Nouveaux antithrombotiques dans les SCA Quel traitement pour quel malade ? Quel rapport efficacité/risque hémorragique ?

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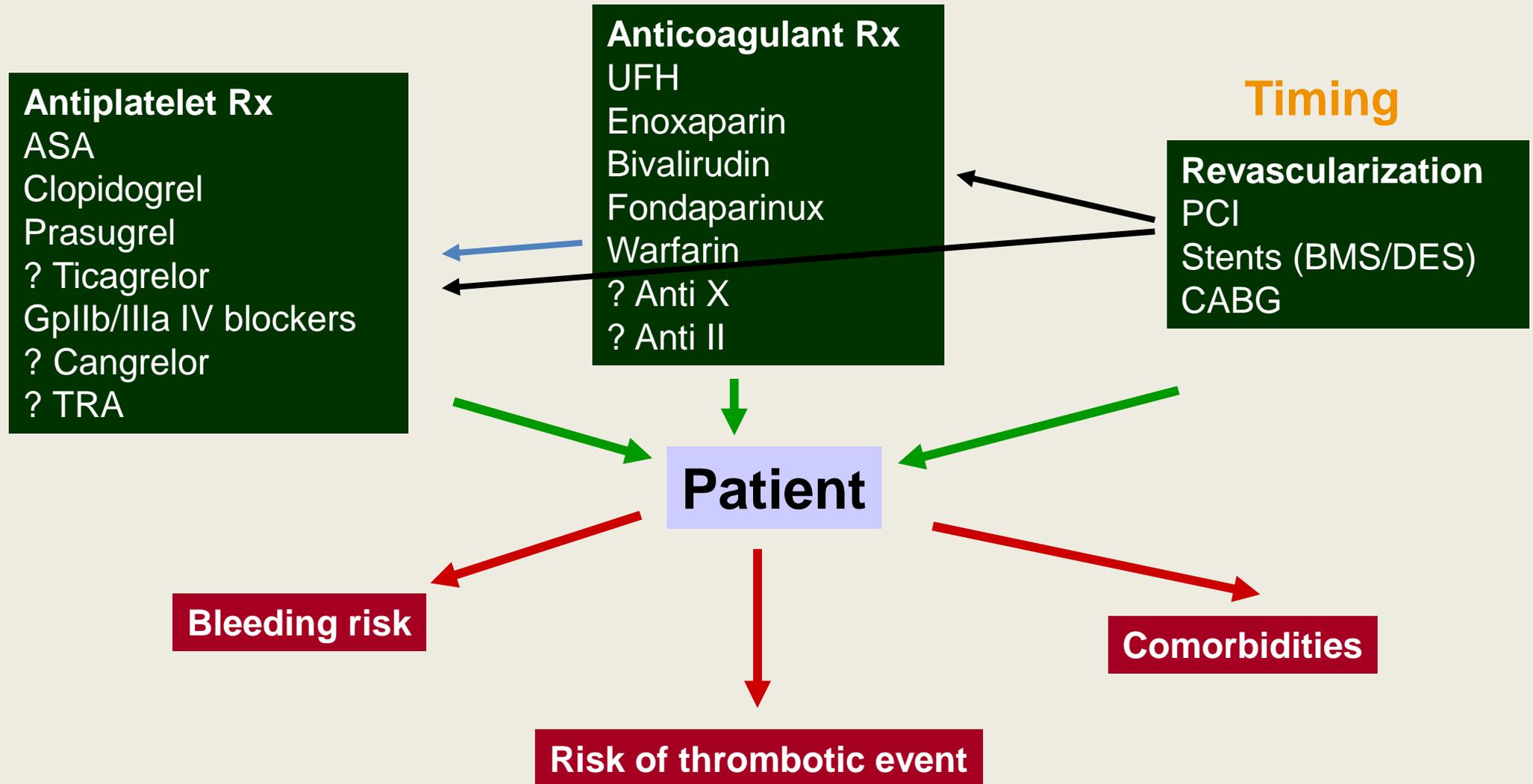
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Ph. Gabriel Steg - Disclosures

- **Research grant:** Servier

- **Speaking or consulting:** Amgen, Astellas, AstraZeneca,Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo-Lilly, Eisai, GSK, Merck, Pfizer, Roche, sanofi-aventis, Servier, The Medicines Company

- **Stockholding:** Aterovax

Antithrombotiques dans les SCA

- **C'est compliqué**

Treatment of ACS is a jungle !

Antiplatelet Rx
ASA
Clopidogrel
Prasugrel
? Ticagrelor
GpIIb/IIIa IV blockers
? Cangrelor
? TRA

Anticoagulant Rx
UFH
Enoxaparin
Bivalirudin
Fondaparinux
Warfarin
? Anti X
? Anti II

Timing

Revascularization
PCI
Stents (BMS/DES)
CABG

Patient

Bleeding risk

Risk of thrombotic event

Comorbidities

Antithrombotiques dans les SCA

- C'est compliqué
- **Les essais cliniques nous donnent quelques informations**

TRITON-TIMI38 Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA   N= 13,600

Double-blind

CLOPIDOGREL 300 mg LD/ 75 mg MD		PRASUGREL 60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

Planned PCI for :

Known
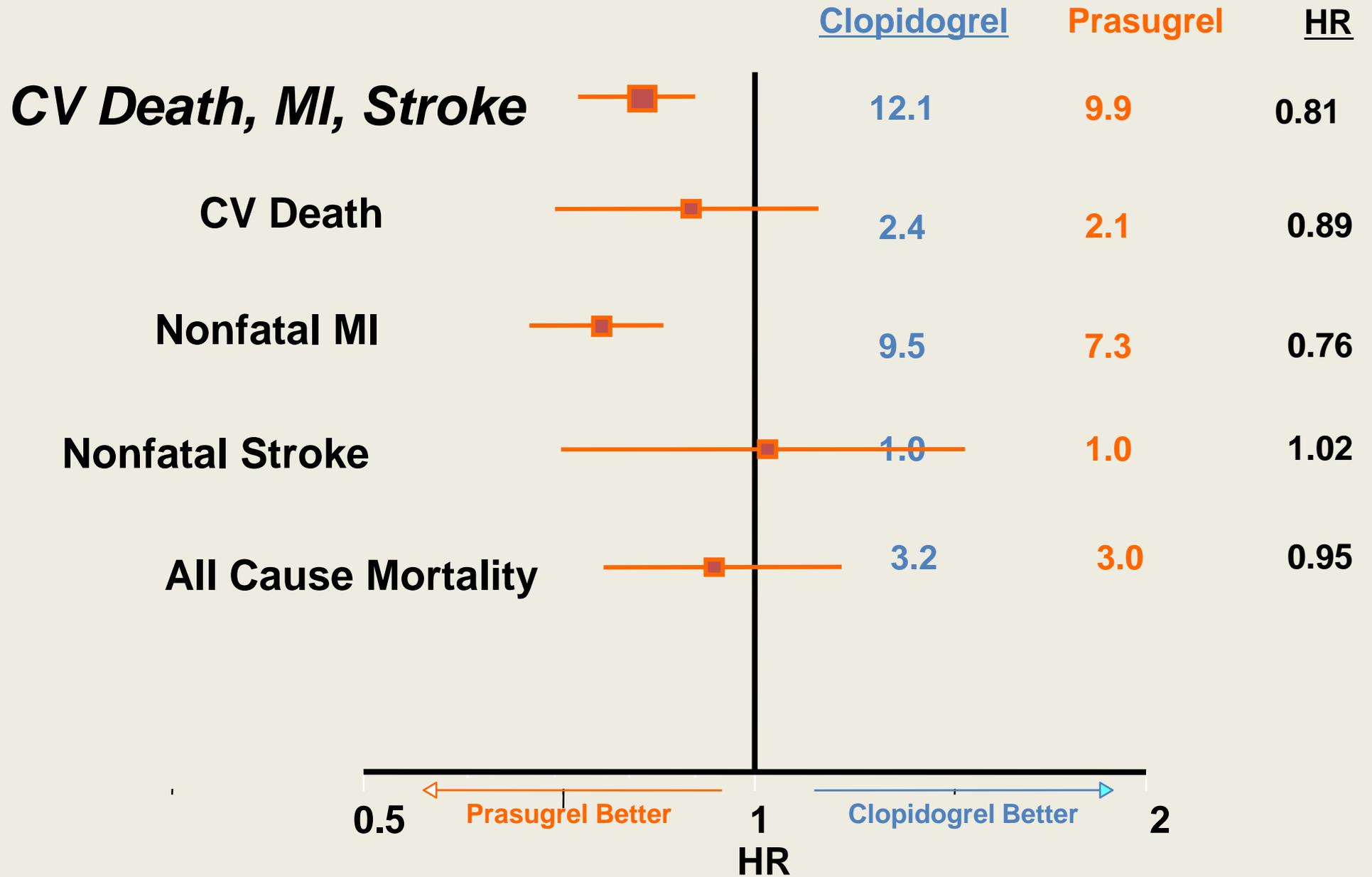*Anatomy*
         Mod-High Risk UA/NSTEMI (TRS $\geq$ 3)
         STEMI: $\leq$ 14 days (ischemia or Rx strategy)
         STEMI: Primary PCI

Index Procedure

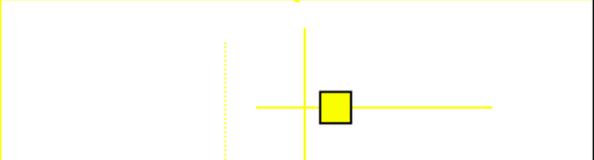|	Clopidogrel (N=6795) %	Prasugrel (N=6813) %
PCI / CABG	99 / 1	99 / 1
Any Stent	95	94
BMS	47	48
DES	47	47
Multivessel PCI	14	14
UFH / LMWH / Bival	65 / 8 / 3	66 / 9 / 3
GP IIb/IIIa	55	54
LD of Study Rx Pre PCI During PCI Post PCI	25 74 1	26 73 1

# Se méfier des analyses en sous-groupe

- La valeur du « p » dans un sous groupe importe peu

  – Faux positifs dans une analyse: 5%

  – SI 5 analyses de sous groupe: 23%

  – Si 10 analyses: 40%... (PLATO: 31 sous-groupes !)

ISIS 2

Subgroup analysis by Astrological Birth Signs Vascular Deaths (Isis 2, Lancet, 1988, 2,349-360)

	Vascular deaths/patients (% dead)		Odds ratio & 95% CI	
	Aspirin	Placebo tablets	Aspirin better	Placebo better
Gemini/Libra	150/1357 (11.1%)	147/1442 (10.2%)		
Other	654/7228 (9.0%)	868/7157 (12.1%)		
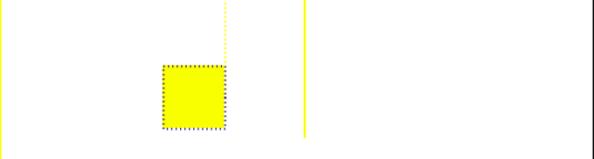
BHAT Hazard Ratios for All-Cause Mortality

Hazard ratios and 95% CIs for all-cause mortality according to randomization center in the BHAT trial.
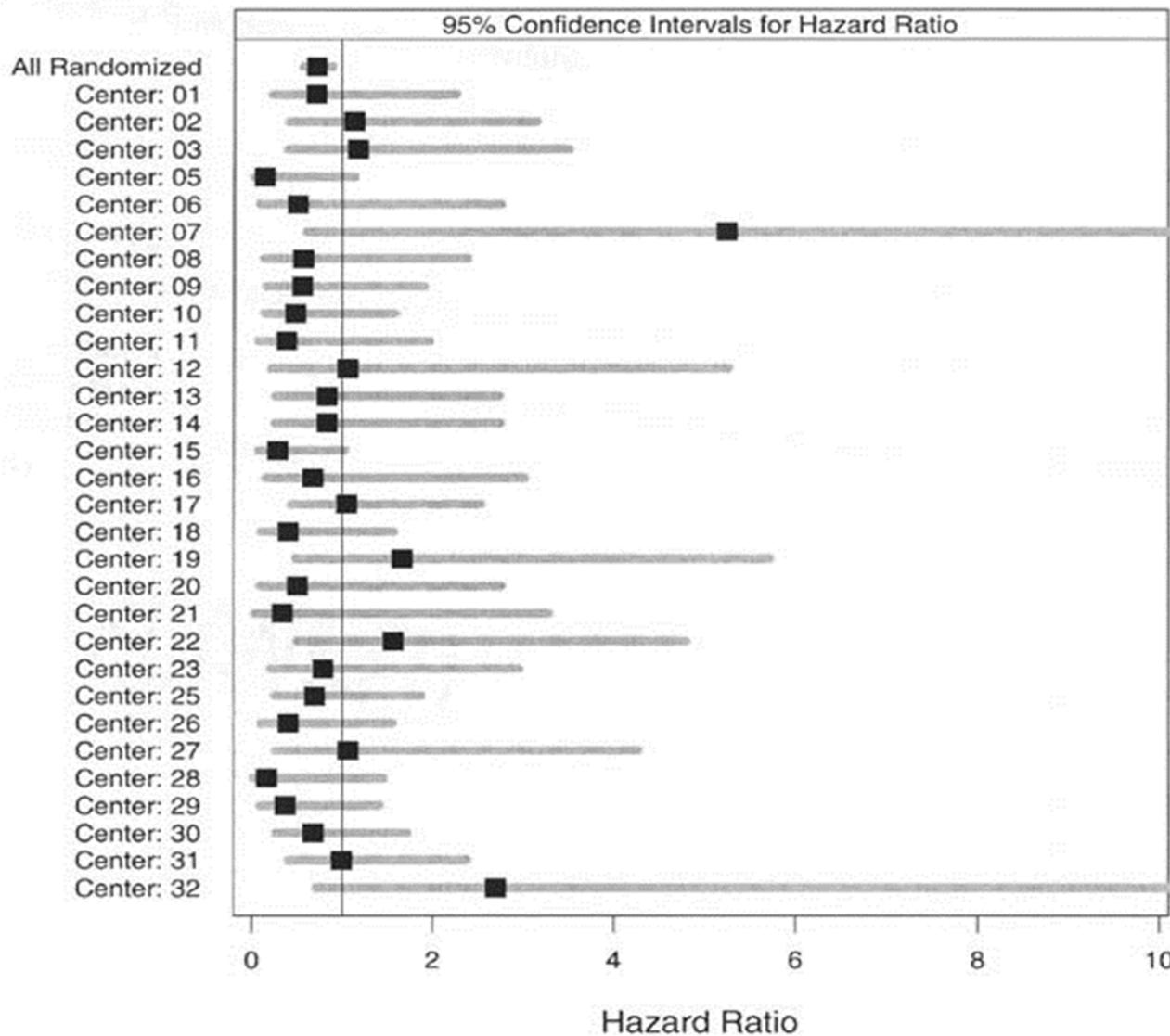
Variations across study centers in BHAT

O'Shea JC, DeMets DL. *Am Heart J* 142:21-8

Quand prêter attention à un sous-groupe ?

- Analyse pré-spécifiée

- Plausibilité biologique

- Puissance statistique

- Interaction statistiquement significative entre effet du traitement et sous groupe (rare…)

- Sinon: l'effet du traitement dans chaque sous groupe est au mieux estimé par l'effet global

Antithrombotiques dans les SCA

- C'est compliqué
- Les essais cliniques nous donnent quelques informations
- **Les traitements ont un bénéfice et un risque**

Risk versus benefit

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

	1 year Estimate
Both MI and Major Bleed (N=94)	28.9%
Major Bleed only (without MI) (N=551)	12.5%
MI only (without Major Bleed) (N=611)	8.6%
No MI or Major Bleed (N=12,557)	3.4%

Mortality (%)

Days from Randomization

Stone GW. ACC 2007

Time-updated covariate adjusted Cox model relating 30-day events to outcomes in HORIZONS-AMI
- Complete model with MACE components and major bleeding -

Risk Factor	HR [95% CI]	P-value	Attributable Deaths
Reinfarction Incidence 69 (2.2%) 10 deaths with event	9.75 [2.72,34.91]	<0.001	9.0* [6.3, 9.7]
Major bleeding (Non CABG) Incidence 238 (6.8%) 26 deaths with event	4.66 [2.84, 7.63]	<0.001	20.4** [16.8, 22.6]

0.01   0.1   1   10   100

Hazard Ratio [95% CI]

*9.7% of 93 total deaths
**21.9% of 93 total deaths

C-statistic = 0.87
Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR – 1)/adj. HR

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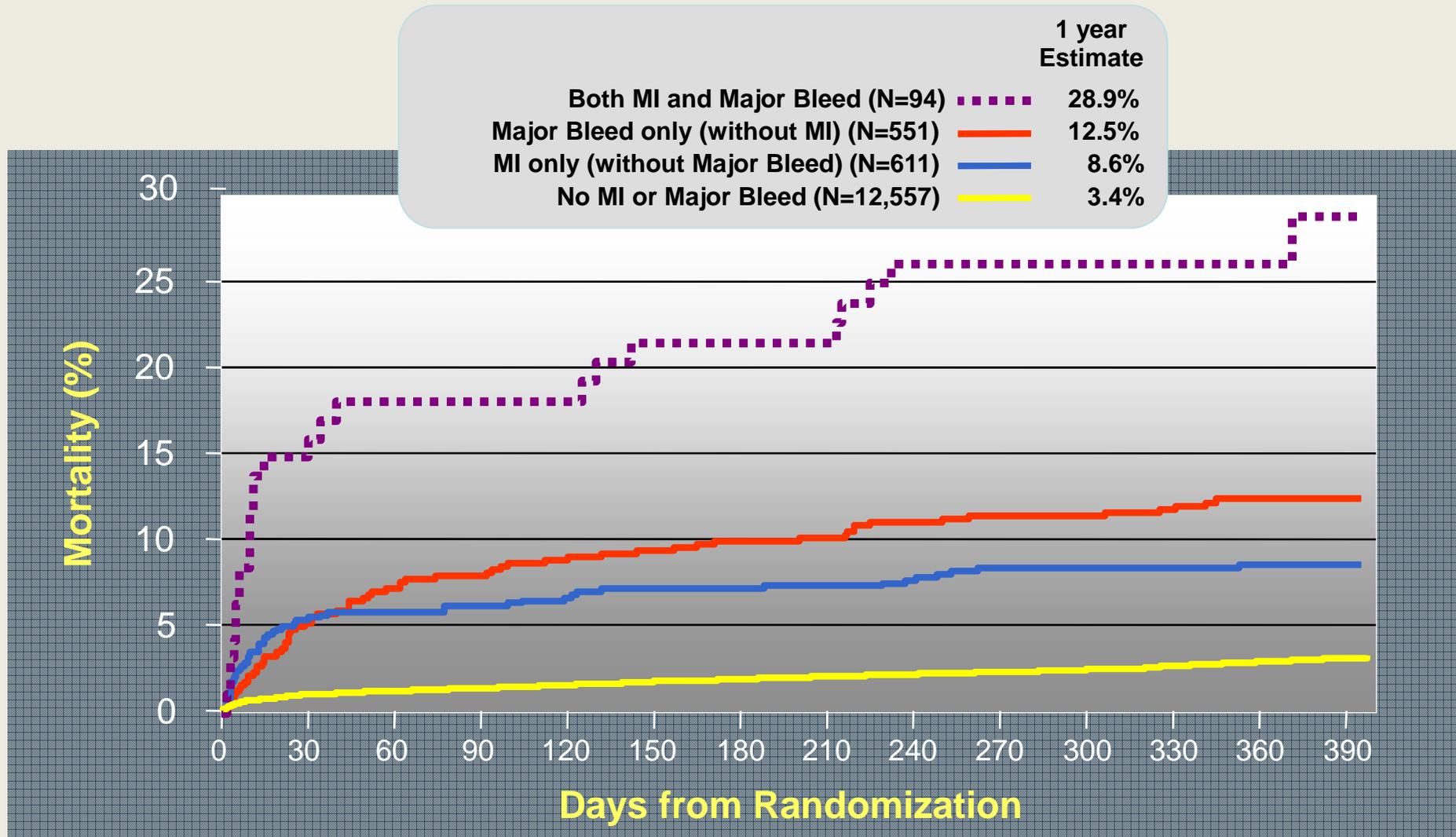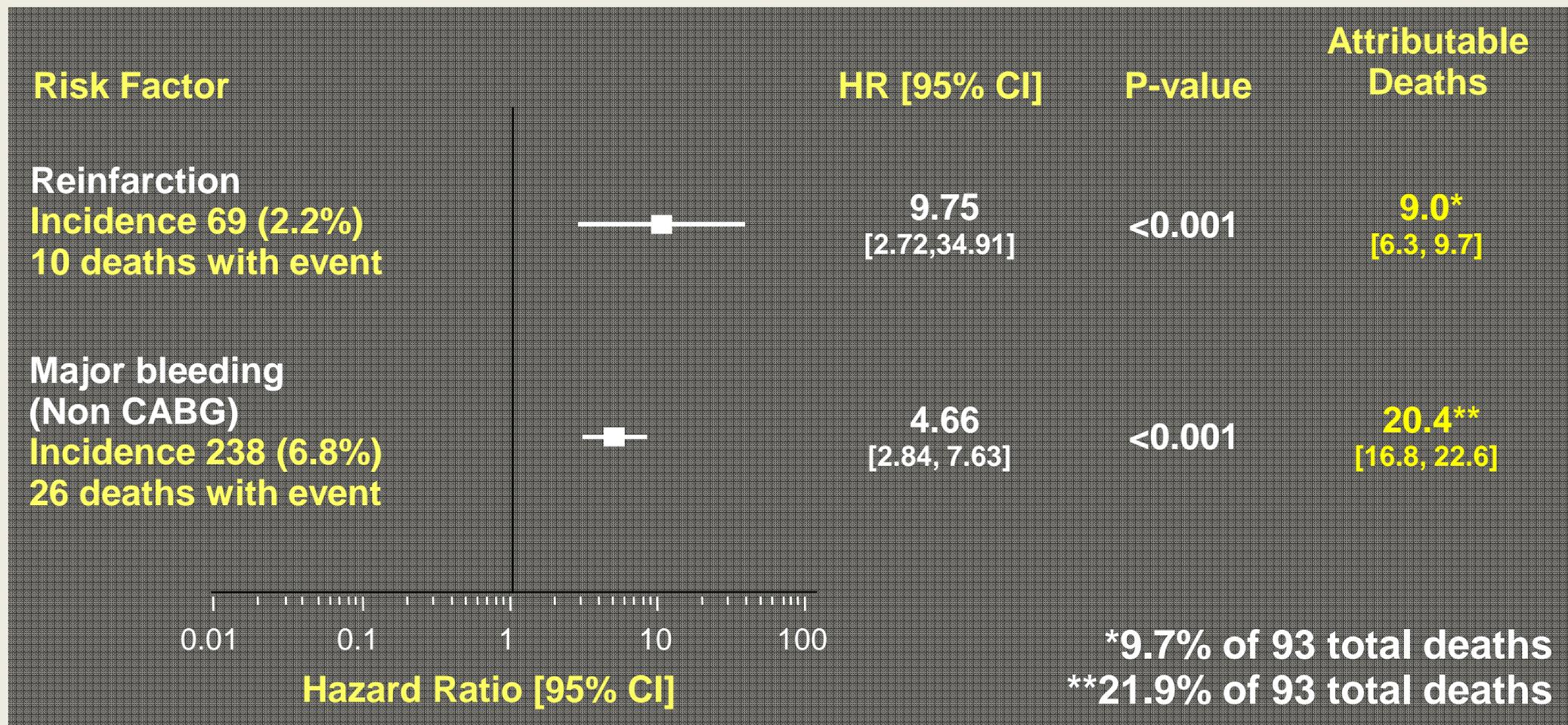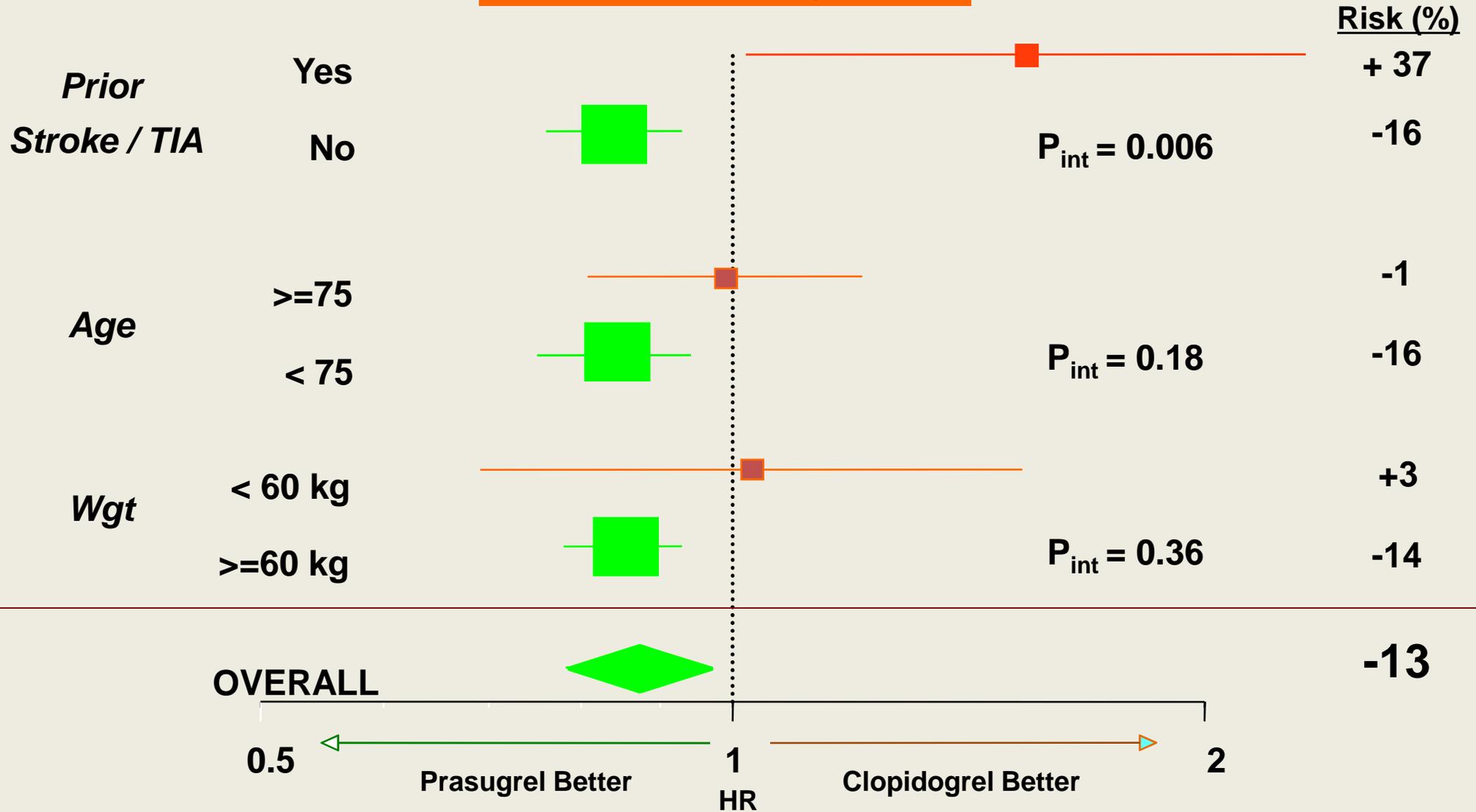- Les traitements ont un bénéfice et un risque
- **L'efficacité antithrombotique n'est pas parfaitement corrélée au bénéfice clinique**

GRAVITAS

Successful PCI with DES without major complication or GPIIb/IIIa use

N ~ 6600

Post-PCI VerifyNow P2Y12 Assay (PRU) 12-24 hours post-PCI

PRU ≥ 230?

Yes — **Non-Responder**

No — **Responder** → Random Selection

A N = 1100 — *"Tailored Therapy"* clopidogrel 150-mg/day

B N = 1100 — "Standard Therapy" clopidogrel 75mg +placebo/day

C N = 583 — "Standard Therapy" clopidogrel 75mg +placebo/day

Clinical Follow-up And VerifyNow Assessment at 30 days, 6 months

Primary Endpt: 6 month CV Death, Non-Fatal MI, ARC Def/Prob Stent Thrombosis

GRAVITAS Pharmacodynamics: Effect of SD vs HD Clopidogrel
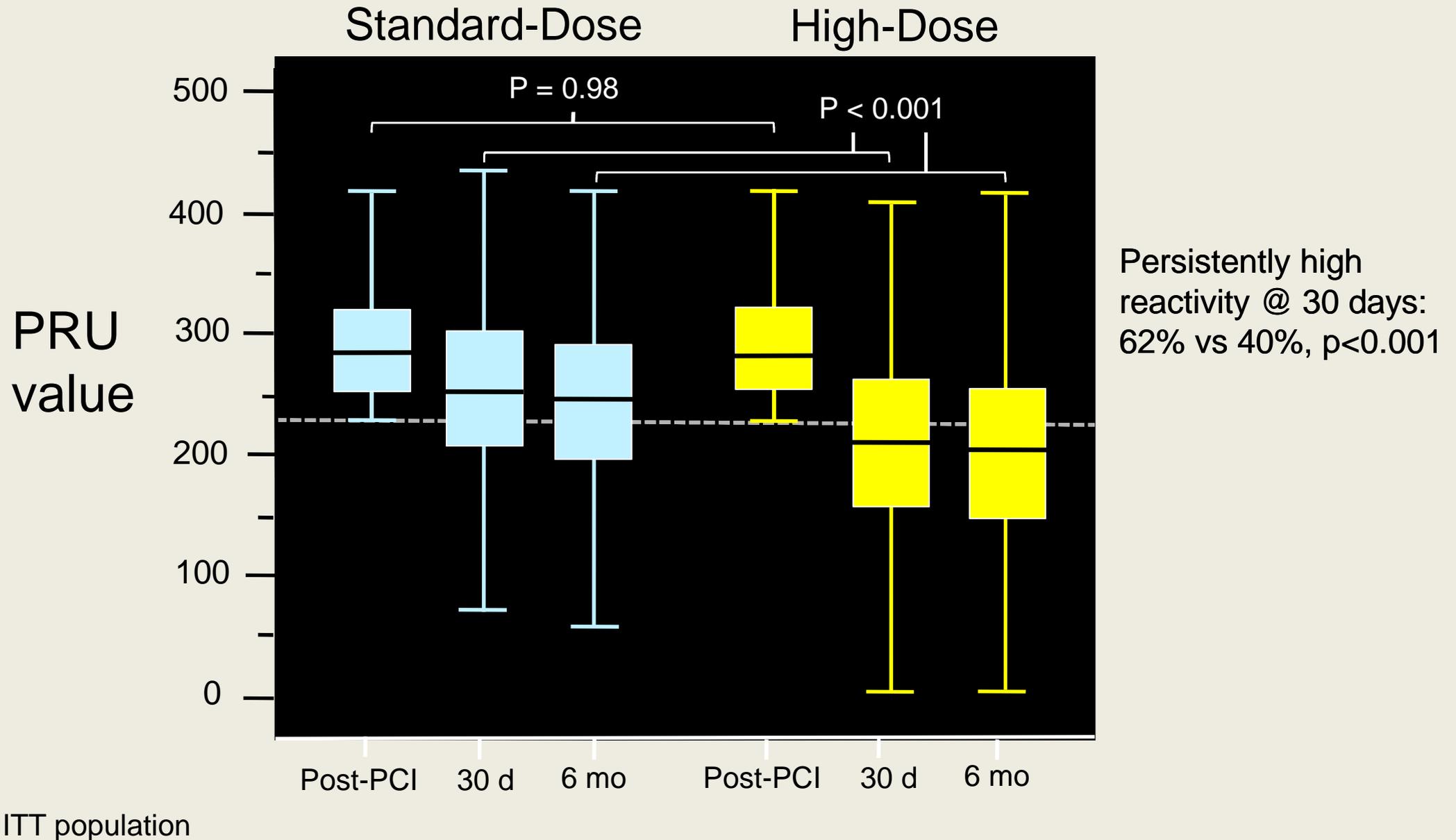
GRAVITAS : CV Death, MI, Stent Thrombosis

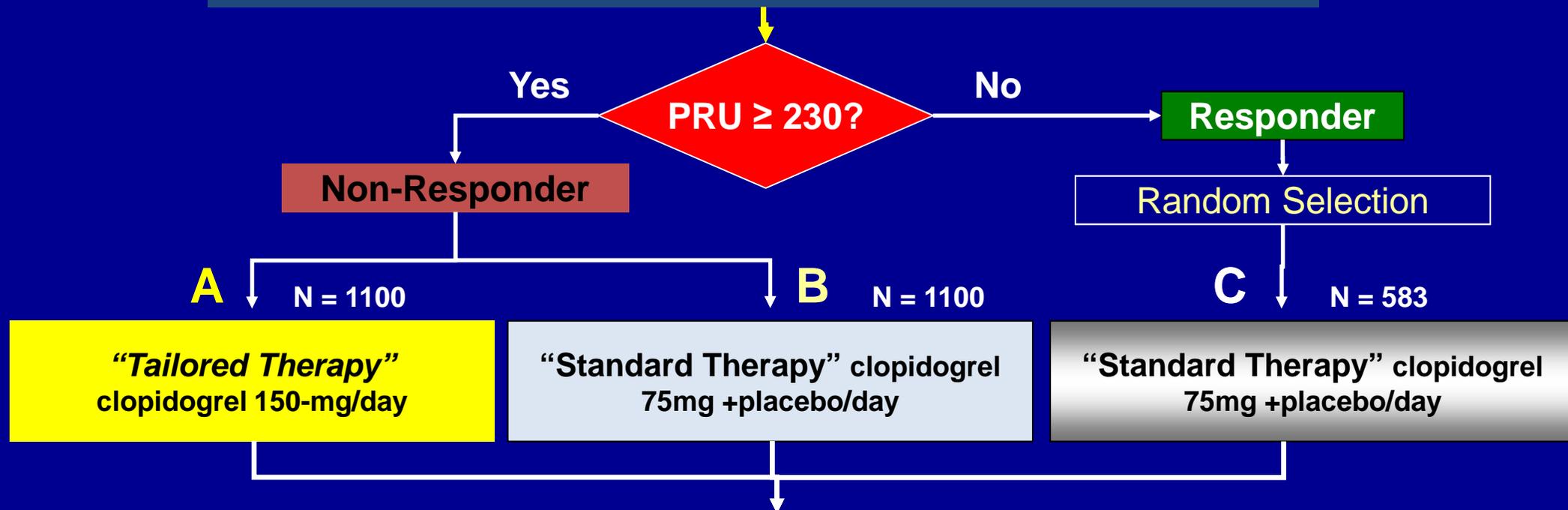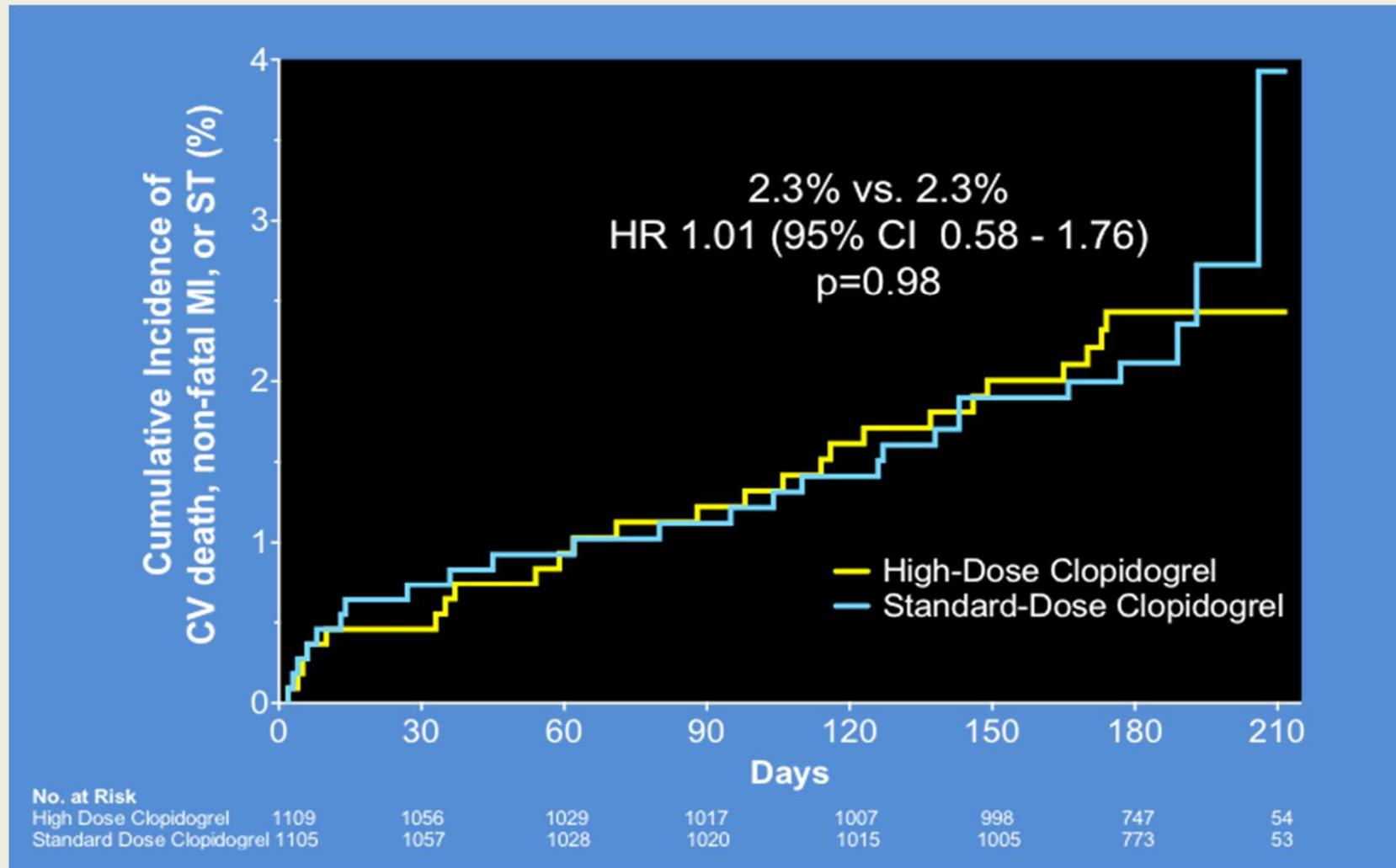Price et al. **JAMA** 2011;305:1097-1105

Antithrombotiques dans les SCA

- C'est compliqué
- Les essais cliniques nous donnent quelques informations
- Les traitements ont un bénéfice et un risque
- L'efficacité antithrombotique n'est pas parfaitement corrélée au bénéfice clinique
- **L'objectif du traitement est un bénéfice clinique**

« Ne pas perdre de vue la balle »

Objectifs du traitement

1. Efficacité anti-thrombotique

2. Prévention des thromboses

3. Réduction des hémorragies

4. Réduction de la morbi-mortalité

« Ne pas perdre de vue la balle »

Objectifs du traitement

1. ~~Efficacité anti-thrombotique~~

2. ~~Prévention des thromboses~~

3. ~~Réduction des hémorragies~~

4. ~~Réduction de la morbi-mortalité~~

5. Réduction de la morbi-mortalité au meilleur coût possible en termes de risque hémorragique

Antithrombotiques dans les SCA

- C'est compliqué
- Les essais cliniques nous donnent quelques informations
- Les traitements ont un bénéfice et un risque
- L'efficacité antithrombotique n'est pas parfaitement corrélée au bénéfice clinique
- L'objectif du traitement est un bénéfice clinique
- **Les principes du traitement: 2 AAP et un anticoagulant**

Mechanisms of interindividual variability in clopidogrel responsiveness

Genetic Factors
- Polymorphisms of CYP
- Polymorphisms of GPIa
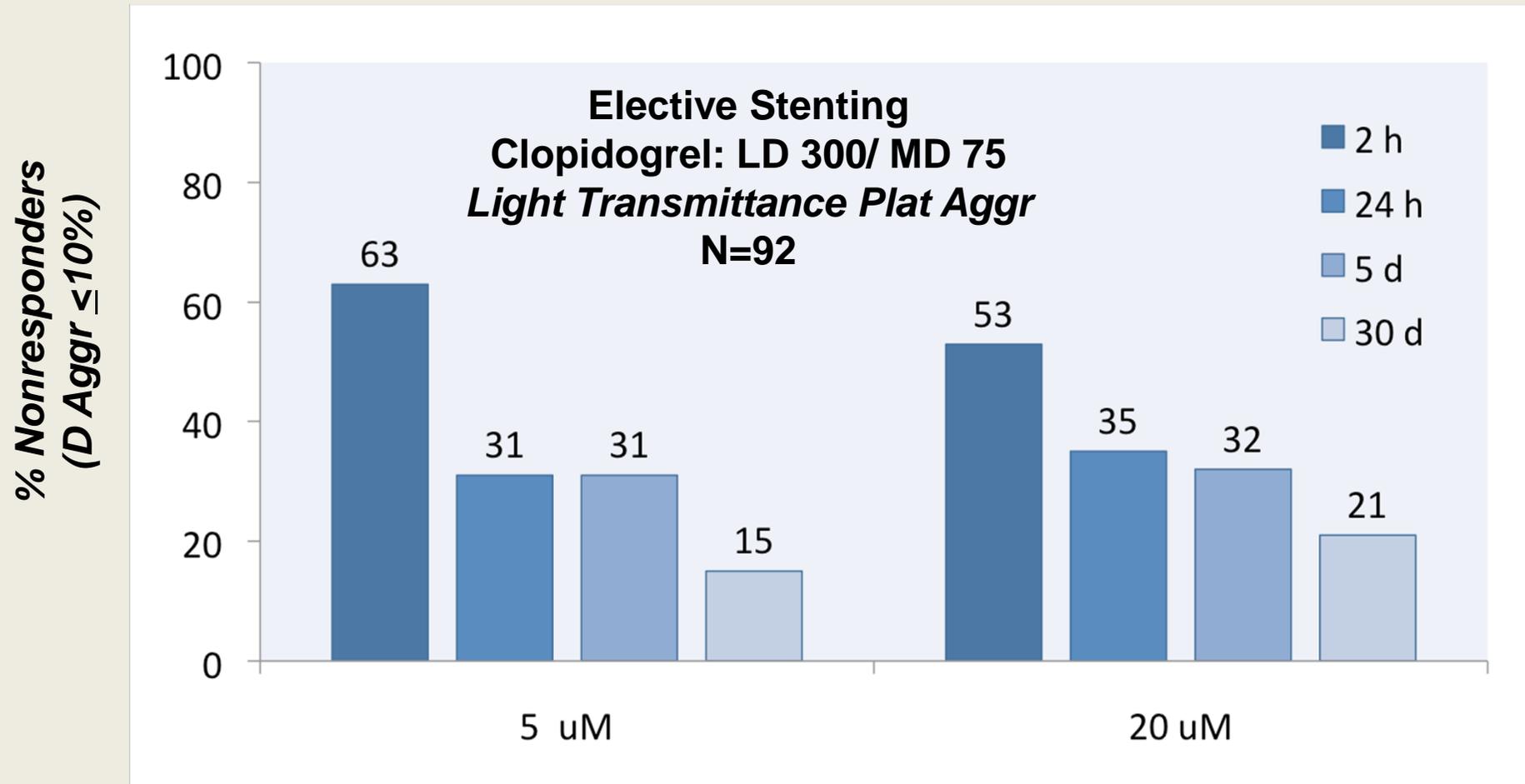- Polymorphisms of $P2Y_{12}$
- Polymorphisms of GPIIIa

Suboptimal Clopidogrel Response

Cellular Factors
- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the $P2Y_{12}$ pathway
- Up-regulation of the $P2Y_1$ pathway
- Up-regulation of P2Y–independent pathways (collagen, epinephrine, thomboxane A_2, thrombin)

Clinical Factors
- Failure to prescribe/Poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes Mellitus/Insulin resistance
- Elevated body mass index

Clopidogrel for Coronary Stenting
Response Variability, "Drug Resistance"

Gurbel et al. *Circulation* 2003;107:2908
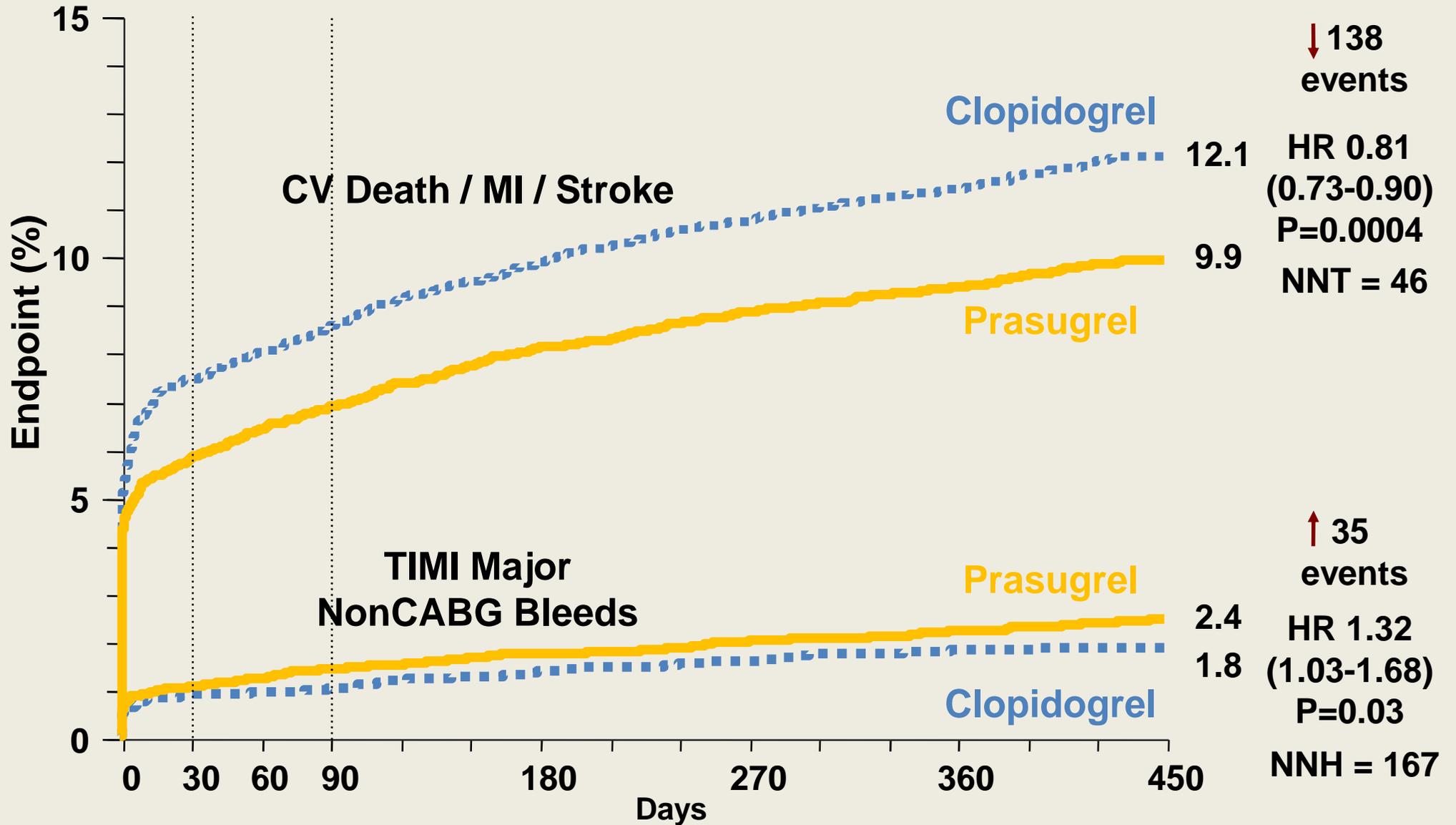
CV Death, MI, Stroke
Major Subgroups

Reduction in risk (%)

UA/NSTEMI	18
STEMI	21
Male	21
Female	12
Age <65	25
Age 65-74	14
Age ≥75	6
No DM	14
DM	30
BMS	20
DES	18
GPI	21
No GPI	16
CrCl < 60	14
CrCl ≥ 60	20
OVERALL	19

P_{inter} = NS

0.5 — Prasugrel Better — 1 HR — Clopidogrel Better — 2
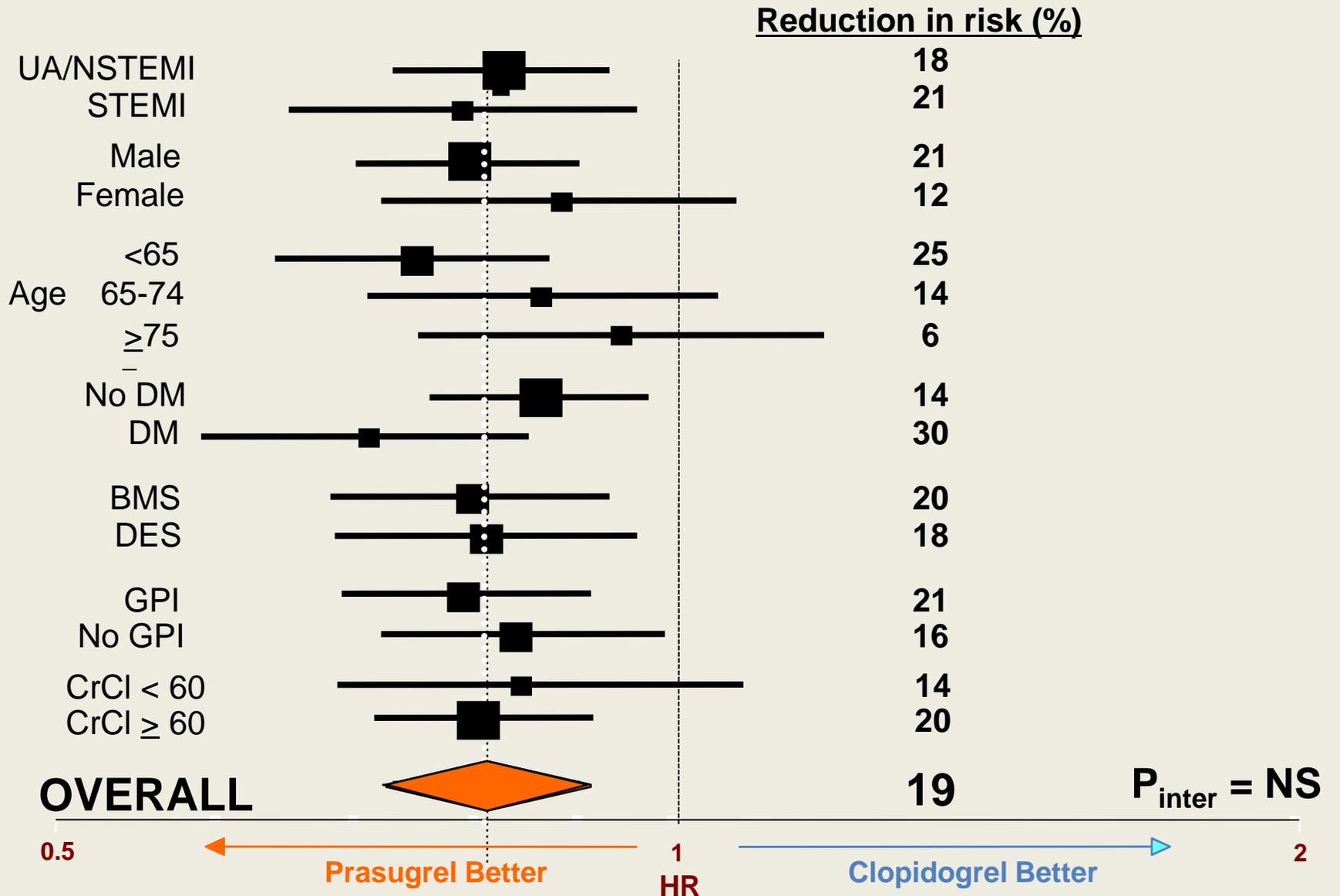
PLATO: ticagrelor vs clopidogrel in all types of ACS
Primary endpoint time to CV death, MI or stroke

Clopidogrel 11.7

9.8

Ticagrelor

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Cumulative incidence (%)
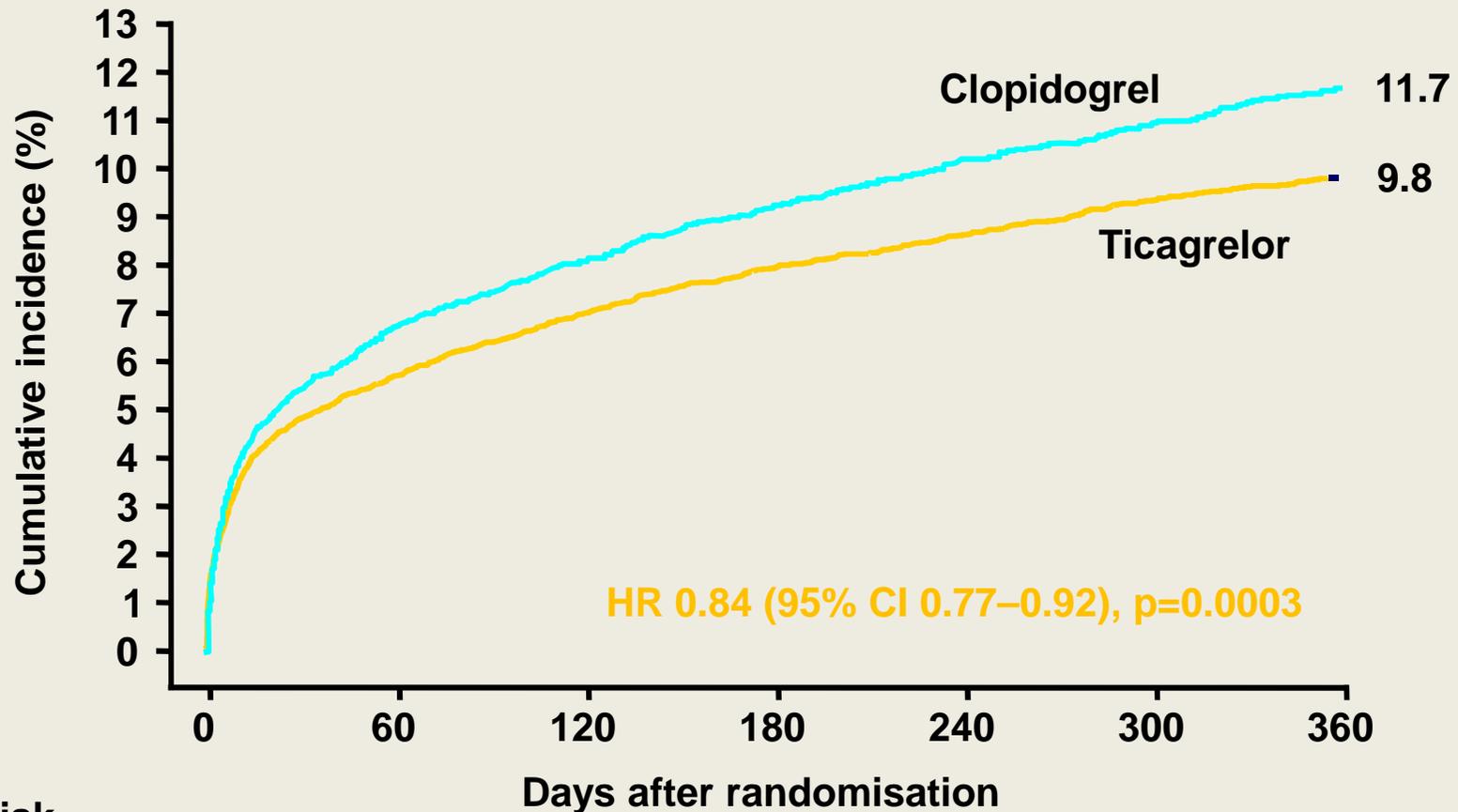
Days after randomisation

No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

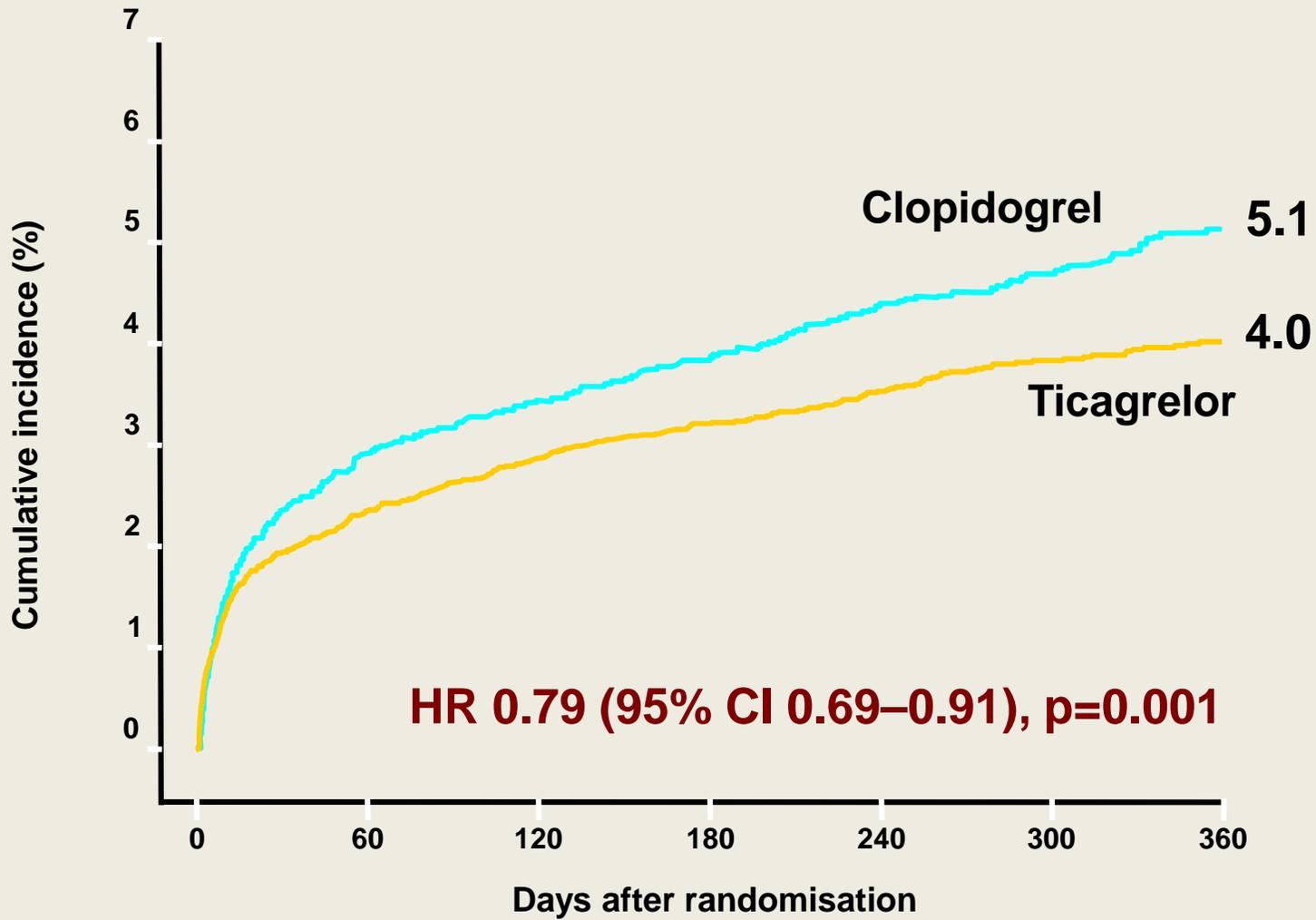Wallentin et al NEJM 2009

PLATO: Hierarchical testing major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

The percentages are K-M estimates of the rate of the endpoint at 12 months.

Wallentin et al NEJM 2009

PLATO: Cardiovascular death over time

Cumulative incidence (%)

Clopidogrel 5.1

4.0 Ticagrelor

HR 0.79 (95% CI 0.69–0.91), p=0.001

Days after randomisation

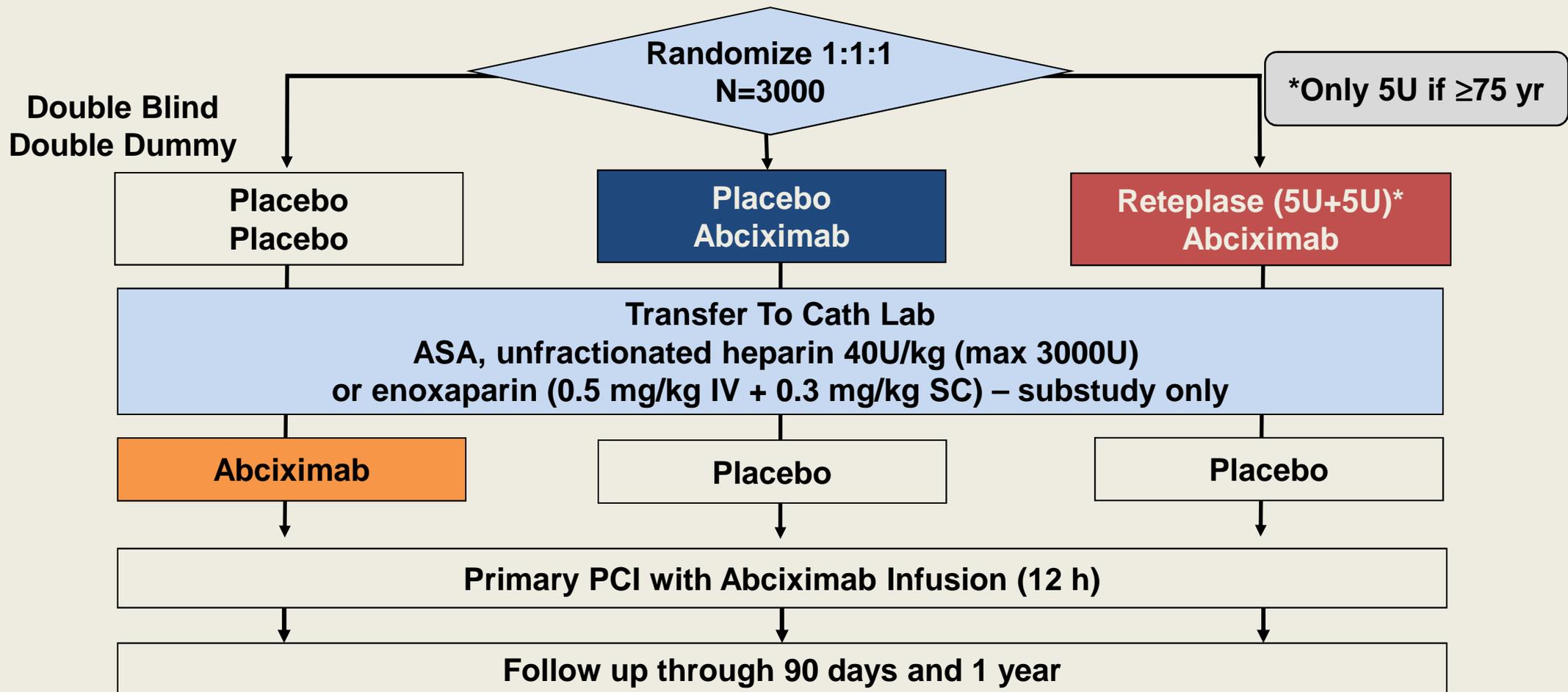|						
9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

PLATO : consistency of effect on primary endpoint

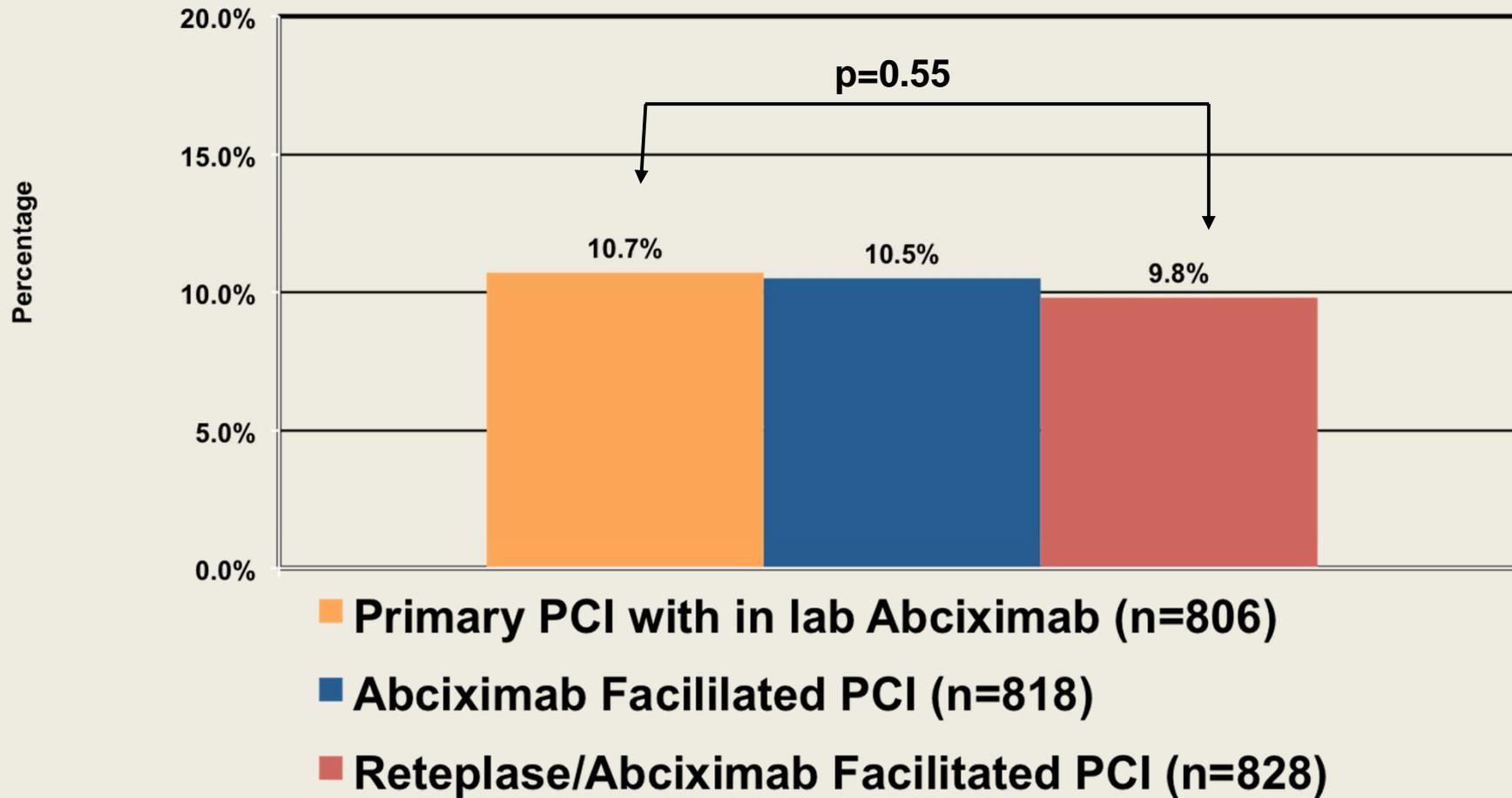| Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 CI.	HR (95% CI)	P value (Interaction)
Overall Treatment Effect						
Primary Endpoint		18624	9.8	11.7	0.84 (0.77, 0.92)	
New ST elevation/LBBB at rand.						0.68
No		11074	10.1	12.3	0.83 (0.74, 0.93)	
Yes		7544	9.4	10.8	0.87 (0.75, 1.01)	
TIMI Risk Score: STEMI						0.32
0-2		3889	4.7	6.2	0.76 (0.58, 1.01)	
≥3		3137	13.1	15.2	0.86 (0.71, 1.04)	

Wallentin et al NEJM 2009

FINESSE: Study Design

Acute ST Elevation MI (or New LBBB) within 6h pain onset

Presenting at Hub or Spoke with estimated time to Cath between 1 and 4 hours

Randomize 1:1:1
N=3000

**Double Blind
Double Dummy**

*Only 5U if ≥75 yr

| Placebo Placebo | Placebo Abciximab | Reteplase (5U+5U)* Abciximab |

Transfer To Cath Lab
ASA, unfractionated heparin 40U/kg (max 3000U)
or enoxaparin (0.5 mg/kg IV + 0.3 mg/kg SC) – substudy only

| Abciximab | Placebo | Placebo |

Primary PCI with Abciximab Infusion (12 h)

Follow up through 90 days and 1 year

Primary Endpoint

Primary Composite Endpoint at Day 90

p=0.55

- 10.7%
- 10.5%
- 9.8%

■ **Primary PCI with in lab Abciximab (n=806)**

■ **Abciximab Facililated PCI (n=818)**

■ **Reteplase/Abciximab Facilitated PCI (n=828)**

Adjunctive antithrombotic Rx for STEMI PCI: what do the ESC revascularization guidelines say ?

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

f: primarily if more efficient agents are contraindicated
d: depending on approval and availability

Wijns & Kohl, *Eur Heart J* 2010

UFH for PCI: no placebo-controlled randomized trial !
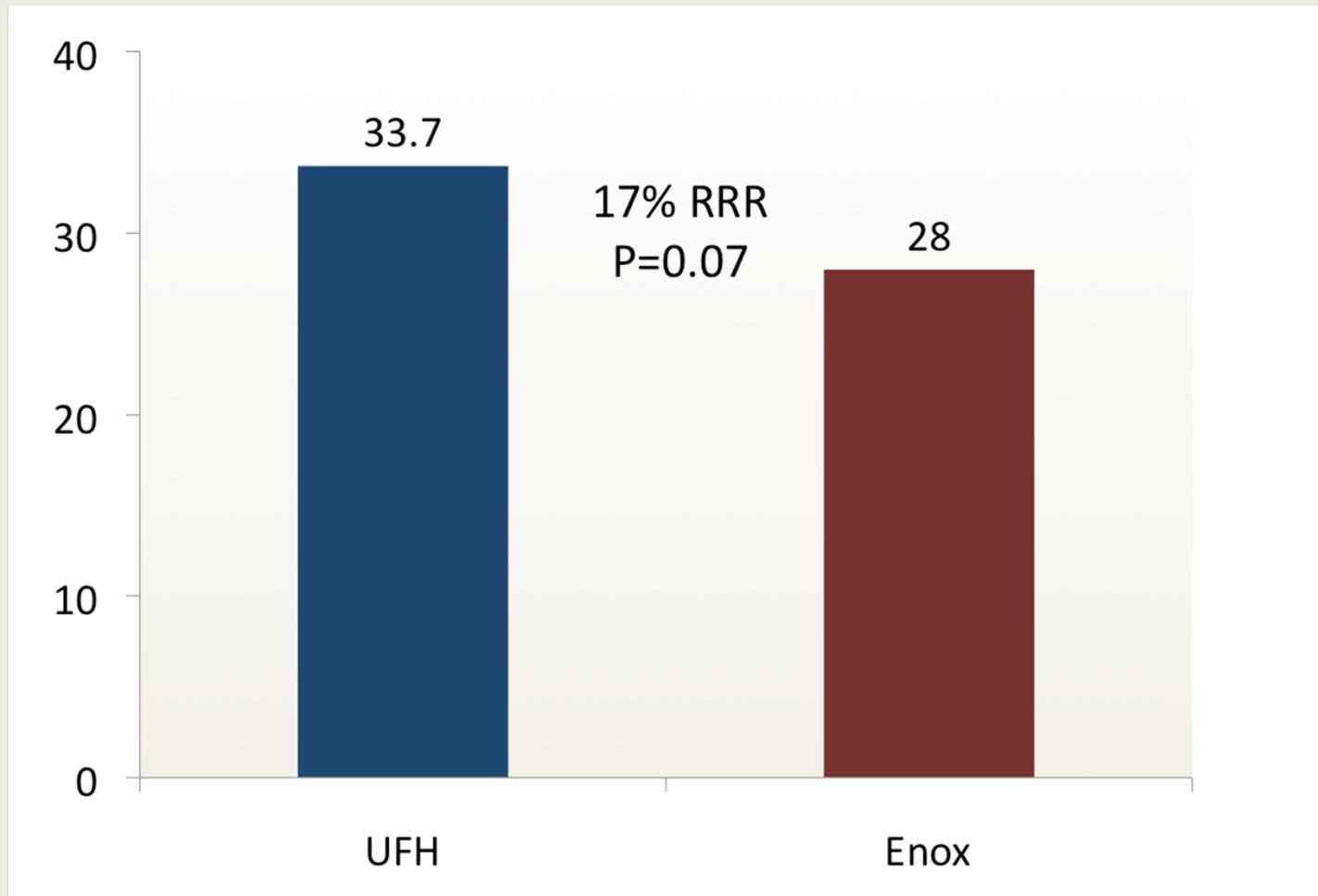
ATOLL Trial design

Randomization as *early* as possible (MICU +++)
Real life population (shock, cardiac arrest included)
No anticoagulation and no lytic **before** Rx
Similar antiplatelet therapy in both groups

STEMI → Primary PCI

**ENOXAPARIN IV
0.5 mg/kg**
with or without GPIIbIIIa

IVRS

UFH IV
50-70 IU with GP IIbIIIa
70-100IU without GP IIbIIIa
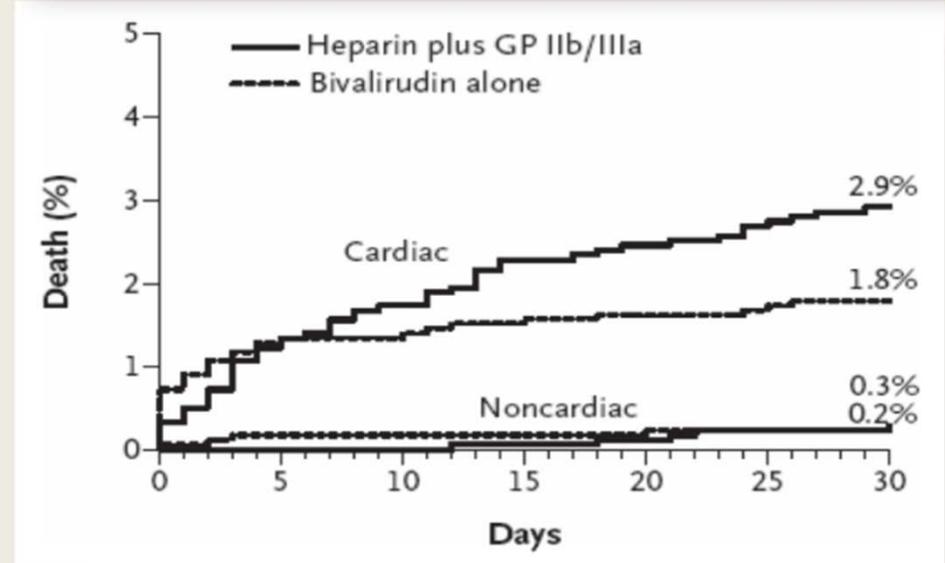**(Dose ACT-adjusted)**

Primary PCI

ENOXAPARIN SC
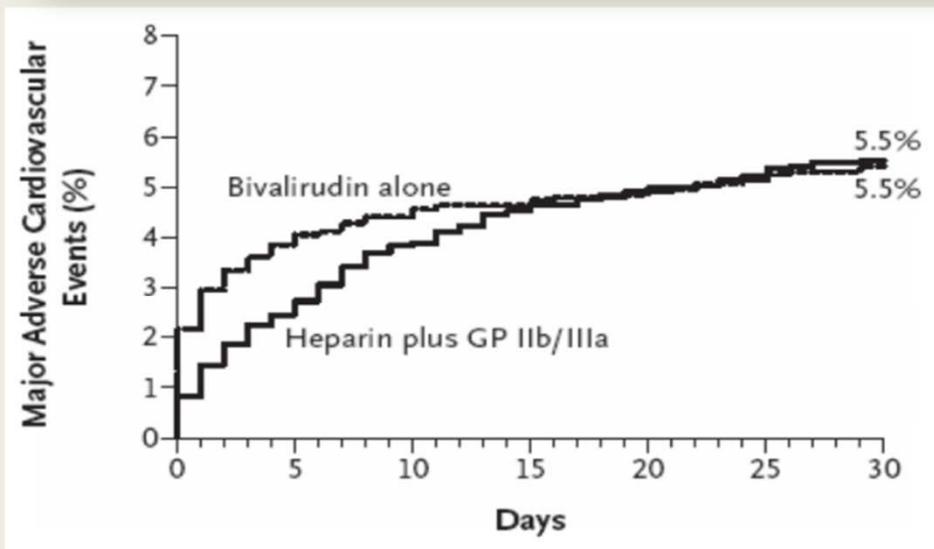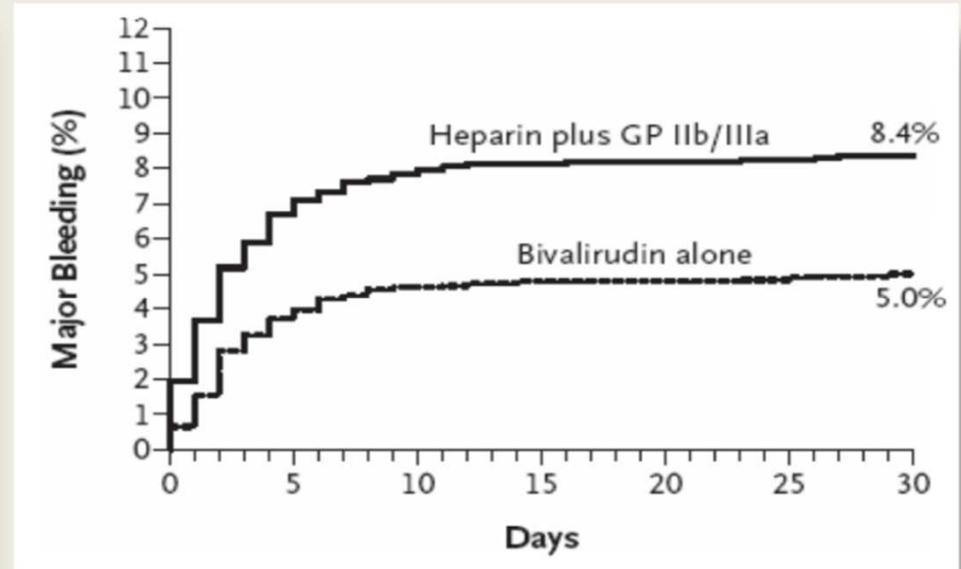
UFH IV or SC

30-day results
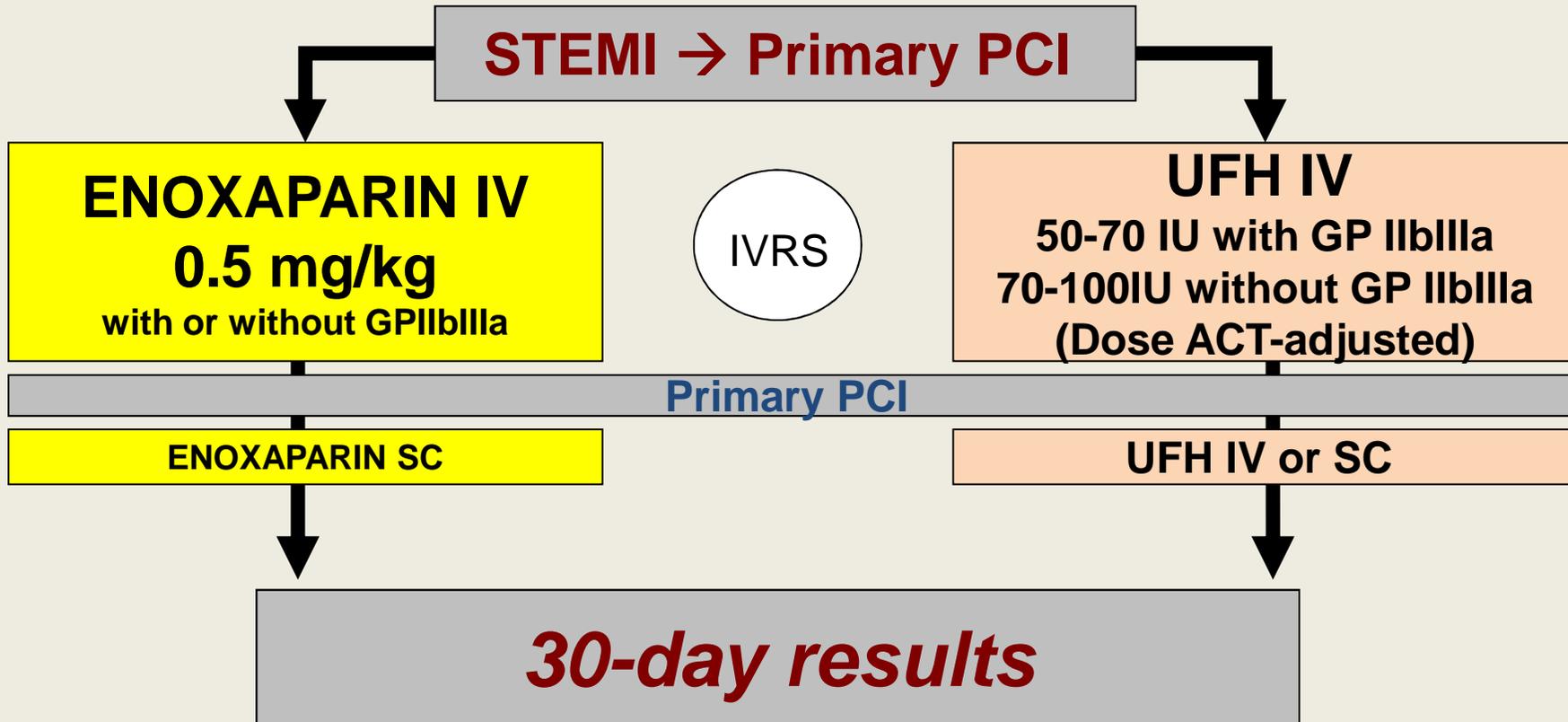
ATOLL: Enox vs UFH for primary PCI

Primary Endpoint: **Death, Complication of MI, Procedure Failure or Major Bleeding**

Montalescot, ESC 2010

1-Year All-Cause Mortality

HORIZONS AMI

- Bivalirudin alone (n=1800)
- Heparin + GPIIb/IIIa (n=1802)

4.8%

Δ = 1.4%

3.4%

3.1%

2.1%

Δ = 1.0%
P=0.049

Diff [95%CI] =
-1.5% [-2.8,-0.1]
HR [95%CI] =
0.69 [0.50, 0.97]
P=0.029

Mortality (%)

Time in Months
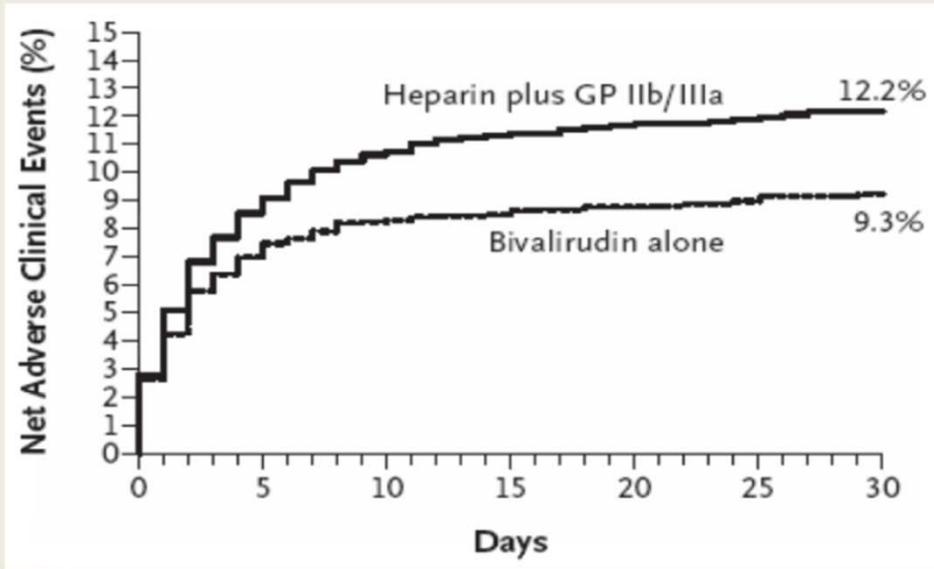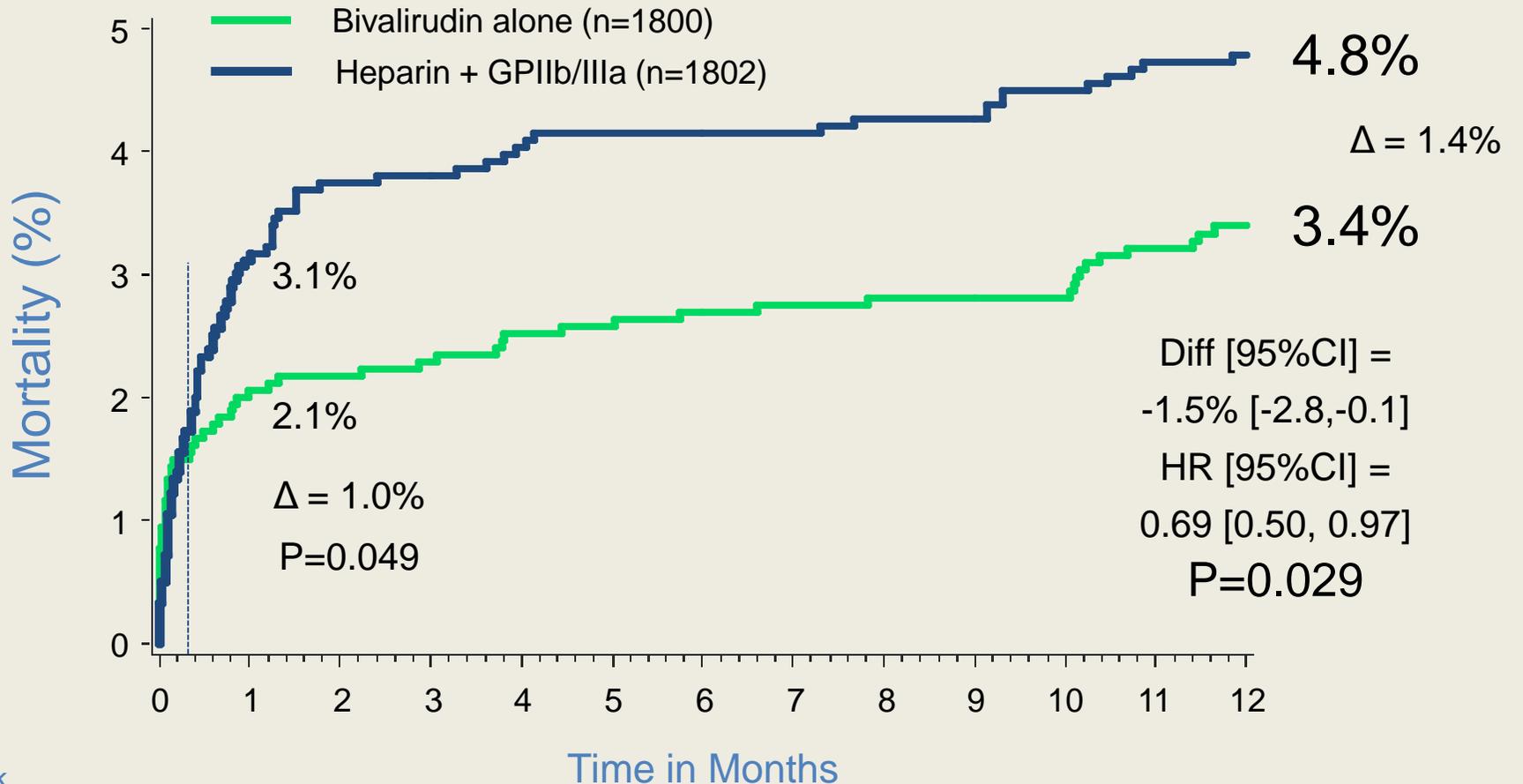
Number at risk

Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1486

Mehran, Lancet 2009

HORIZONS: 1-Year Stent Thrombosis

Stent Thrombosis (%)

- Bivalirudin alone (n=1611)
- Heparin + GPIIb/IIIa (n=1591)

Δ = 0.3%

3.5%
3.2%

2.7%

2.2%

Δ = 0.5%
P=0.31

HR [95%CI] =
1.11 [0.76, 1.63]

P=0.59

Time in Months

Number at risk					
Bivalirudin alone	1611	1525	1504	1486	1356
Heparin+GPIIb/IIIa	1591	1495	1475	1457	1315

EUROMAX
Primary PCI ambulance trial

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

R 1:1

Aspirin and thienopyridine

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

Bivalirudin monotherapy with prolonged infusion
(Gp IIb/IIIa for bailout only)
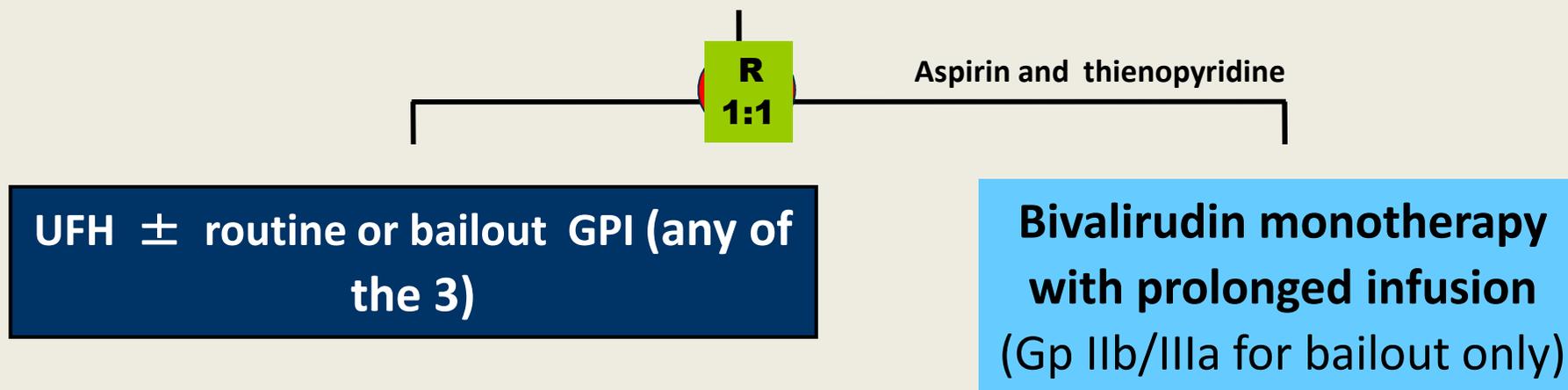
Primary endpoint
30-day death, MI or non-CABG related major bleeding

Clinical FU at 30 days and 1 year

Pre-Specified Subgroup Analyses

Death or MI at 30 days

	N	UFH/Placebo	Fonda		Interaction P value
Overall	12092	11.2%	9.7%		
Initial Reperfusion Rx					0.04
None	2867	15.1	12.2		
Thrombolytic	5436	13.6	10.9		
Primary PCI	3789	4.9	6.0		
GRACE Risk Score					0.03
< 112	5958	4.3	4.6		
>=112	6134	18.0	14.5		

0.5   0.7 0.8   1.0   1.2 1.4 1.6   2.0

← **Fonda better** | **UFH/Plac better** →

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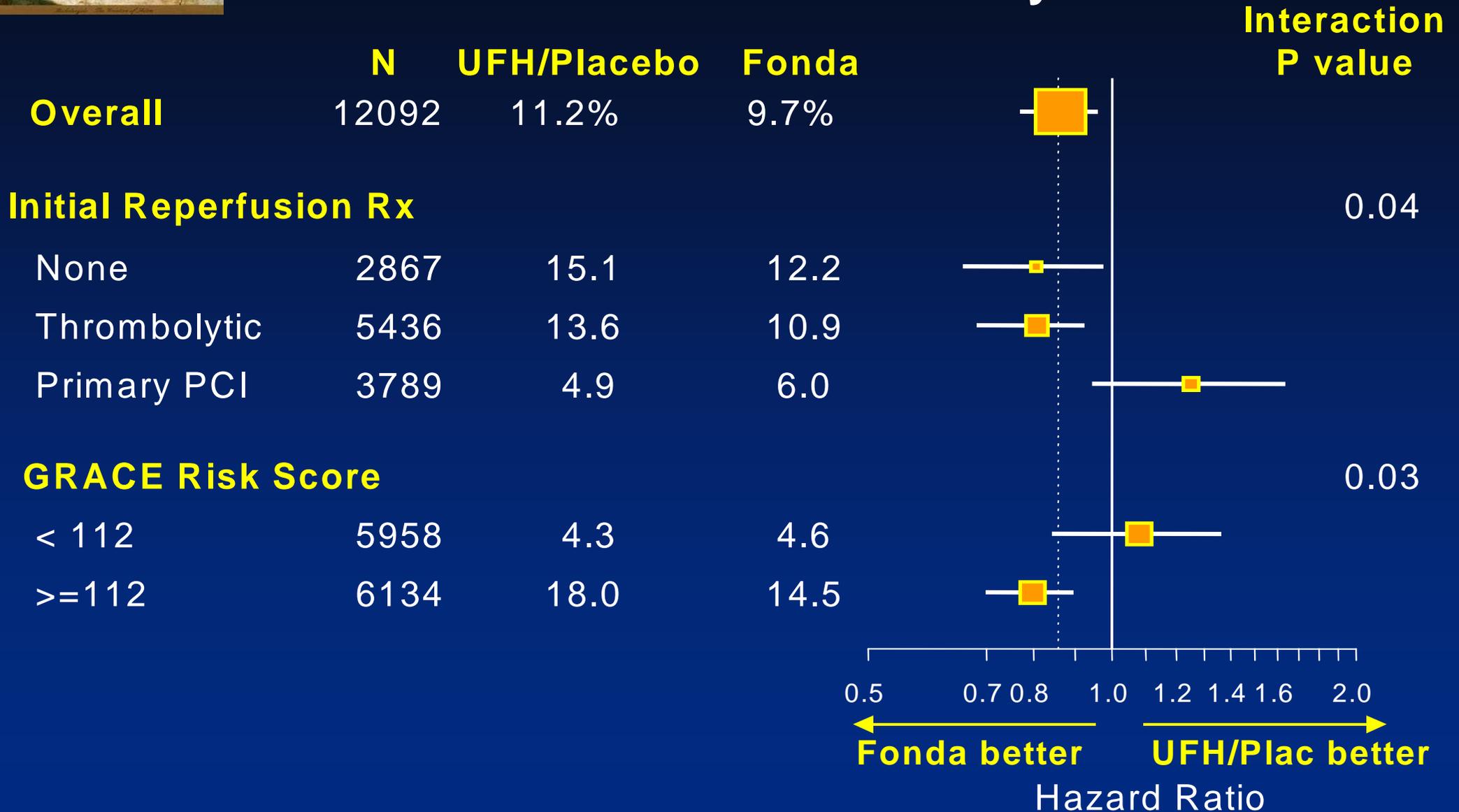
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Antiplatelet therapy				
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	Clopidogrel[f] (with 600 mg loading dose as soon as possible)		I	C
	Prasugrel[d]		I	B
	Ticagrelor[d]		I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary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

Wijns & Kohl, *Eur Heart J* 2010

Mon algorithme

STEMI – Angioplastie primaire

- Aspirine
  - Charge 500 mg
  - Entretien 75 mg/j
- Prasugrel (sf si age, poids, AVC/AIT*)
  - Charge 60 mg
  - Entretien 10 mg
- Bivalirudine (prolongée 4 h post PCI)
- Abciximab si bailout

SCA sans sus décalage de ST

- Aspirine
  - Charge 500 mg
  - Entretien 75 mg/j
- Prasugrel (sf si age, poids, AVC/AIT*)
  - Charge 60 mg
  - Entretien 10 mg
- Fondaparinux
- Eptifibatide si PCI et troponine +

- Si CI au prasugrel: clopidogrel 600/75
- Demain: remplacer Prasugrel par Ticagrelor

Antithrombotiques dans les SCA

- C'est compliqué
- Les essais cliniques nous donnent quelques informations
- Les traitements ont un bénéfice et un risque
- L'efficacité antithrombotique n'est pas parfaitement corrélée au bénéfice clinique
- L'objectif du traitement est un bénéfice clinique
- Les principes du traitement
- Nécessité d'un algorithme par consensus local

The spectrum of ACS care

- A wide spectrum of clinical presentation
  - Chest pain
  - STEMI, NSTEMI, UA
  - Variations related to age, gender, prior medical history

- A spectrum of care locations
  - Pre-hospital and ambulance
  - Emergency Room
  - CCU
  - Cath lab

- Multiple stakeholders
  - Emergency physicians
  - CCU Cardiologists
  - Interventionalists
  - Cardiac Surgeons
  - Anesthesiologists, Intensive Care
  - Referring Cardiologists

- Multiple therapeutic strategies
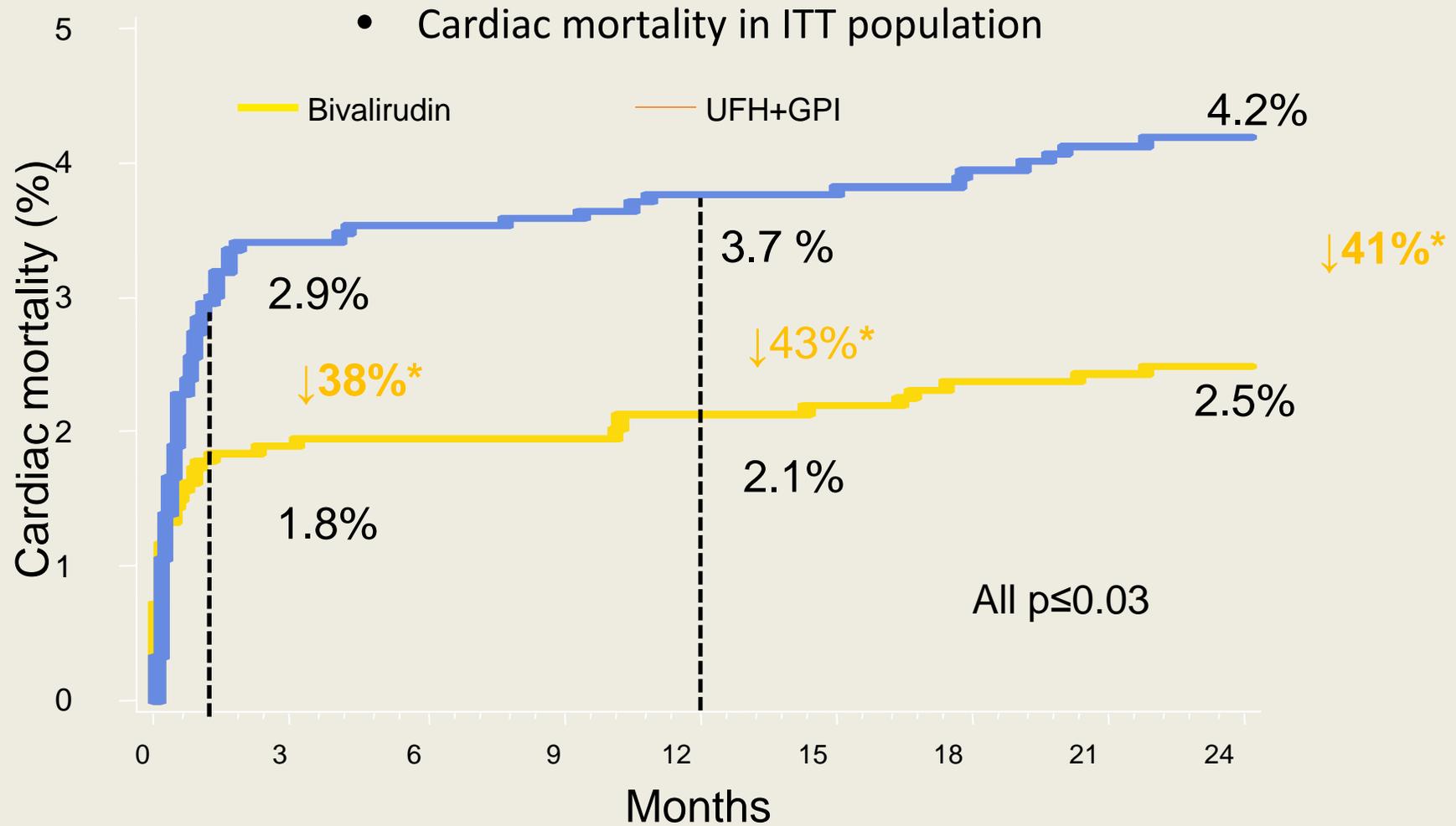 - PCI
  - CABG
  - Medical therapy

Conclusions

- Le choix d'une stratégie antithrombotique doit intégrer risque ischémique et risque hémorragique

- La combinaison aux nouveaux agents est intéressante:
  - Ex les nouveaux antiplaquettaires oraux peuvent éviter le besoin d'antiGpIIb/IIIa et optimiser l'efficacité des anticoagulants

- La réduction de la mortalité doit rester le facteur de choix principale d'une stratégie thérapeutique

- La mise en oeuvre peut être problématique
  - Multiplicité des intervenants
  - Contecte d'urgence
  - Continuité des soins (pre-hospital/Urgences/USIC/Cath lab)

- Nécessité de consensus loco-régionaux

Thank you !

Backup slides

TRITON-STEMI - Efficacy endpoints at 15 months

Proportion of population (%)

Legend: ■ Clopidogrel ■ Prasugrel

- All Death: p=0.11
- MI: p=0.02
- UTVR: p=0.09
- Stent Thrombosis: p=0.02
- CV Death/MI: p=0.007
- CV Death/MI/UTVR: p=0.03
- CV Death/MI/Stroke: p=0.02
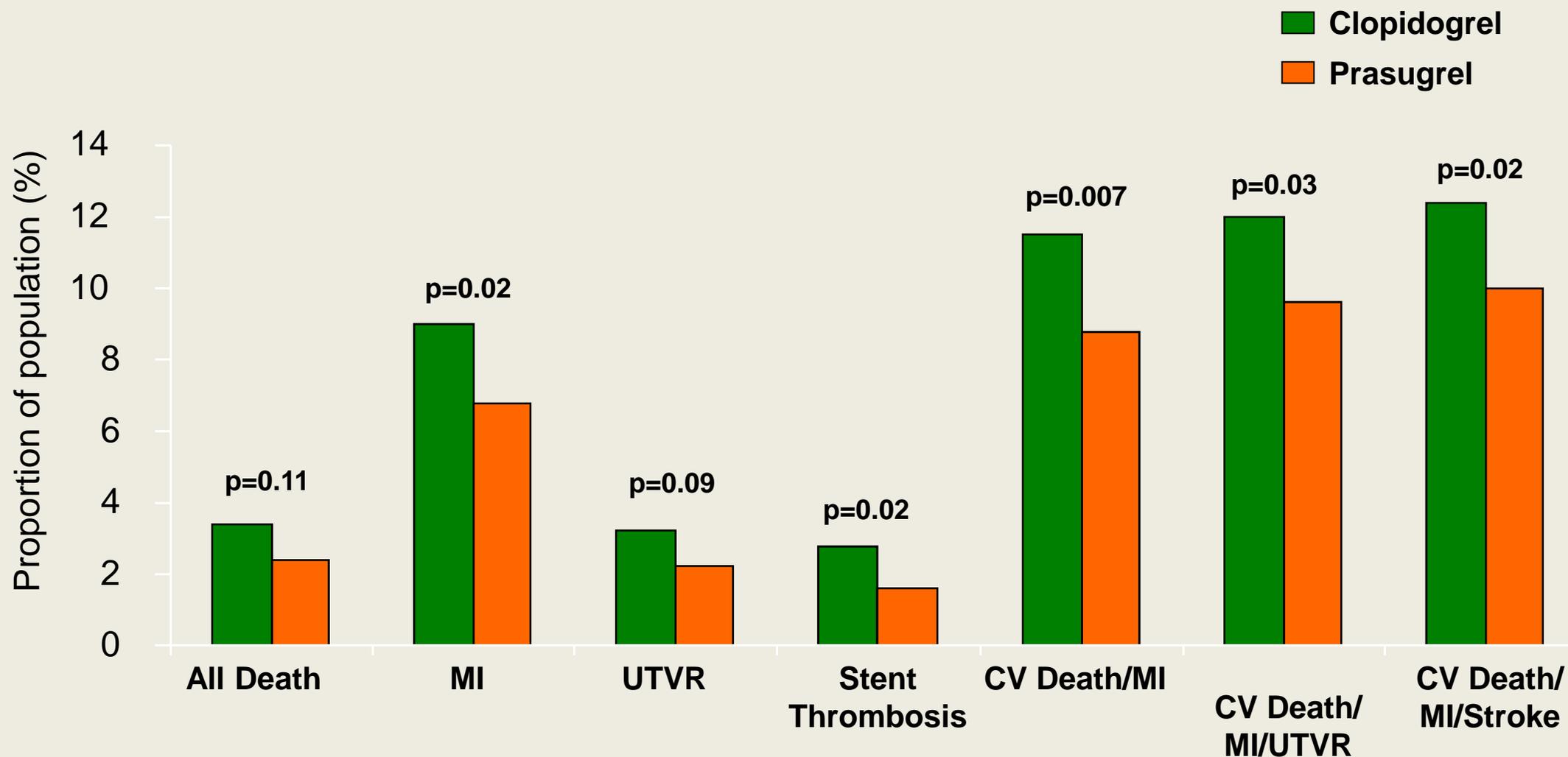
CV   = Cardiovascular
MI   = Myocardial infarction
UTVR = Urgent target-vessel revascularisation

Montalescot et al. ESC 2008

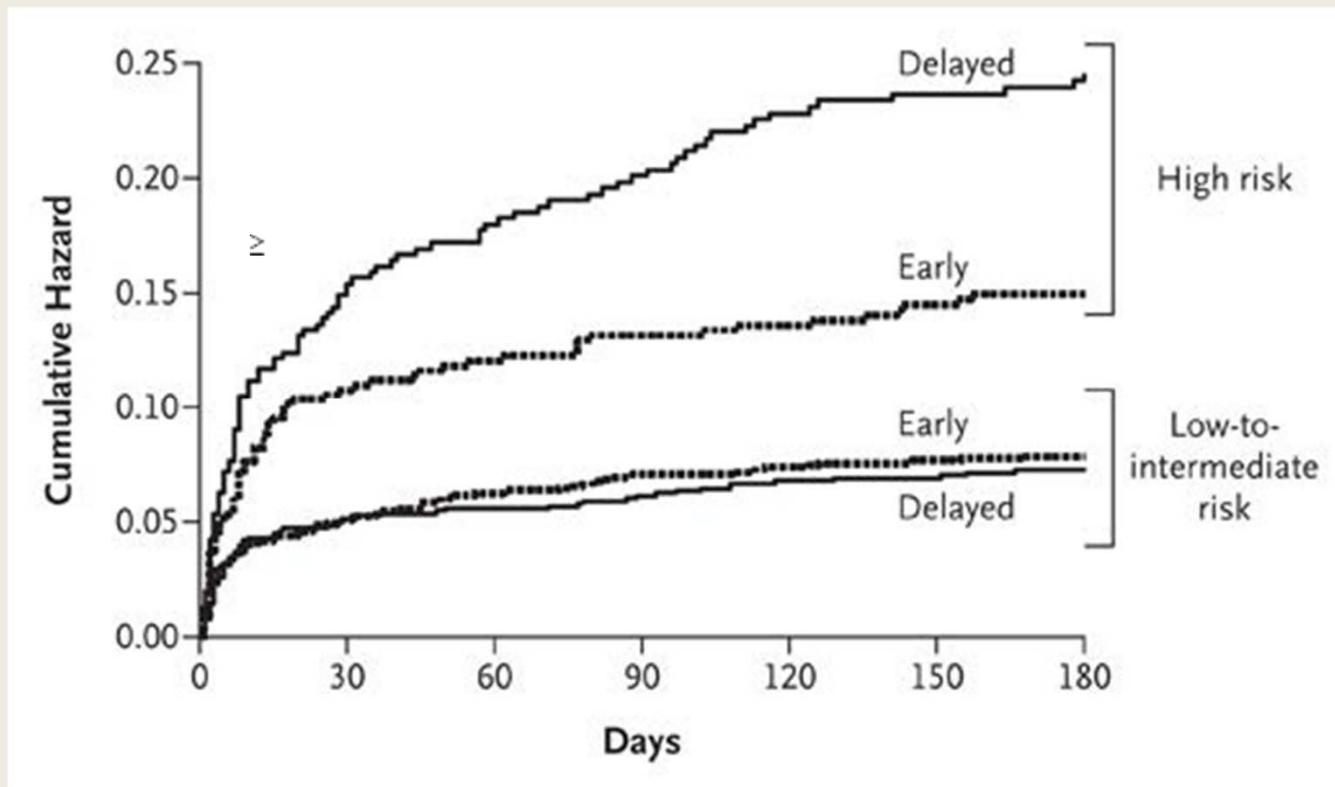| Specification	Class[a]	Level[b]	Ref.[c]
An invasive strategy is indicated in patients with: • GRACE score >140 or at least one high-risk criterion. • recurrent symptoms. • inducible ischaemia at stress test.	I	A	64, 68–70
An early invasive strategy (<24 h) is indicated in patients with GRACE score >140 or multiple other high-risk criteria.	I	A	63, 64, 66, 70–72
A late invasive strategy (within 72 h) is indicated in patients with GRACE score <140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia.	I	A	59, 66, 68
Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (<2 h).	IIa	C	—
An invasive strategy should not be performed in patients: • at low overall risk. • at a particular high-risk for invasive diagnosis or intervention.	III	A	59, 68

ESC guidelines: recommendations for revascularization in NSTE-ACS

Wijns & Kohl, *Eur Heart J* 2010

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb–IIIa antagonists	III	B
Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B

Wijns & Kohl, *Eur Heart J* 2010

Benefit of early vs delayed intervention according to GRACE risk score in ACS in the TIMACS trial

3031 pts randomized to undergo either routine early intervention (coronary angiography, < 24 hrs) or delayed intervention (coronary angiography >36 hrs)
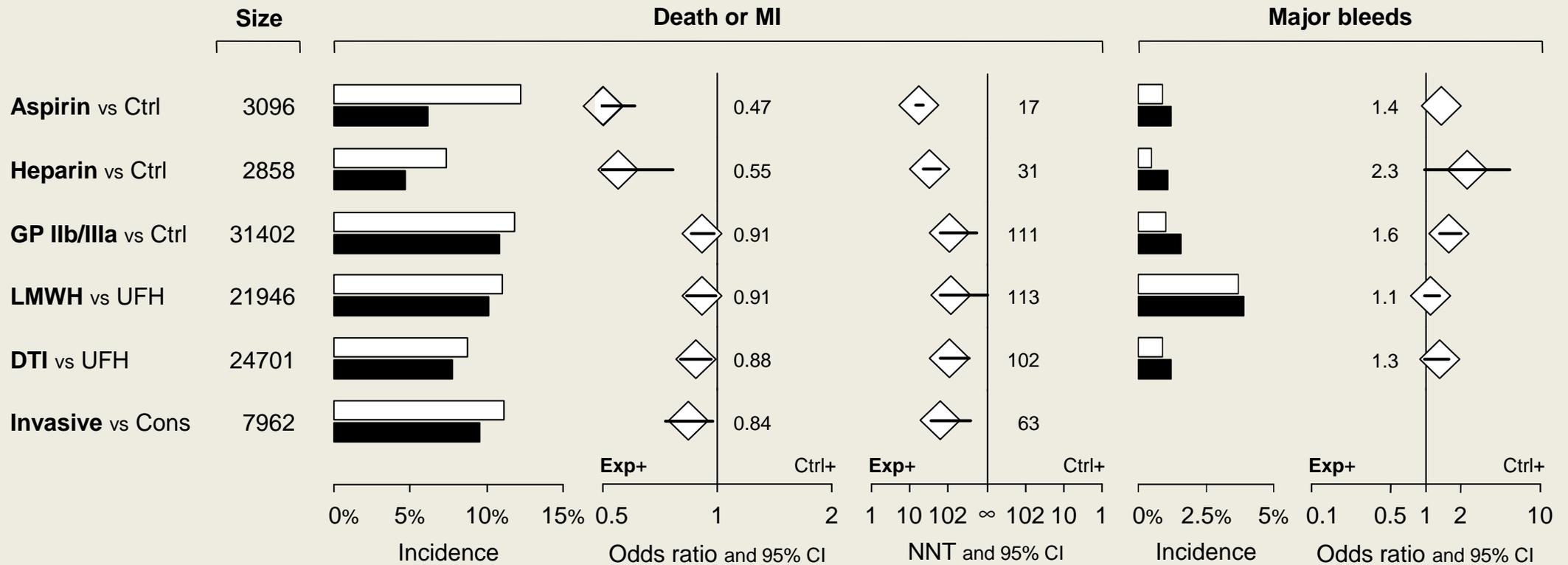
Kaplan–Meier Cumulative Risk of the Primary Outcome (death/MI/Stroke)

High-risk = GRACE risk score > 140

Interaction P = 0.01

Mehta et al NEJM 2009:360:2165-75

NSTE-ACS – Summary of Treatment Approaches

	Size	Death or MI			Major bleeds	
		Incidence / Odds ratio and 95% CI	NNT and 95% CI		Incidence / Odds ratio and 95% CI	
Aspirin vs Ctrl	3096	0.47	17		1.4	
Heparin vs Ctrl	2858	0.55	31		2.3	
GP IIb/IIIa vs Ctrl	31402	0.91	111		1.6	
LMWH vs UFH	21946	0.91	113		1.1	
DTI vs UFH	24701	0.88	102		1.3	
Invasive vs Cons	7962	0.84	63			

Randomized trials of UFH/LMWH (dark bars) vs Control

Size	Death or MI at end study medication			Major bleeds	

Death or MI at end study medication — Incidence | Odds ratio and 95% CI | NNT and 95% CI

Major bleeds — Incidence | Odds ratio and 95% CI

	Size
Theroux '88	243
Cohen '90	69
RISC '90	399
Cohen '94	214
Holdright '94	285
Gurfinkel '95	143
FRISC '96	1506
All	2859

Heparin+ / Ctrl+

0% 20% 40% — Incidence
0.25 0.5 1 2 — Odds ratio and 95% CI
1 10 102 ∞ 102 10 1 — NNT and 95% CI
0% 3% 6% — Incidence
0.1 0.5 1 2 10 — Odds ratio and 95% CI

4.7% vs 7.4%   0.55 (0.39-0.77)   31 (23-62)   **1.1**% vs 0.5%   2.3 (0.97-5.4)

Randomized trials
Enoxaparin (dark bars) vs UFH (open bars)

	Size	Death or MI at 30 days			Major bleeds	

Trial	Size
ESSENCE '97	3171
TIMI-11B '99	3910
ACUTE-II '02	525
INTERACT '03	746
A to Z '04	3620
SYNERGY '04	9974
All	21946

Incidence
0% 10% 20%

Odds ratio and 95% CI
LMWH+   UFH+
0.5   1   2

NNT and 95% CI
LMWH+   UFH+
1 10 102 ∞ 102 10 1

Incidence
0% 5% 10%

Odds ratio and 95% CI
LMWH+   UFH+
0.1 0.5 1 2 10

10.1% vs 11.0%   0.91 (0.83-0.99)   113 (61-1438)   **3.9**% vs 3.7%   1.1 (0.96-1.3)
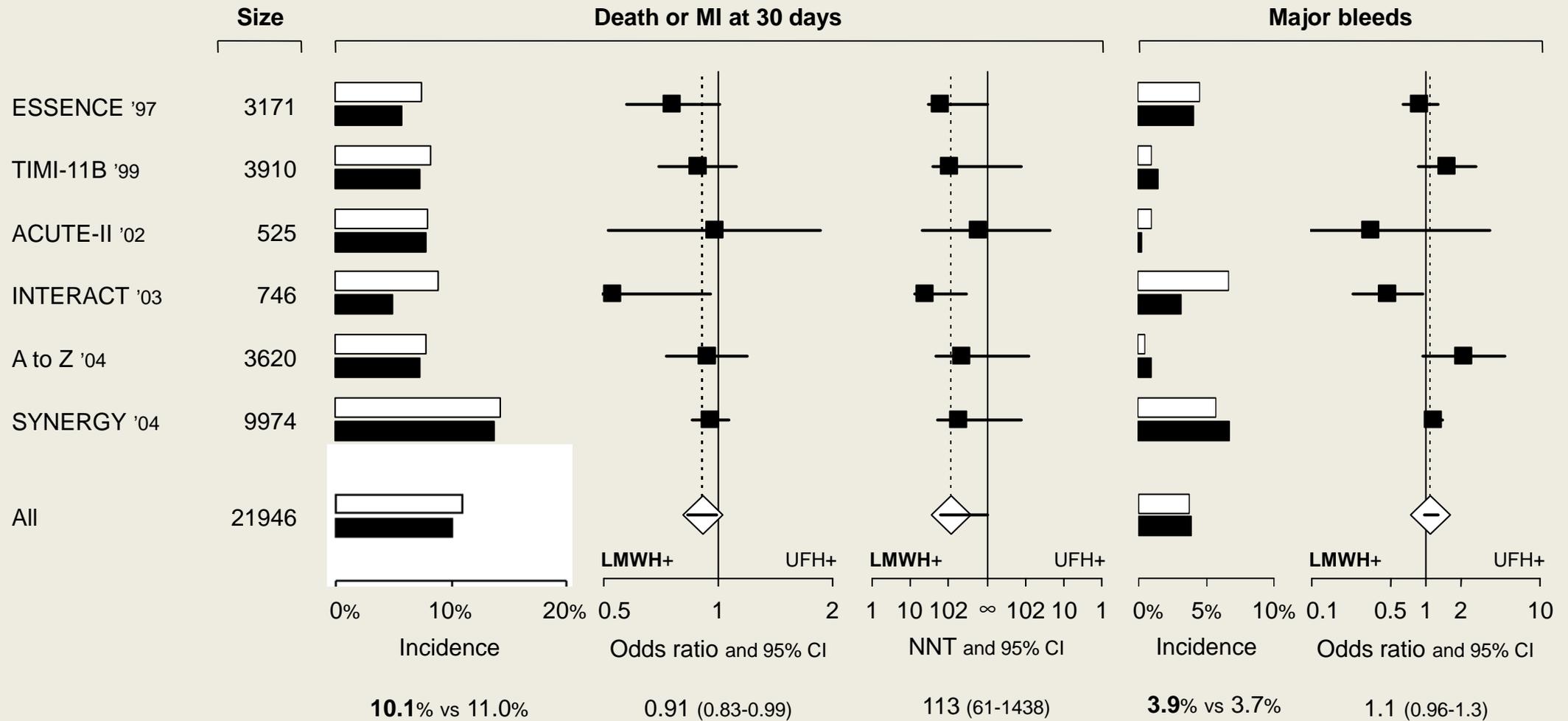
OASIS 5: bleeding reduction and mortality benefit for Fondaparinux vs Enoxaparin

OASIS 5 Investigators. N Engl J Med 2006;354:1464-76
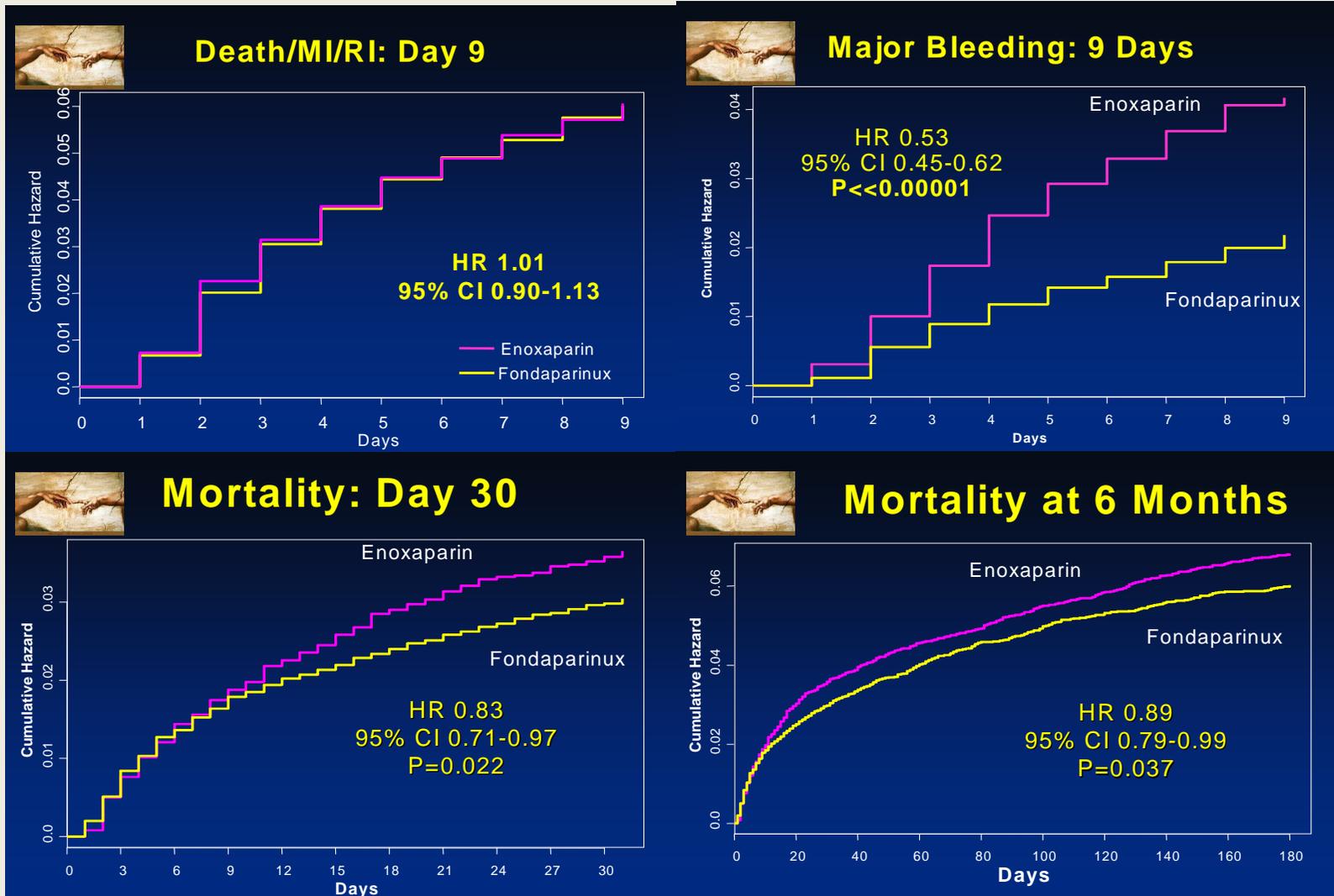
OASIS 5
(Randomized trial (n=20, 078) of Fondaparinux vs. Enoxaparin in ACS)

Major Bleeding at 9 days

Enoxaparin 4.1 %

HR: 0.52
95% CI: 0.44 -0.61
p<0.0001

48% relative risk reduction

Fondaparinux 2.2 %

Days

Mortality at 30 days

Enoxaparin 3.5 %

17 % RRR

Fondaparinux 2.9 %

HR: 0.83
95% CI: 0.71 -0.97
p=0.02

Days
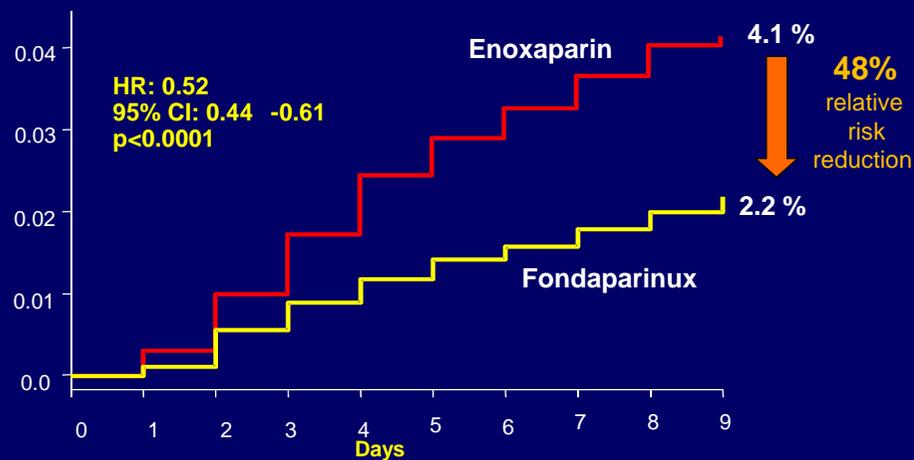
Fondaparinux: 295 deaths
Enoxaparin: 352 deaths
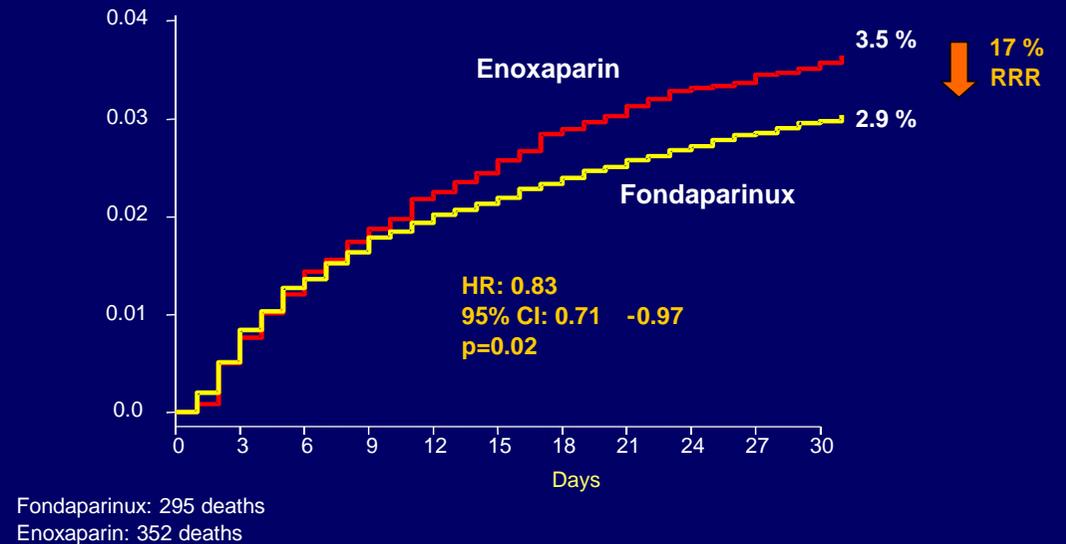
OASIS 5 Trial: Fondaparinux vs. Enoxaparin reduced major bleeding by 48% and mortality by 17% in NSTEACS

Randomized trials
Direct thrombin inhibitors (DTIs) (dark bars) vs UFH/LMWH

	Size	Death or MI at 30 days		Major bleeds	
GUSTO-2B '95	12142				
OASIS pilot '97	909				
OASIS '99	10141				
Klootwijk '99	300				
ACUITY '06	9207				
All	32699				

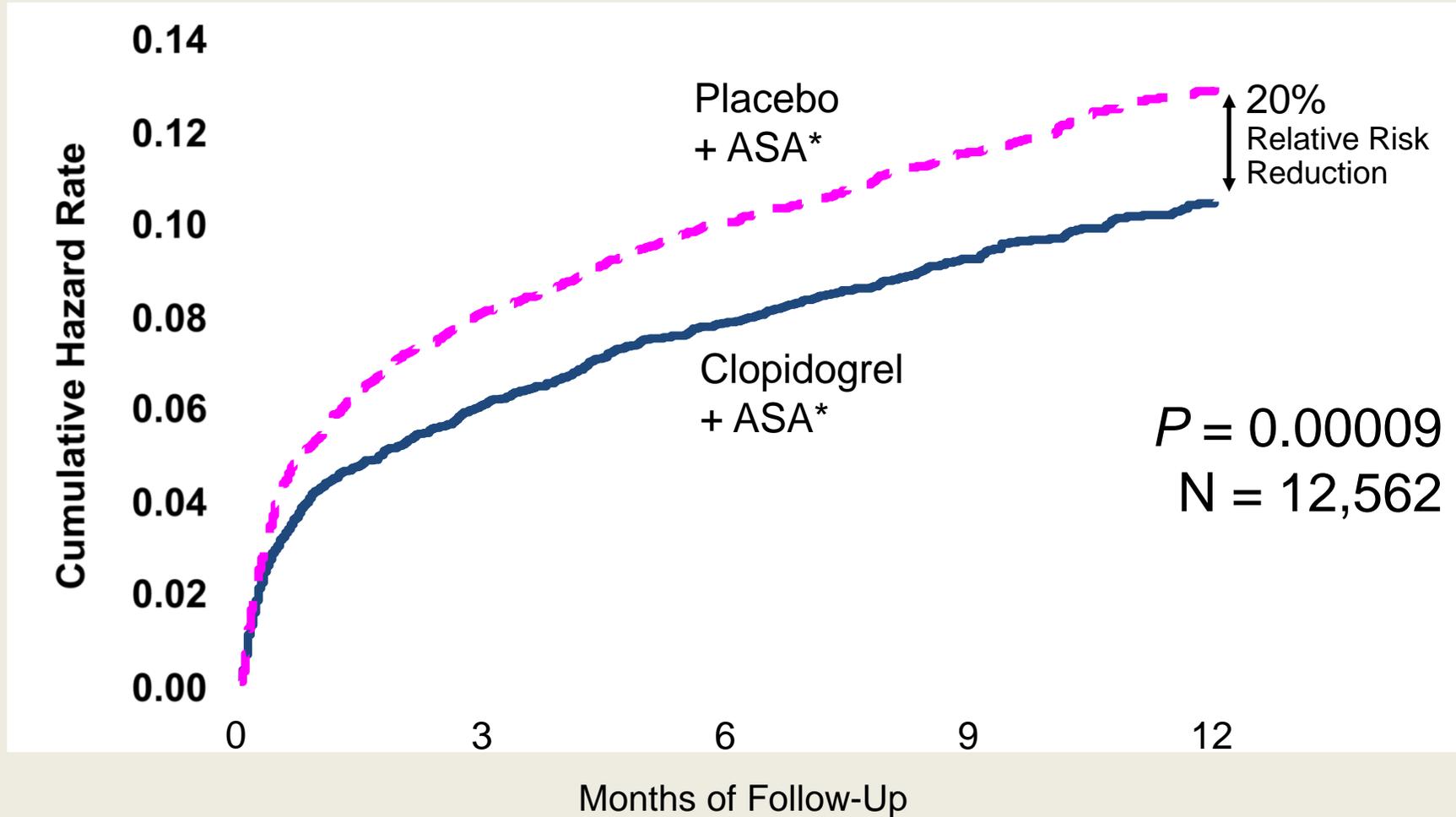| Incidence	Odds ratio and 95% CI	NNT and 95% CI	Incidence	Odds ratio and 95% CI
7.7% vs 8.3%	0.93 (0.85-1.0)	176 (89-∞)	**2.3**% vs 2.3%	1.0 (0.89-1.2)
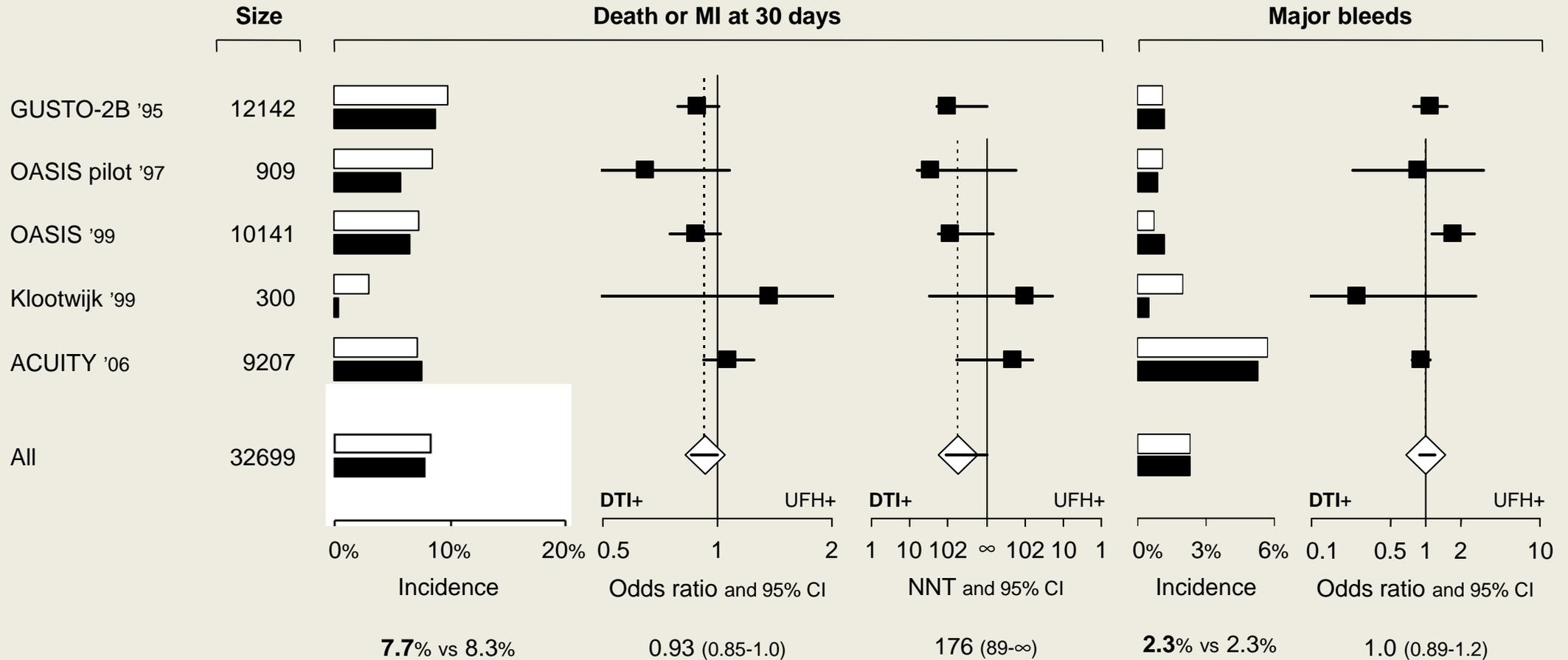
Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients
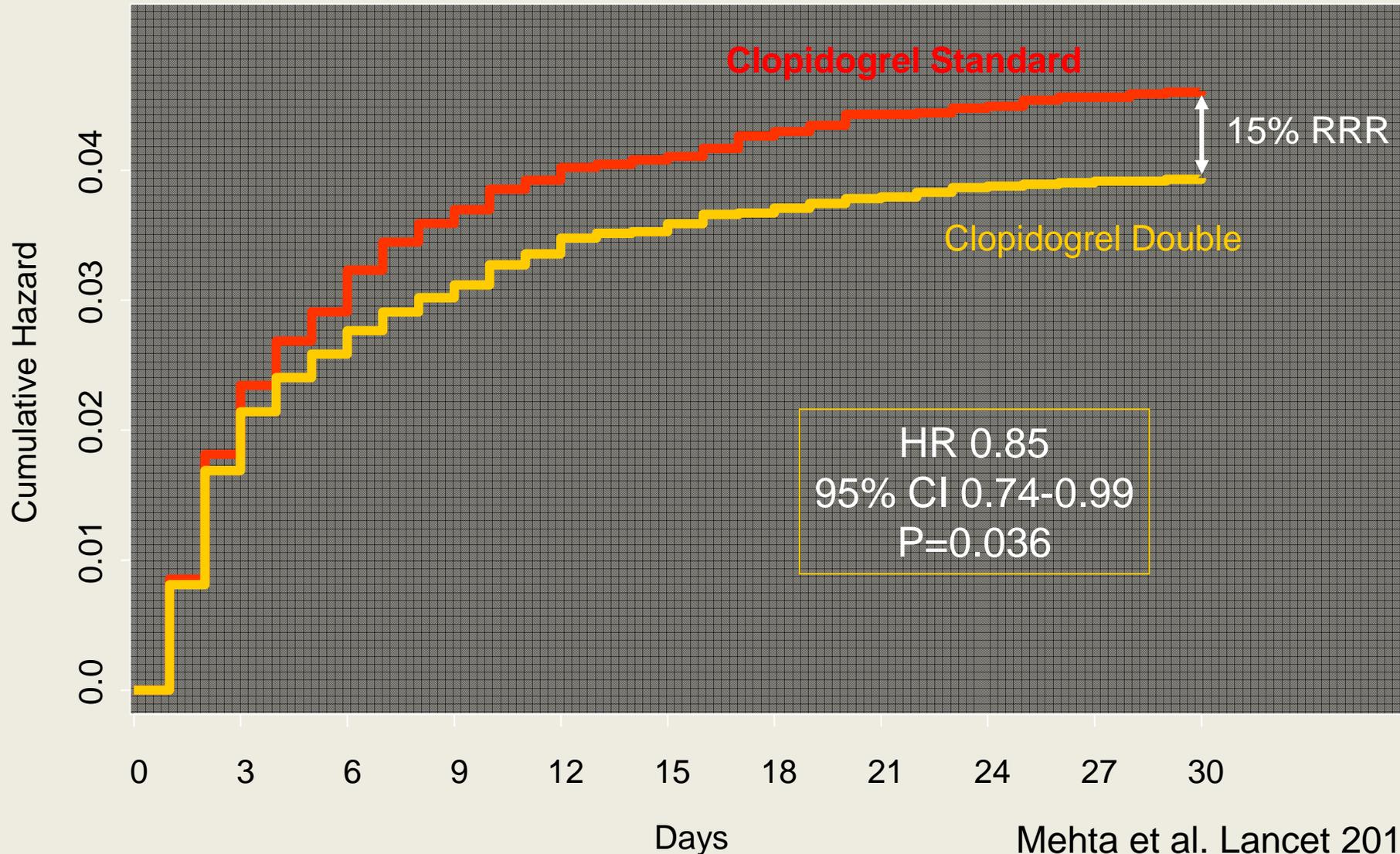
Antithrombotic Trialists' Collaboration

| Category of trial | No of trials with data | No (%) of vascular events | | Observed-expected | Variance | Odds ratio (CI) Antiplatelet:control | % Odds reduction (SE) |
		Allocated antiplatelet	Adjusted control				
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6		25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2		30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8		22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3		11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0		26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6		25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**		**22 (2)**

Heterogeneity of odds reductions between:
5 categories of trial: $\chi^2=21.4$, df=4; P=0.0003
Acute stroke v other: $\chi^2=18.0$, df=1; P=0.00002

Antiplatelet better   Antiplatelet worse
Treatment effect P<0.0001

Primary Outcome – MI/Stroke/CV Death

Placebo + ASA*

20% Relative Risk Reduction

Clopidogrel + ASA*

$P = 0.00009$

N = 12,562

Cumulative Hazard Rate

Months of Follow-Up

* In addition to other standard therapies.
CURE Investigators. *N Engl J Med.* 2001;345:494

EARLY ACS
no benefit of routine upstream eptifibatide in NSTE-ACS

Death, MI, RIUR or TBO (%)

Delayed provisional eptifibatide

10.0%

9.3%

Routine early eptifibatide

P = 0.23
(stratified for intended early clopidogrel use)

Time Since Randomization (Hours)
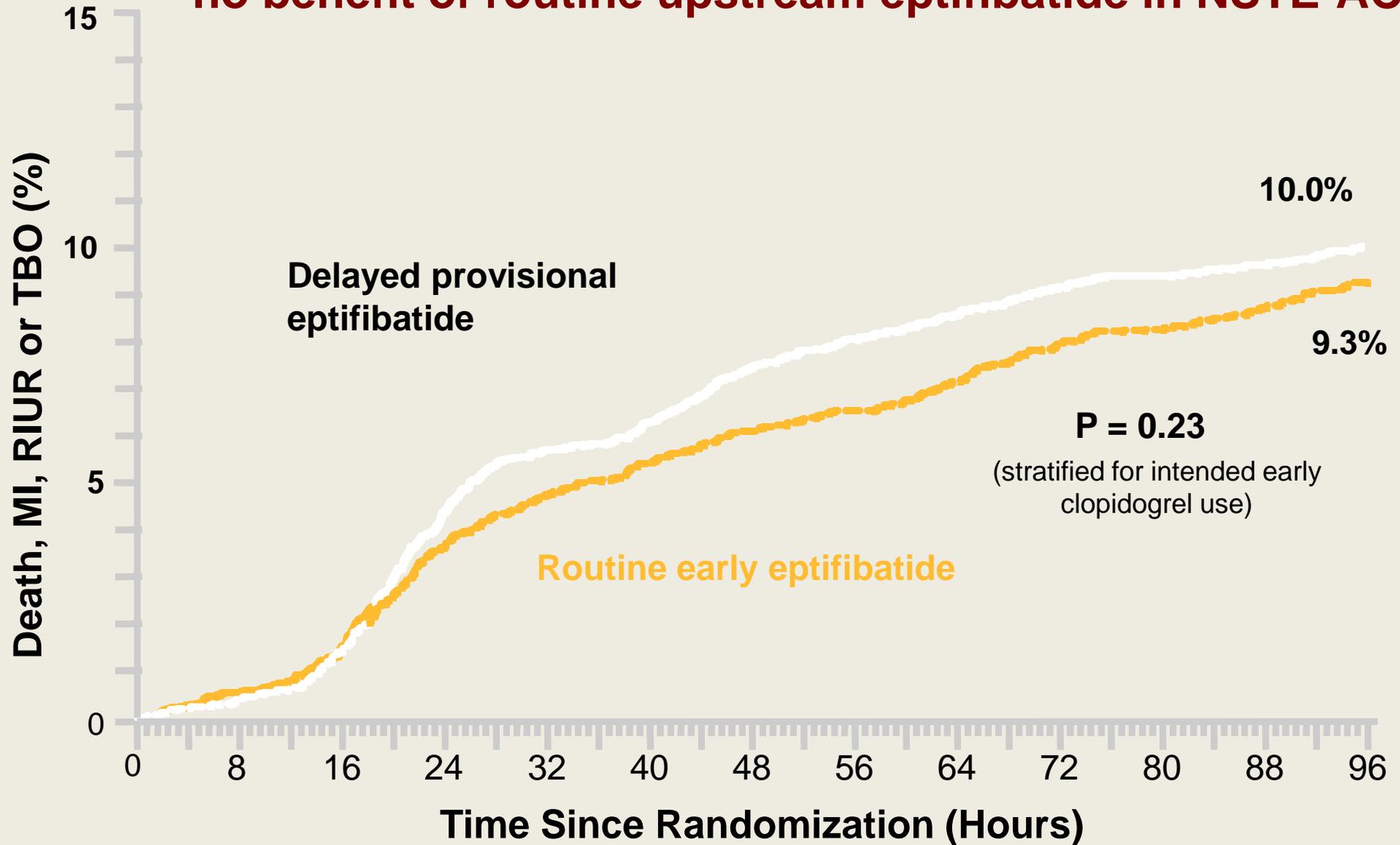
EARLY ACS:
Kaplan-Meier Curves for 30-day Death or MI

Death or MI (%)

15

10

5

0

Delayed provisional eptifibatide — 12.4%

Routine early eptifibatide — 11.2%

P = 0.079

(stratified for intended early clopidogrel use)

Time Since Randomization (Days)

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
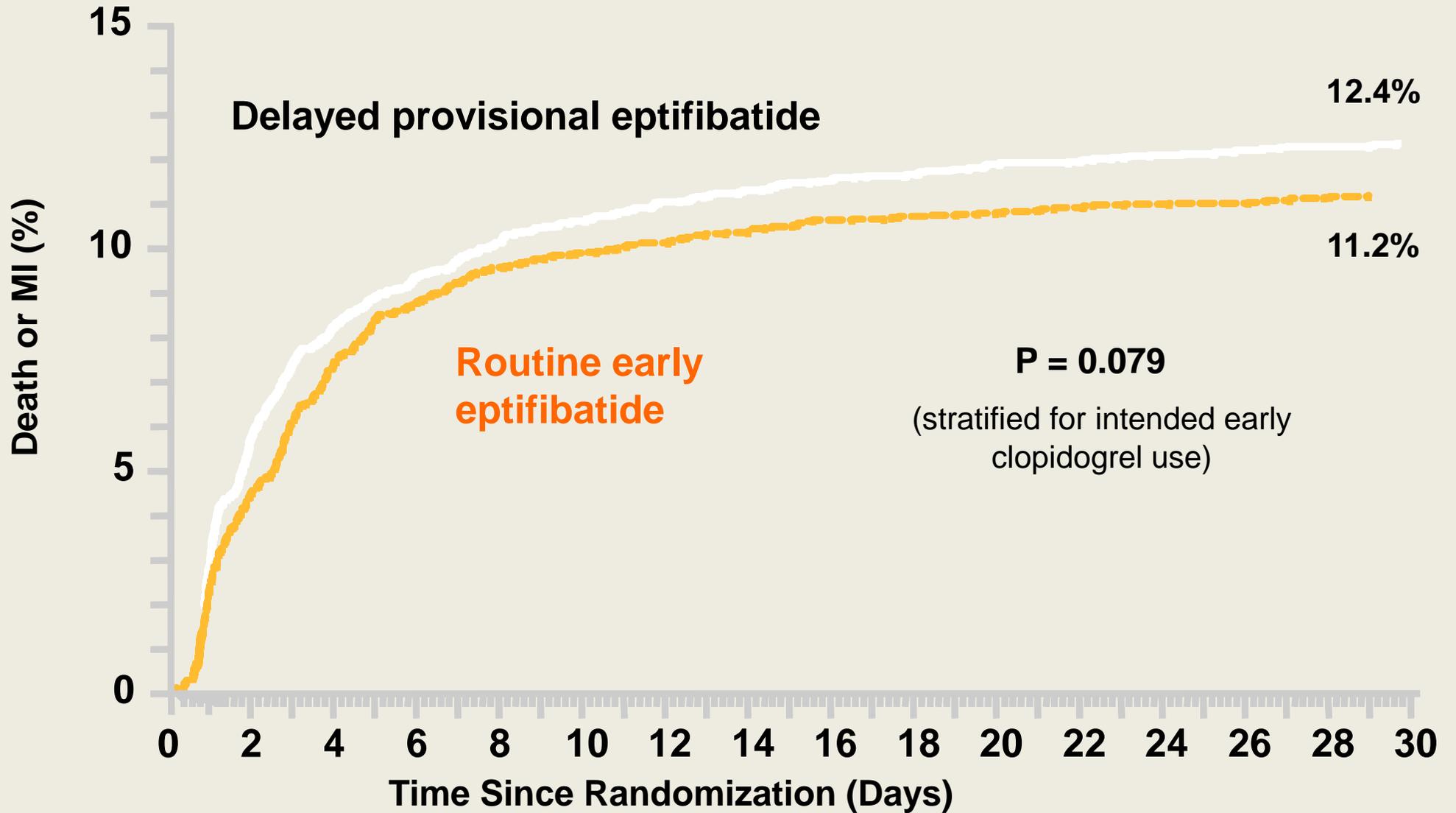
ISAR REACT -2

Death, Myocardial Infarction, or Urgent Target Vessel Revascularization

Kastrati et al. JAMA 2006
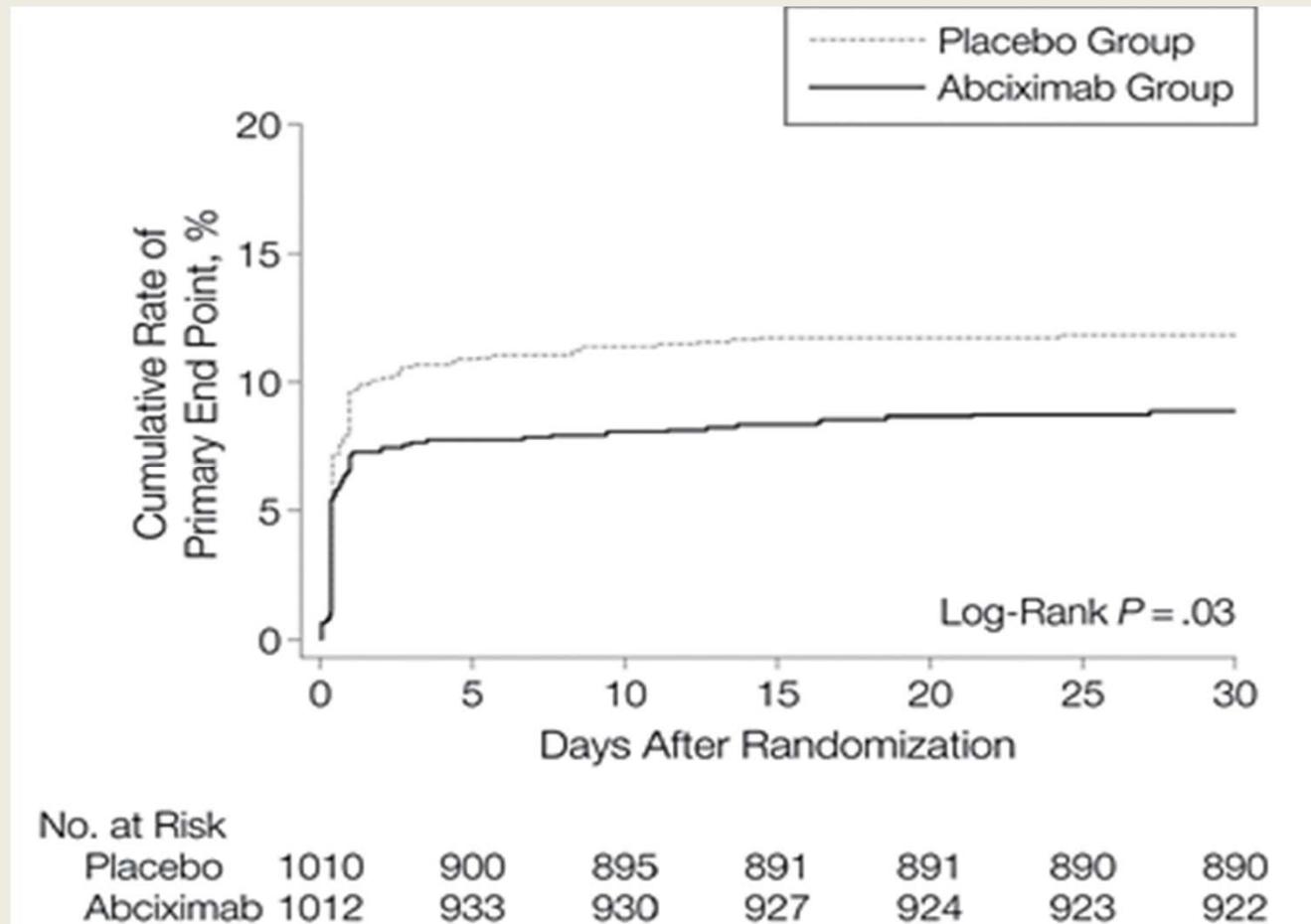
ISAR REACT -2

Benefit of GpIIb/IIIa blockade according to Troponin Levels (>0.03 µg/L)
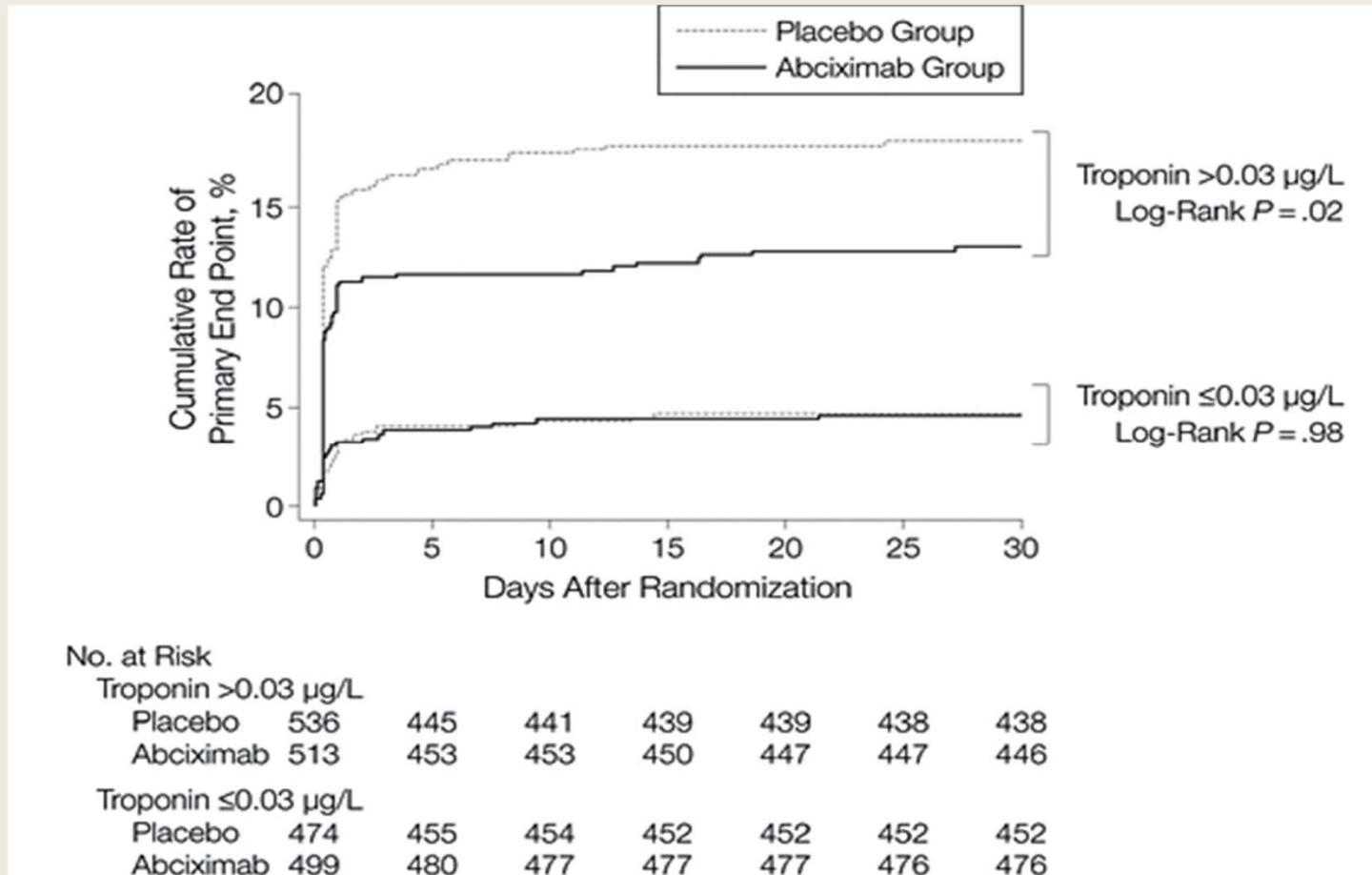
Benefit of Ticagrelor over Clopidogrel in PLATO consistent regardless of LOF genotype

(K-M) estimate of the primary endpoint in relation to CYP2C 19 lof allele
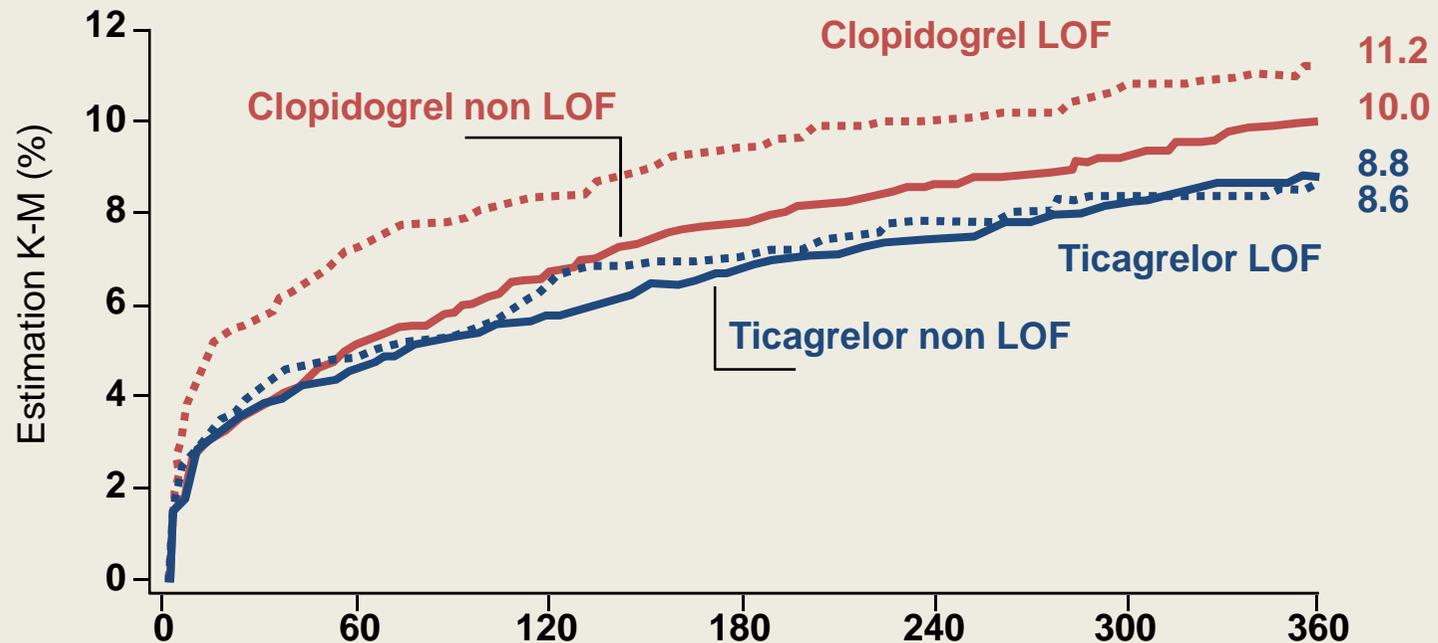
Nbr of patients							
Clopidogrel LOF*	1,388	1,275	1,259	1,226	1,027	801	658
Clopidogrel non LOF**	3,516	3,321	3,256	3,186	2,691	2,123	1,757
Ticagrelor LOF*	1,384	1,305	1,274	1,250	1,053	834	683
Ticagrelor non LOF**	3,554	3,352	3,301	3,222	2,718	2,127	1,761

Wallentin *et al.* **Lancet** 2010:376,

Association of CYP2C19*2 (rs4244285) Loss-of-Function Variant With Adenosine Diphosphate-Stimulated Platelet Aggregation Before and After Clopidogrel
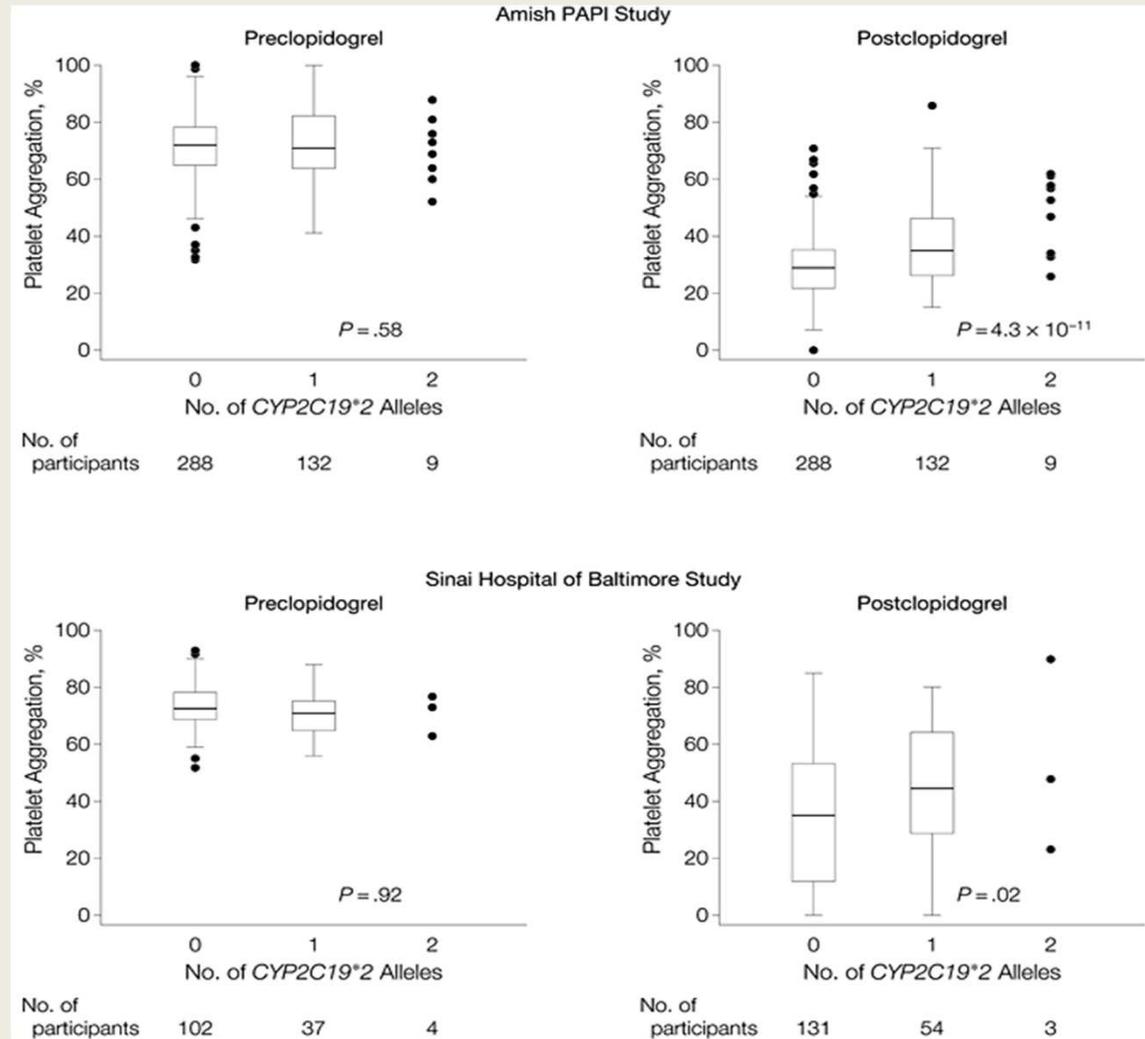
CYP2C19*2 accounts for 12% of the variability
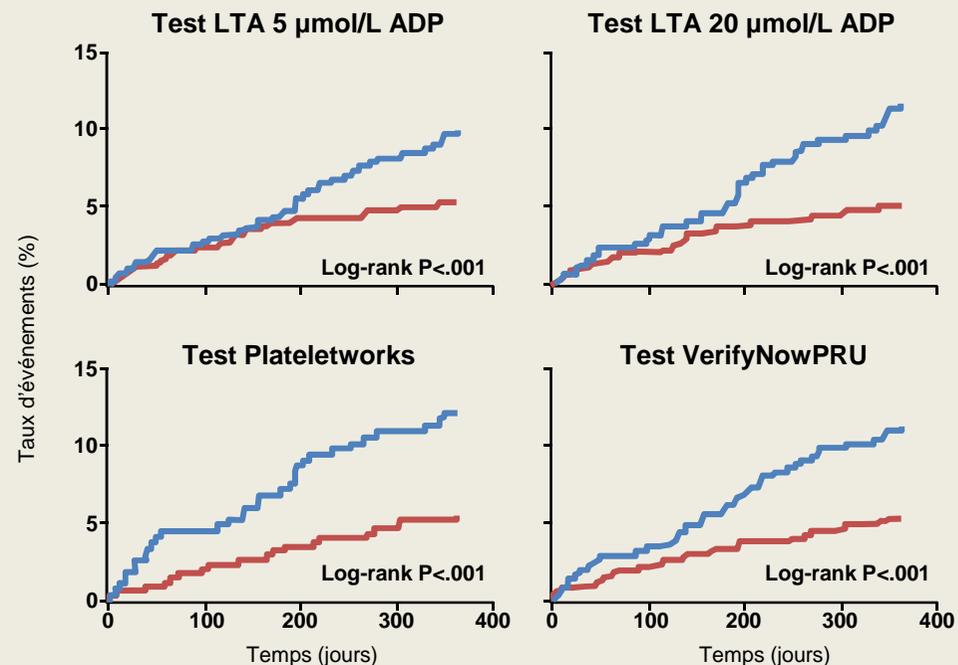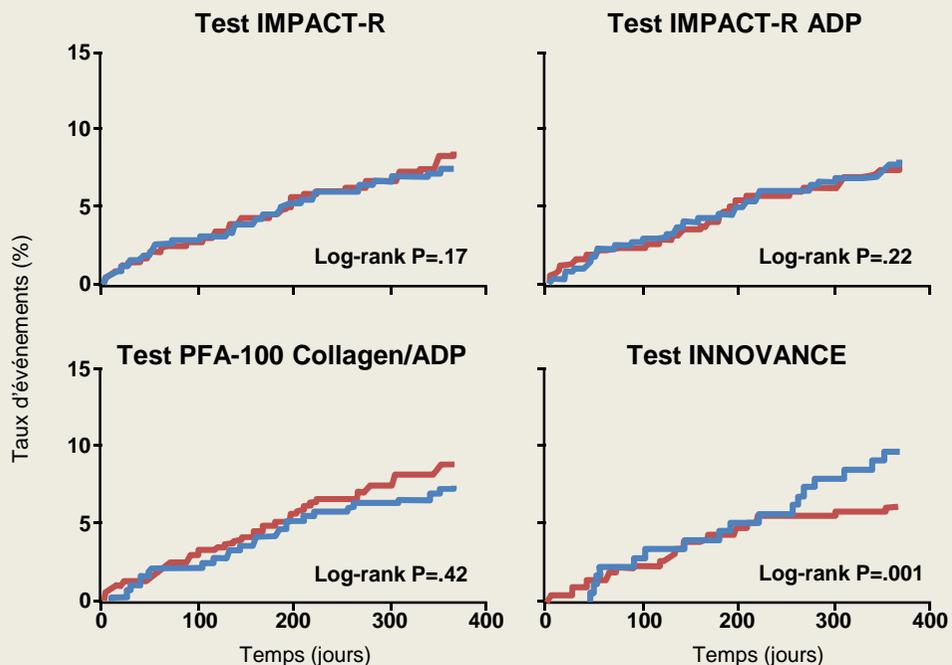
JAMA

Paraoxonase-1 is a major determinant of clopidogrel efficacy

Kaplan-Meier curves for individuals with coronary stent implantation and their pharmacokinetic and pharmacodynamic responses to clopidogrel
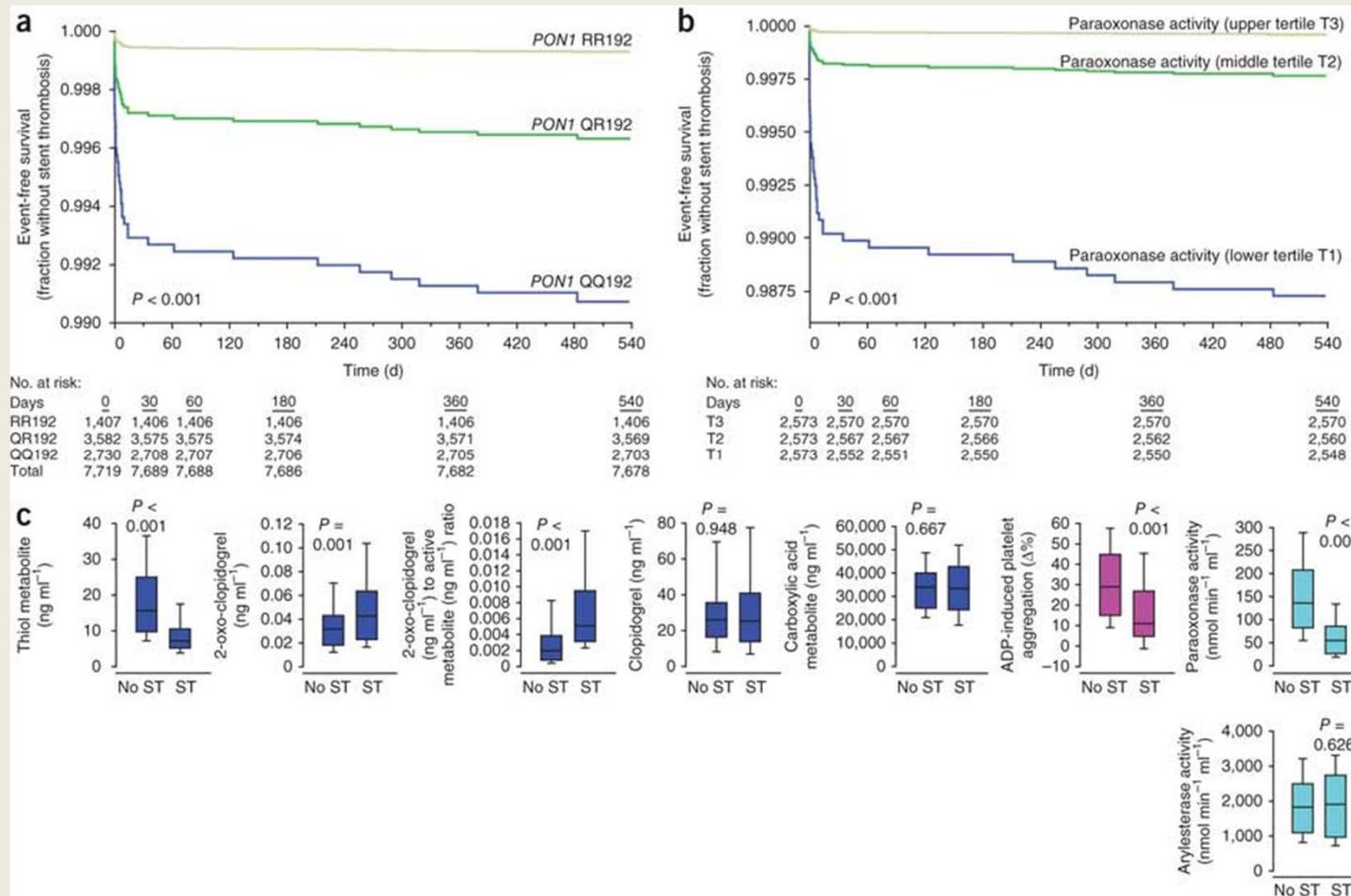
Predictive value of platelet function tests following stenting
Survival free from MI, stent thrombosis and stroke

Breet *et al. JAMA* 2010;303(8):754-62

The problems of bespoke therapy

- When to measure response to clopidogrel ?

- How to select poor responders ?

- Which therapy for poor responders ?

- Where are the clinical proofs of benefit ?

  - GRAVITAS ?

  - Trigger-PCI ?

  - CLOVIS ?

  - ARCTIC ?

CLOVIS-2: using high doses of clopidogrel to overcome genetic resistance
Pharmacokinetic Response According to CYP2C19*2 and Clopidogrel LDs
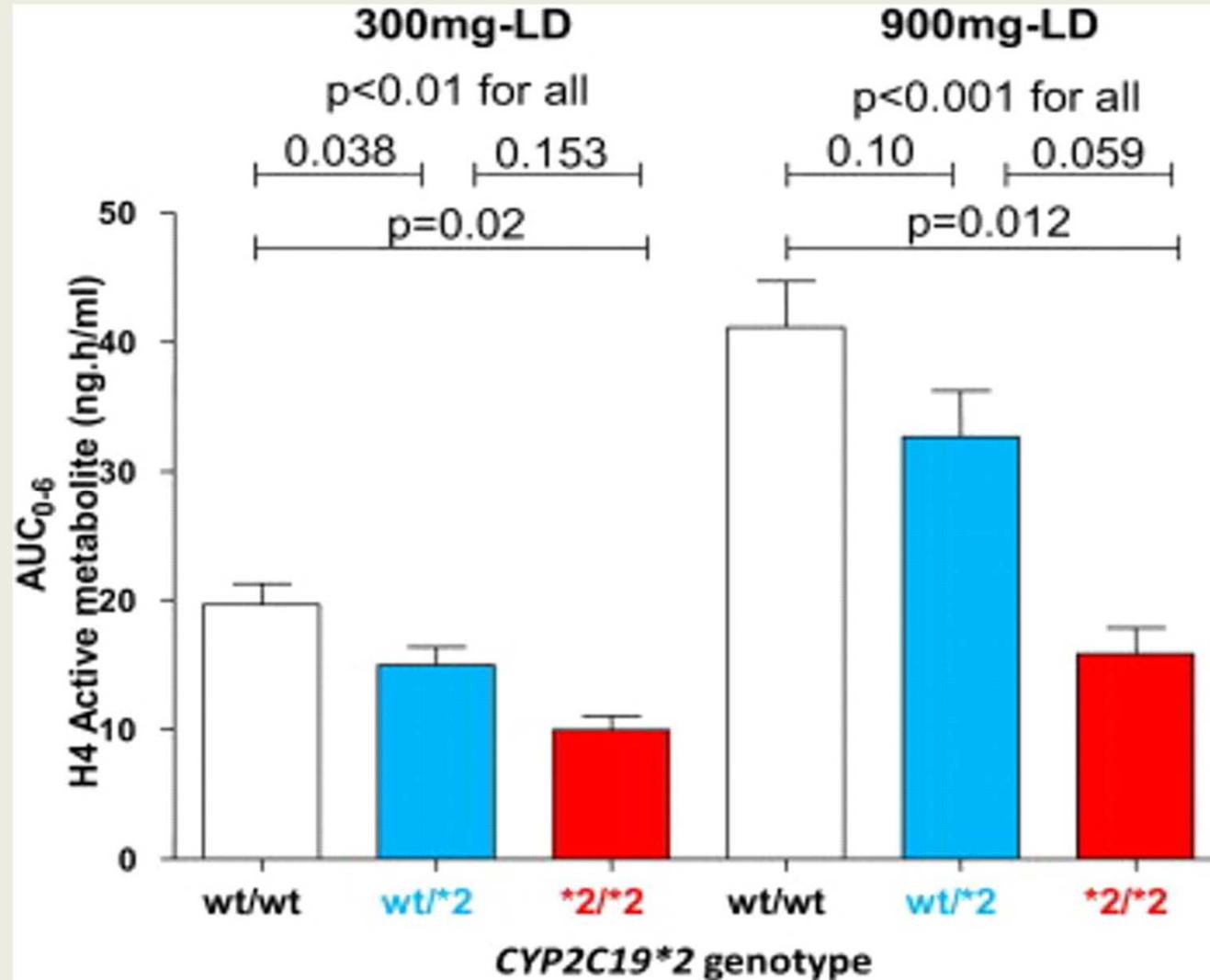
Collet, et al. *J Am Coll Cardiol Intv* 2011;4:392-402

The case for ready-to wear antiplatelet therapy

Ford Model T