Torino

6° Joint meeting with Mayo Clinic

Great Innovation in Cardiology

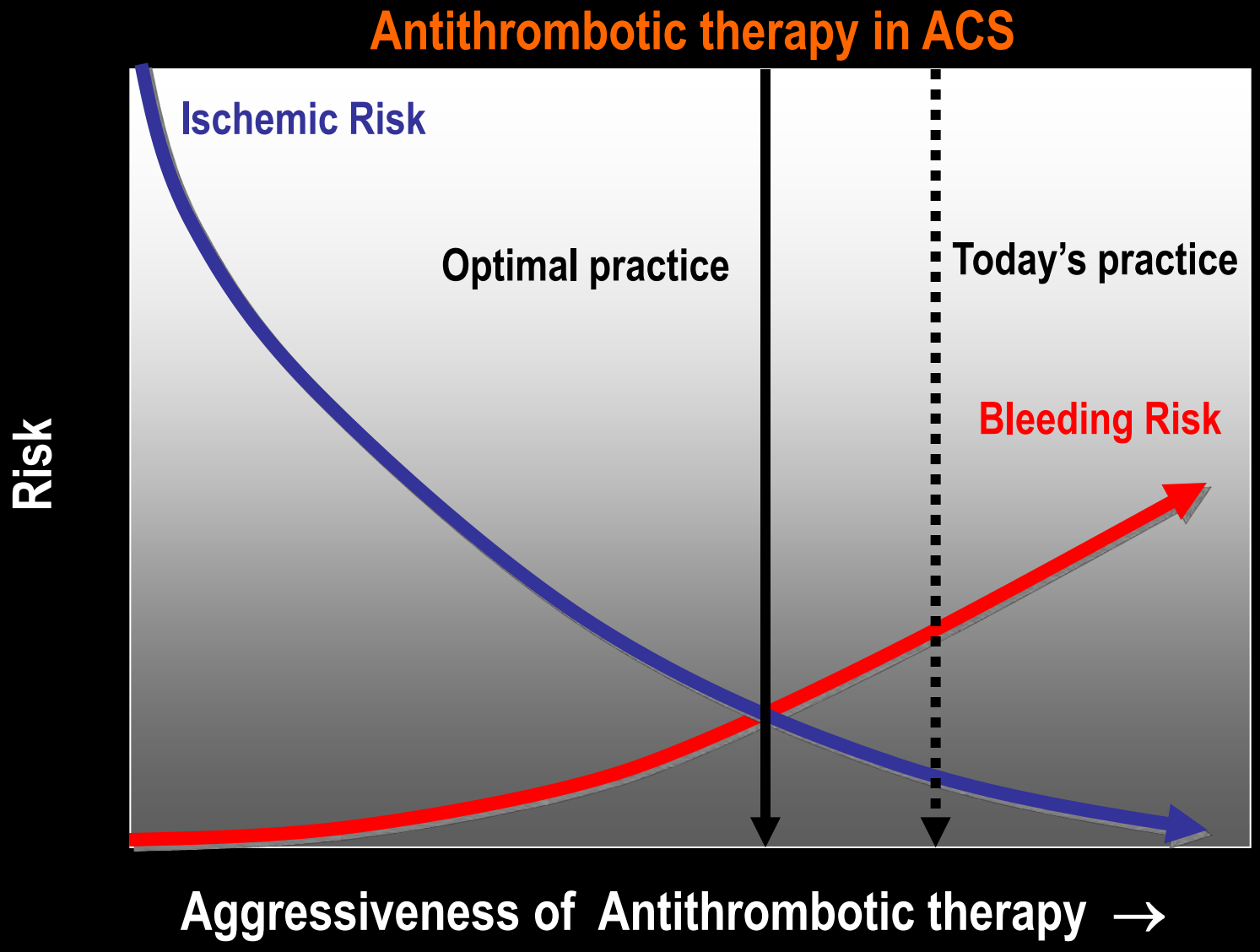
14-15 Ottobre 2010

Optimal antiplatelet and anticoagulant therapy for patients treated in STEMI network

Diego Ardissino

Parma

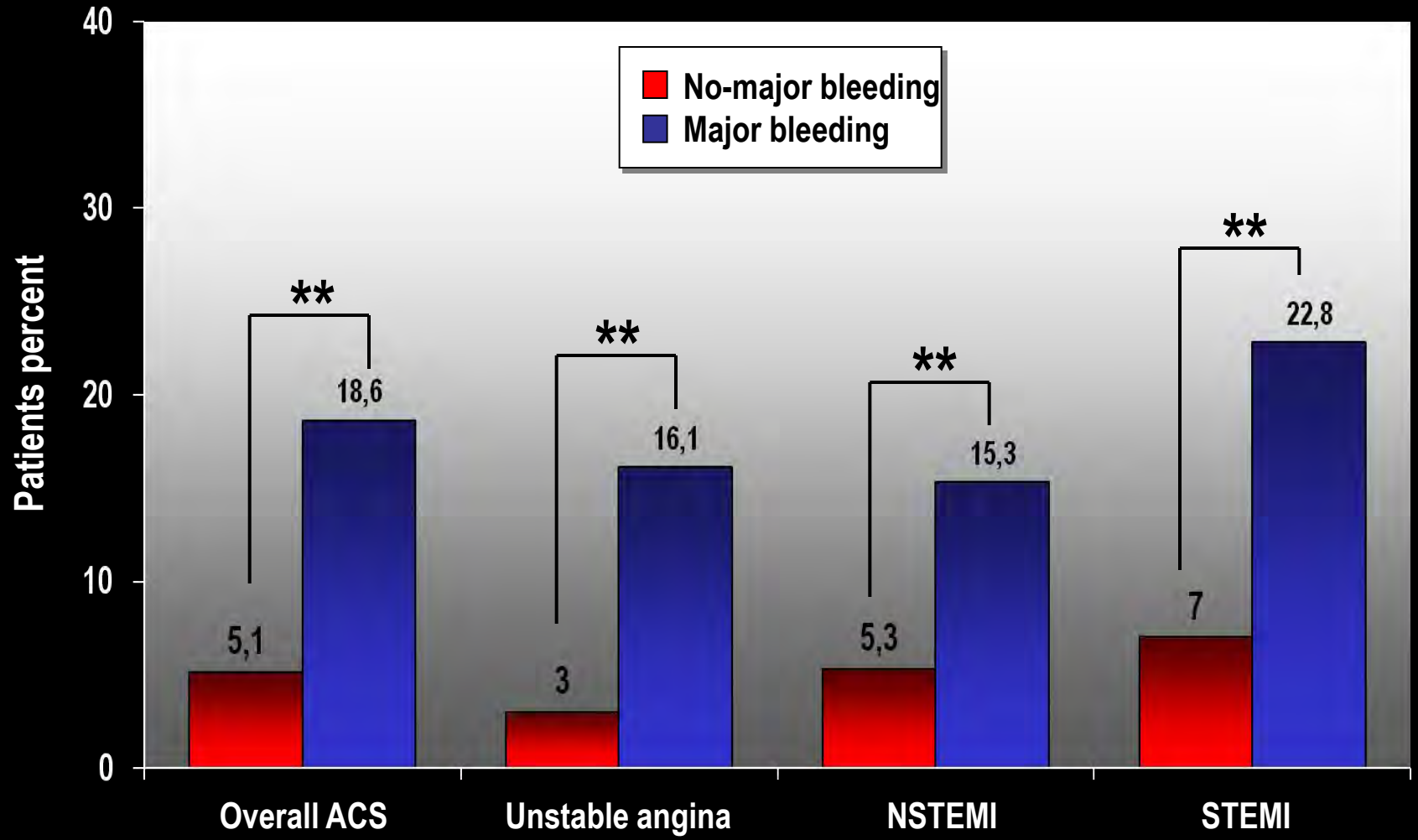
Ischemic vs Bleeding Risk in ACS



Divisione di Cardiologia
Parma

GRACE Registry

In-hospital Death Rates in Patients who Developed or not Major Bleeding



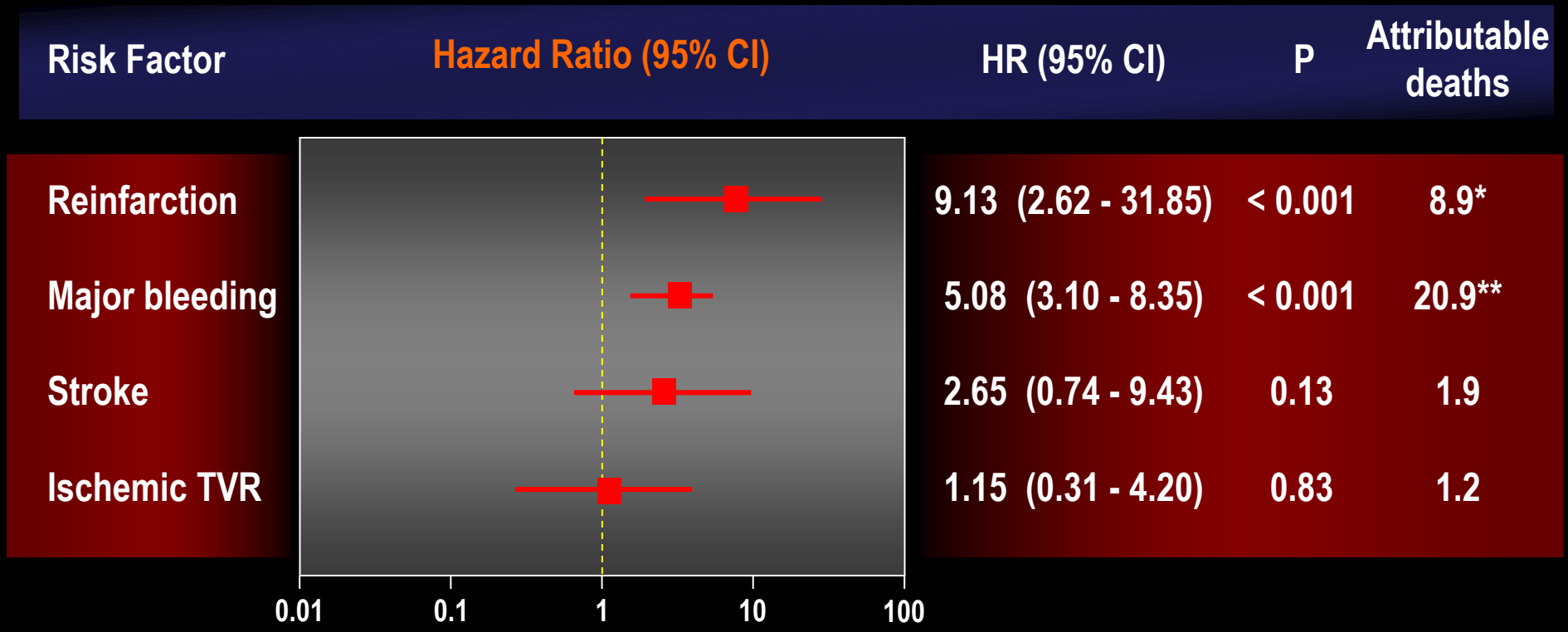
** P < 0.001 for differences in unadjusted death rates

Moscucci M, et al. EHJ 2003; 24: 1815-1823

Divisione di Cardiologia Parma

Time-update Covariate Adjusted Cox Model Relating Single 30-day Events to 30-day Mortality

Complete model with MACE components and major bleeding



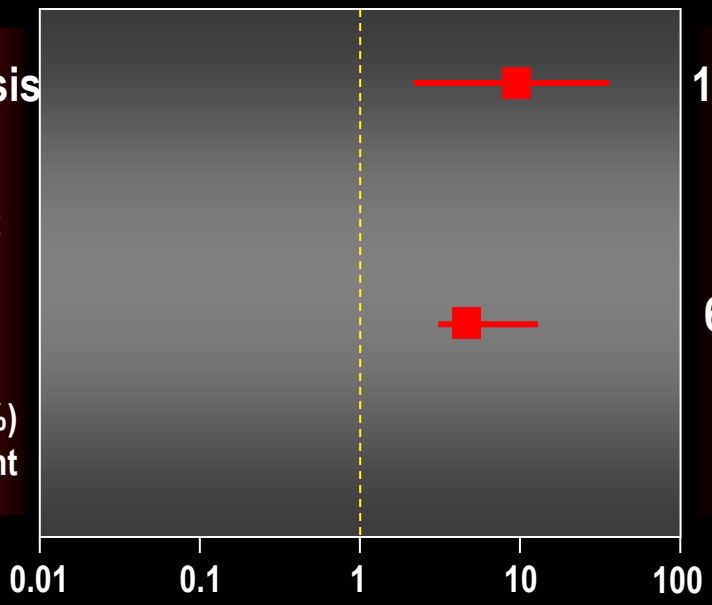
C = statistic = 0.87 Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR-1) / adj. HR

* 9.6% of 93 total deaths ** 22.5% of 93 total deaths

Divisione di Cardiologia Parma

Time-update Covariate Adjusted Cox Model Relating Single 30-day Events to 30-day Mortality

Complete model in 3.124 pts with succesfully implanted stents

Risk Factor	Hazard Ratio (95% CI)	HR (95% CI)	P	Attributable deaths
Stent thrombosis (definite) Incidence 57 (1.8%) 5 deaths with event		10.62 (3.92 - 28.48)	< 0.001	4.5* (3.7 - 4.8)
Major bleeding (Non CABG) Incidence 195 (6.2%) 18 deaths with event		6.22 (3.33 - 11.60)	< 0.001	15.1** (12.6 - 16.4)

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

* 8.3% of 54 total deaths ** 28.0% of 54 total deaths

Divisione di Cardiologia Parma

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

ANTITHROMBOTIC THERAPY IN PRIMARY PCI

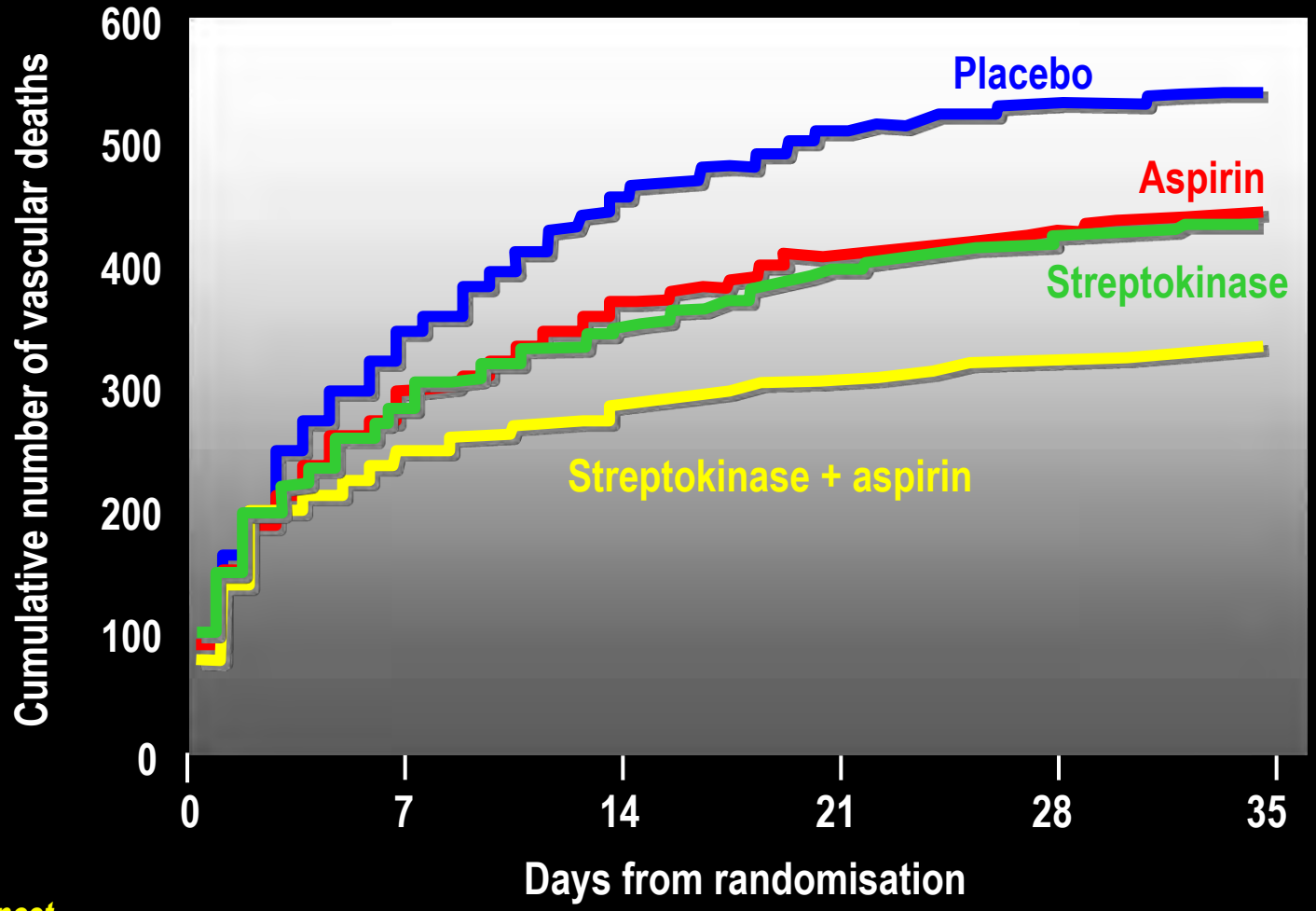
Aspirin should be given to all patients with a STEMI as soon as possible after the diagnosis is deemed probable. It should be started at a dose of 150-325 mg in a chewable form (no enteric-coated) and an alternative approach is i.v. administration at a dose of 250-500 mg.

CLASS I

EVIDENCE B

Aspirin in Acute Myocardial Infarction

Cumulative vascular mortality in days 0 - 35



The Lancet

Divisione di Cardiologia
Parma

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

ANTITHROMBOTIC THERAPY IN PRIMARY PCI

Clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI at a loading dose of at least 300 mg, but a 600 mg loading dose achieves a more rapid and stronger inhibition of platelet aggregation.

CLASS I

EVIDENCE C

ESC/ EACTS Guidelines on myocardial revascularization 2010

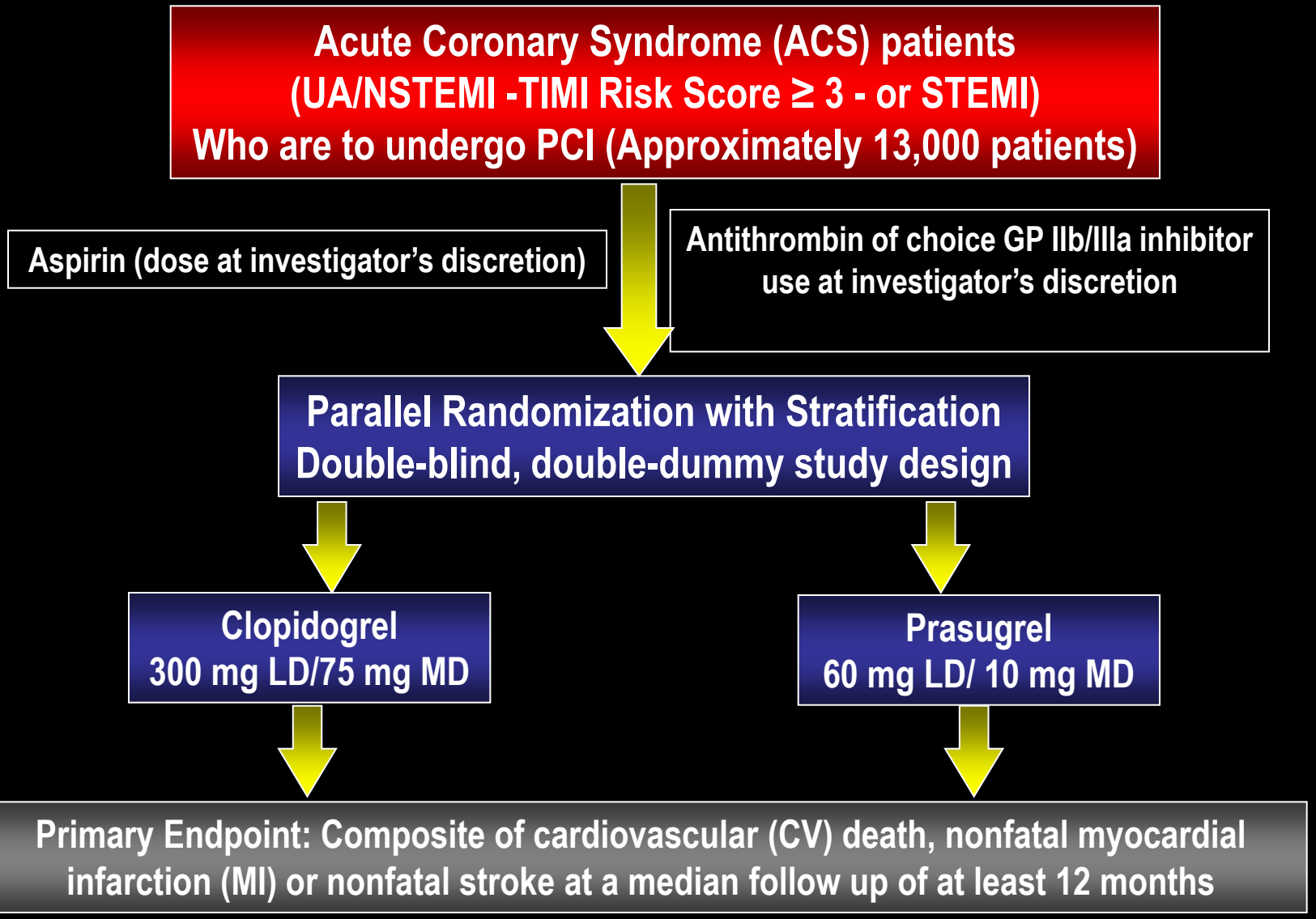
Antithrombotic treatment options in myocardial revascularization

STEMI ANTITHROMBOTIC THERAPY

Dual antiplatelet therapy consists of aspirin 150-300mg per os or 250-500 mg bolus iv followed by 75-100 mg daily, and prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily, depending on drug availability.

Clopidogrel 600 mg loading dose, followed by 75 mg daily should be used primarily if the more effective ADP receptor blockers are controindicated or unavailable.

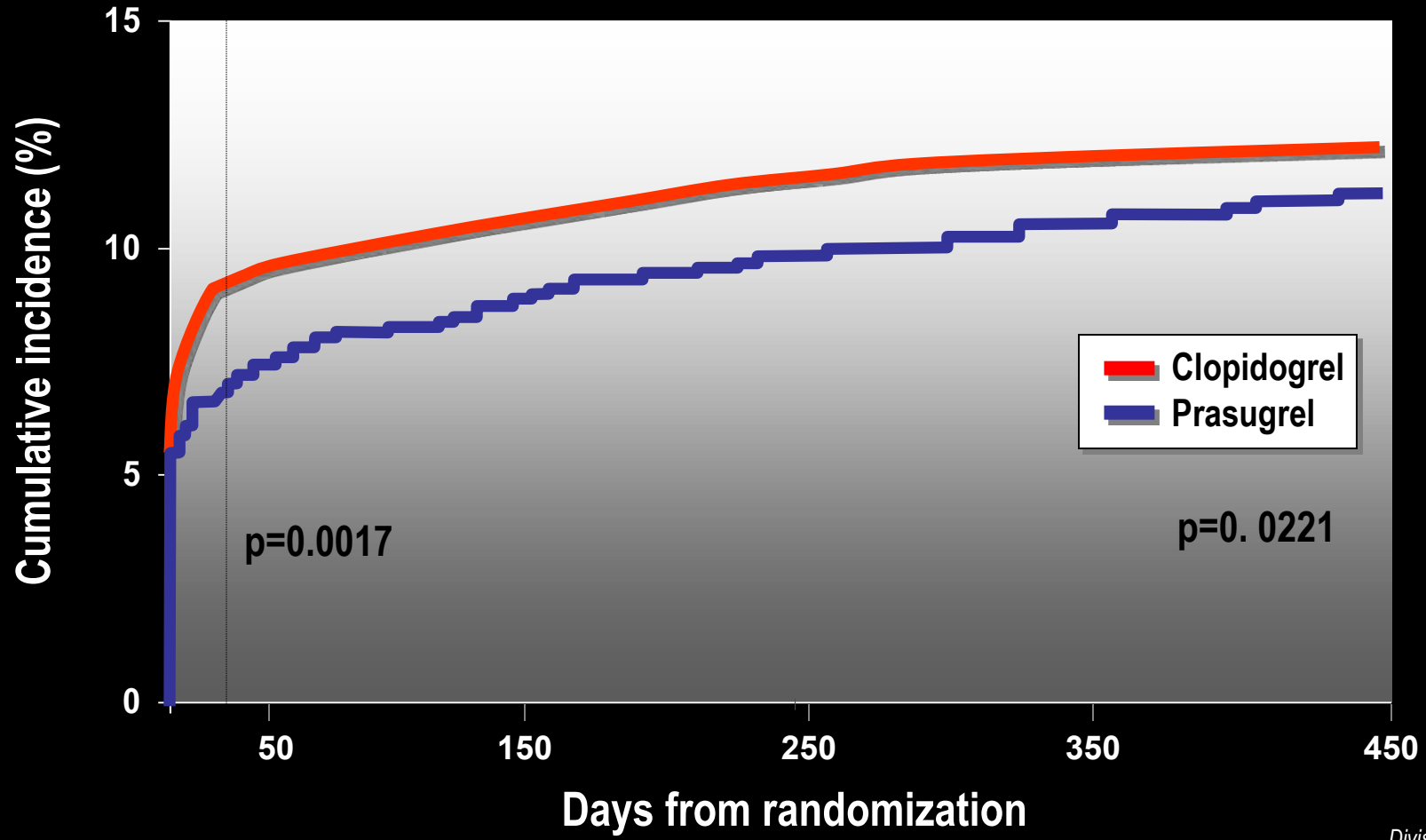
Triton - TIMI 38
Study Protocol



Prasugrel vs clopidogrel in primary PCI

TRITON TIMI-38 trial

Primary endpoint: Cardiovascular death, non-fatal MI, non-fatal stroke



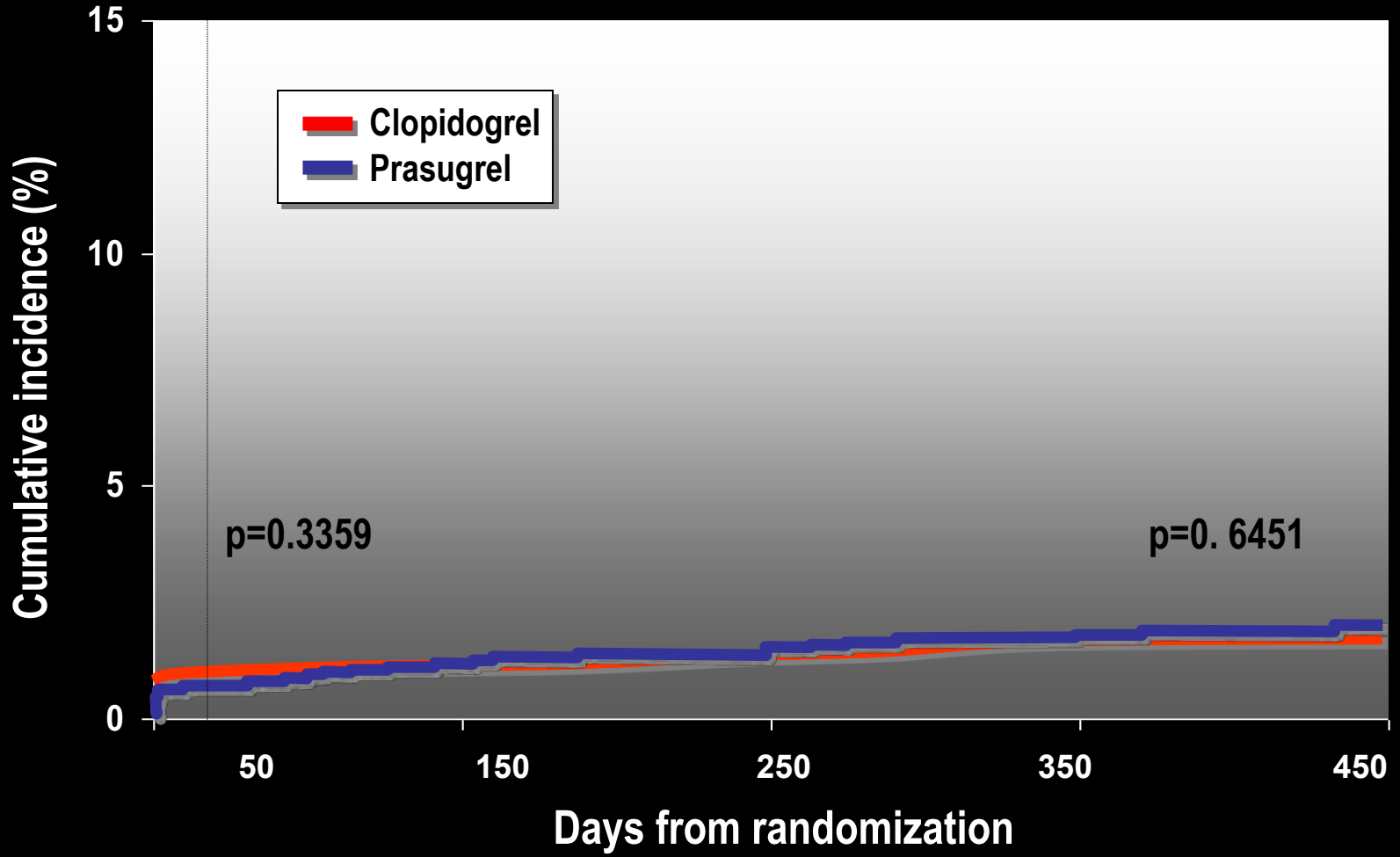
Montalescot G et al, Lancet 2009; 373: 723-31

Divisione di Cardiologia
Parma

Prasugrel vs clopidogrel in primary PCI

TRITON TIMI-38 trial

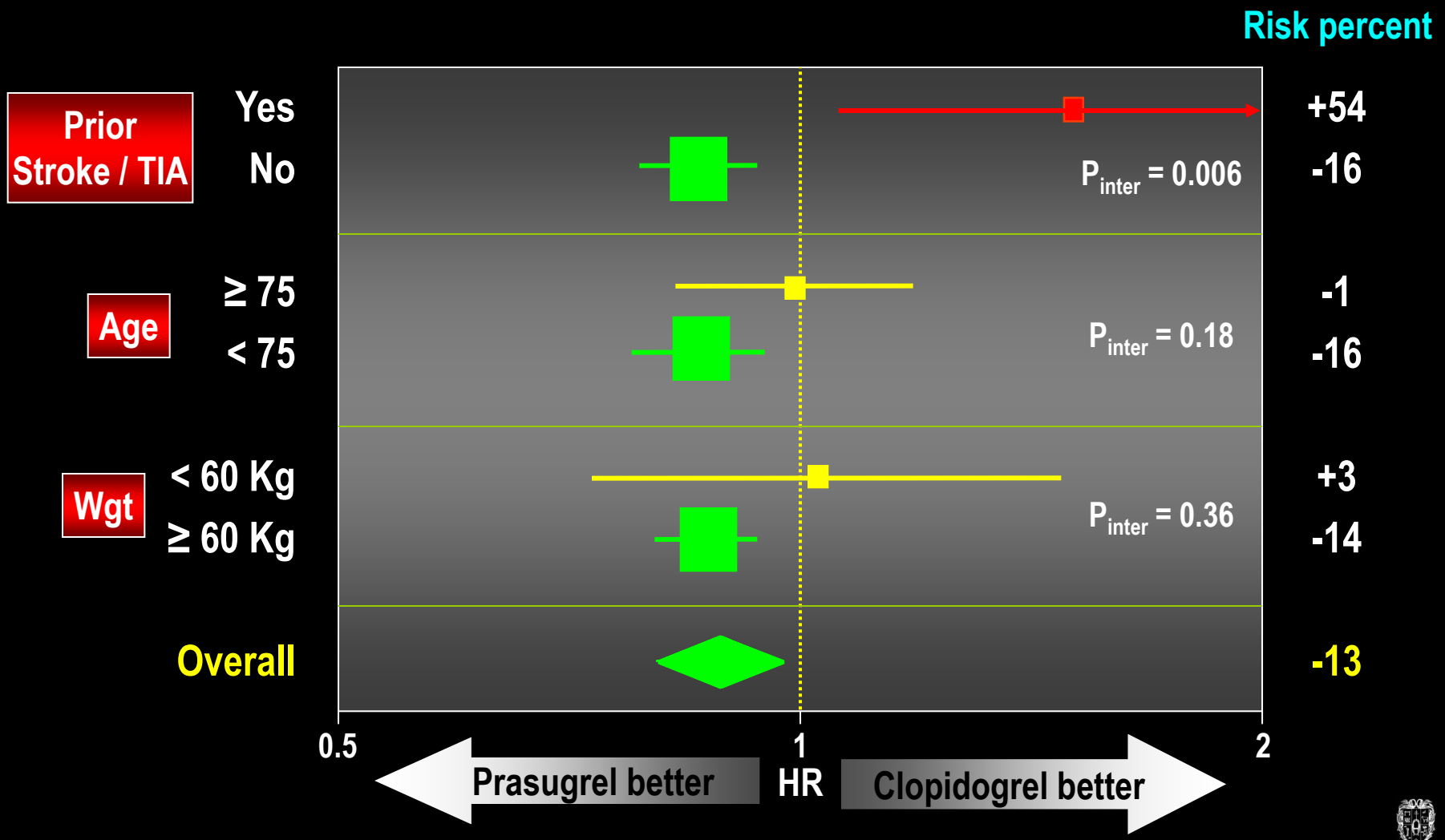
TIMI major bleeding



Montalescot G et al, Lancet 2009; 373: 723-31

Net Clinical Benefit

Bleeding Risk Subgroups Post-hoc Analysis



Divisione di Cardiologia Parma

ESC/ EACTS Guidelines on myocardial revascularization 2010

Antithrombotic treatment options in myocardial revascularization

Prasugrel is superior to clopidogrel in reducing combined ischaemic endpoints and stent thrombosis in STEMI patients without increasing the risk of severe bleeding.

CLASS I

EVIDENCE B

ESC/ EACTS Guidelines on myocardial revascularization 2010

Antithrombotic treatment options in myocardial revascularization

…A predefinite subgroup analysis has demonstrated that STEMI patients referred to PCI significantly benefit from ticagrelor vs clopidogrel, with similar bleeding rates.

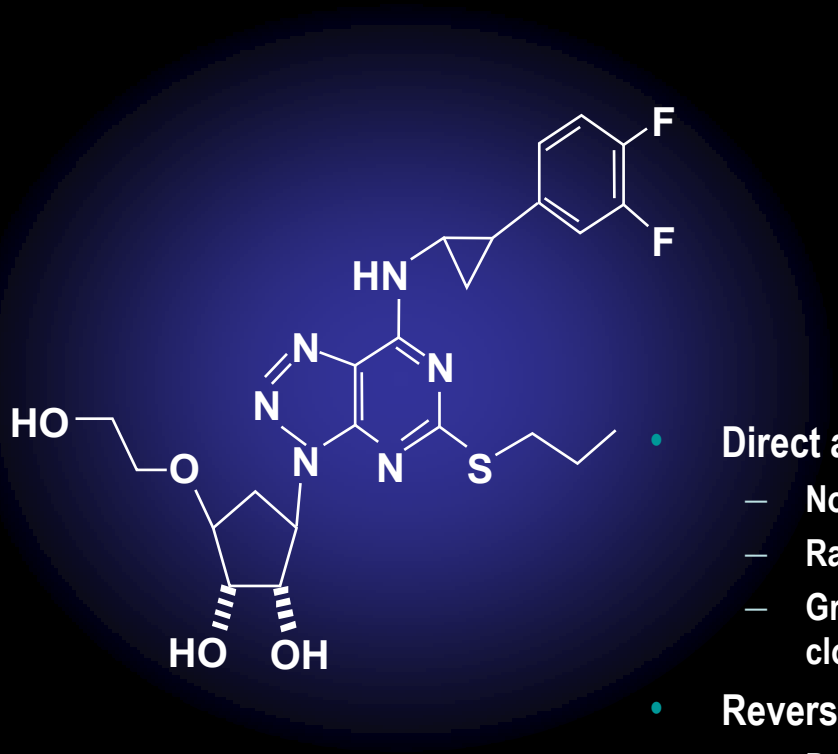
CLASS I

EVIDENCE B

Ticagrelor (AZD 6140)

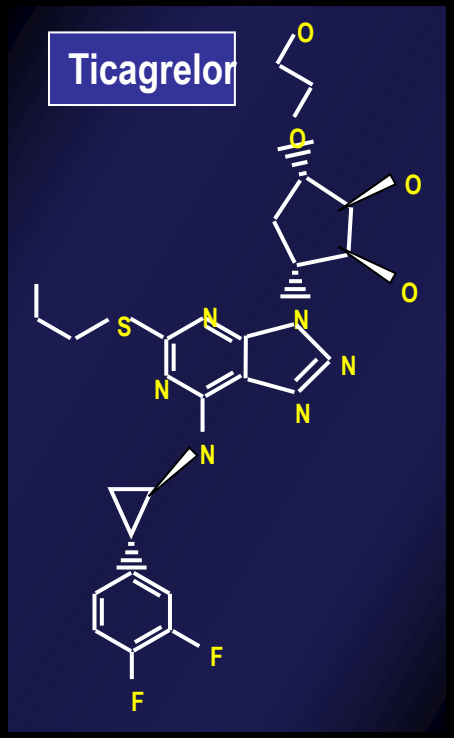
A new and selective oral reversible platelet ADP P2Y12 receptor antagonist

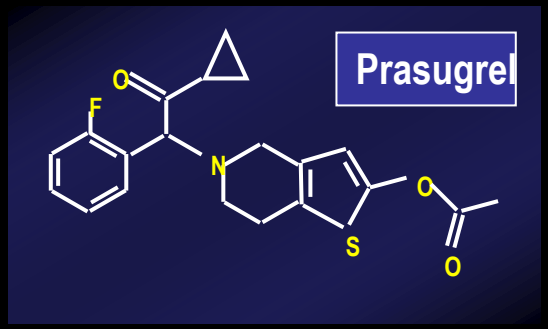
Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine

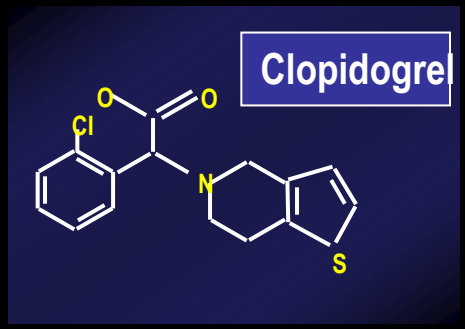


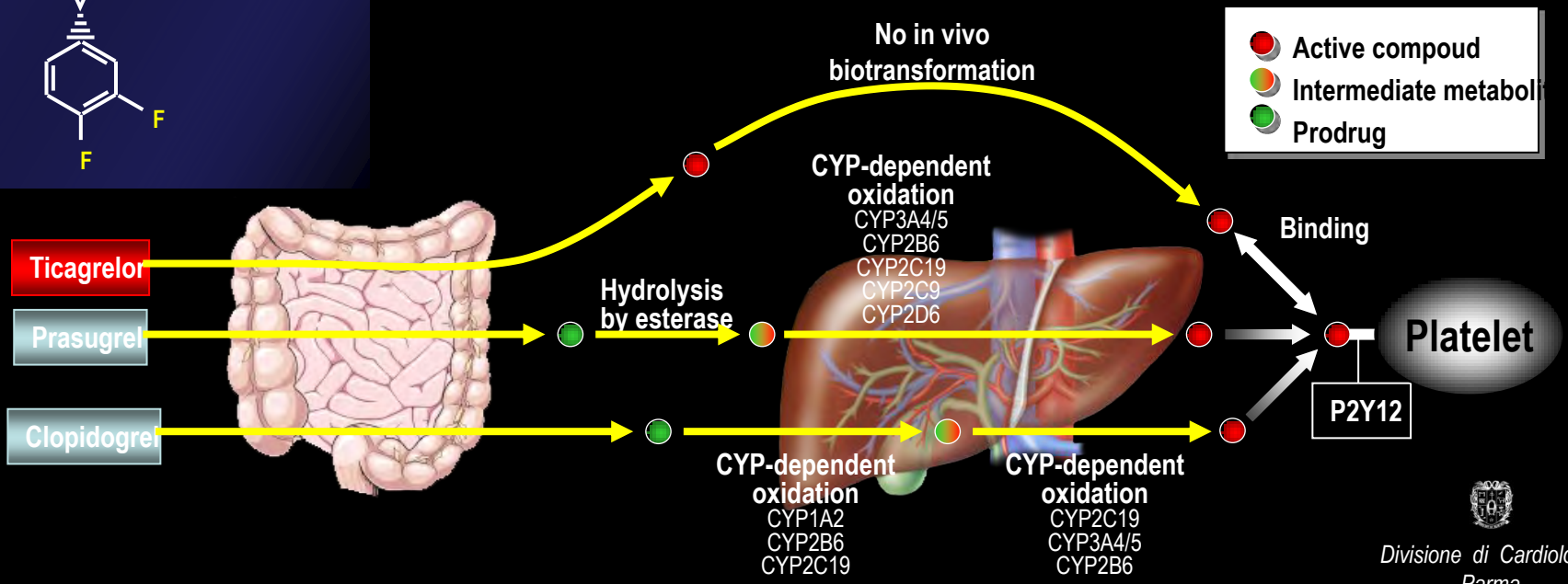
- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater and more consistent inhibition of platelet aggregation versus clopidogrel
- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

Ticagrelor metabolism









PLATO *Study design*

UA / NSTEMI (moderate to high risk)
STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or -naïve; randomised within 24 h of index event

(*n* = 18,000)
Event driven

Clopidogrel
300 mg loading dose,
then 75 mg od maintenance;
(additional 300 mg allowed pre-PCI)

AZD 6140
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

12-month maximum exposure
(Minimum 6-month exposure of last included patient)

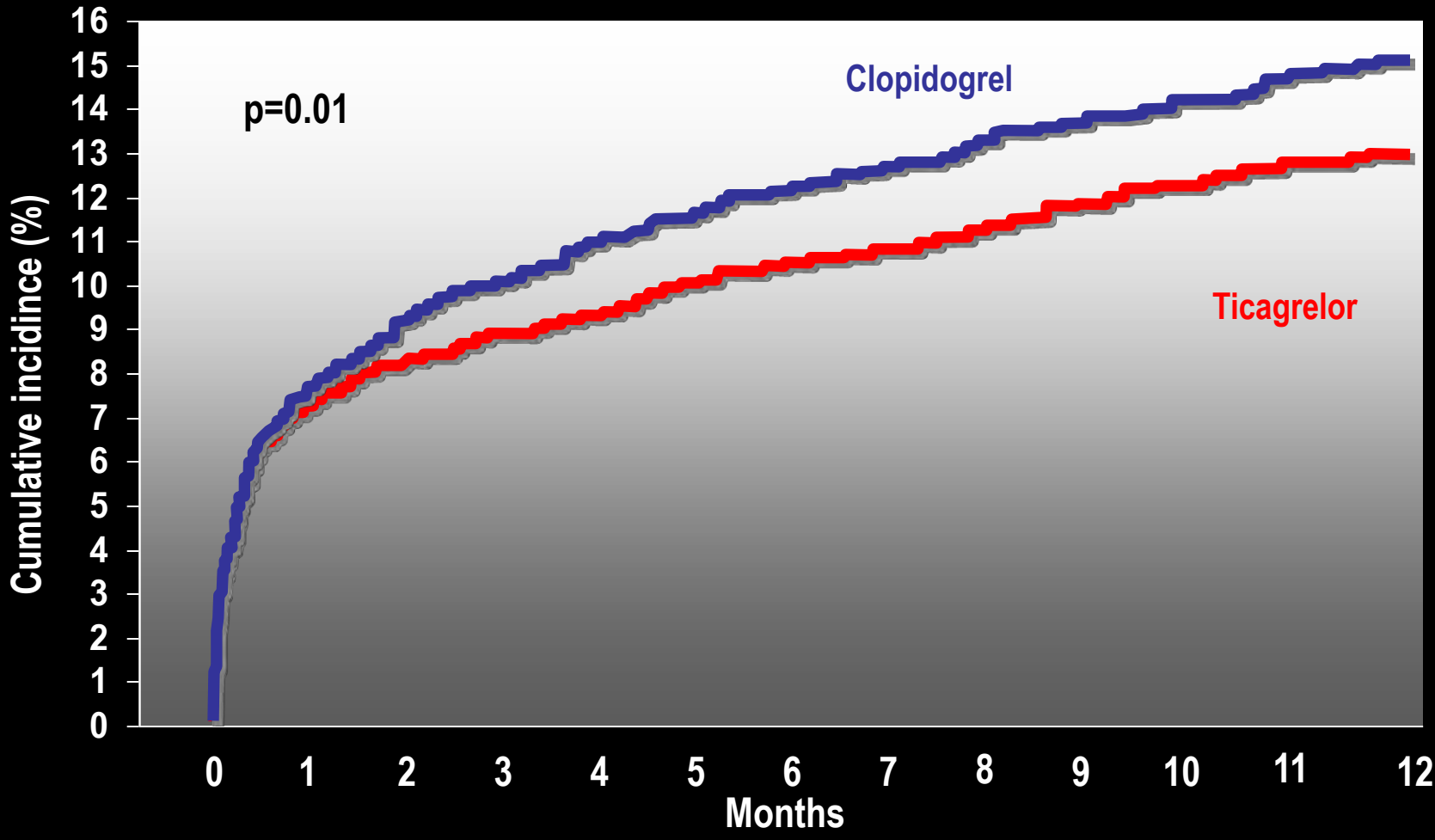
Primary endpoint:
- **CVD / MI / stroke**

Secondary endpoint:
- **CVD / MI / stroke in patients with intent for inv. management**
- **CVD / MI / stroke / recurrent ischaemia / TIA / other arterial thrombotic events**

Recruitment October 2006 – July 2008

bid, twice daily; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; od, once daily; TIA, transient ischaemic attack.

Ticagrelor vs clopidogrel in STEMI treated with primary PCI
All cause death



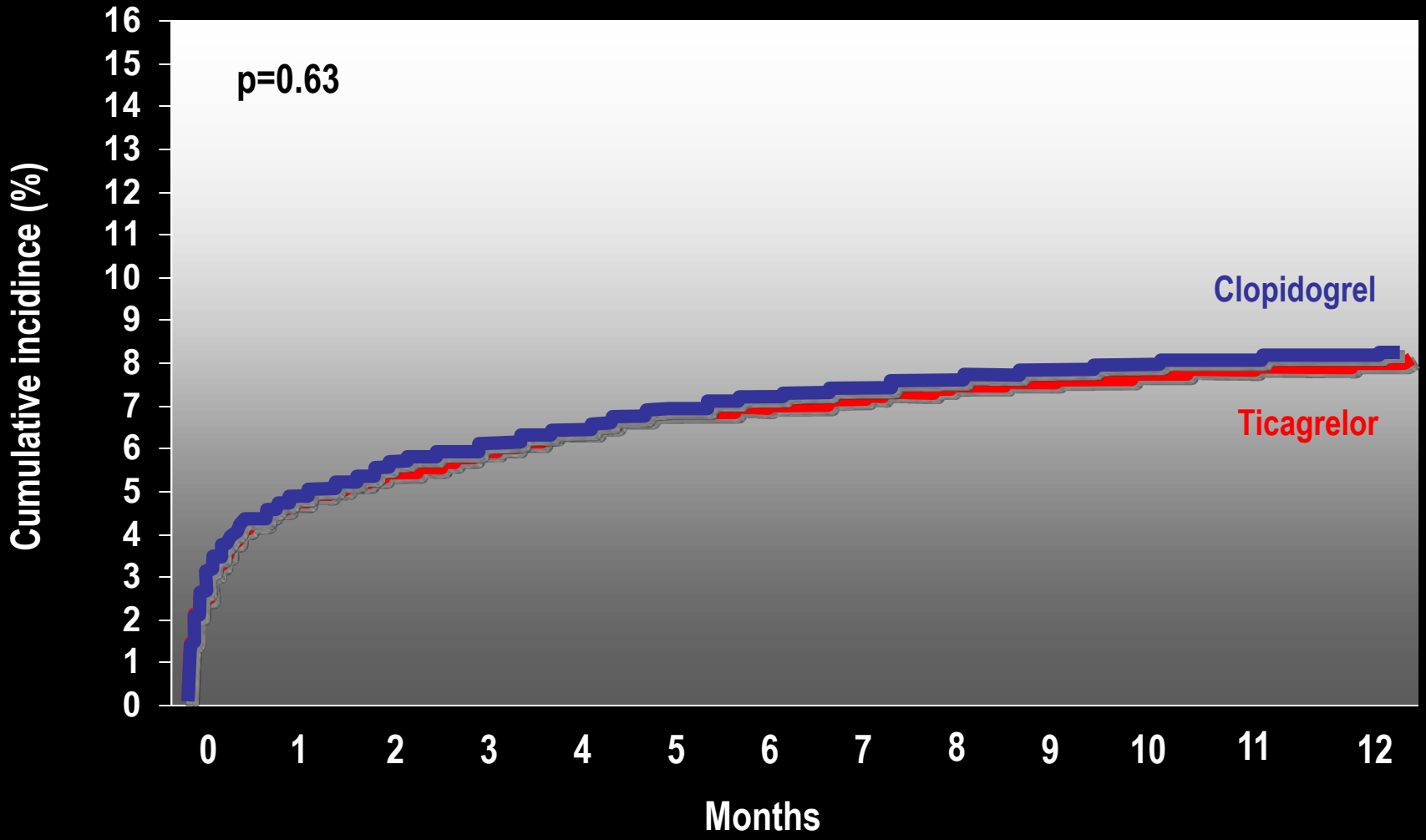
T	4201	3793	3712	3598	2889	2183	1794
C	4229	3908	3688	3576	2878	2221	1777

Steg PG et al, Circulation 2010,

Divisione di Cardiologia
Parma

Ticagrelor vs clopidogrel in STEMI treated with primary PCI

Major bleeding according to PLATO definition



T	4165	3431	3254	3137	2440	1786	1640
C	4181	3430	3297	3159	2441	1804	1635

Steg PG et al, Circulation 2010,

Divisione di Cardiologia Parma

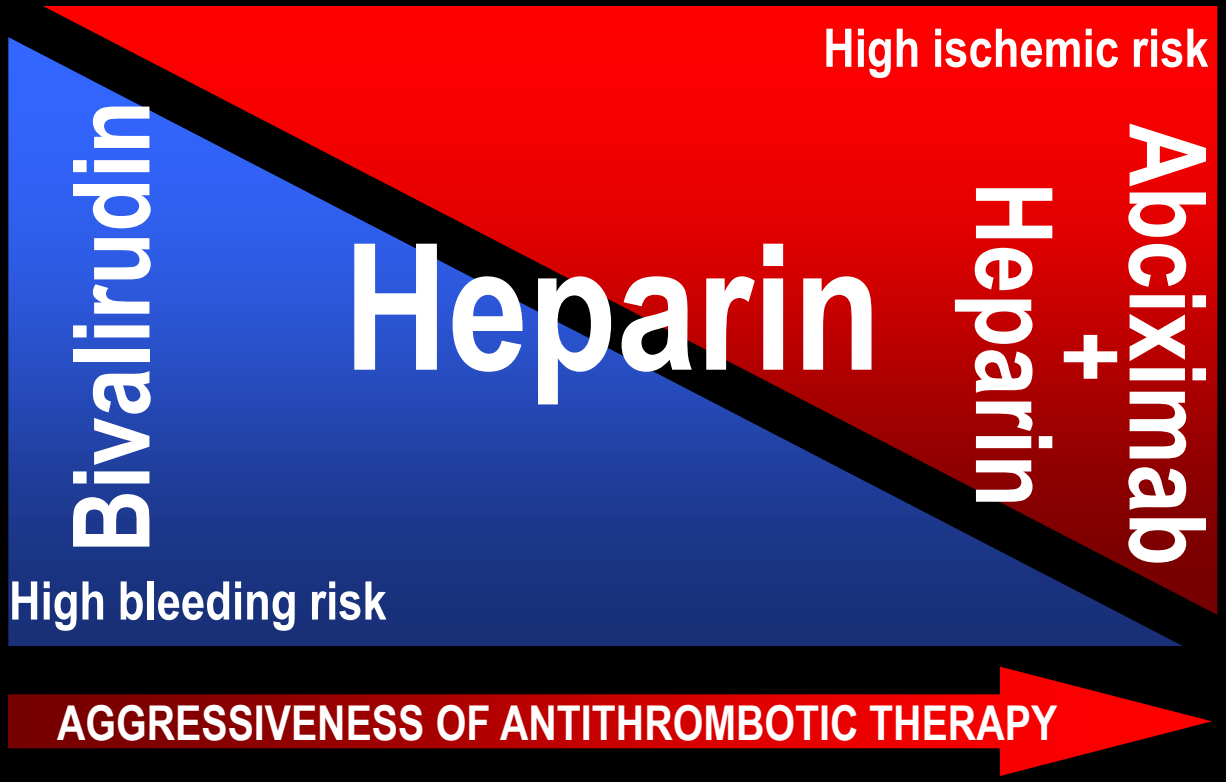
PLATO trial

Major efficacy end-point

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

ANTITHROMBOTIC THERAPY IN STEMI

Abciximab vs heparin vs bivalirudin



Divisione di Cardiologia
Parma

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

ANTITHROMBOTIC THERAPY IN PRIMARY PCI

Unfractionated heparin is standard anticoagulant therapy during PCI.

- i.v. bolus: 100 U/Kg (60 U/Kg if GP IIb/IIIa antagonists are used)
- target ACT during procedure: 250-350 seconds (200-250 seconds if GP IIb/IIIa antagonists are used)

CLASS I

EVIDENCE C

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

ANTITHROMBOTIC THERAPY IN PRIMARY PCI

Abiciximab can be administered in primary PCI.

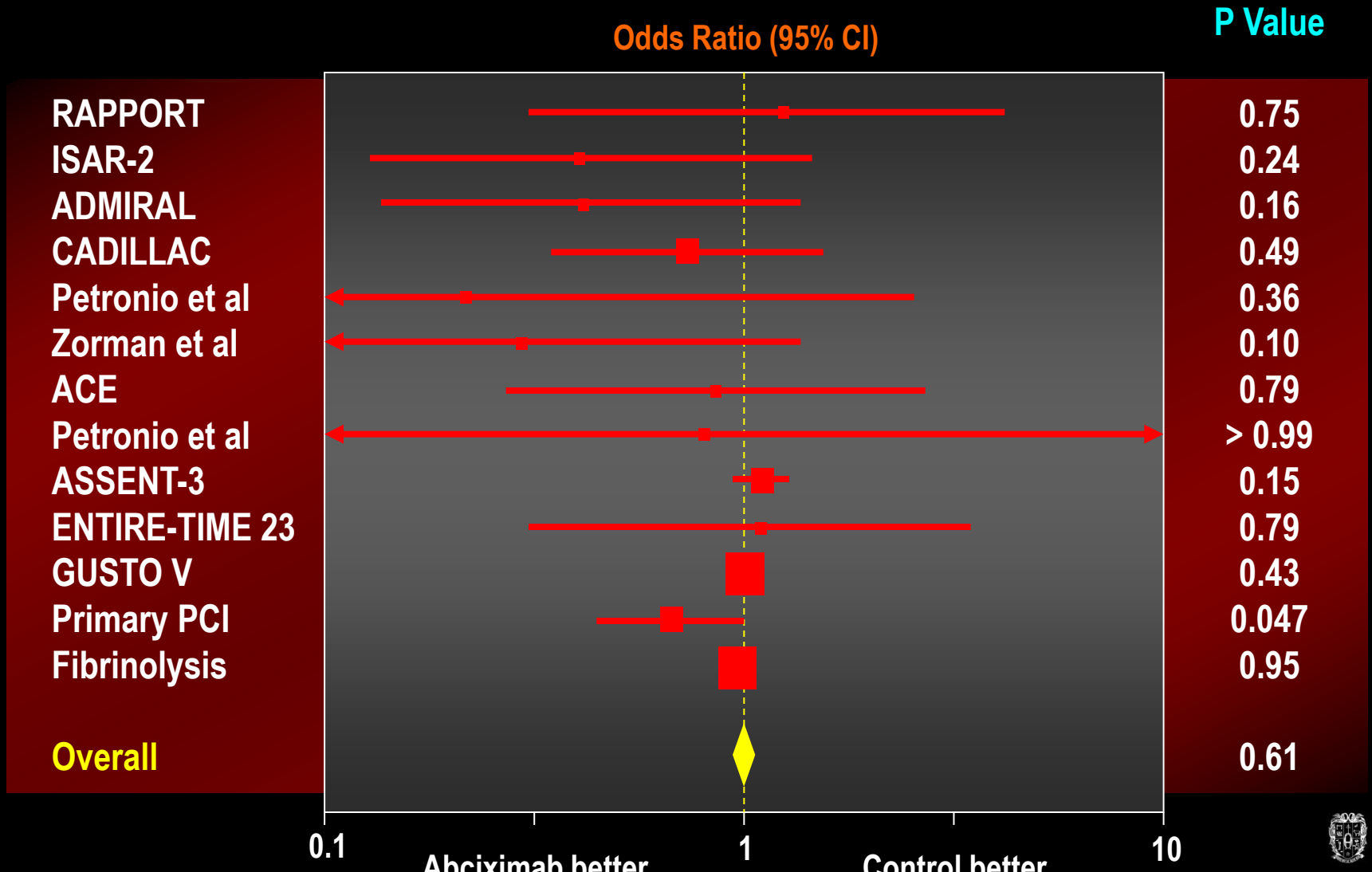
- i.v. bolus: 0.25 mg/kg
- Infusion: 0.125 mcg/Kg/min (maximum 10 mcg/min for 12 hours)

CLASS IIa

EVIDENCE A

Abciximab as Adjunctive Therapy to Reperfusion in STEMI

30-day mortality

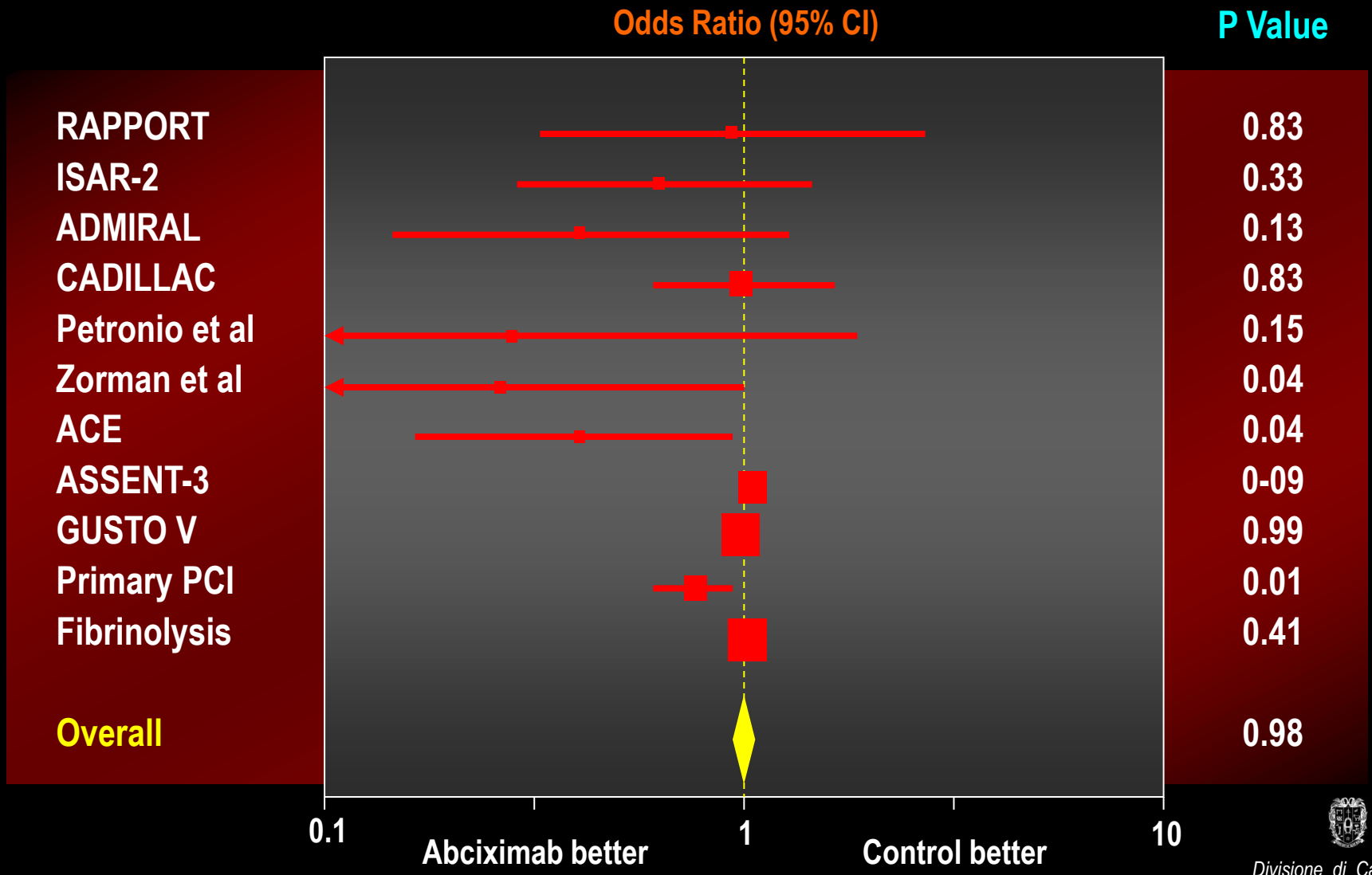


De Luca G. et al, JAMA 2005; 293: 1759-65

Divisione di Cardiologia Parma

Abciximab as Adjunctive Therapy to Reperfusion in STEMI

Long-term (6 and 12 month) mortality



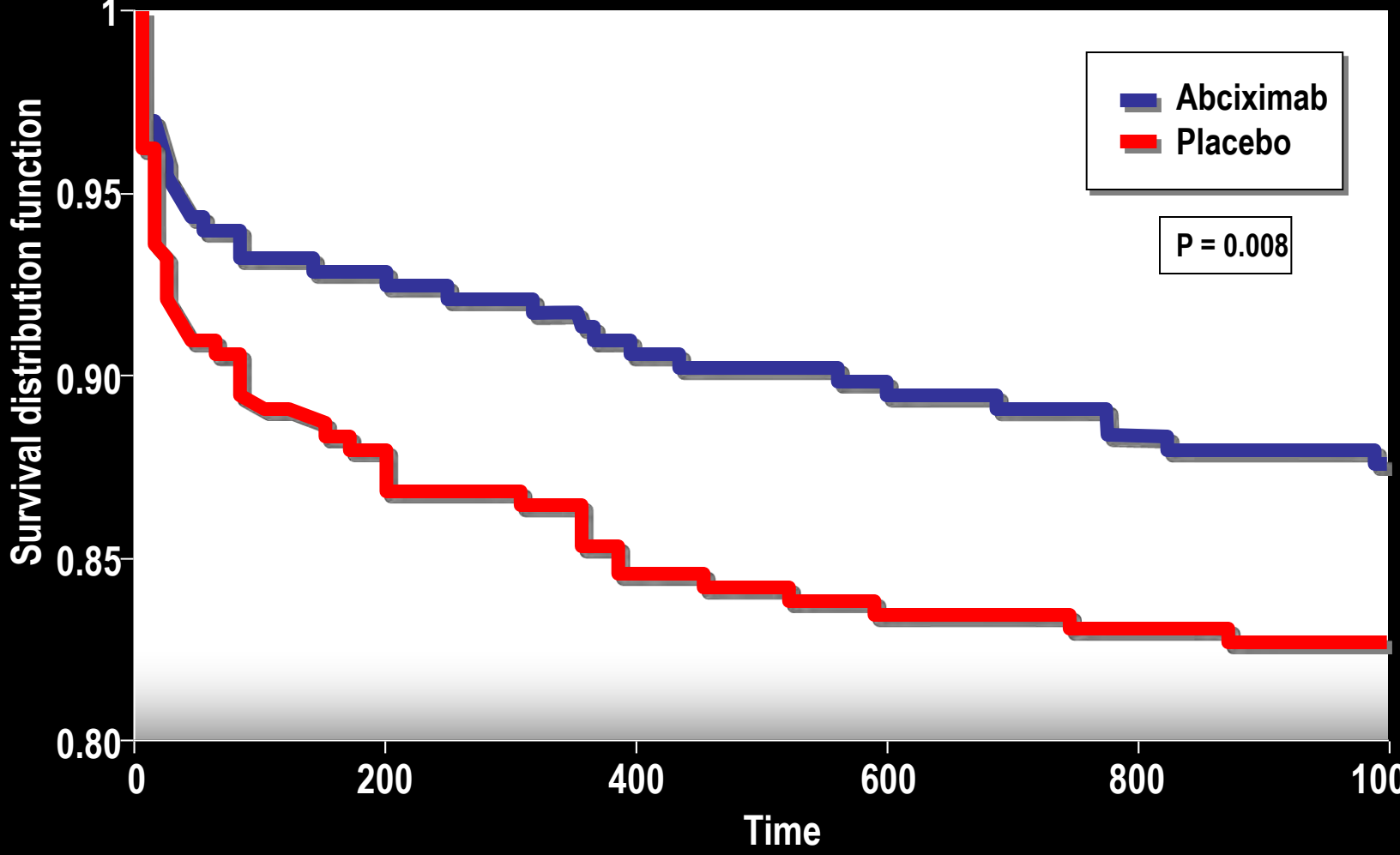
De Luca G. et al, Jama 2005; 293: 1759-65

Divisione di Cardiologia Parma

Abciximab vs Placebo in Primary PCI

Death or re-infarction over 3 years of follow-up

Trials: ACE, ADMIRAL and ISAR

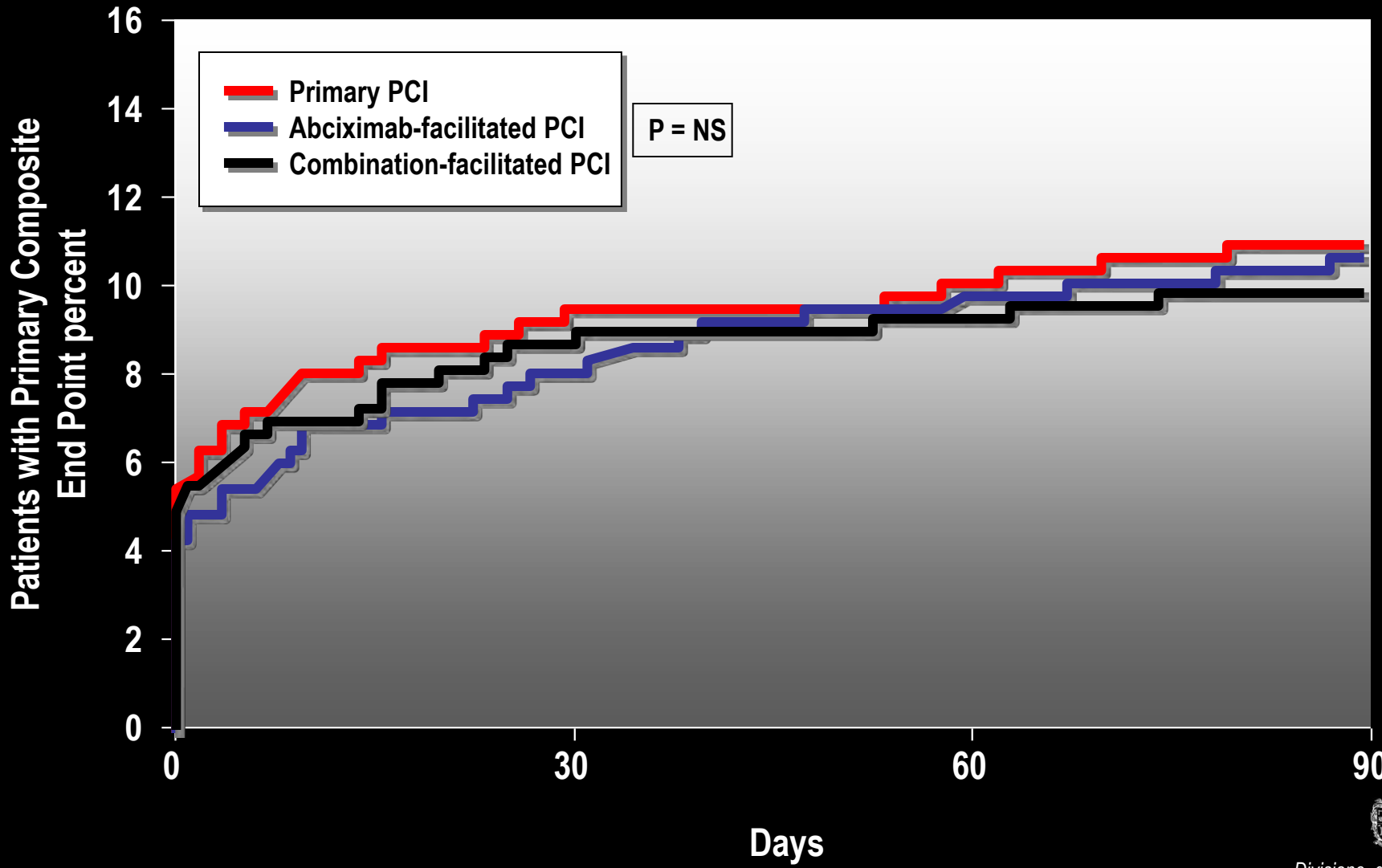


Montalescot G. et al, Eur Heart J 2007; 28: 443-449

Divisione di Cardiologia Parma

Facilitated PCI in Patients with STEMI

The FINESSE trial



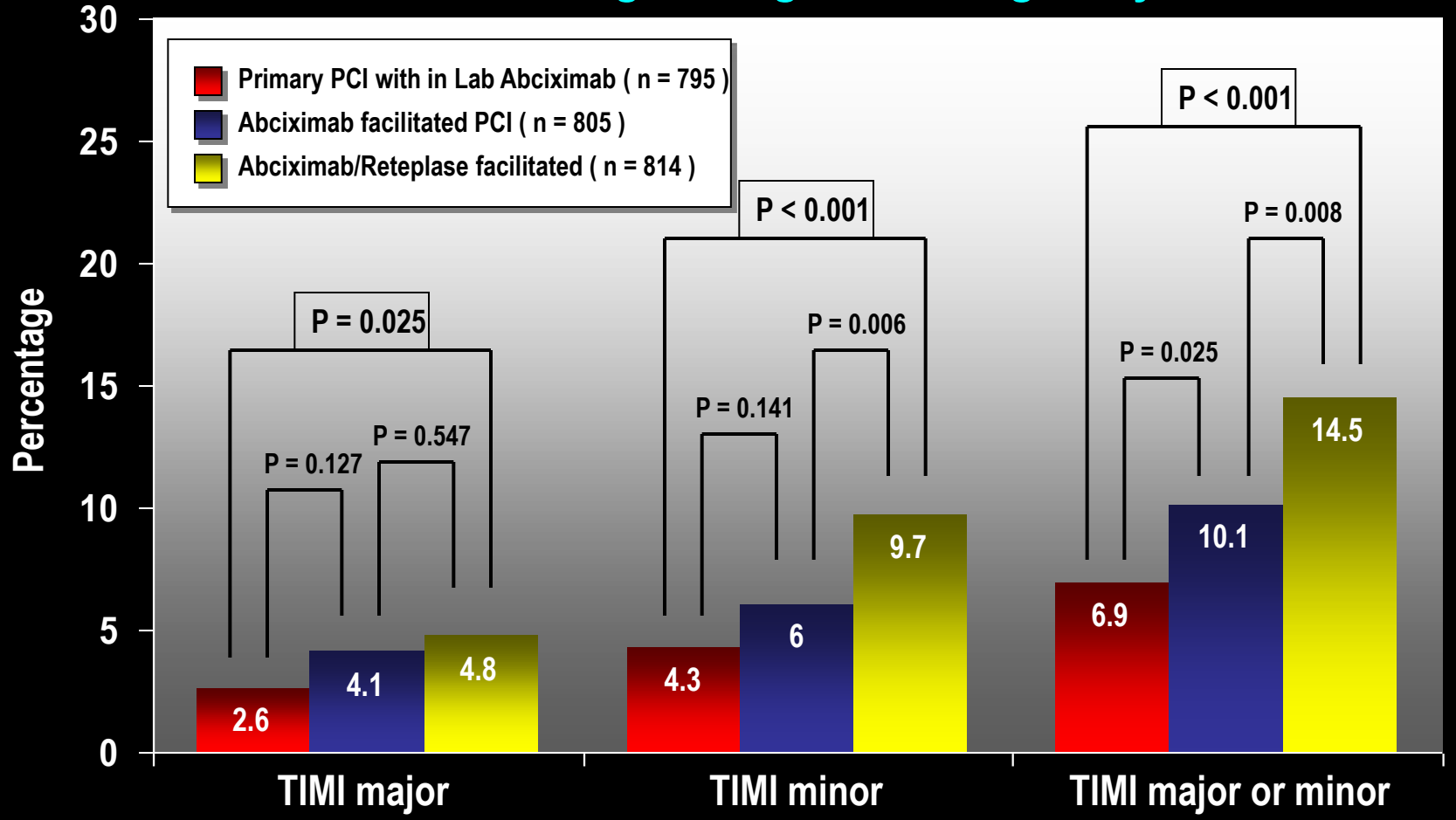
Ellis SG. et al, N Engl J Med 2008; 358: 2205-17

Divisione di Cardiologia Parma

Facilitated PCI in Patients with STEMI

The FINESSE trial

TIMI Bleeding through Discharge/Day 7

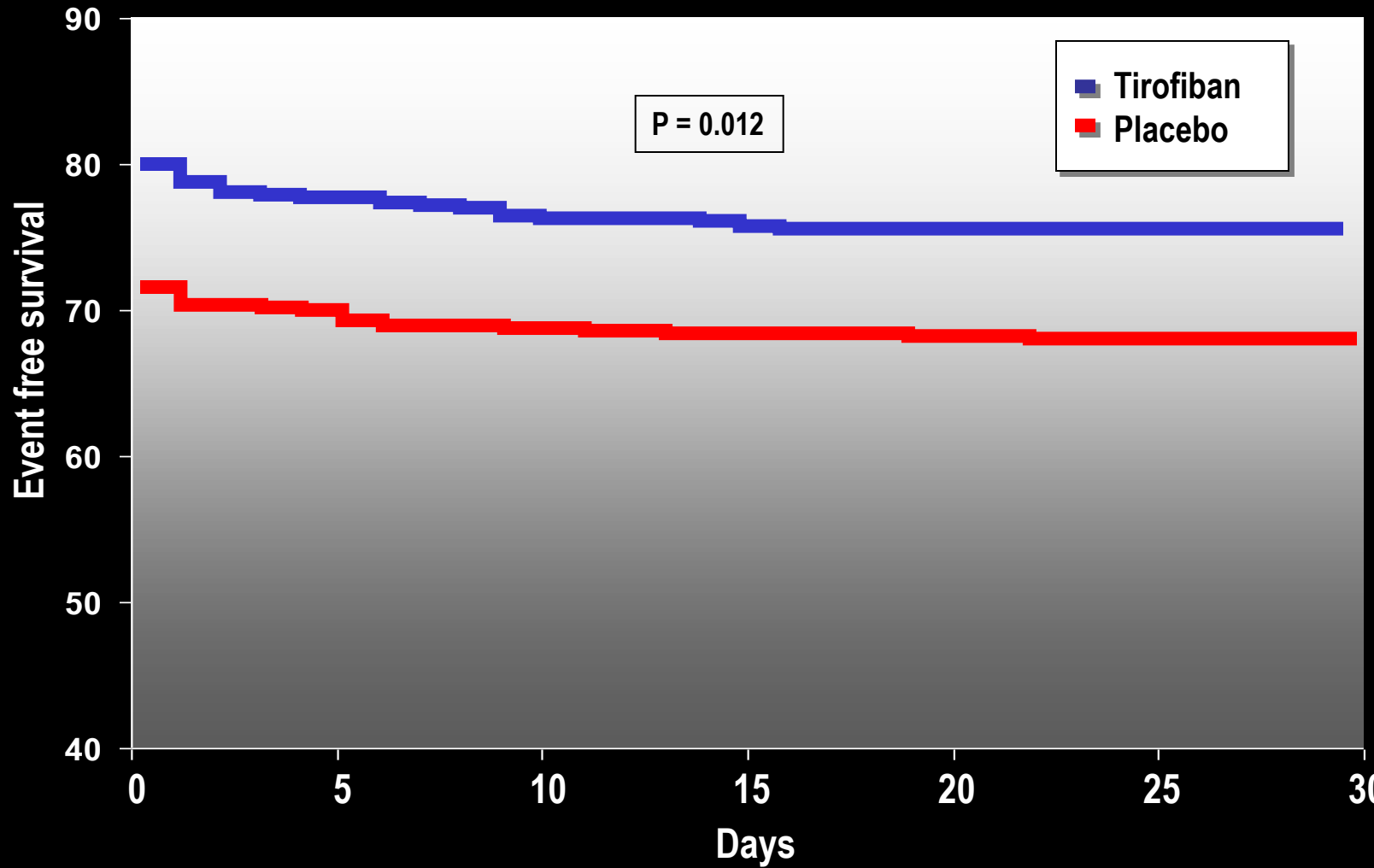


Ellis SG. et al, N Engl J Med 2008; 358: 2205-17

Divisione di Cardiologia Parma

Event free survival

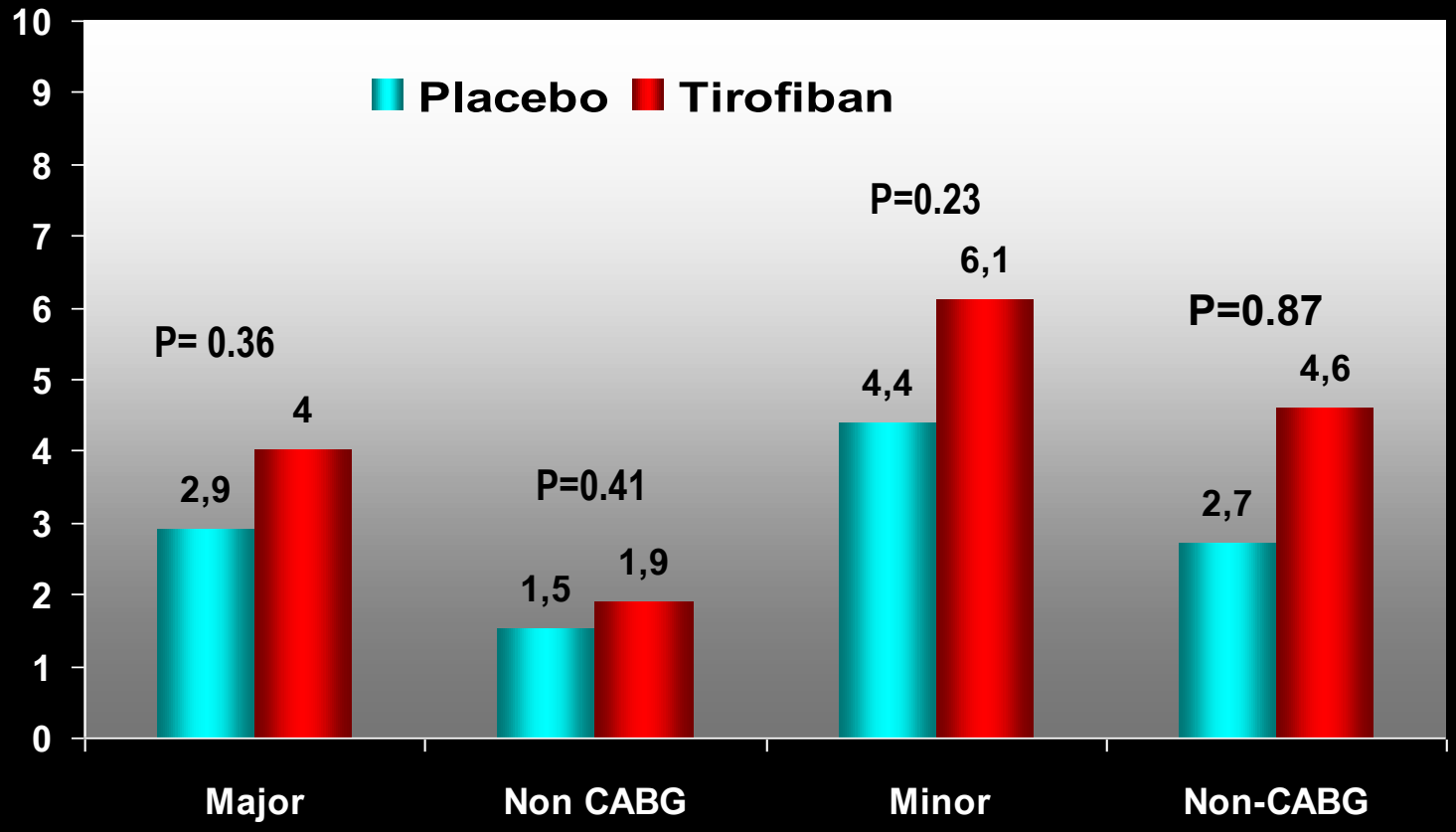
ON-TIME –2 trial



A W J van't Hof et al Lancet 2008; 372: 537-46

Safety Endpoint: Bleeding

ON-TIME –2 trial



A W J van't Hof et al Lancet 2008; 372: 537-46

Divisione di Cardiologia
Parma

UPSTREAM GP IIb/IIIa INHIBITORS

….the controversial literature data, the negative outcome of the only prospecitve RCT and the beneficial effects of faster acting and more efficacious ADP receptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GPIIb/IIIa inhibitors.

CLASS III

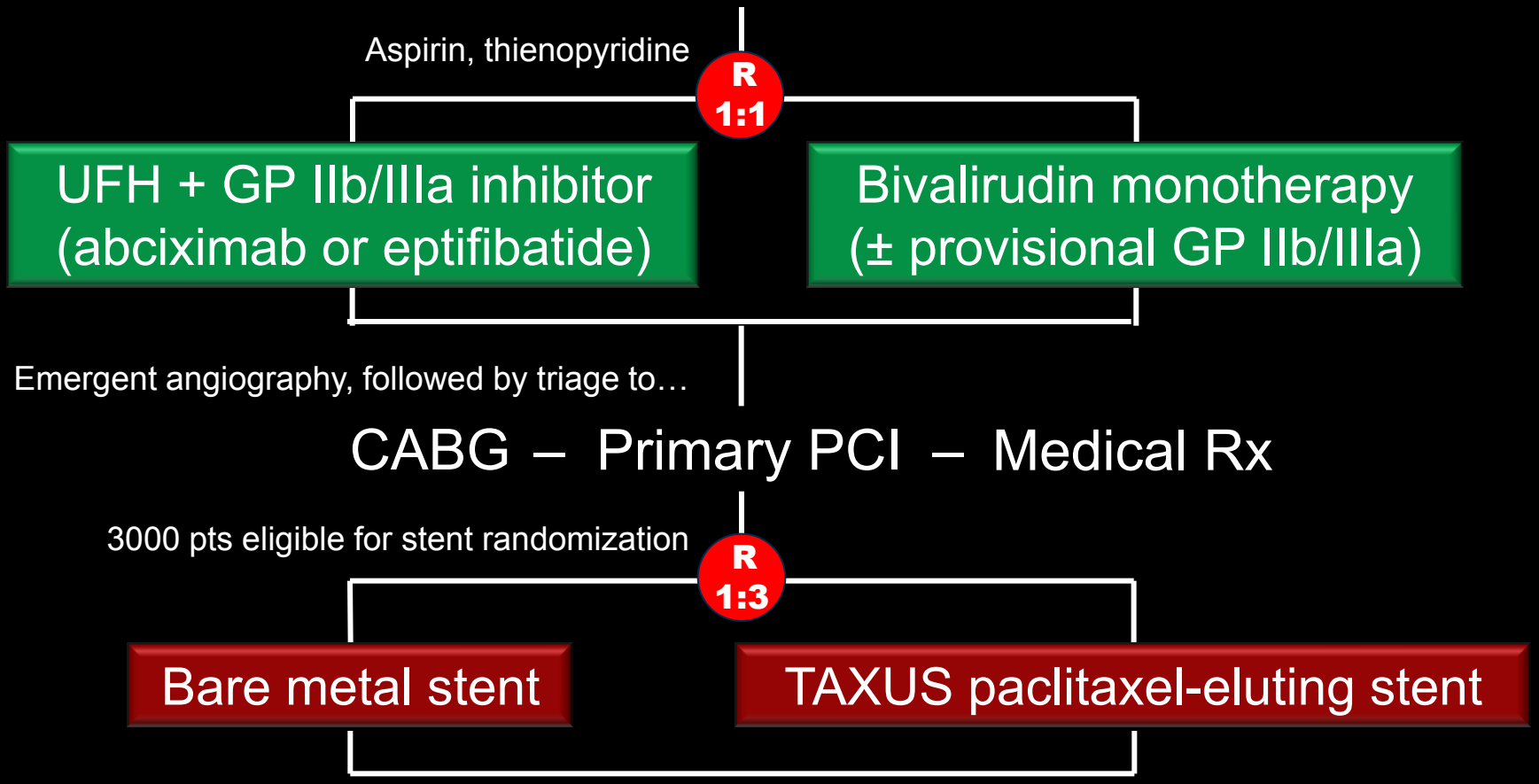
EVIDENCE B

Bivalirudin During Primary PCI in STEMI

The HORIZONS-AMI study design

Harmonizing Outcomes with Revascularization and Stents in AMI

≥3400* pts with STEMI with symptom onset ≤12 hours

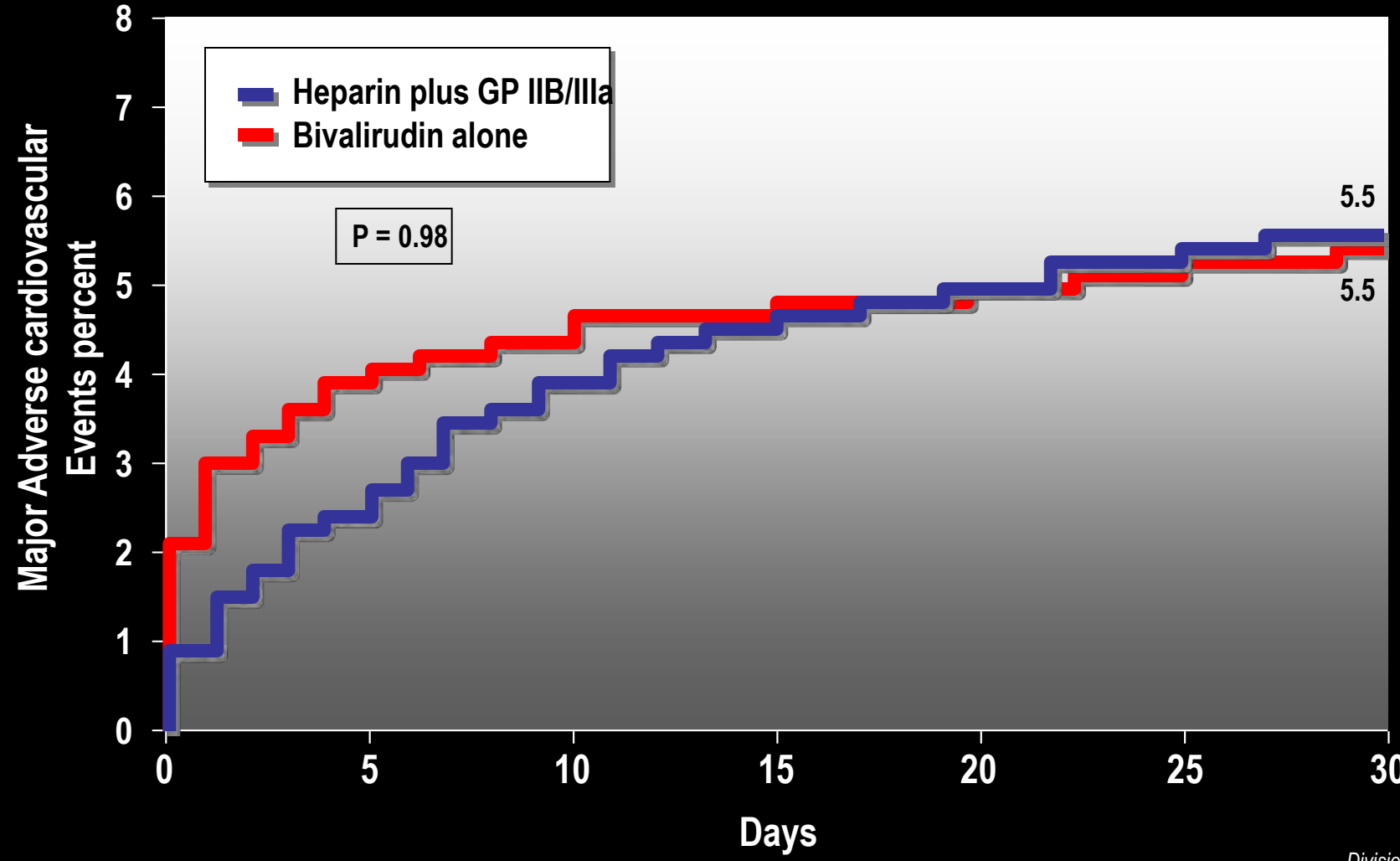


Clinical FU at 30 days, 6 months,
1 year, and then yearly through 5 years

*To rand 3000 stent pts

Bivalirudin During Primary PCI in STEMI
The HORIZONS-AMI trial

Major adverse cardiovascular events



BRAVE 4 TRIAL

Flow of Study Participants

STEMI patients within 24 hours
1,200 Patients

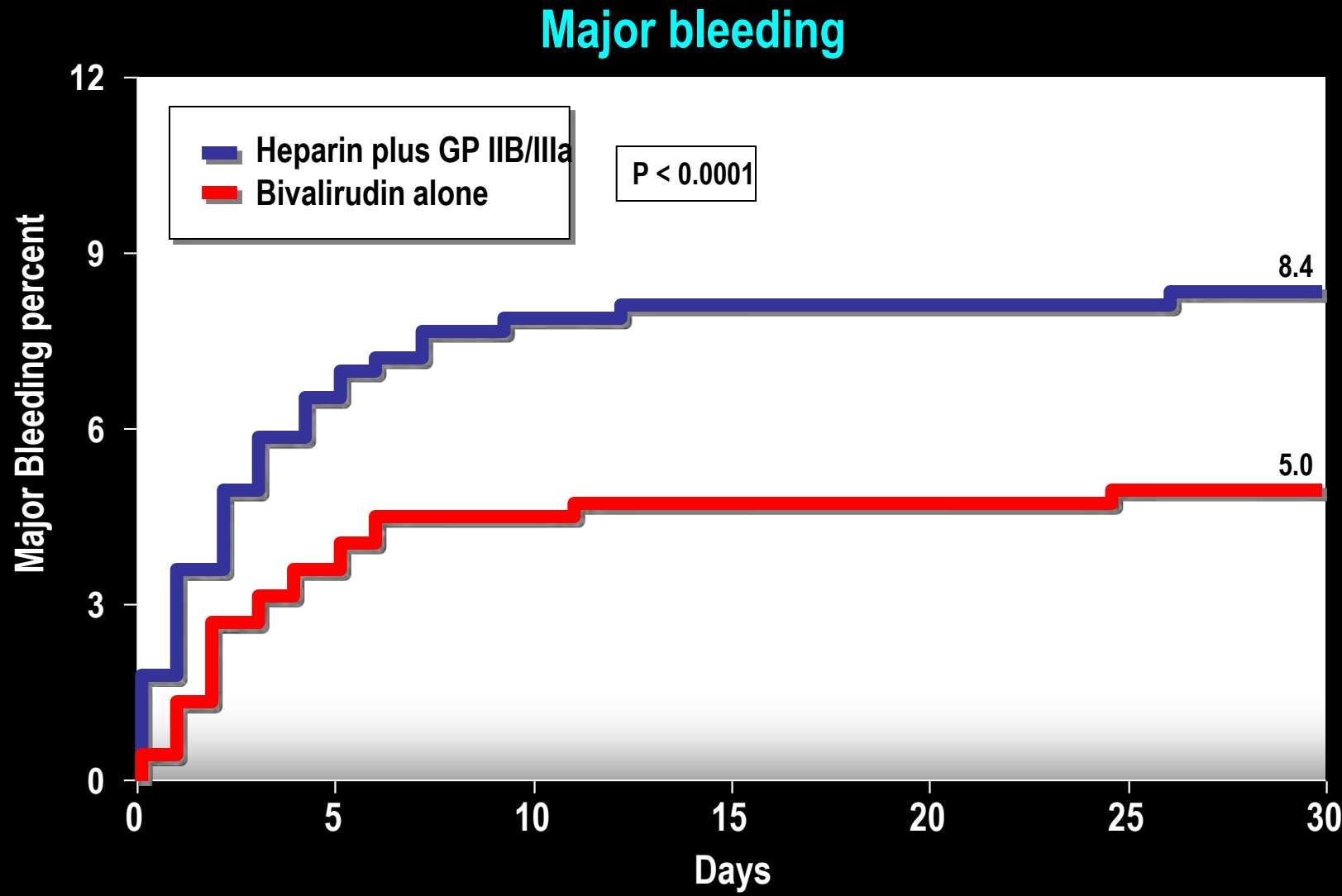
Prasugrel + Bivalirudin

Clopidogrel + Heparin

Efficacy endpoint: Composite of death, recurrent myocardial infarction, urgent infarct-related artery revascularization, stroke, definite stent thrombosis or major bleeding at 30 days

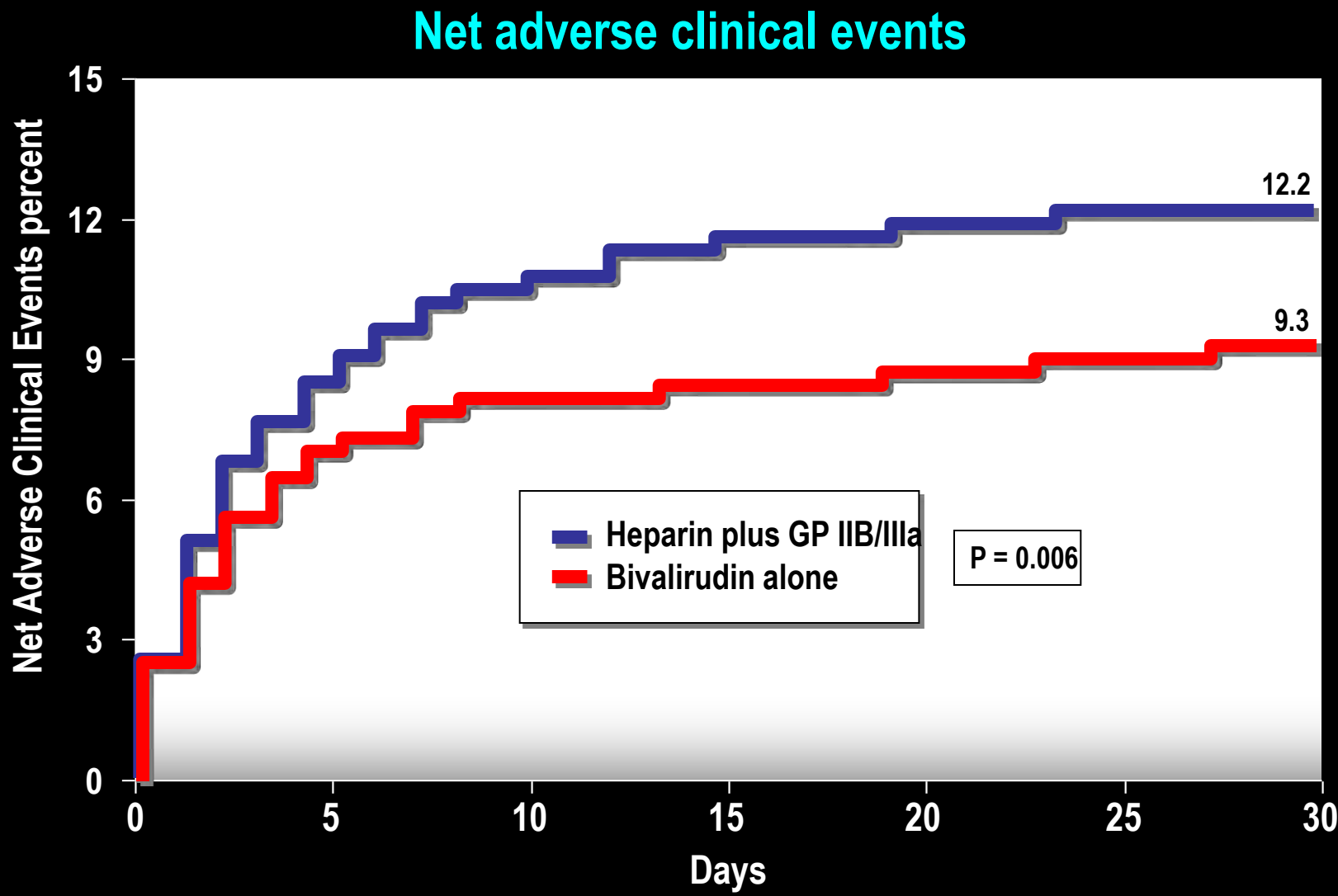
Divisione di Cardiologia
Parma

Bivalirudin During Primary PCI in STEMI
The HORIZONS-AMI trial



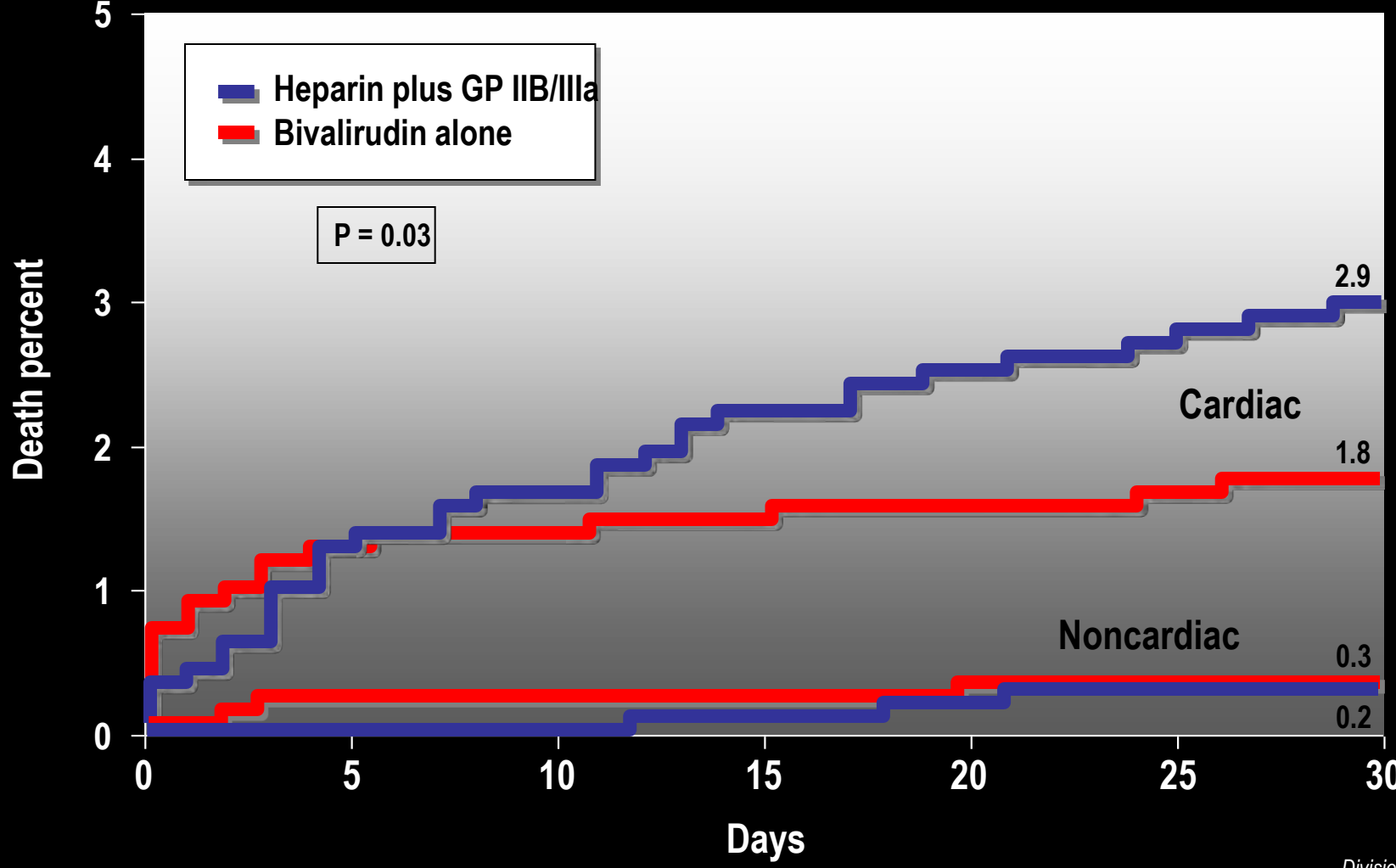
Bivalirudin During Primary PCI in STEMI

The HORIZONS-AMI trial



Bivalirudin During Primary PCI in STEMI
The HORIZONS-AMI trial

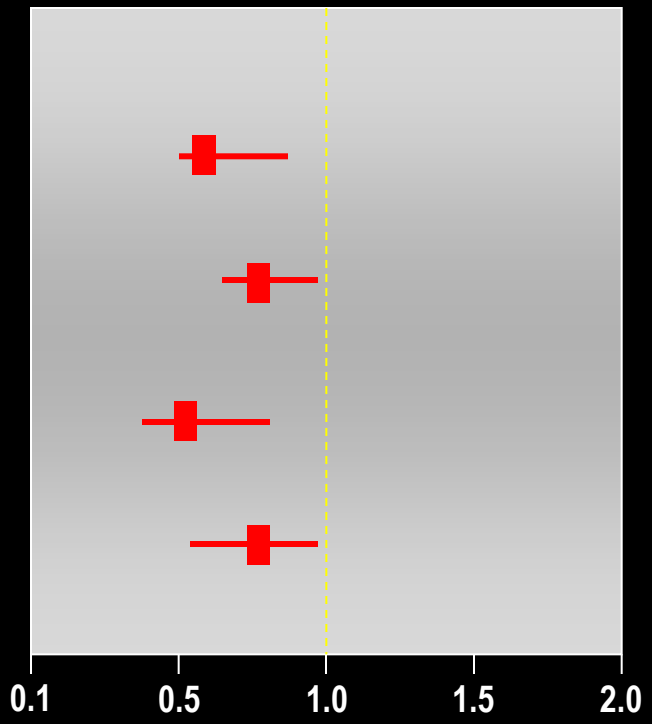
Death from cardiac and non cardiac causes



Stone GW. et al, N Engl J Med 2008; 358: 2218-30

Divisione di Cardiologia Parma

Bivalirudin During Primary PCI in STEMI
The HORIZONS-AMI trial 3-years follow up



Endpoint	Bival (%)	Hep+GP IIb/IIIa (%)	HR (95% CI)	p
Major bleeding	6.9	10.5	0.64 (0.51-0.80)	<0.001
All-cause mortality	5.9	7.7	0.75 (0.58-0.97)	0.03
Cardiac mortality	2.9	5.1	0.56 (0.40-0.80)	0.001
Reinfarction	6.2	8.2	0.76 (0.59-0.92)	0.04

Stone GW. et al, TCT 2010

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

ANTITHROMBOTIC THERAPY IN PRIMARY PCI

Bivalirudin is recommended as an alternative to unfractionated heparin in primary PCI, expecially among patients at high-risk for bleeding complications.

- i.v. bolus: 0.75 mg/kg
- infusion: 1,75 mg/kg/h not titrated to ACT and usually terminated at the end of the procedure)

CLASS IIa

EVIDENCE B

ESC/ EACTS Guidelines on myocardial revascularization 2010

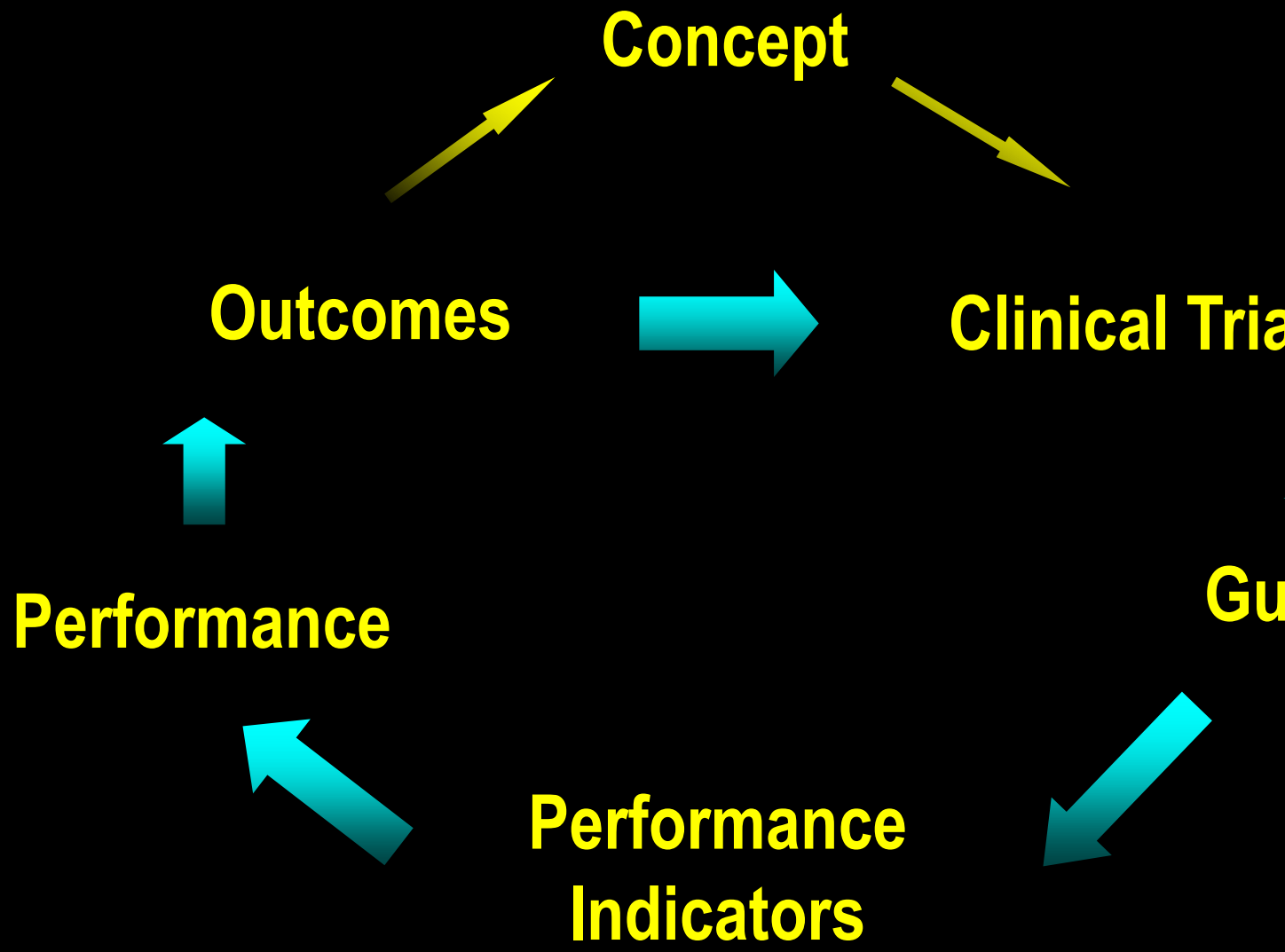
Antithrombotic treatment options in myocardial revascularization

….bivalirudin may be preferred in STEMI patients at high risk of bleeding…

CLASS I

EVIDENCE B

The cycle of continuous quality improvement



Califf RM et al. JACC 2002;40:1895-901