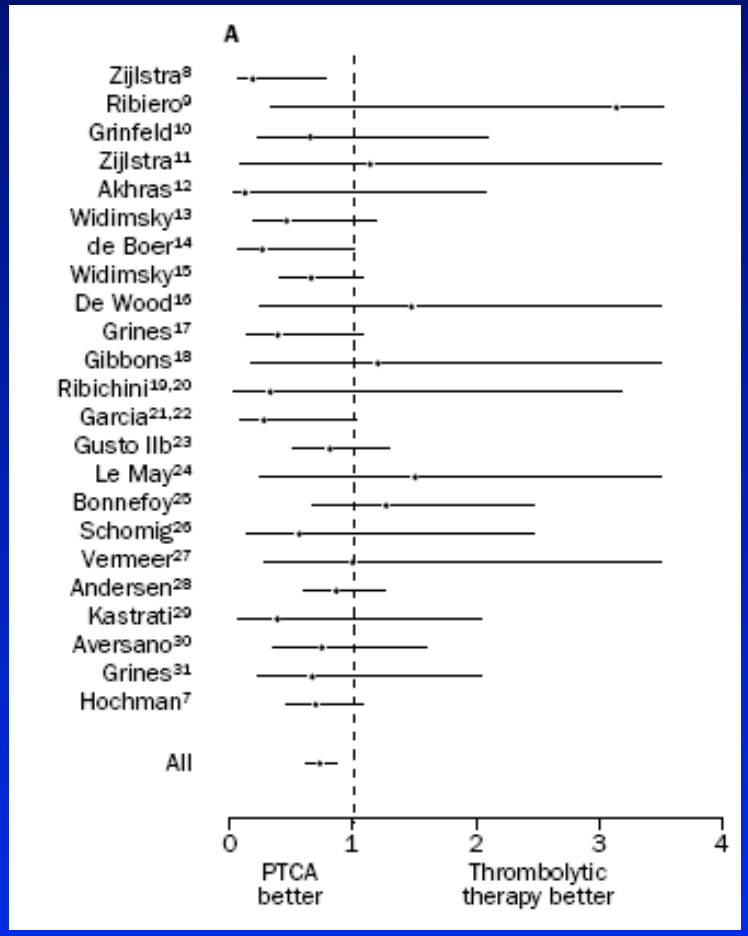
Développement de réseau: orientation optimale du malade



Registre FAST-MI

In-hospital mortality according to pathway
(SAMU alone vs SAMU+ emergency department)

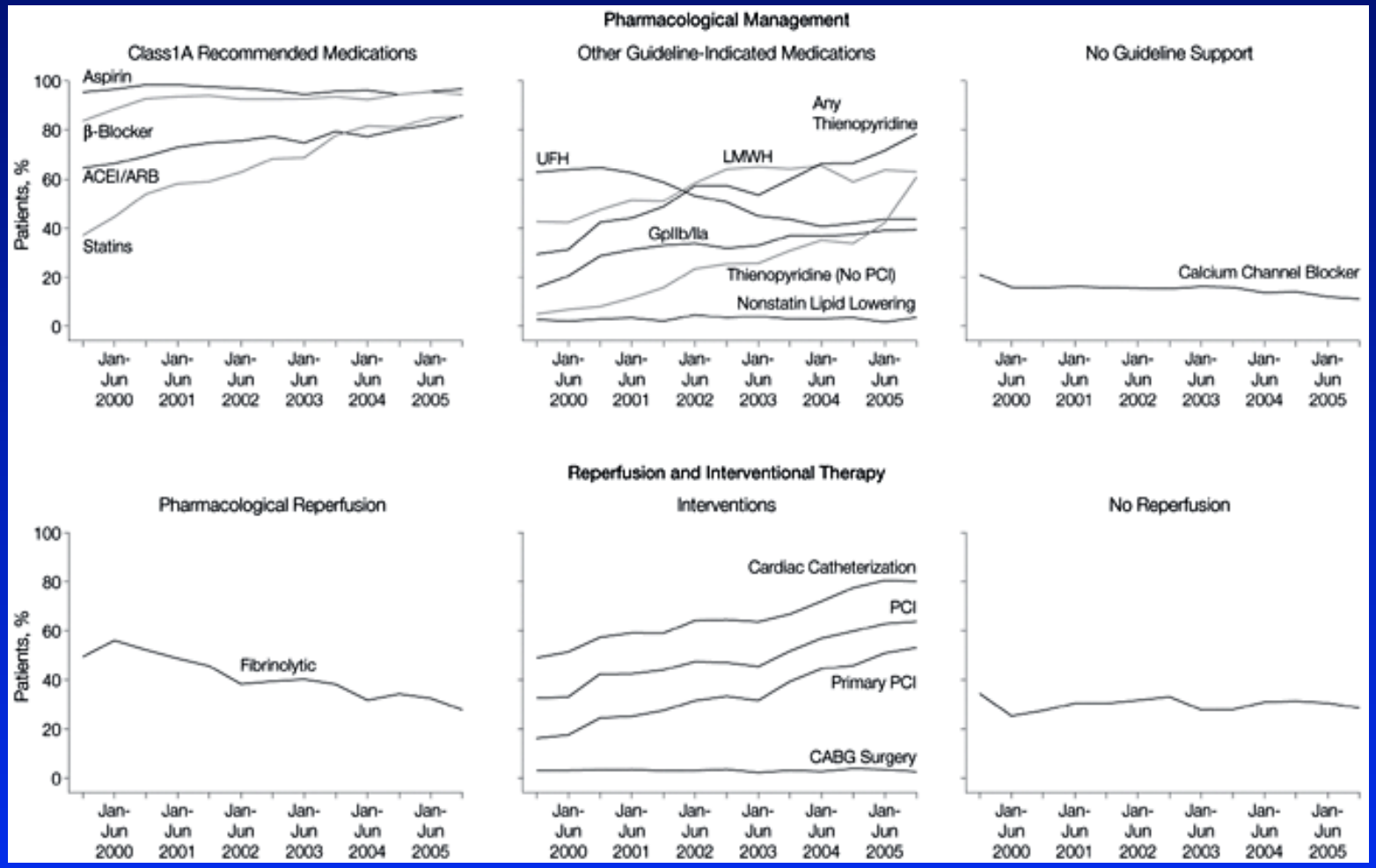
Généralisation d'un stratégie invasive: STEMI



Short term death

Keeley Lancet 2006

Adhérence aux guidelines



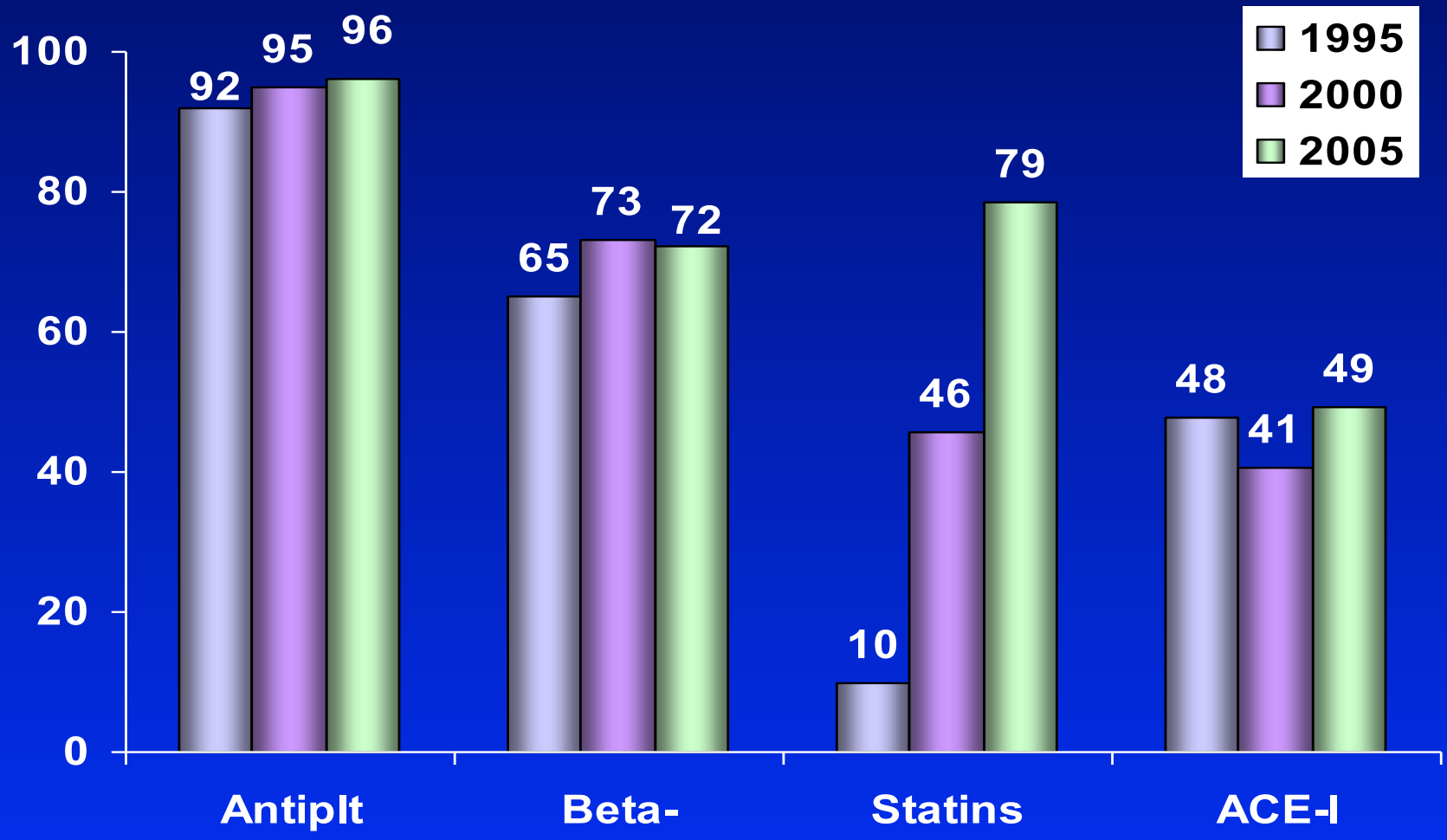
JAMA

Fox KAA et al. *JAMA* 2007

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

Adhérence aux guidelines: données françaises



Données tirées des registres USIK 1995; USIC 2000 et FAST MI

Cambou, Ann Cardiol Angeiol 2004

Cambou, Arch Mal Coeur Vaiss 2007

Pouvons nous encore diminuer la mortalité ?

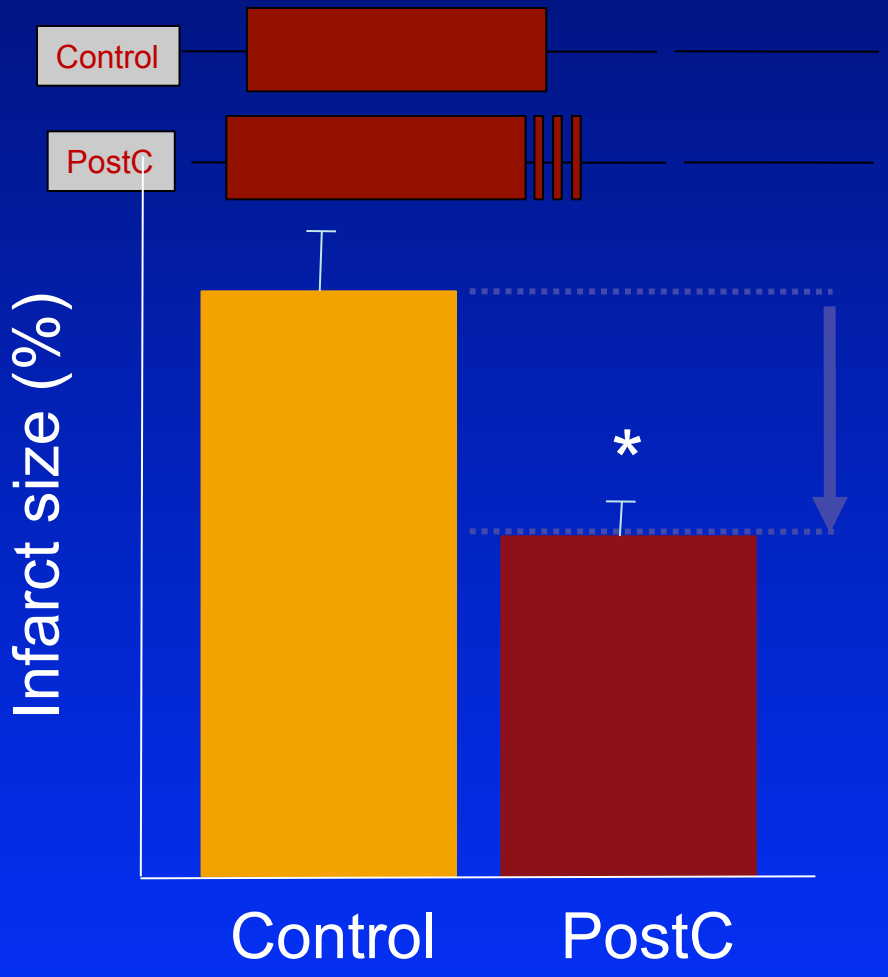
Pouvons nous encore réduire la mortalité ?

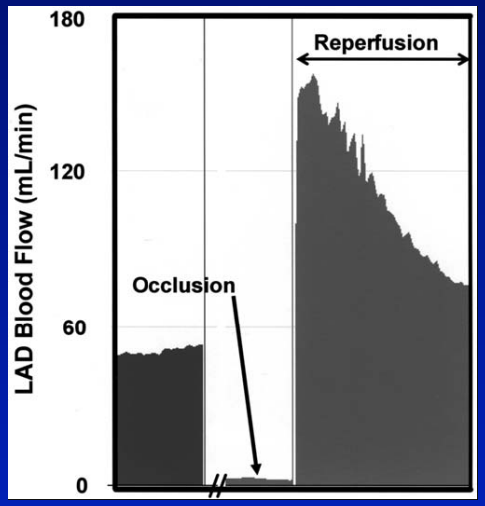
- **Post-conditionnement**

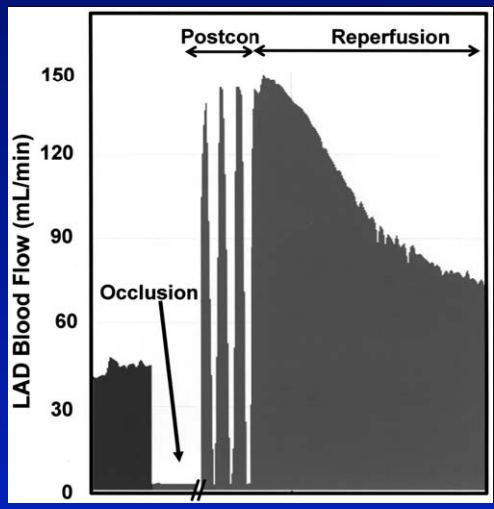
- Diminuer les événements ischémiques
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

- Diminuer les événements hémorragiques
  - Intérêt de la voie radiale
  - Pharmacologie
    - Fondaparinux
    - Bivalirudine

Intérêt du post-conditionnement







Zhao ZQ et al. Am J Physiol 2003

Post-conditionnement : intérêt de la cyclosporine

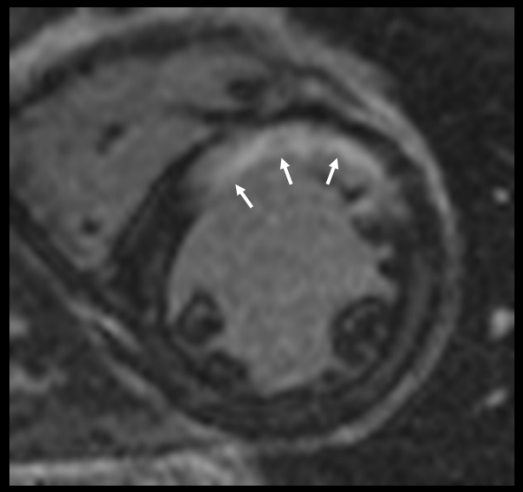
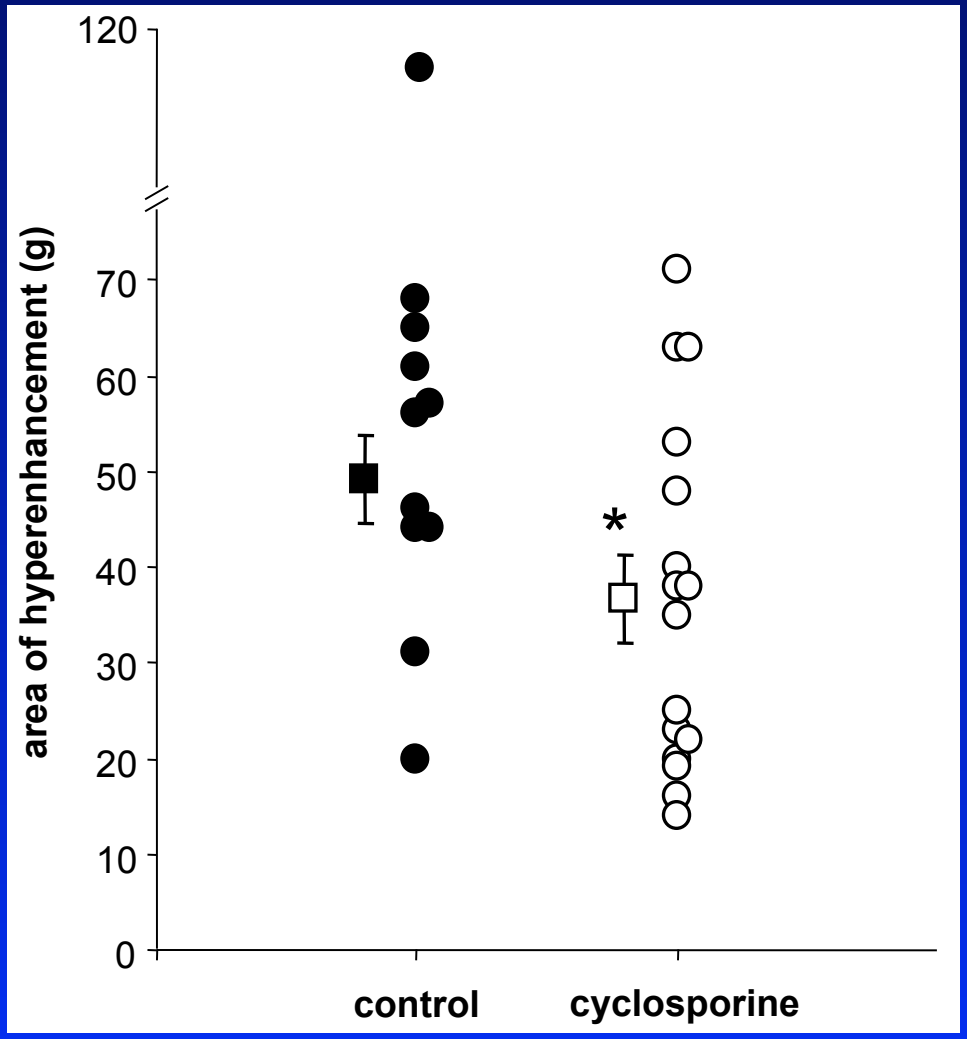


Figure: MRI infarct size
Short axis view of the left ventricle showing an area of hyper-enhancement within the anterior wall (arrows), indicative of myocardial infarction



Piot et al. NEJM 2008

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

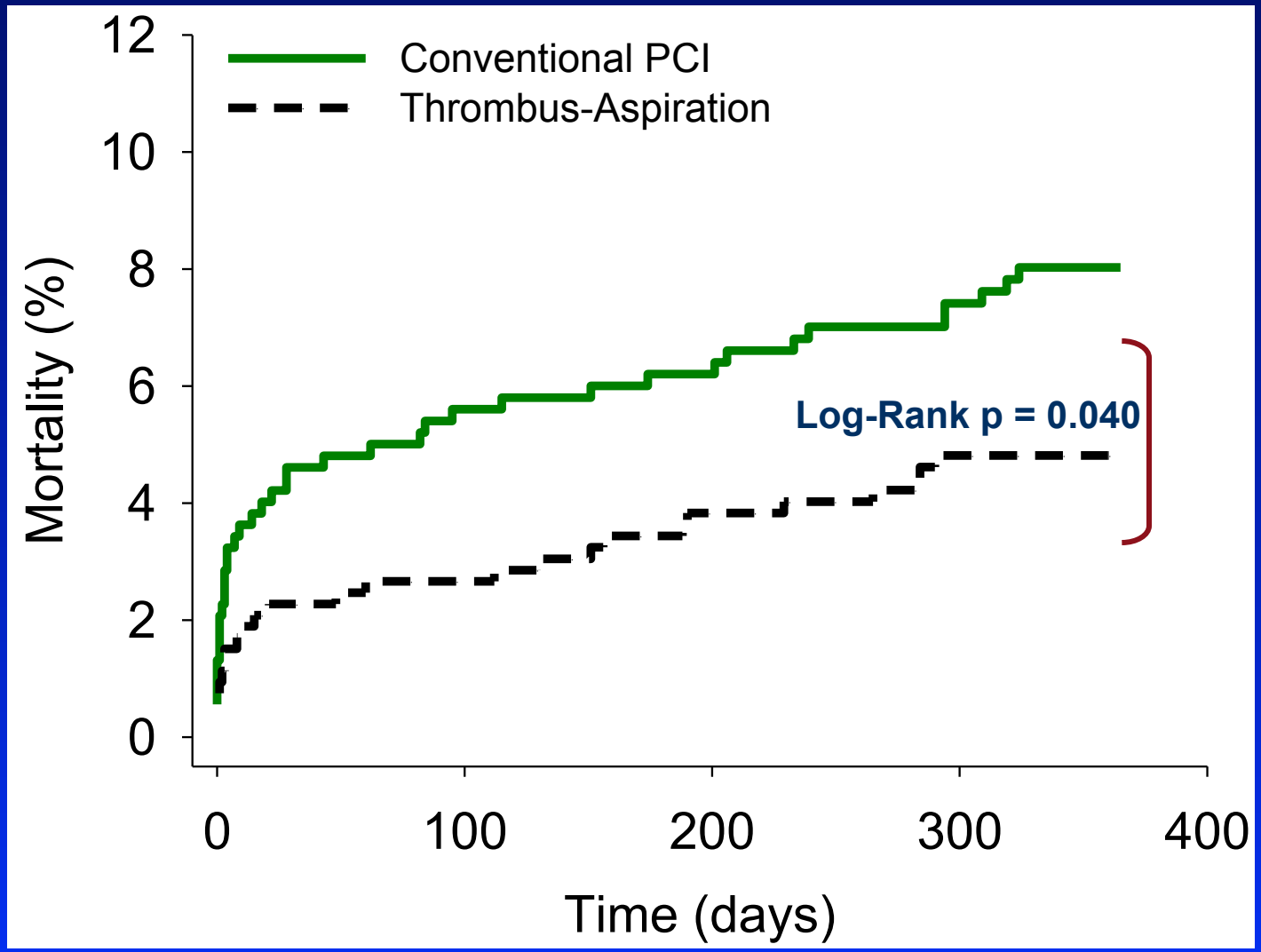
Pouvons nous encore diminuer la mortalité dans le SCA à haut risque ?

- Post-conditionnement

- **Diminuer les événements ischémiques**
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

- Diminuer les événements hémorragiques
  - Intérêt de la voie radiale
  - Pharmacologie
    - Fondaparinux
    - Bivalirudine

Etude TAPAS: mortalité à 1 an



Vlaar Lancet 2008

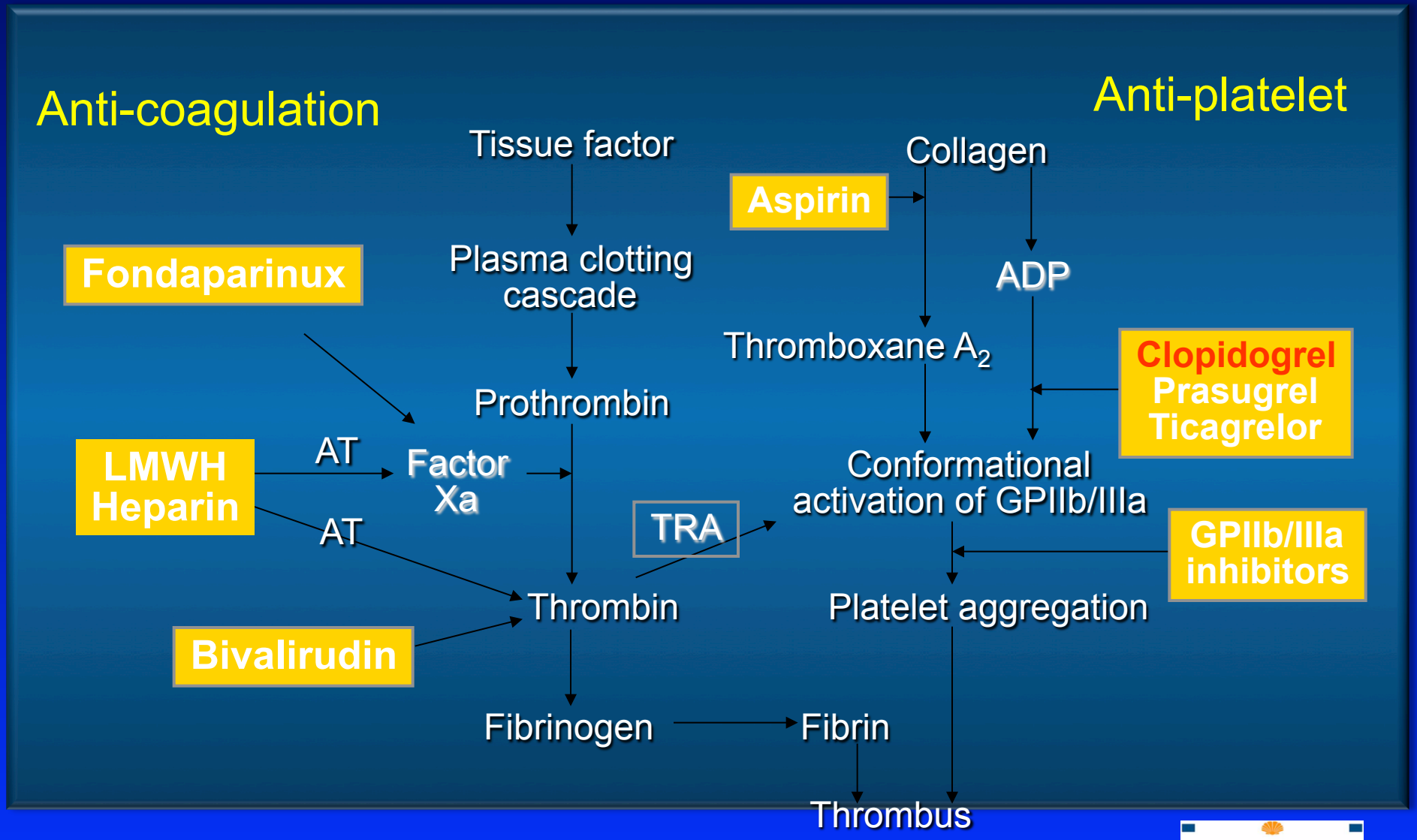
Pouvons nous encore diminuer la mortalité dans le SCA à haut risque?

- Post-conditionnement

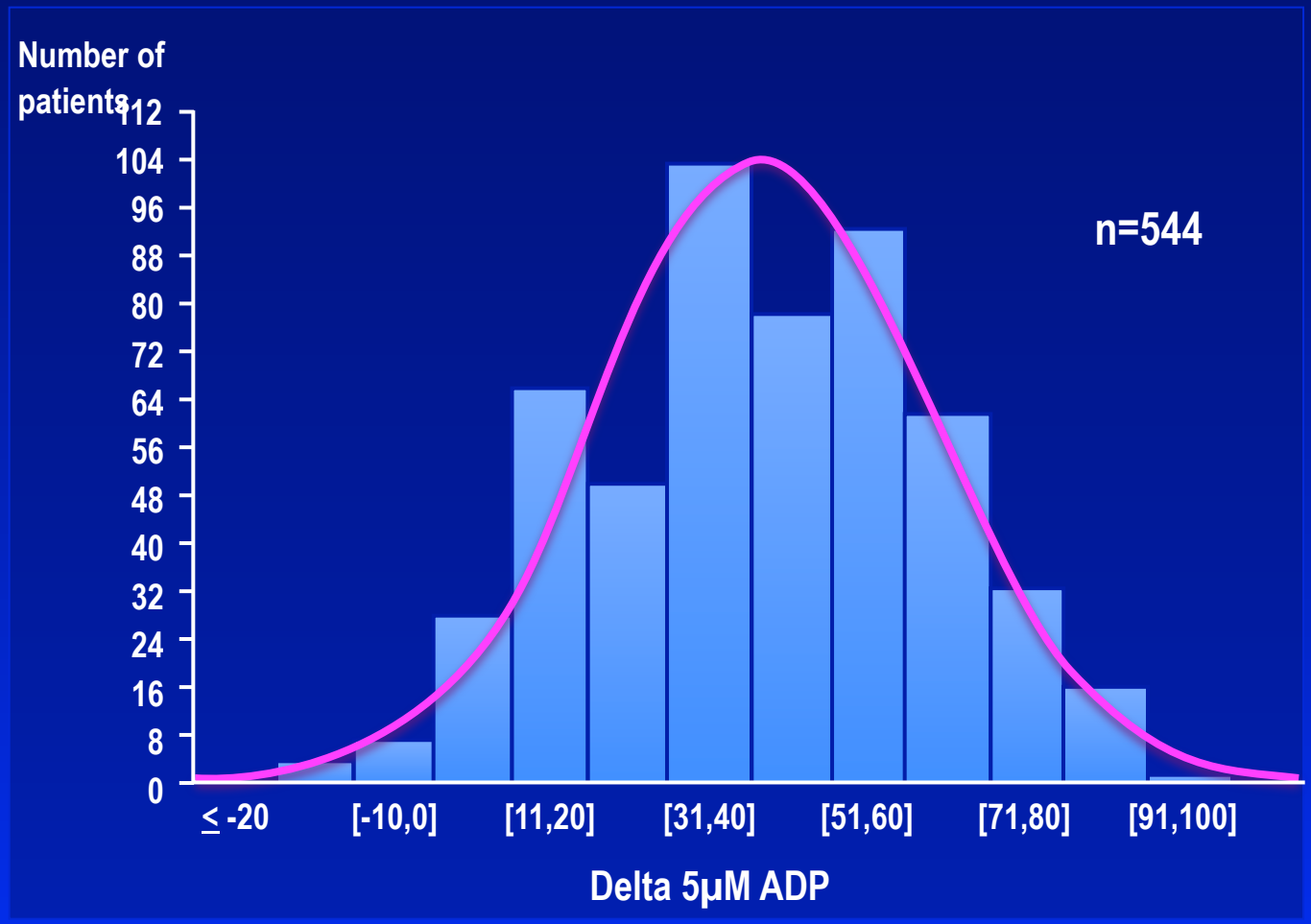
- **Diminuer les événements ischémiques**
  - Thromboaspiration
  - **Pharmacologie**
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

- Diminuer les événements hémorragiques
  - Intérêt de la voie radiale
  - Pharmacologie
    - Fondaparinux
    - Bivalirudine

Clopidogrel



Hétérogénéité de la réponse au clopidogrel

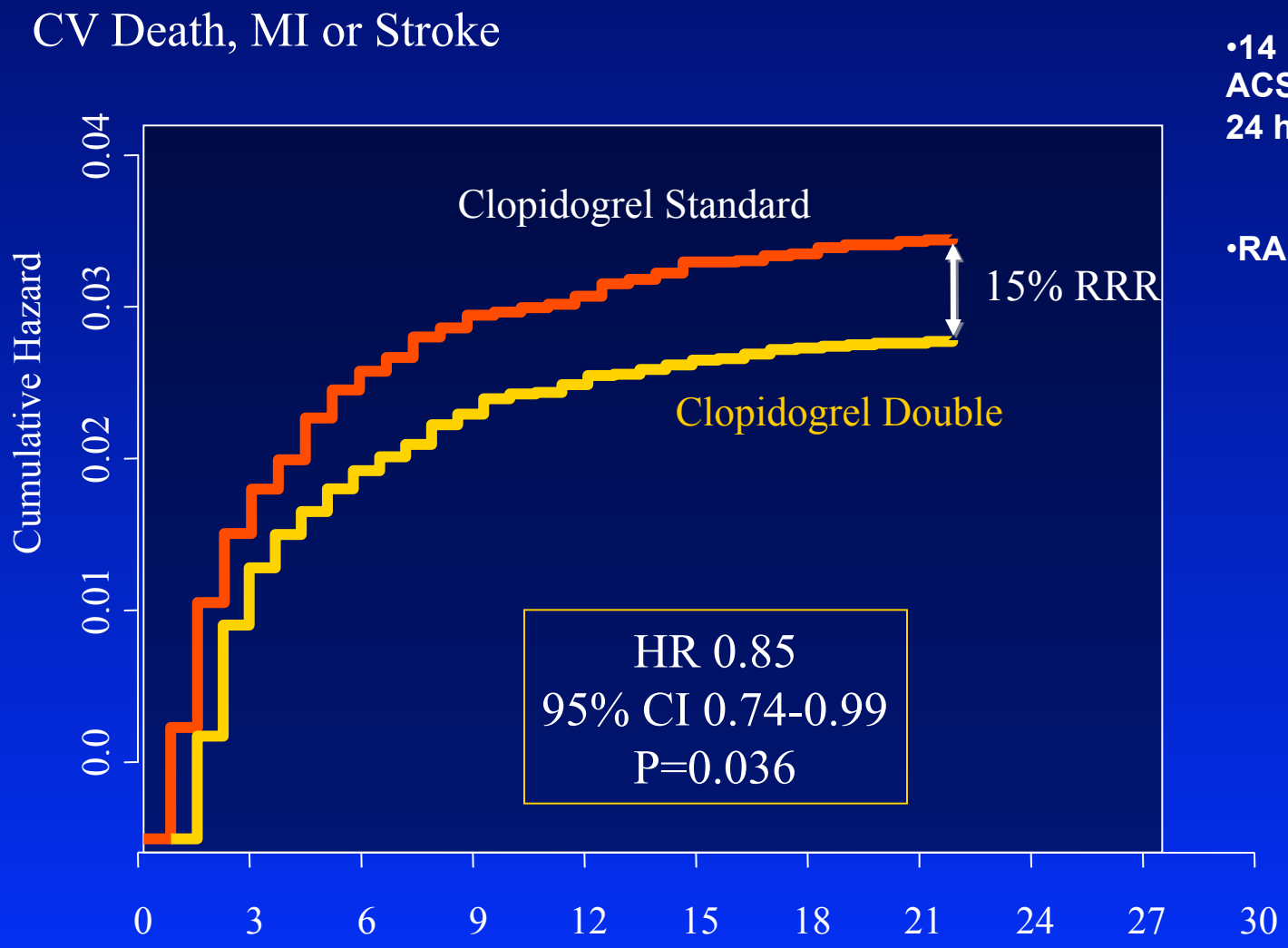


Serebruany et al. *JACC* 2005

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

Intérêt des fortes doses de clopidogrel: Etude CURRENT-OASIS 7



- 14 000 Pts with NSTE ACS & Planned PCI within 24 hrs

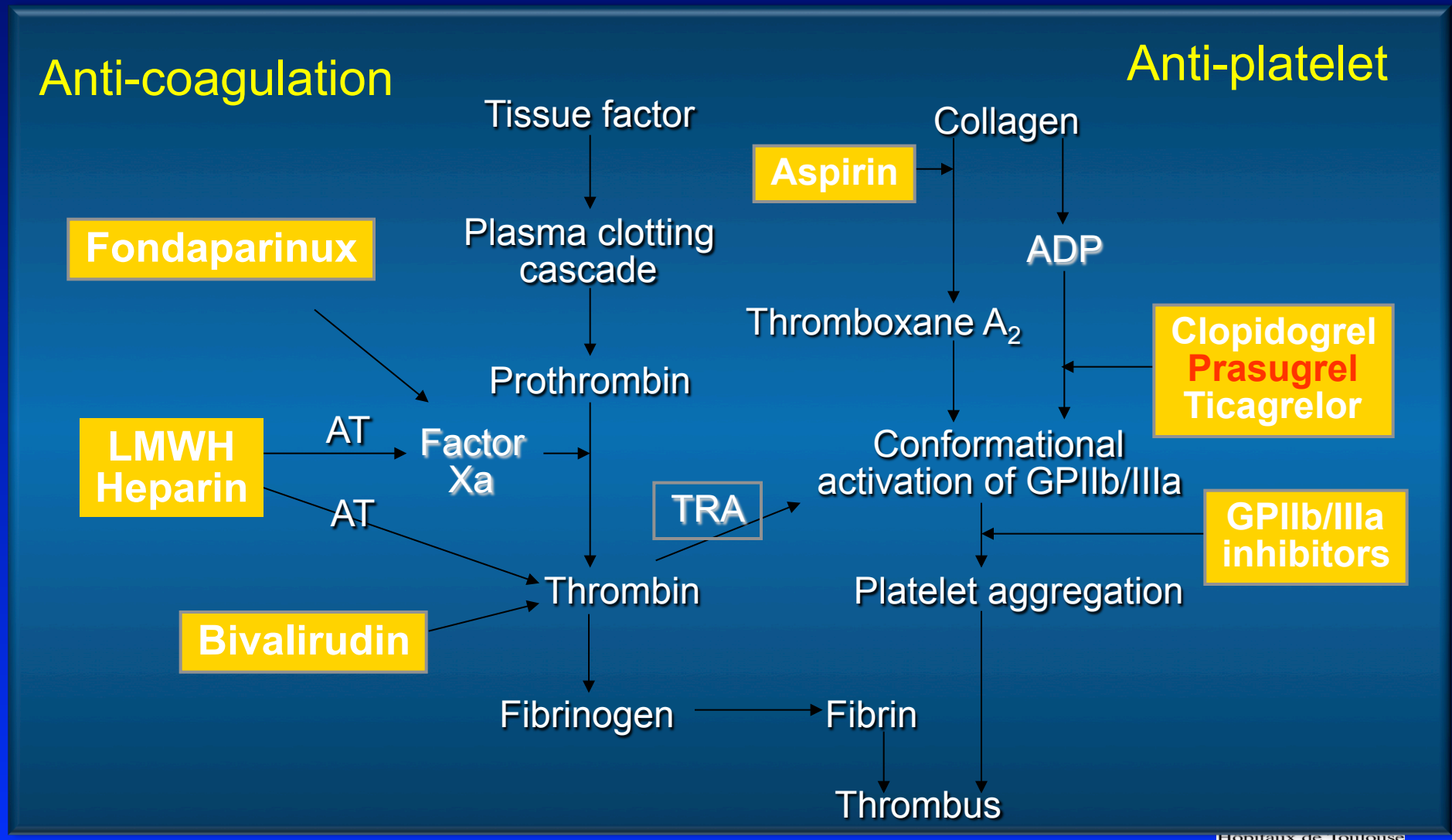
- RANDOMIZATION
  - Clopidogrel 300 mg + 75 mg (Day 2 – 30)
  - Vs.
  - Clopidogrel 600 mg + 150 mg (Day 2 – 7) + 75 mg (Day 8-30)

Mehta; Am Heart J. 2008

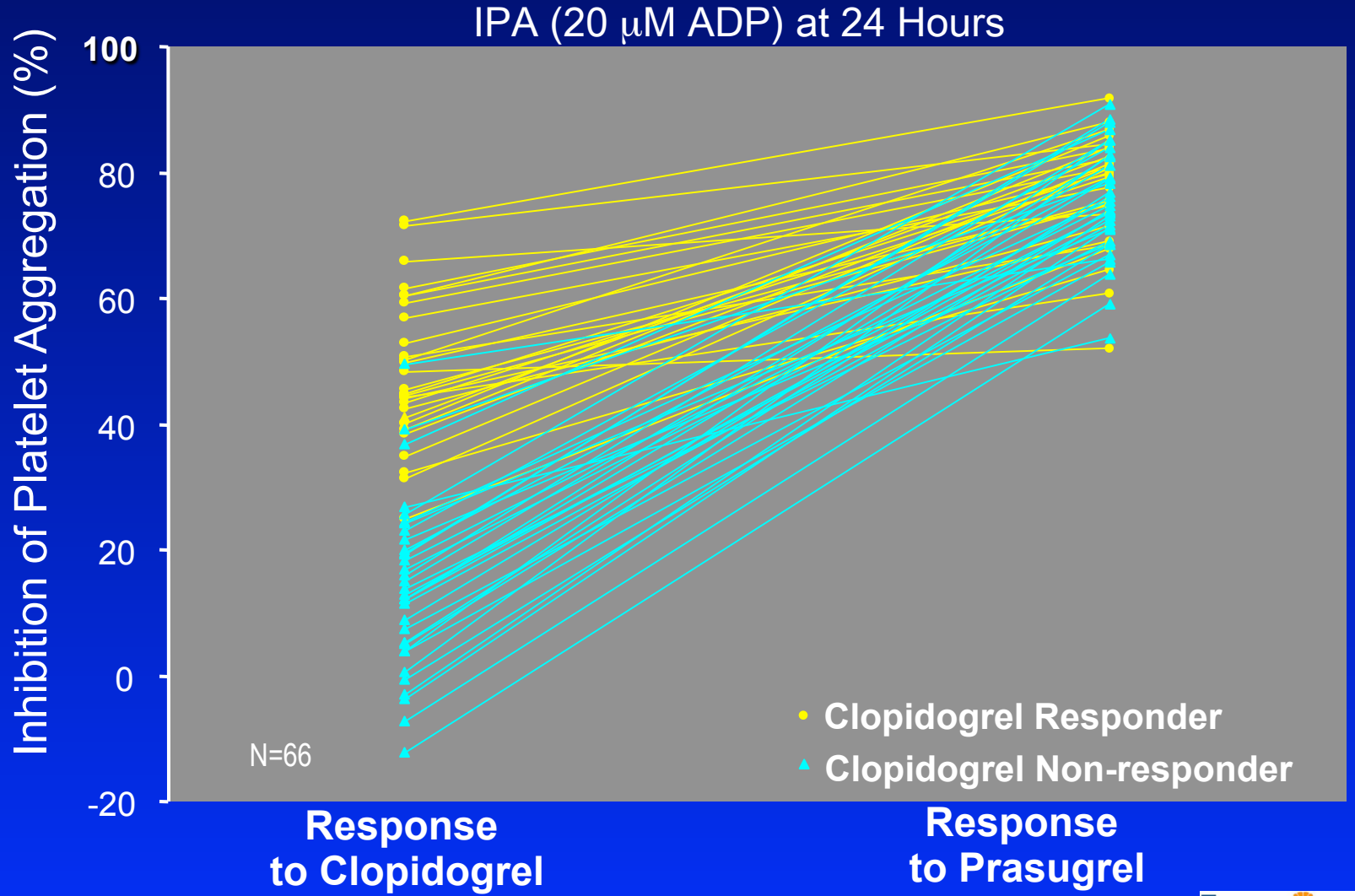
Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

Prasugrel


Anti-coagulation
Anti-platelet
Tissue factor
Collagen
Aspirin
Fondaparinux
Plasma clotting cascade
ADP
Thromboxane A_2
Clopidogrel
Prasugrel
Ticagrelor
Prothrombin
LMWH
Heparin
AT
Factor Xa
Conformational activation of GPIIb/IIIa
AT
TRA
GPIIb/IIIa inhibitors
Thrombin
Platelet aggregation
Bivalirudin
Fibrinogen
Fibrin
Thrombus

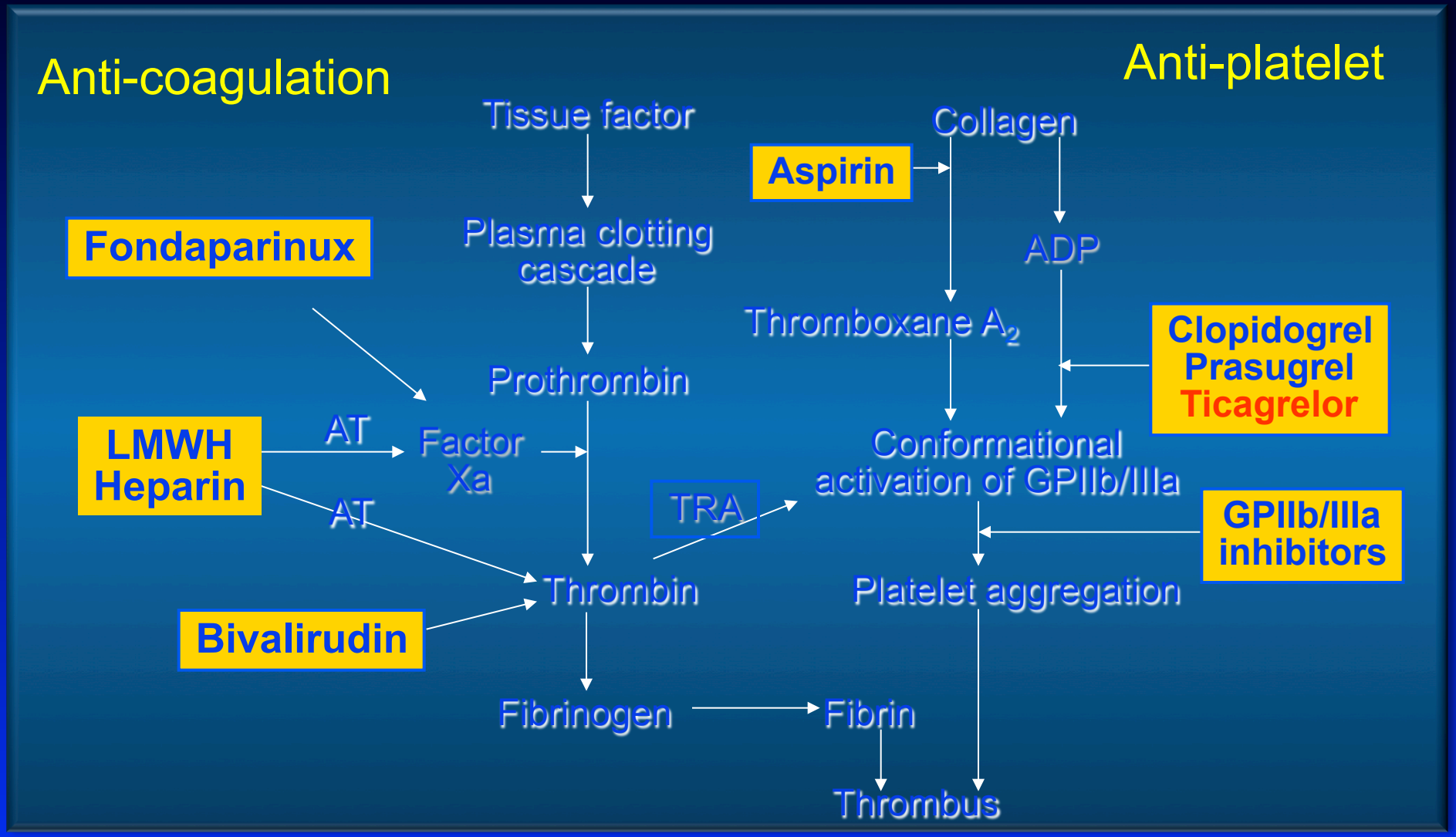
Intérêt du Prasugrel ?



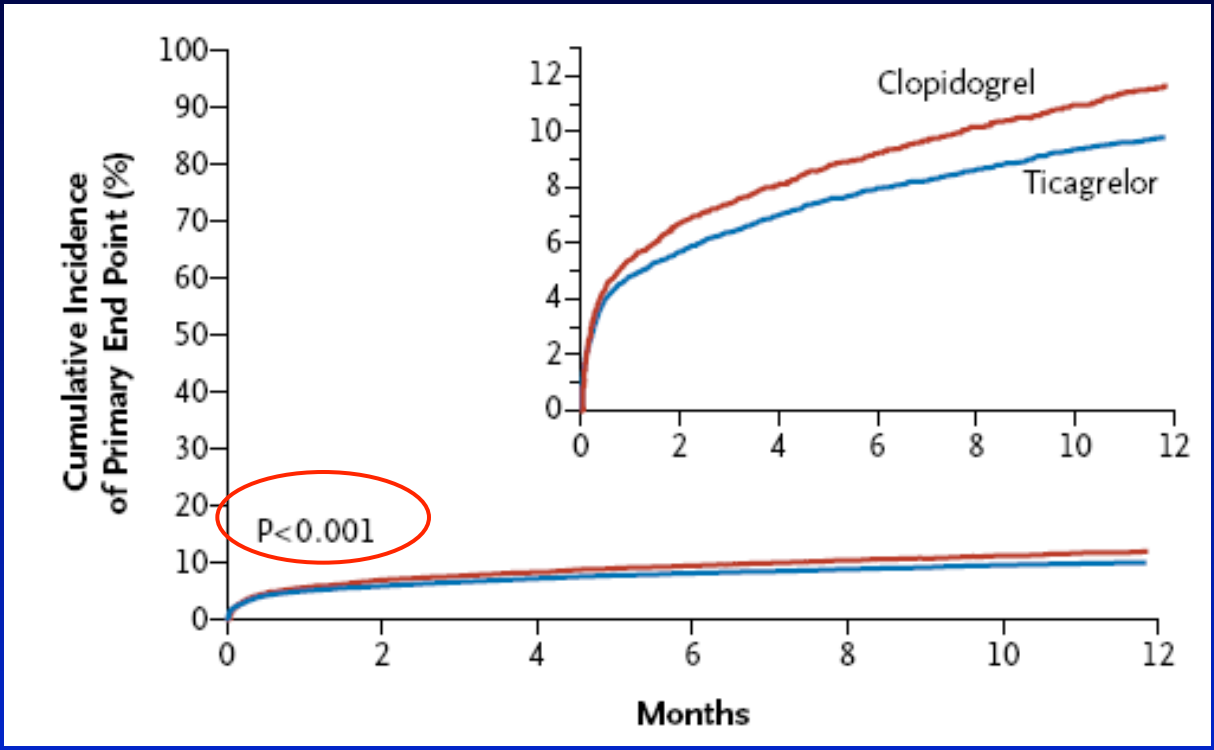
Brandt J, et al. ACC 2005

Hôpitaux de Toulouse
Pôle Cardiovasculaire et Métabolique

Ticagrelor


Anti-coagulation
Anti-platelet
Tissue factor
Collagen
Aspirin
Fondaparinux
Plasma clotting cascade
ADP
Thromboxane A_2
Clopidogrel
Prasugrel
Ticagrelor
Prothrombin
LMWH
Heparin
AT
Factor Xa
Conformational activation of GPIIb/IIIa
TRA
AT
GPIIb/IIIa inhibitors
Thrombin
Platelet aggregation
Bivalirudin
Fibrinogen
Fibrin
Thrombus

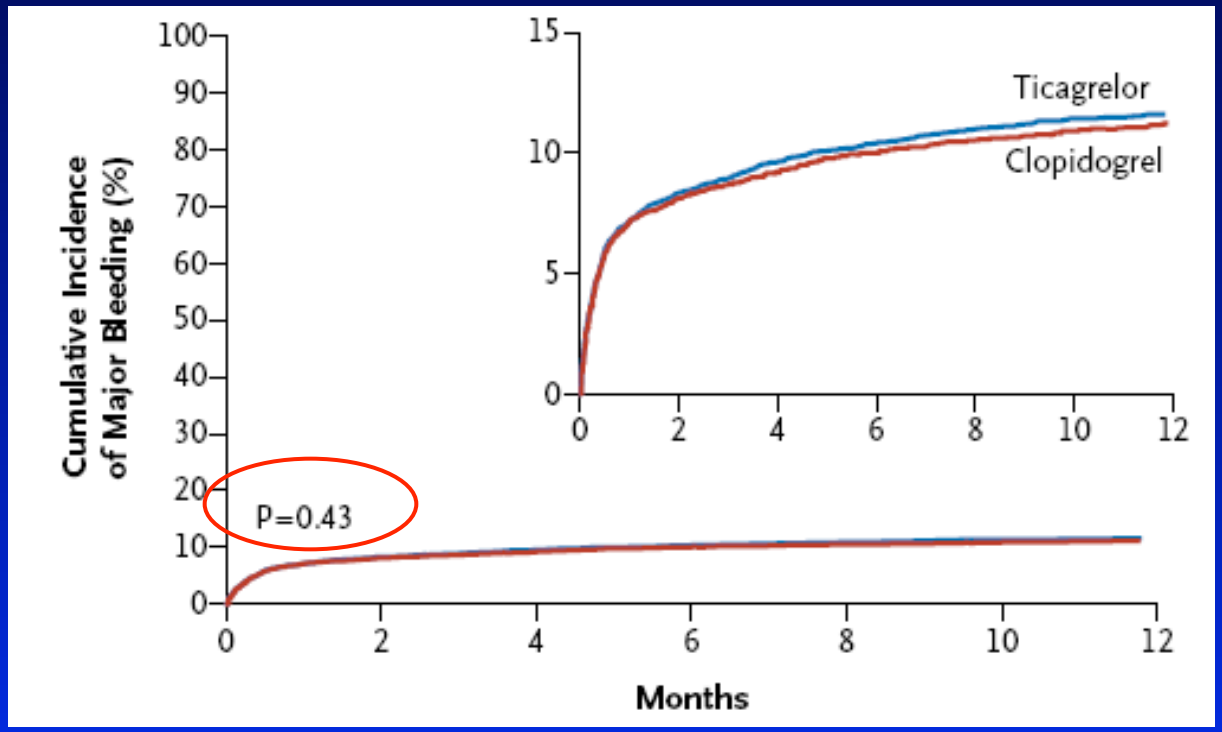
Ticagrelor: Etude PLATO



Evénements ischémiques

Wallentin; NEJM 2009

Ticagrelor: Etude PLATO



Evénements hémorragiques

Wallentin; NEJM 2009

Plato: bénéfice sur la mortalité

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

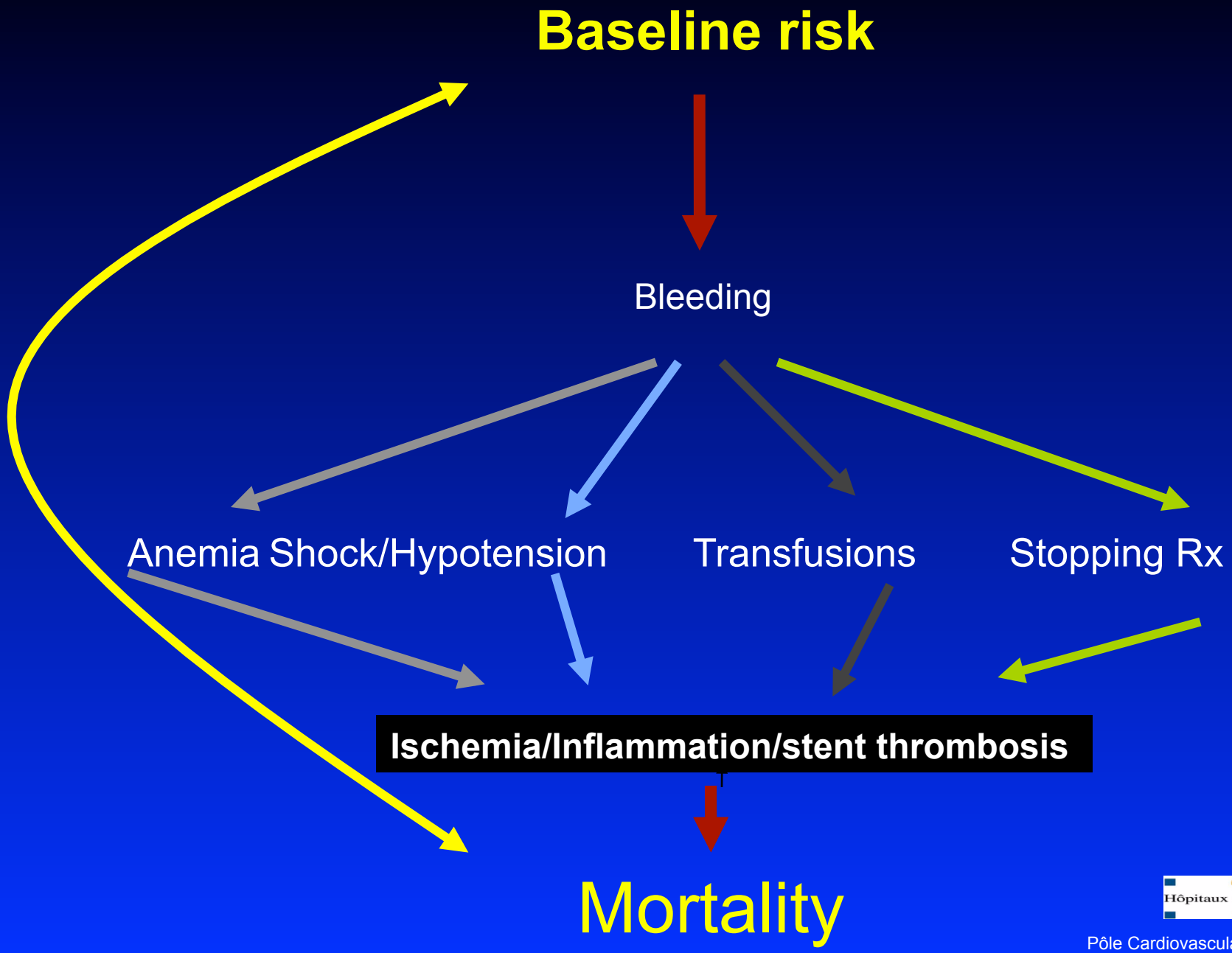
Wallentin; NEJM 2009

Pouvons nous encore diminuer la mortalité dans le SCA à haut risque ?

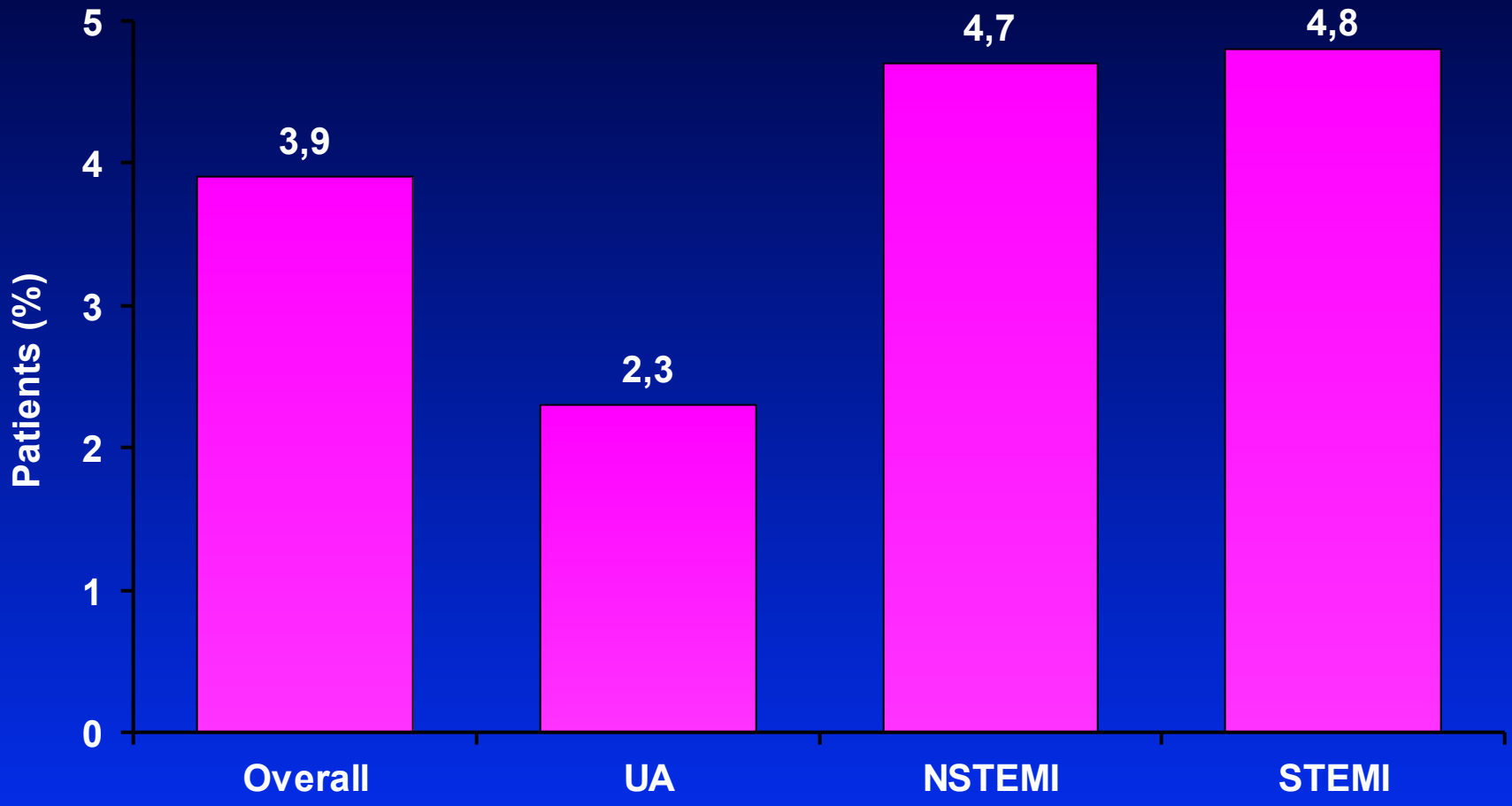
- Post-conditionnement

- Diminuer les événements ischémiques
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

- **Diminuer les événements hémorragiques**
  - Intérêt de la voie radiale
  - Pharmacologie
    - Fondaparinux
    - Bivalirudine

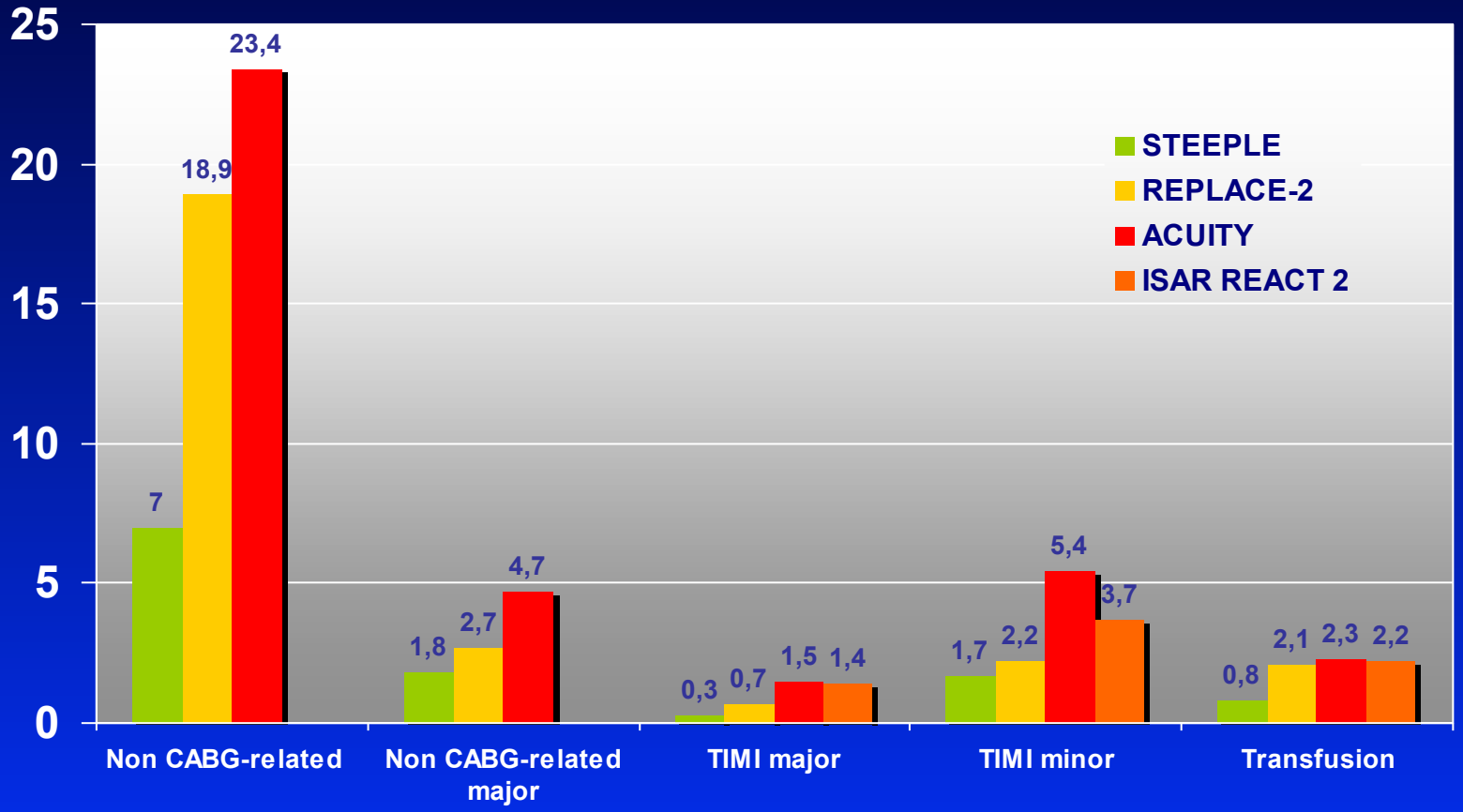

Baseline risk
Bleeding
Anemia Shock/Hypotension
Transfusions
Stopping Rx
Ischemia/Inflammation/stent thrombosis
Mortality

Incidence des saignements majeurs (Registre GRACE)



Moscucci M, et al. Eur Heart J. 2003

Taux de saignement dans les études contemporaines d'angioplastie



Pouvons nous prévoir les saignements ?

Prédicteurs indépendants de saignement : les caractéristiques du patient

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.28	1.21,1.37	<0.0001
Female sex	1.43	1.23,1.66	<0.0001
History of renal insufficiency	1.48	1.19,1.84	0.0004
History of bleeding	2.83	1.94,4.13	<0.0001
Mean arterial pressure (per 20 mmHg decrease)	1.11	1.04,1.19	0.0016
Diuretics	1.69	1.44,1.99	<0.0001
LMWH only[a]	0.70	0.57,0.85	0.0003
Thrombolytics only	1.43	1.14,1.78	0.0017
GP IIb/IIIa blockers only	1.93	1.59,2.35	<0.0001
Thrombolytics and GP IIb/IIIa blockers	2.38	1.69,3.35	<0.0001
IV inotropic agents	2.05	1.68,2.50	<0.0001
Other vasodilators	1.35	1.09,1.68	0.0068
Right-heart catheterization	2.48	1.98,3.11	<0.0001
Percutaneous coronary intervention	1.63	1.36,1.94	<0.0001

[a]Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit Test P-value=0.59; C-statistic=0.75. GP=glycoprotein; LMWH=low-molecular-weight heparin; OR=odds ratio; UFH=unfractionated heparin.

Moscucci M et al. ***Eur Heart J 2003***

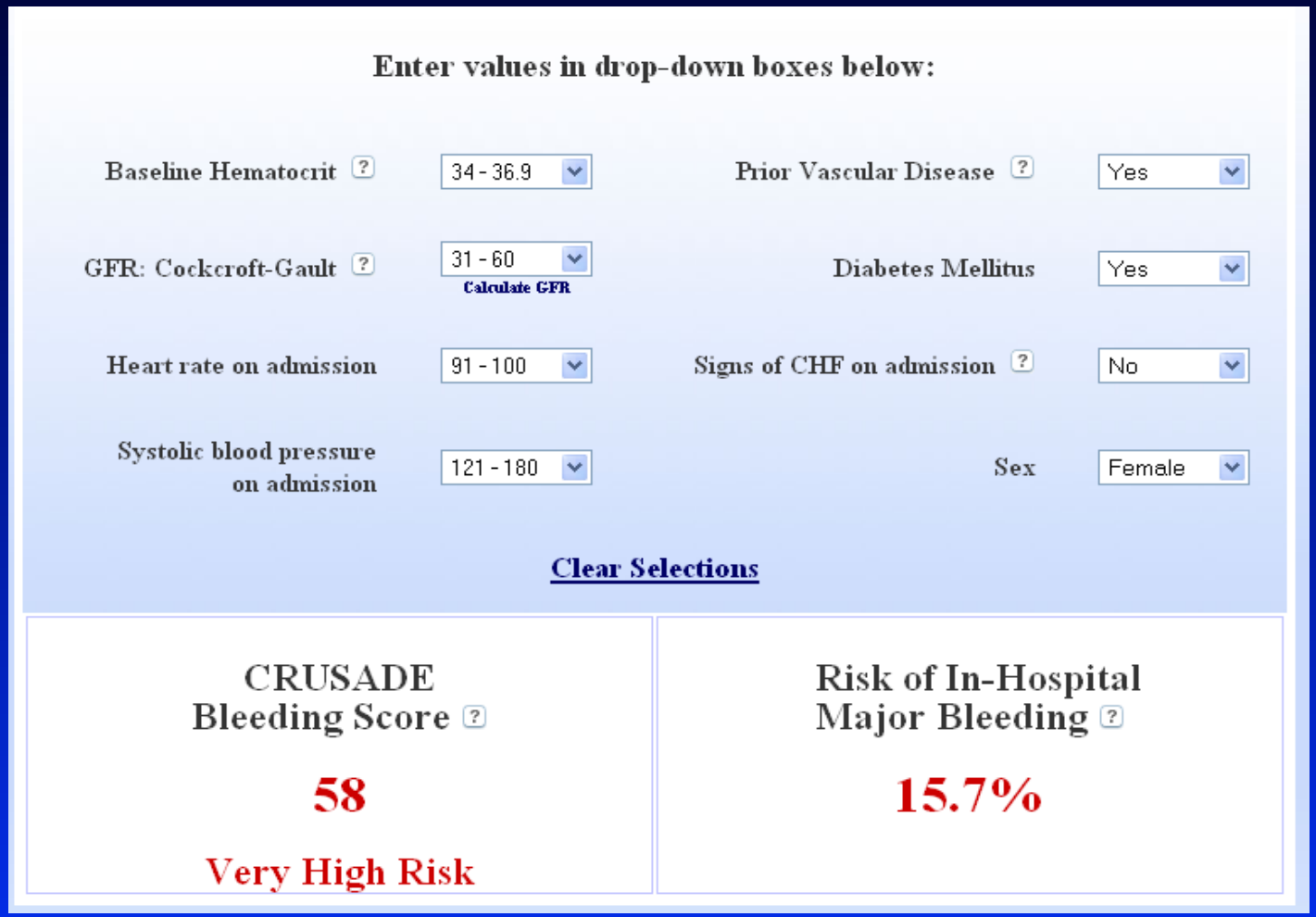
Prédicteurs indépendants de saignement : les traitements

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.28	1.21,1.37	<0.0001
Female sex	1.43	1.23,1.66	<0.0001
History of renal insufficiency	1.48	1.19,1.84	0.0004
History of bleeding	2.83	1.94,4.13	<0.0001
Mean arterial pressure (per 20 mmHg decrease)	1.11	1.04,1.19	0.0016
Diuretics	1.69	1.44,1.99	<0.0001
LMWH only[a]	0.70	0.57,0.85	0.0003
Thrombolytics only	1.43	1.14,1.78	0.0017
GP IIb/IIIa blockers only	1.93	1.59,2.35	<0.0001
Thrombolytics and GP IIb/IIIa blockers	2.38	1.69,3.35	<0.0001
IV inotropic agents	2.05	1.68,2.50	<0.0001
Other vasodilators	1.35	1.09,1.68	0.0068
Right-heart catheterization	2.48	1.98,3.11	<0.0001
Percutaneous coronary intervention	1.63	1.36,1.94	<0.0001

[a]Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit Test P-value=0.59; C-statistic=0.75. GP=glycoprotein; LMWH=low-molecular-weight heparin; OR=odds ratio; UFH=unfractionated heparin.

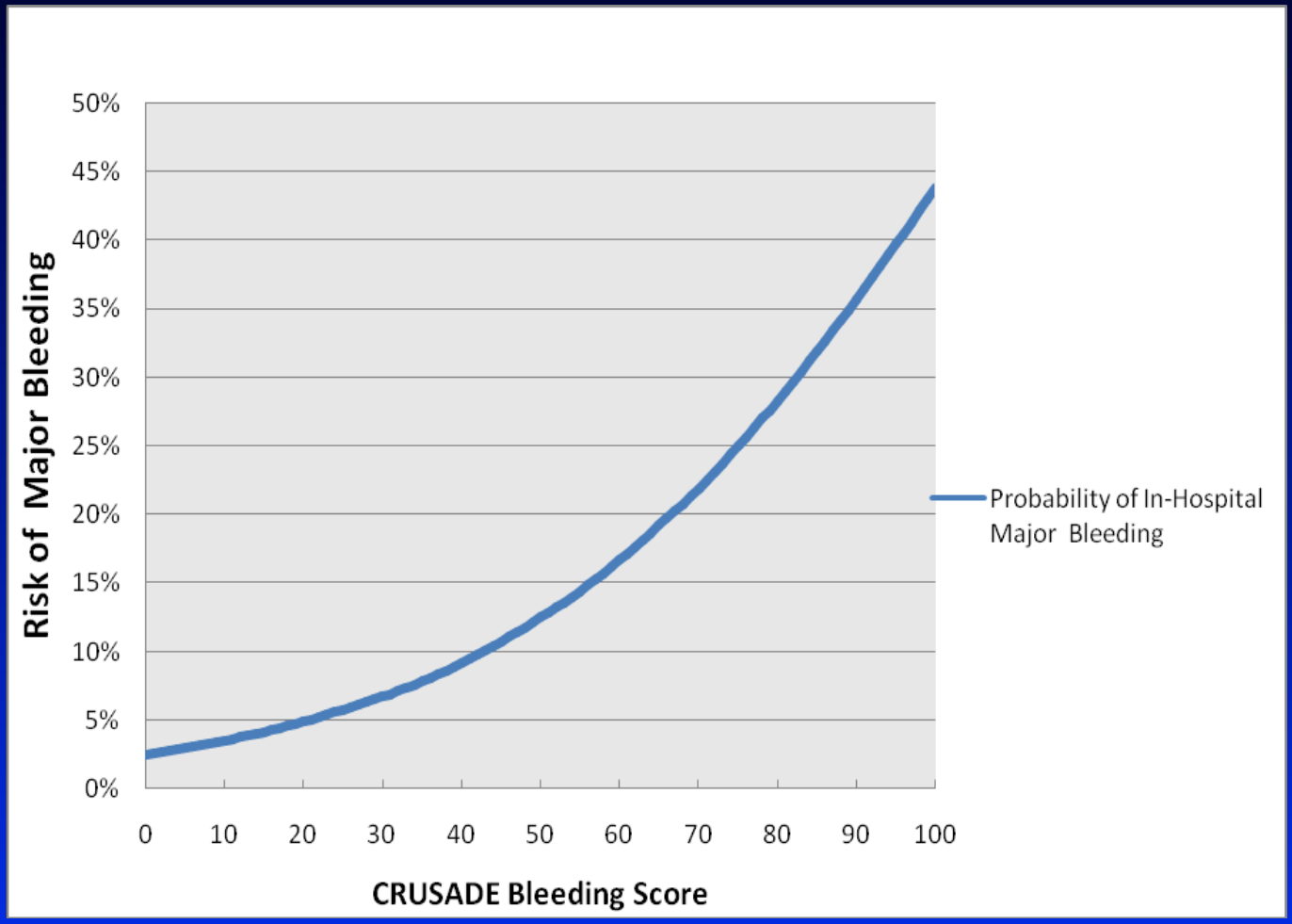
Moscucci M et al. *Eur Heart J* 2003

Score de risque de saignement CRUSADE



Subherwal S et al, Circulation 2009

Score de risque de saignement CRUSADE



p<0.001 for trend; Derivation: C=0.71 Validation: C=0.70

Subherwal S et al, Circulation 2009

Pouvons nous encore diminuer la mortalité dans le SCA à haut risque ?

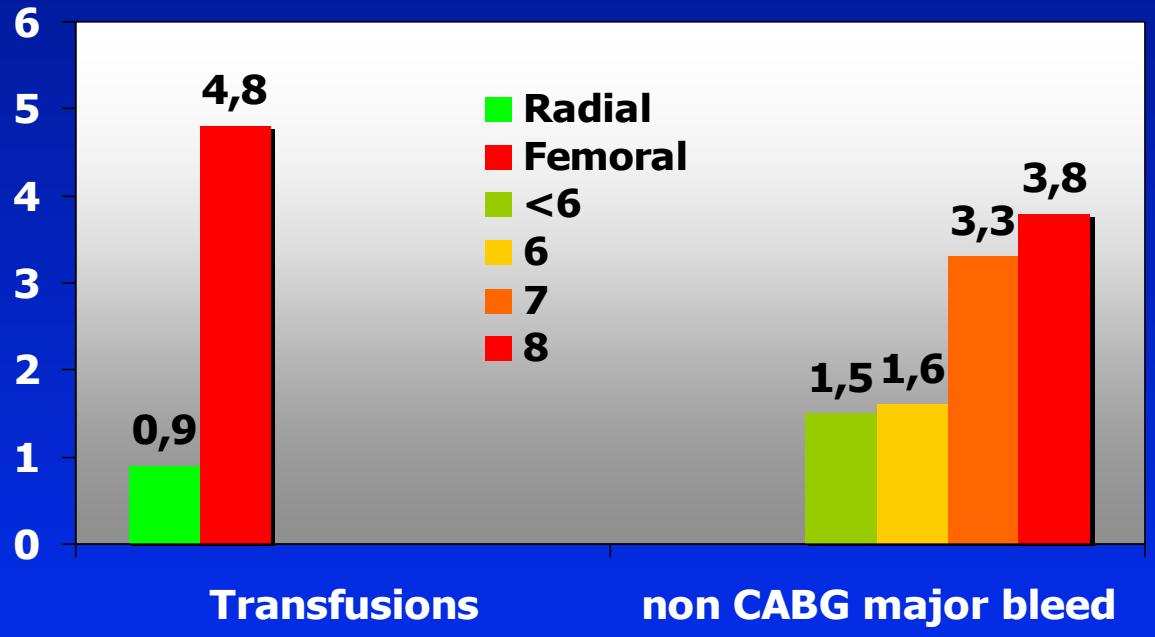
- Post-conditionnement

- Diminuer les événements ischémiques
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

- **Diminuer les événements hémorragiques**
  - Intérêt de la voie radiale
  - Pharmacologie
    - Fondaparinux
    - Bivalirudine

Diminuer les événements hémorragiques: intérêt de la voie radiale

9404 ACS pts from the SYNERGY trial



(for pts with femoral access)

Cantor. Catheter Cardiovasc Interv 2007

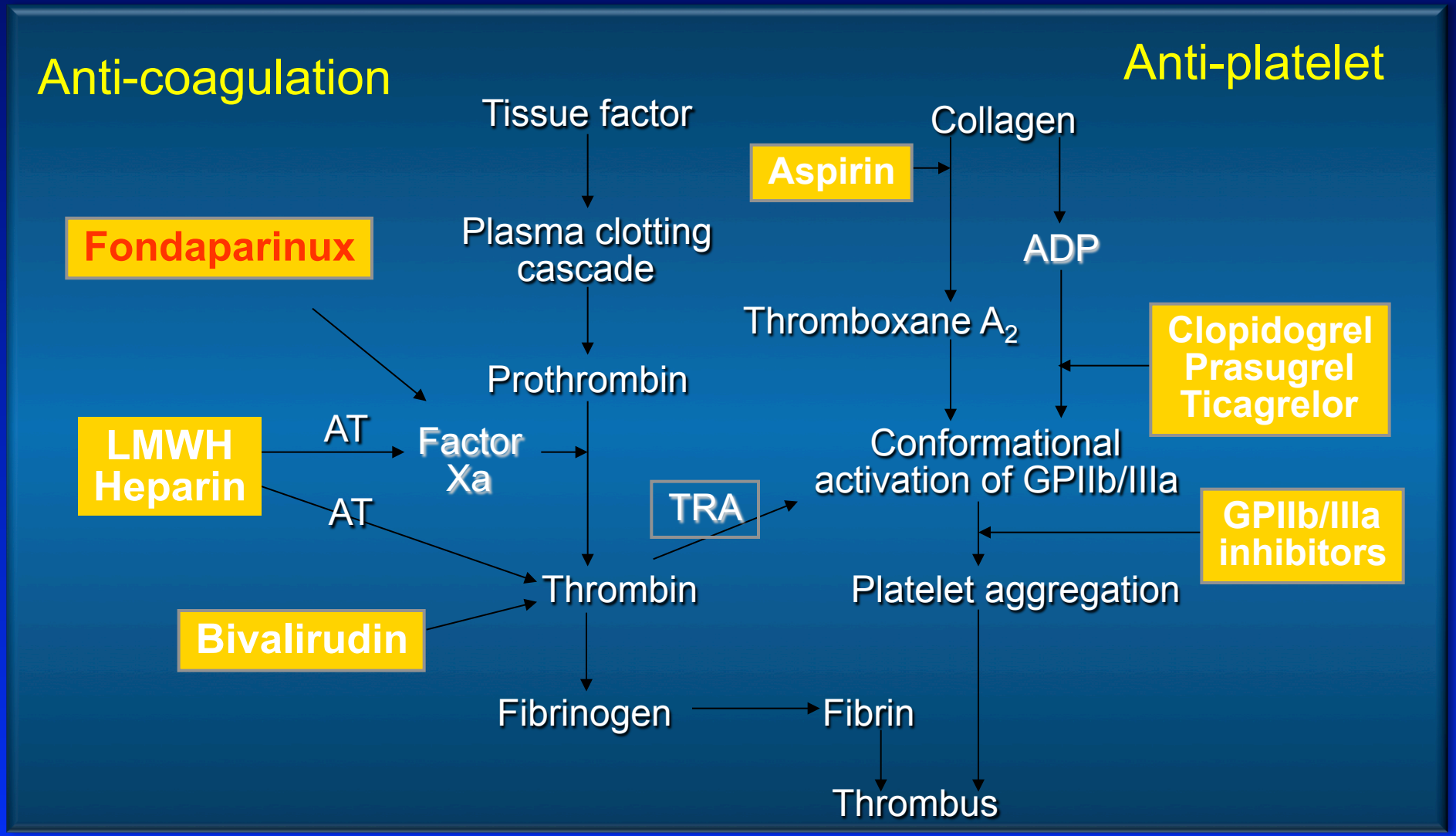
Pouvons nous encore diminuer la mortalité dans le SCA à haut risque ?

- Post-conditionnement

- Diminuer les événements ischémiques
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - Ticagrelor

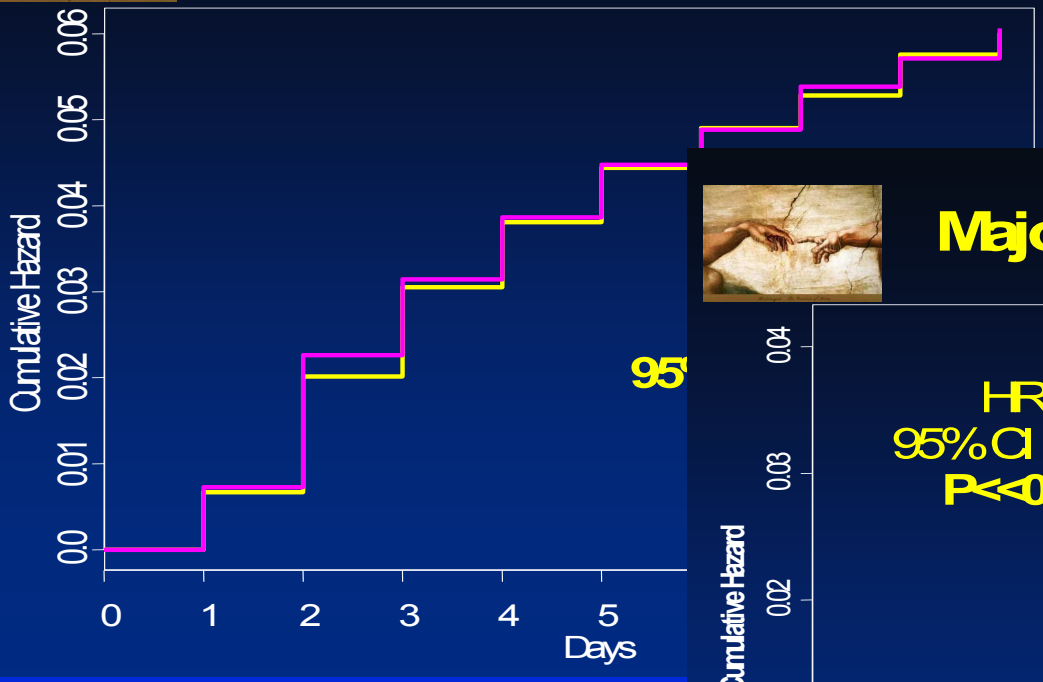
- **Diminuer les événements hémorragiques**
  - Intérêt de la voie radiale
  - **Pharmacologie**
    - **Fondaparinux**
    - Bivalirudine

Fondaparinux

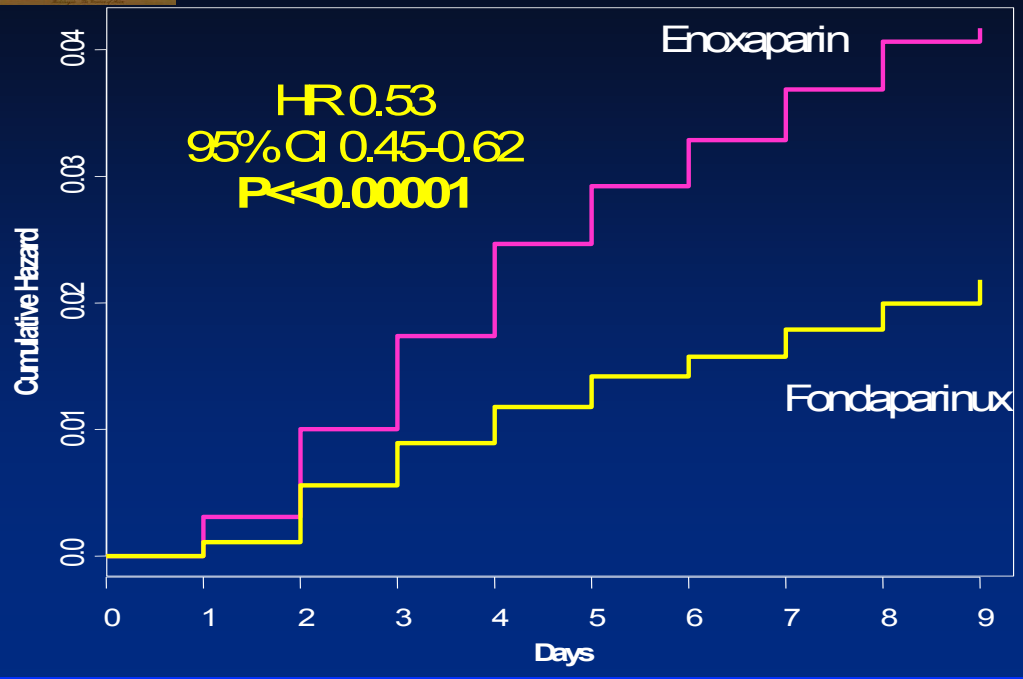


Fondaparinux: Etude OASIS 5

Death/MI/RI: Day 9



Major Bleeding: 9 Days



NEJM 2006

Fondaparinux: Etude OASIS 5

Mortality: Day 30

NEJM 2006

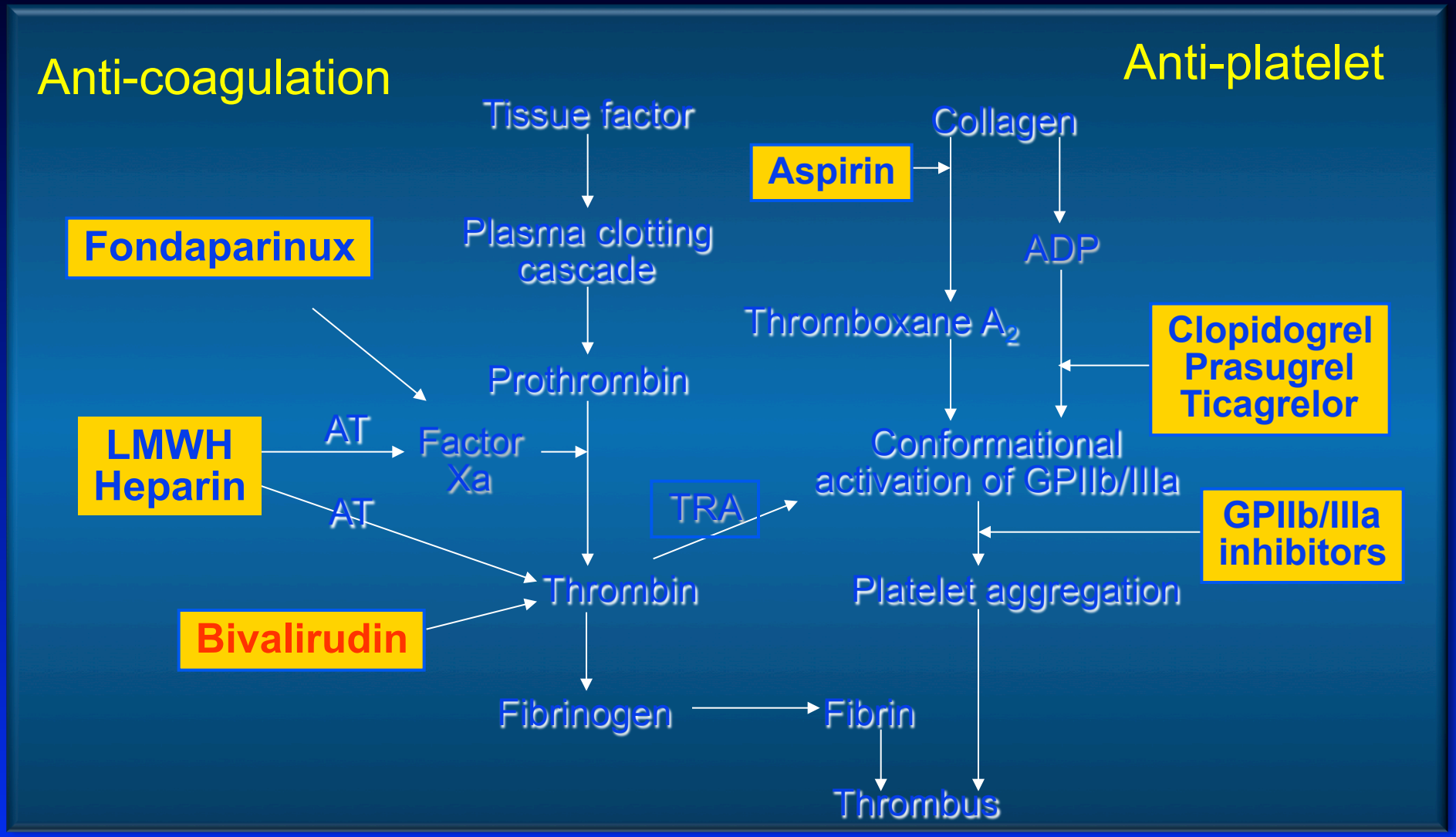
Pouvons nous encore diminuer la mortalité dans le SCA à haut risque ?

- Post-conditionnement

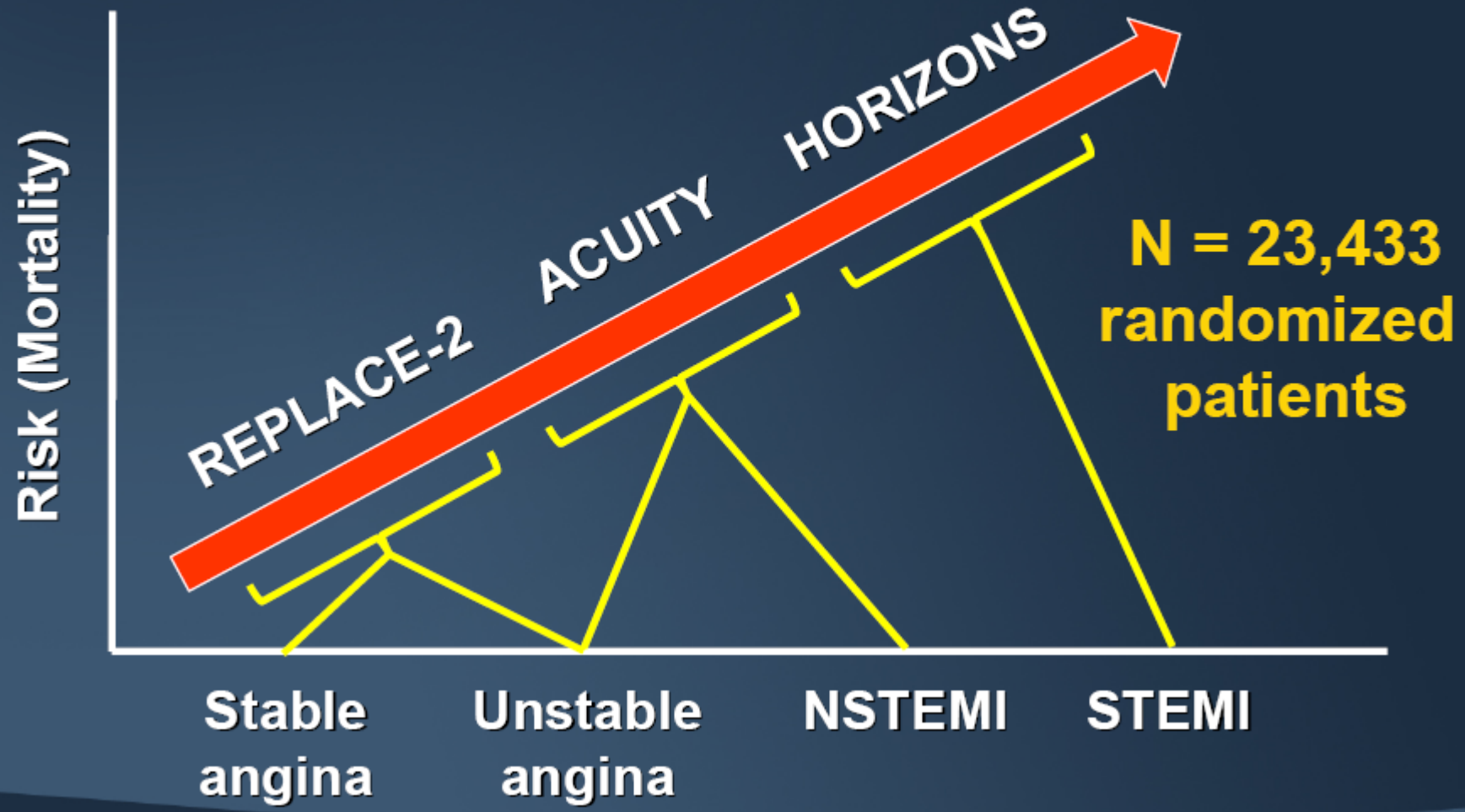
- Diminuer les événements ischémiques
  - Thromboaspiration
  - Pharmacologie
    - Fortes doses de clopidogrel
    - Prasugrel
    - **Ticagrelor**

- **Diminuer les événements hémorragiques**
  - Intérêt de la voie radiale
  - **Pharmacologie**
    - Fondaparinux
    - Bivalirudine

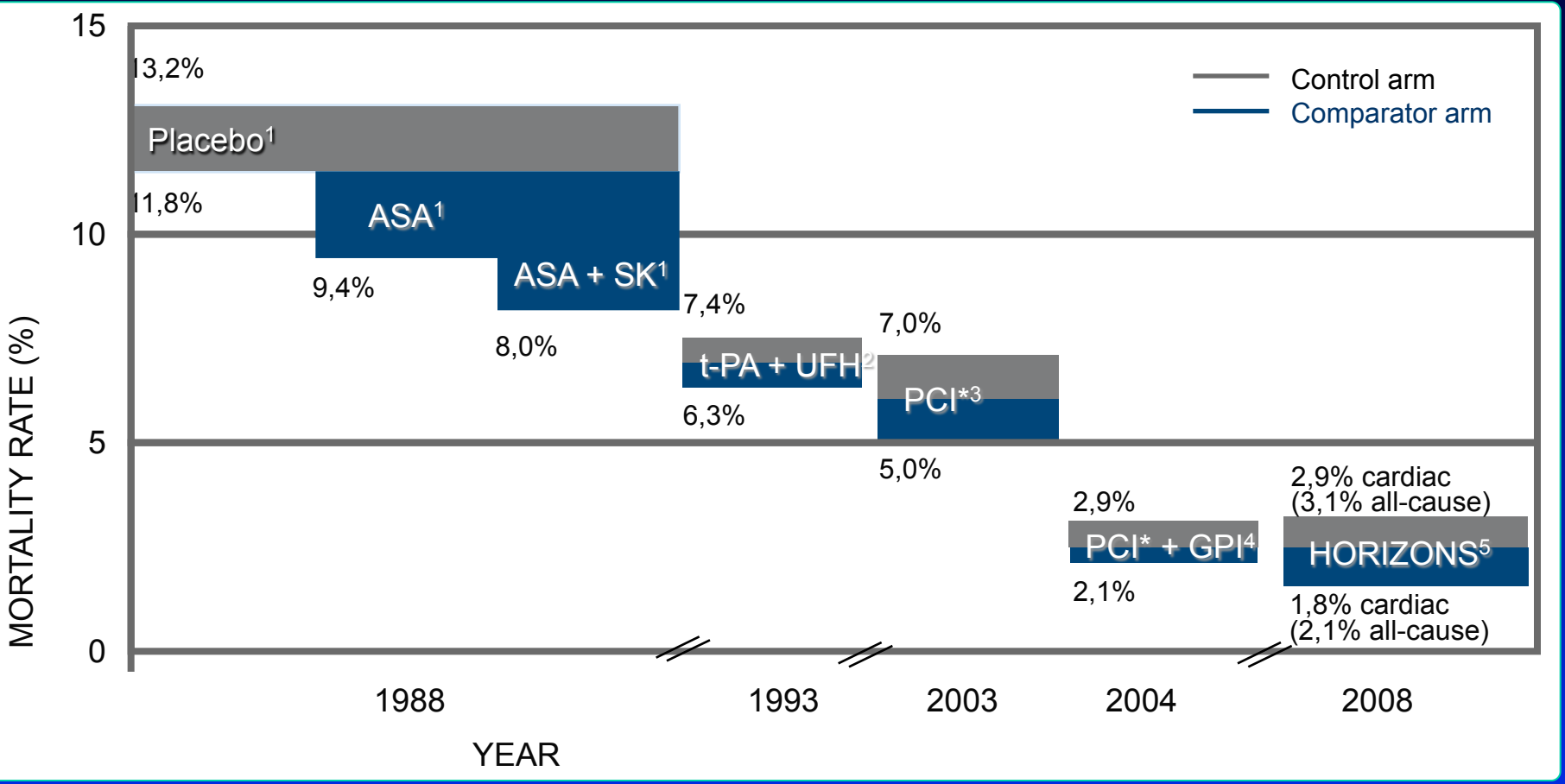
Bivalirudine



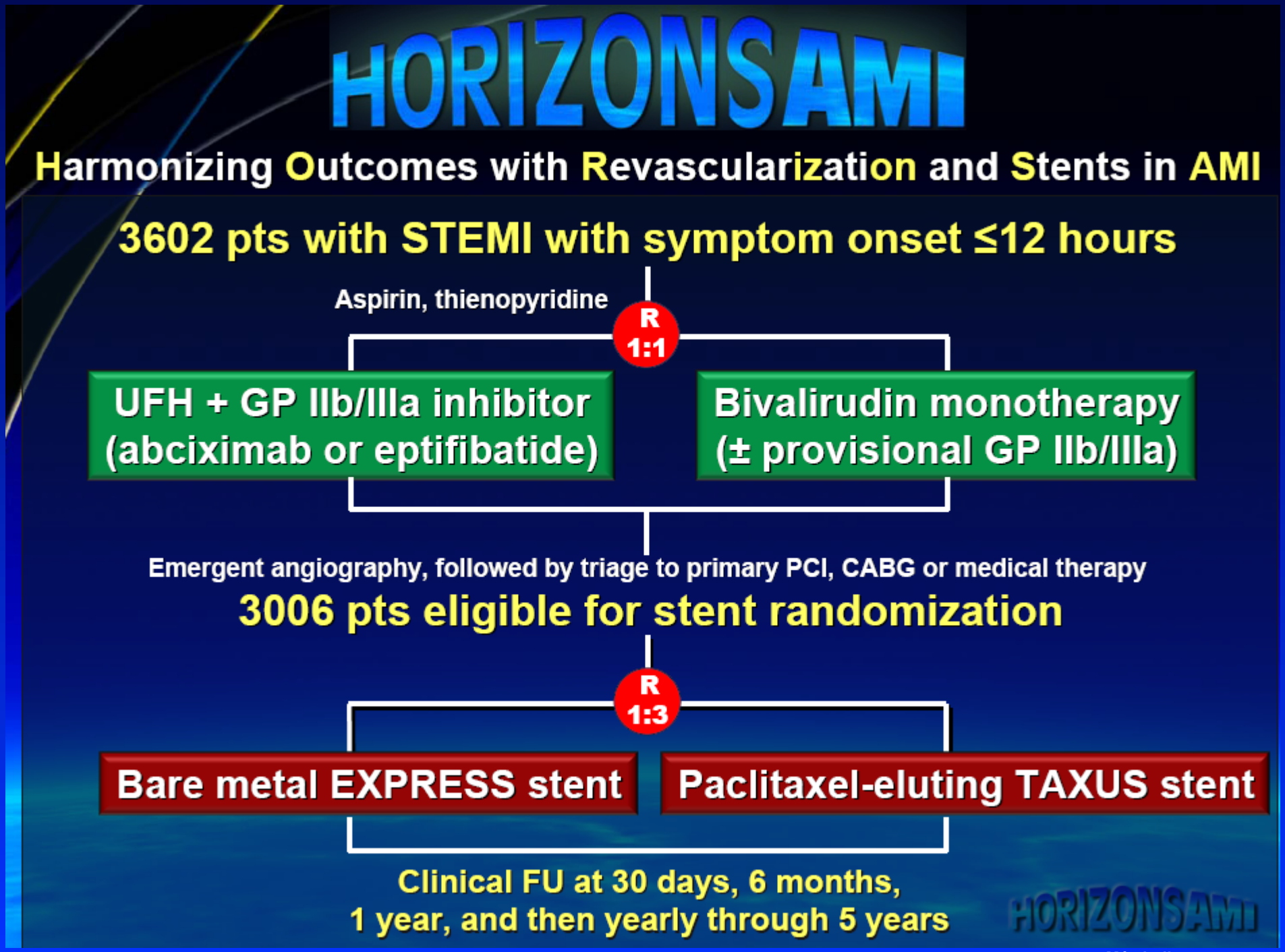
Bivalirudin Across the Spectrum of CAD: Pivotal trials



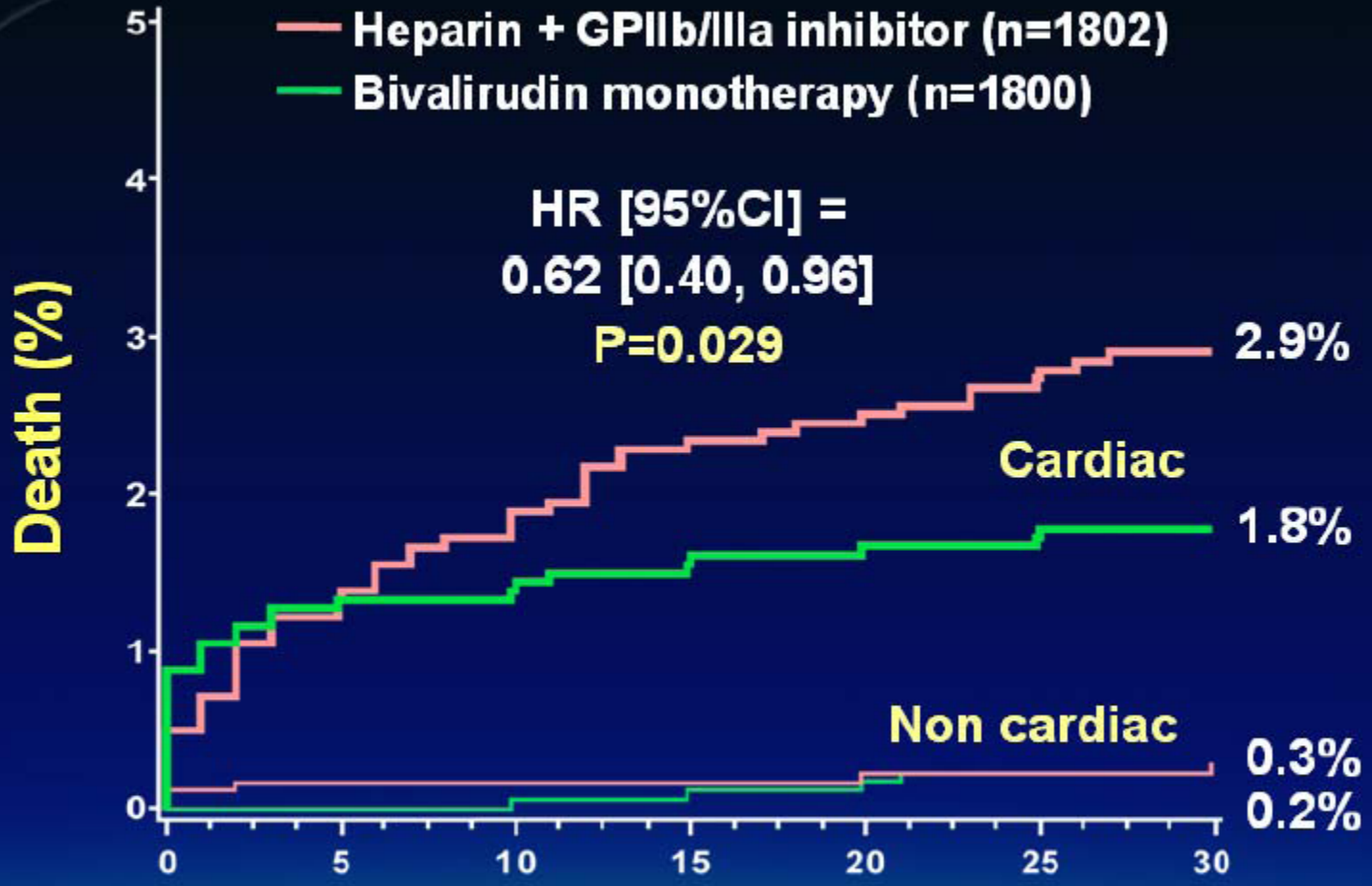
Progrès thérapeutiques à travers les études cliniques dans les SCA ST+



ASA: aspirin; GPI: GP IIb/IIIa inhibitor; SK: streptokinase; STE-ACS: ST-elevation acute coronary syndrome; t-PA: tissue plasminogen activator.
*PCI includes percutaneous transluminal coronary angioplasty (PTCA) ± stent with aspirin and thienopyridine.
1. ISIS-2. *Lancet.* 1988;2:349–60; 2. GUSTO-I. *N Engl J Med.* 1993;329:673–82; 3. Keeley EC et al. *Lancet.* 2003;361:13–20; 4. Kandzari DE et al. *Am Heart J.* 2004;147:457–62; 5. Stone GW et al. *N Engl J Med.* 2008;358:2218–30.


HORIZONS AMI
Harmonizing Outcomes with Revascularization and Stents in AMI
3602 pts with STEMI with symptom onset ≤12 hours
Aspirin, thienopyridine
R 1:1
UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
Bivalirudin monotherapy (± provisional GP IIb/IIIa)
Emergent angiography, followed by triage to primary PCI, CABG or medical therapy
3006 pts eligible for stent randomization
R 1:3
Bare metal EXPRESS stent
Paclitaxel-eluting TAXUS stent
Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years
HORIZONS AMI

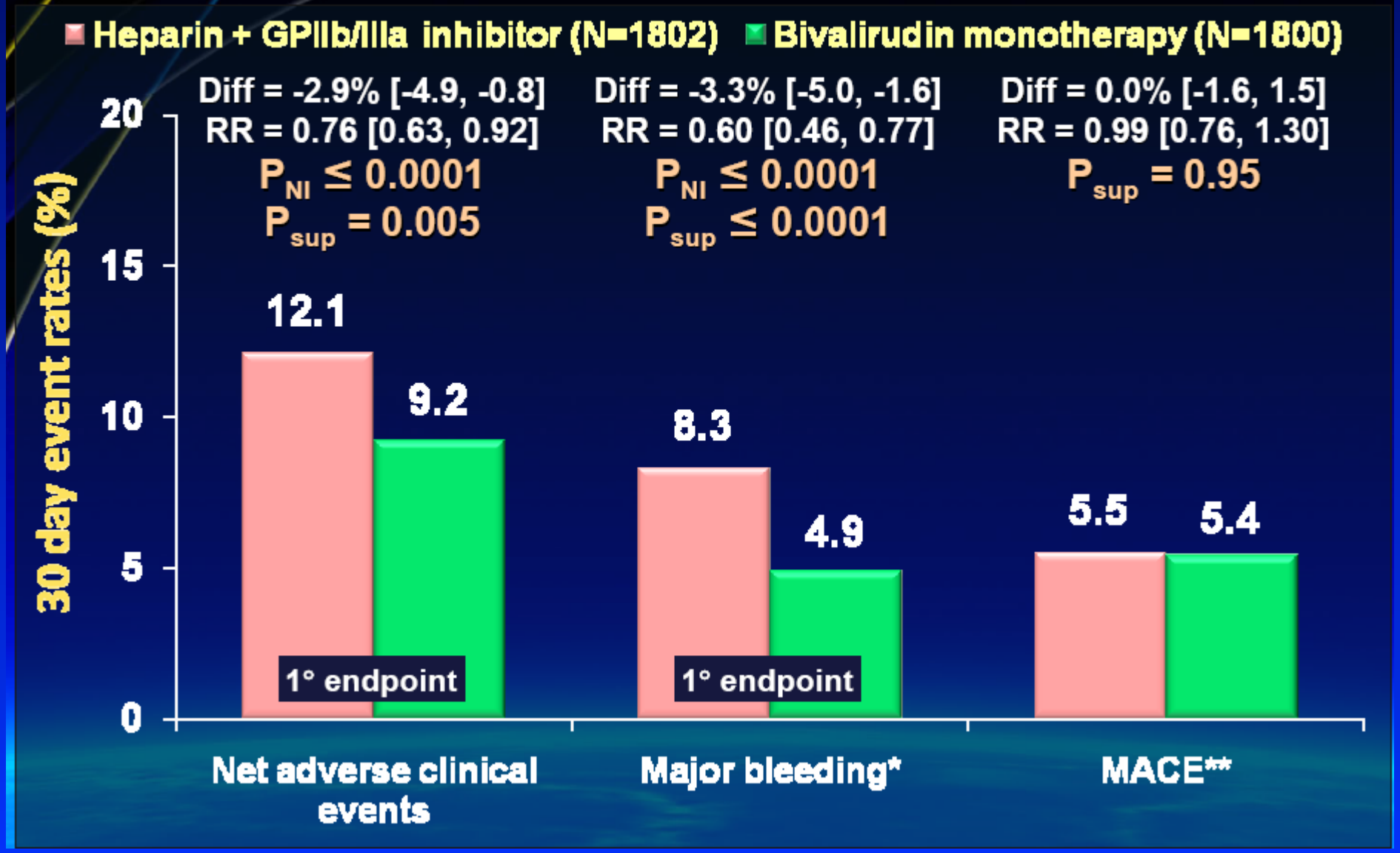
30 Day Mortality: Cardiac and Non Cardiac



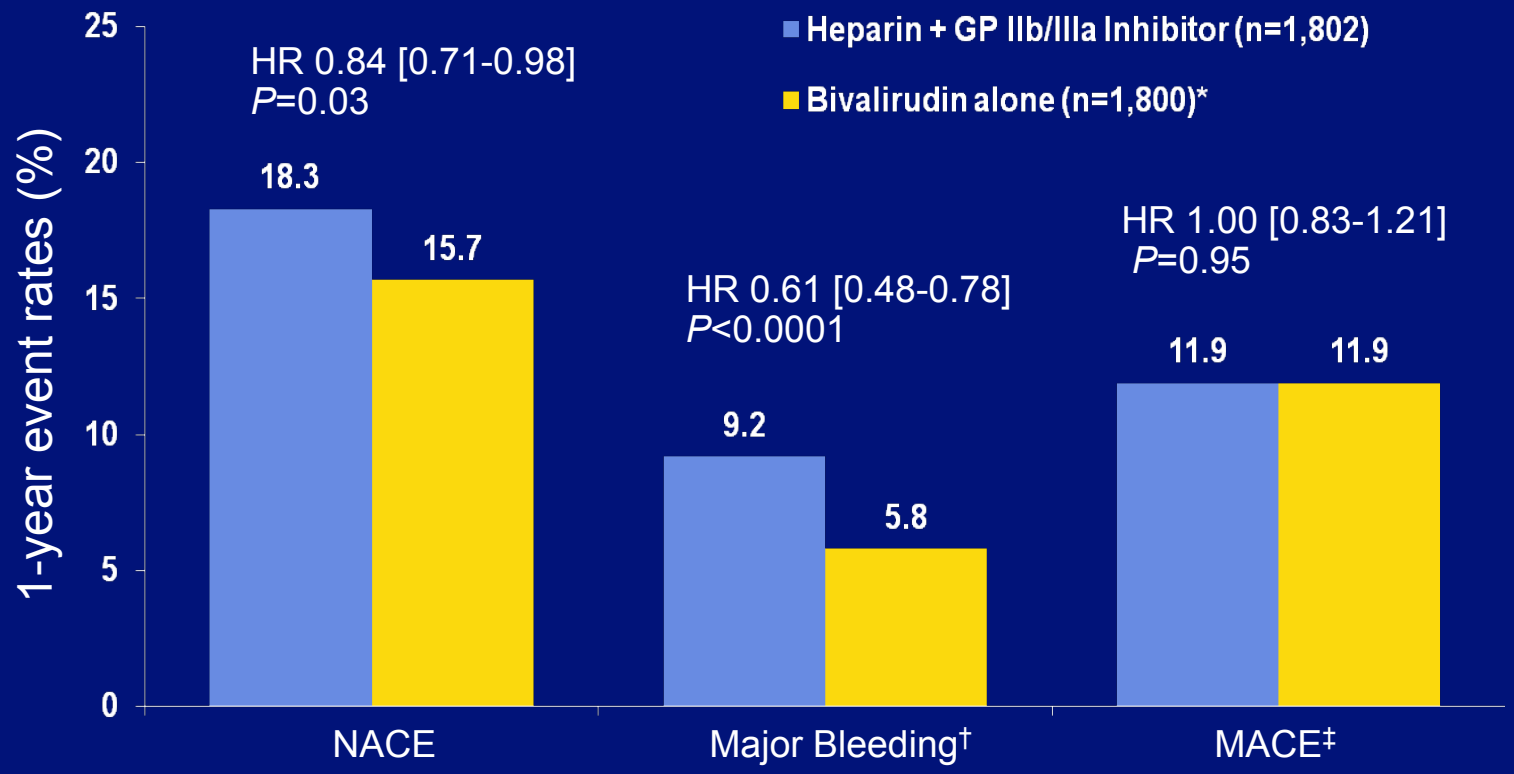
Number at risk

Bivalirudin	1800	1758	1751	1746	1742	1729	1666
Heparin + GPIIb/IIIa	1802	1764	1748	1736	1728	1707	1630

Primary Outcome Measures (ITT)



1-year Outcomes

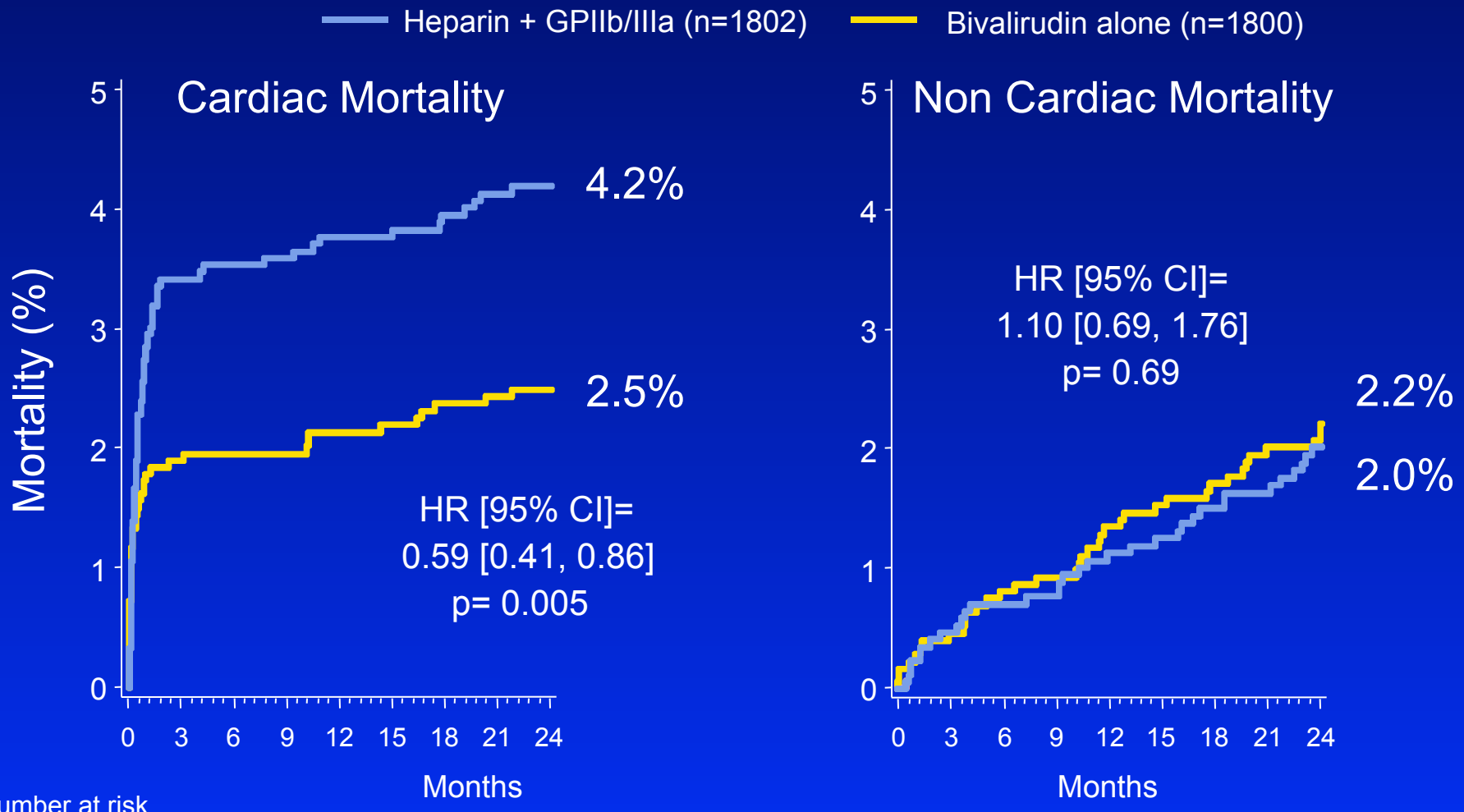


*In HORIZONS AMI, 93% of bivalirudin patients received monotherapy, without provisional GP IIb/IIIa.
†Not related to CABG.
‡MACE=all-cause death, reinfarction, ischaemic TVR, or stroke.

Stone GW. *NEJM* 2008;358:2218-30:

2-Year Mortality : Cardiac & Non Cardiac

HORIZONS AMI



Number at risk

Bivalirudin alone	1800	1690	1658	1627	1359
Heparin+GPIIb/IIIa	1802	1669	1637	1579	1324

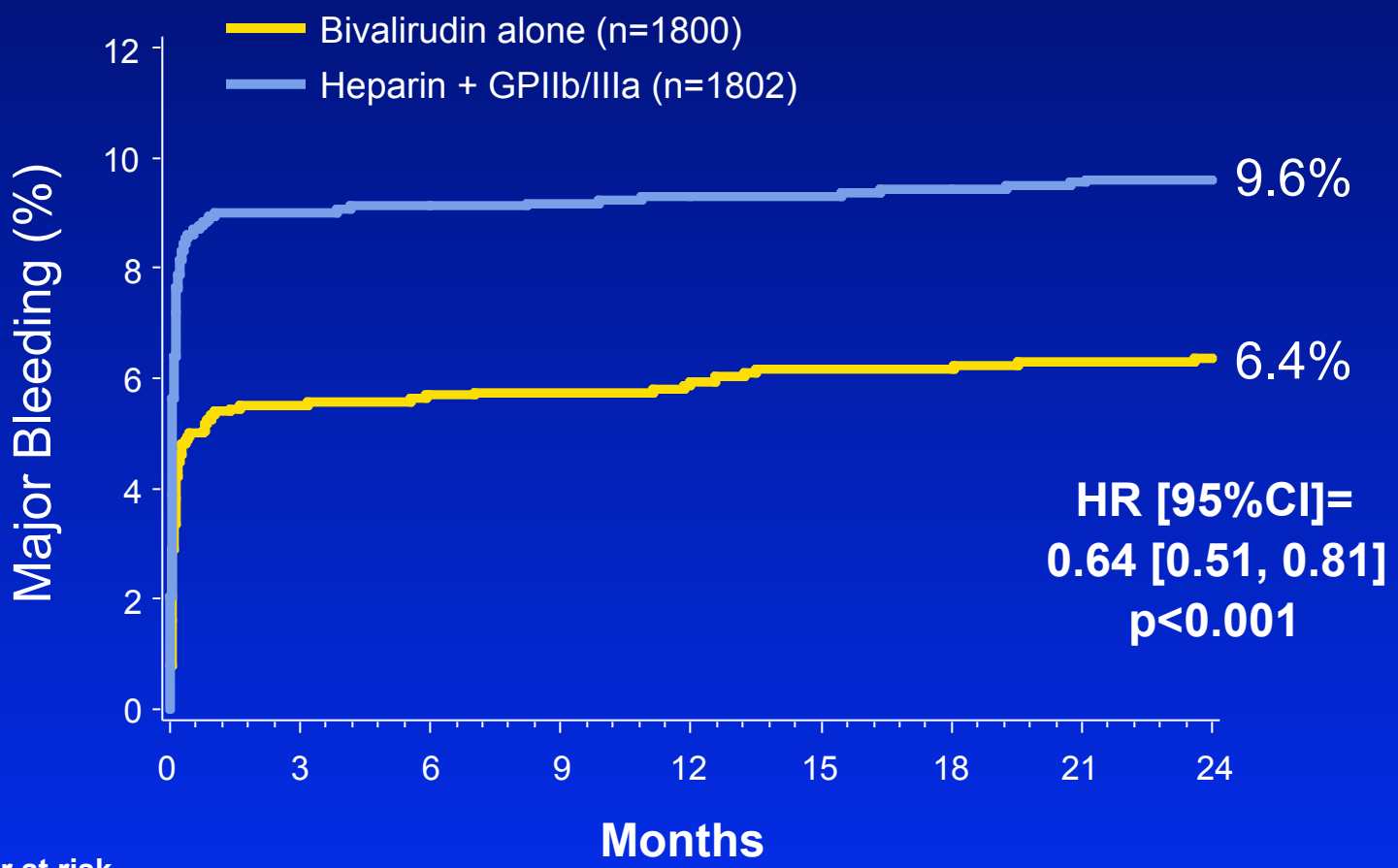
1800	1690	1658	1627	1359	
1802	1669	1637	1579		

Stone GW TCT 2009

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

2-Year Major Bleeding (non-CABG)*



Number at risk

Bivalirudin alone	1800	1603	1571	1540	1290
Heparin+GPIIb/IIIa	1802	1535	1505	1453	1218

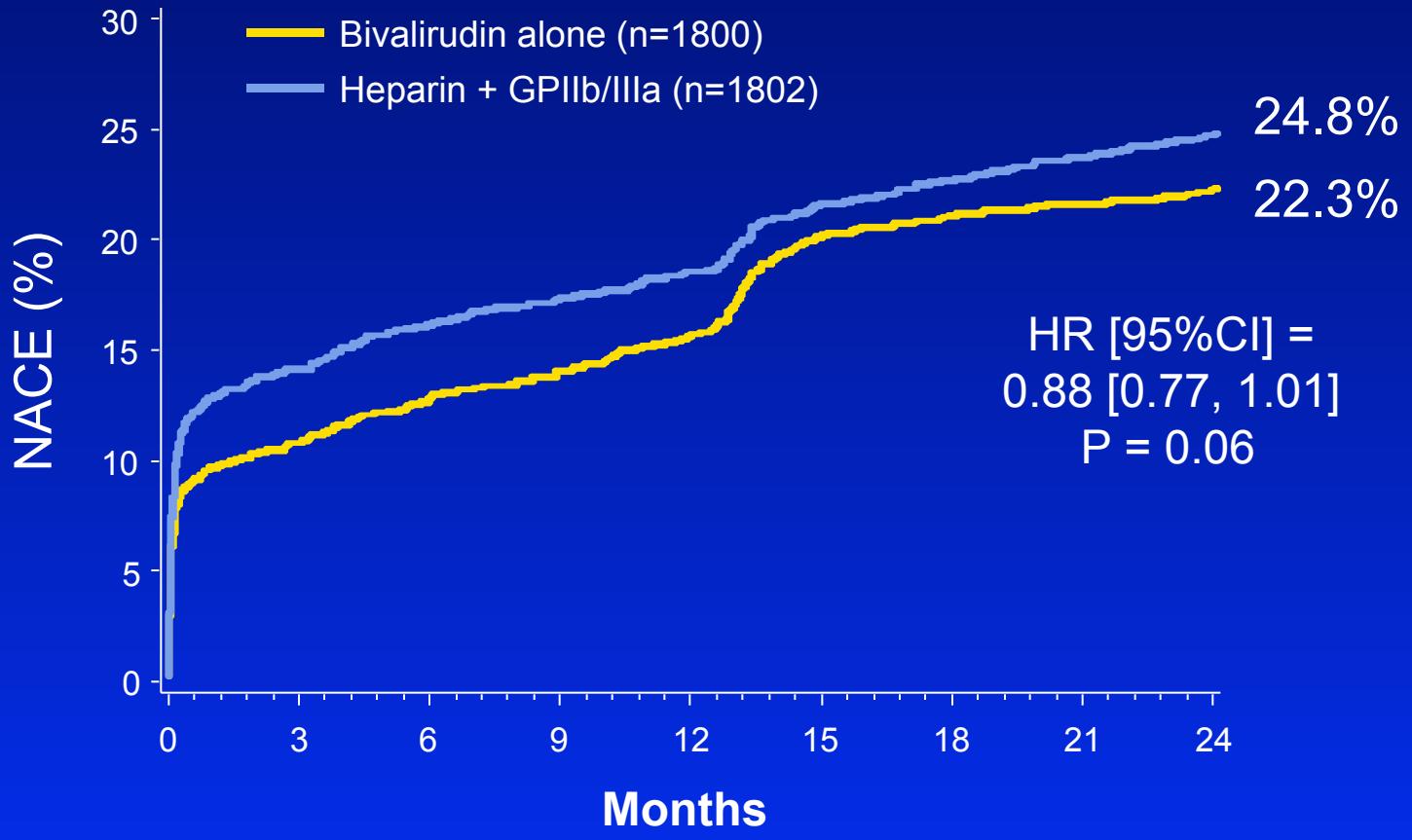
Stone GW TCT 2009

*Intracranial intraocular, retroperitoneal, access site bleed requiring intervention/surgery, hematoma ≥5 cm, hgb ↓ ≥3g/dL with or ≥4g/dL w/o overt source; reoperation for bleeding; or blood product transfusion

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

2-Year Net Adverse Clinical Events*



Number at risk					
Bivalirudin alone	1800	1517	1451	1340	1112
Heparin+GPIIb/IIIa	1802	1460	1405	1294	1059

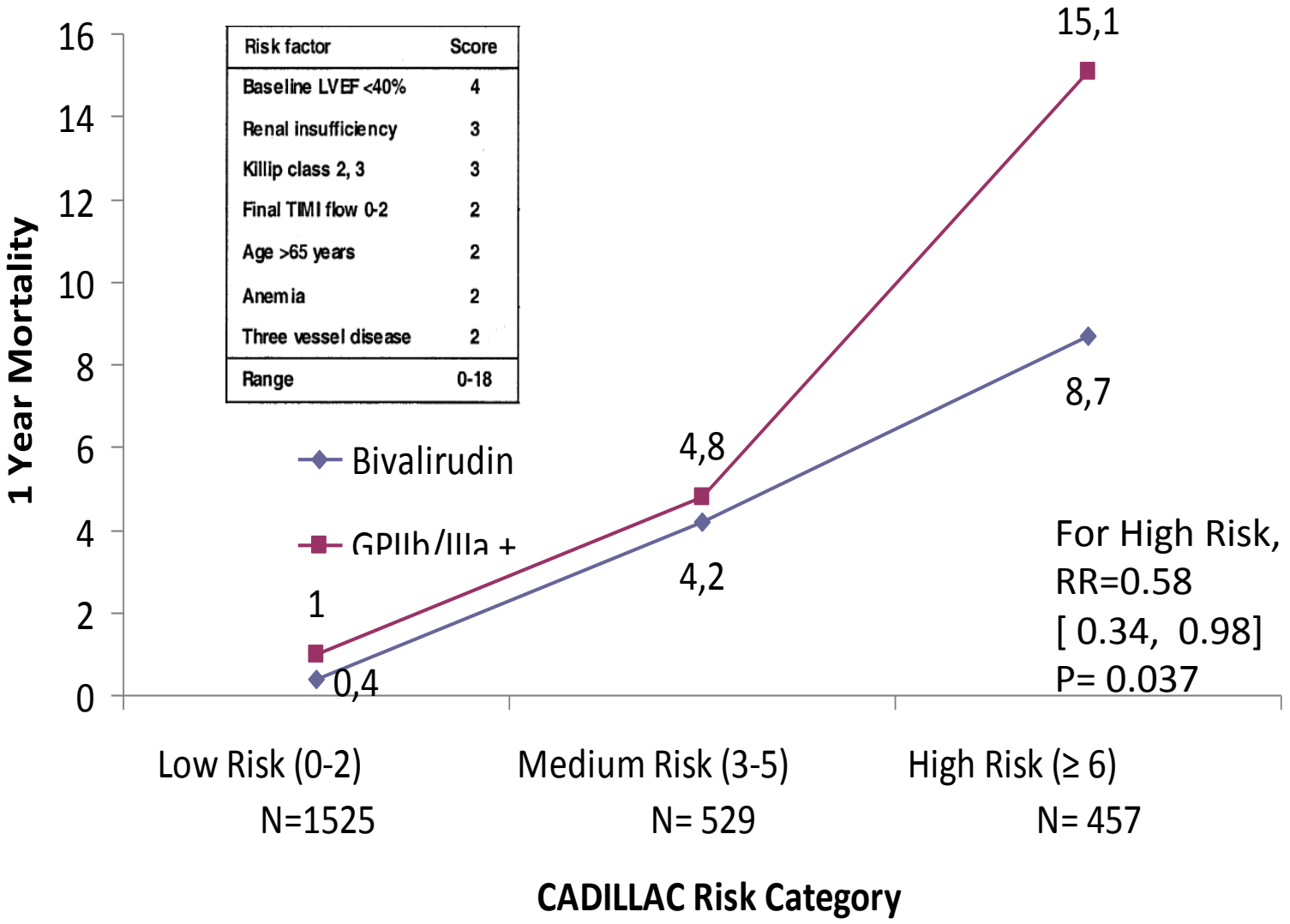
Stone GW TCT 2009

*MACE (death, reMI, iTVR or stroke) or major bleeding (non CABG)

Hôpitaux de Toulouse

Pôle Cardiovasculaire et Métabolique

1-Year Mortality in HORIZONS Based on Randomized Treatment and CADILLAC Risk Score*

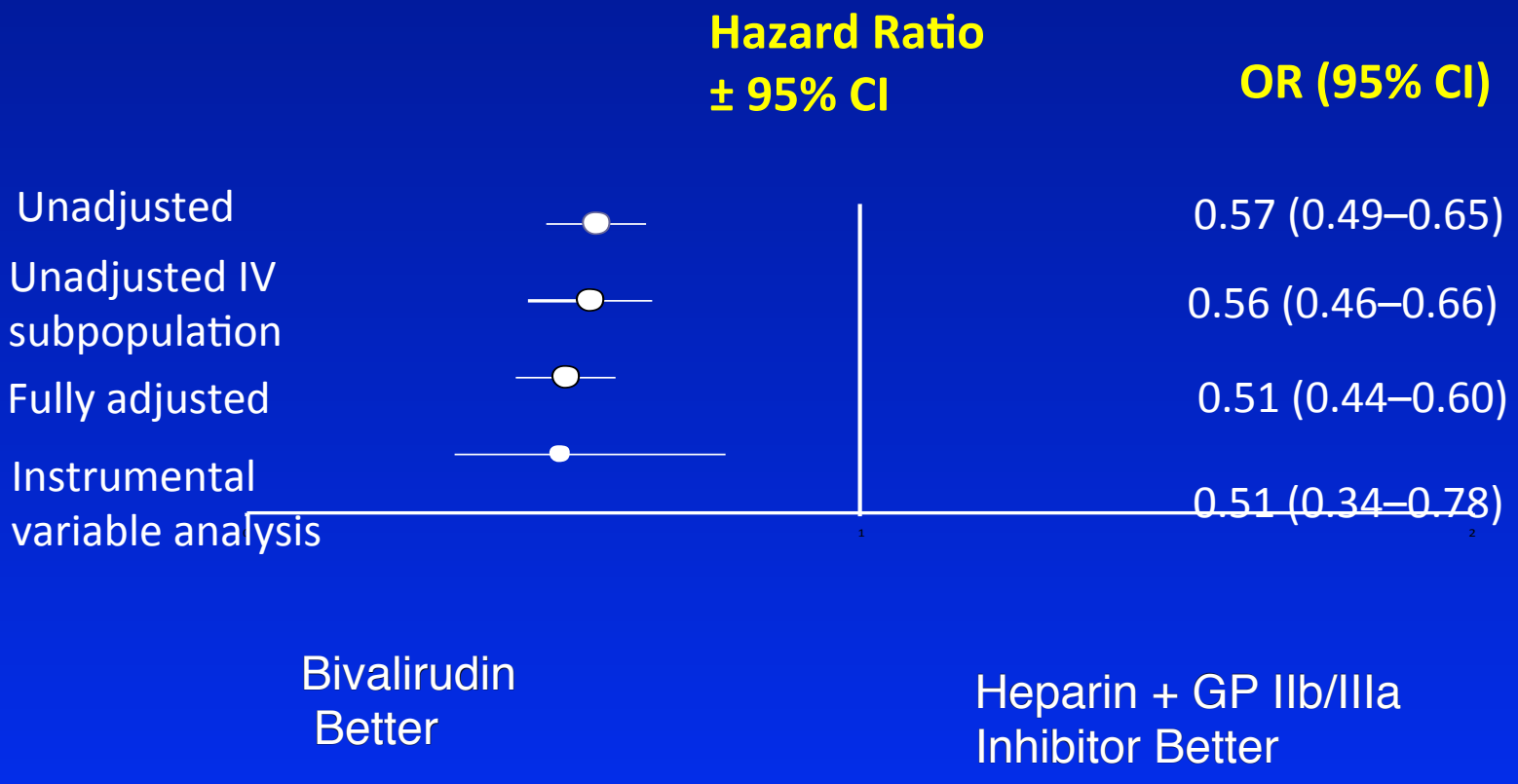


Stone et al. TCT 2009

*Halkin A. J Am Coll Cardiol 2005;45:1397 - 05

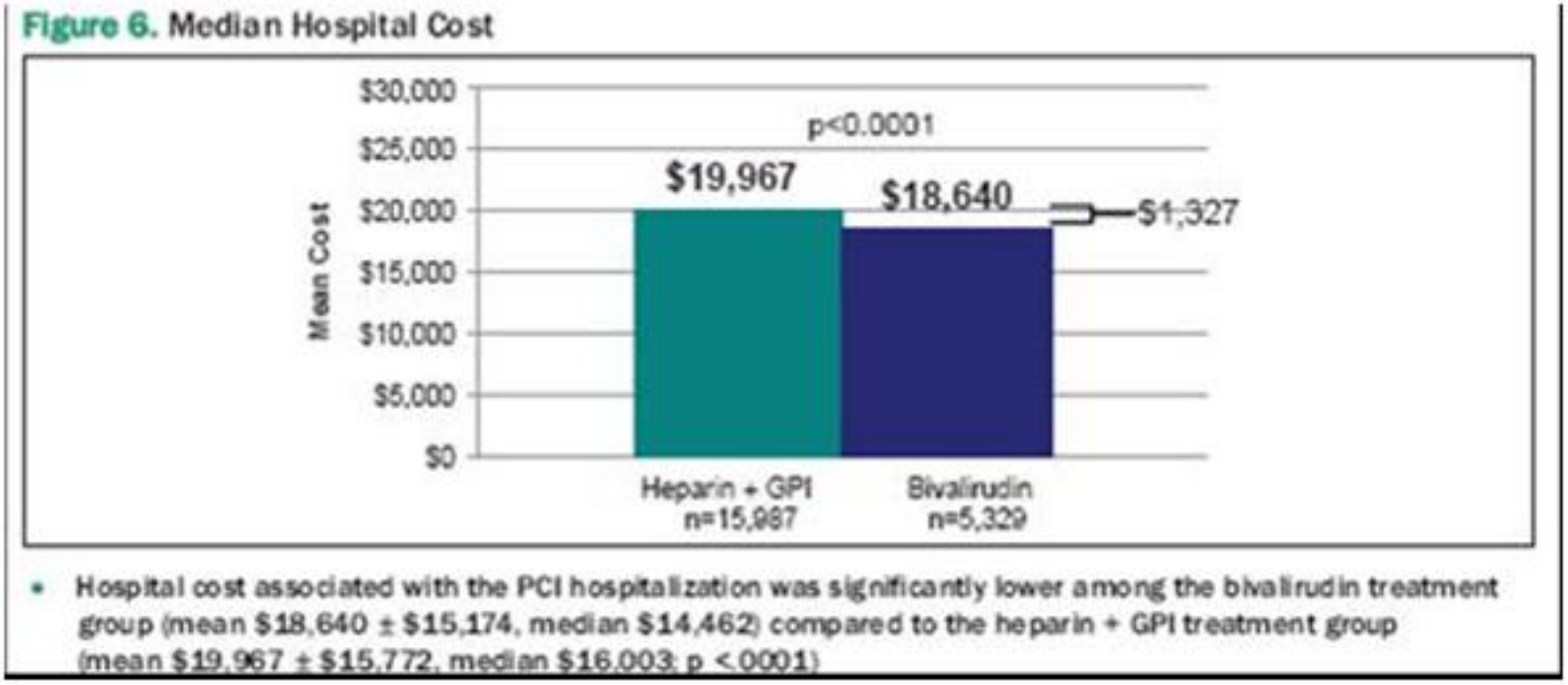
Premier Data over 127 000 patients : Death

In-hospital mortality rate: bivalirudin 0.8%, 2.1% heparin + GPI



Rassen JA et al *Eur Heart J* 2009 On line ahead of print Nov 25 doi:10.1093/eurheartj/ehp437

Logique économique



Cost Analysis for STEMI Patients

•"This large 'real-world' analysis demonstrates that patients treated with bivalirudin had significantly lower bleeding and inpatient mortality rates, shorter LOS, and lower cost when compared to patients treated with heparin + GPI in STEMI patients undergoing PCI."

Pinto DS et al. JACC 2010:55 (10suppl 1): A101

Design EUROMAX

3680 pts with STEMI with symptom onset > 20 min and ≤12 hours in ambulance or non-PCI hospital

UFH ± routine or bailout GPI (any of the 3)

Bivalirudin monotherapy with prolonged infusion
(Gp IIb/IIIa for bailout only)

Primary endpoint
30-day death, MI or non-CABG related protocol major bleeding

Clinical FU at 30 days and 1 year

Conclusion

- **Réduction très significative de la mortalité globale depuis 25 ans.**
- **Rôle majeur du risque hémorragique parmi les déterminants de la mortalité.**
- **Adapter et privilégier les stratégies médicamenteuses et interventionnelles en fonction du risque hémorragique.**