Pushing the envelope for bivalirudin monotherapy: Design, rationale and status of ISAR-REACT 4 and HORIZONS

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Periprocedural Antithrombotic Therapy

- Aspirin
- Clopidogrel
- Heparins (UFH or LMWH)
- IIb/IIIa Inhibitors
- Bivalirudin

- Stable/Unstable Angina
- NSTE Acute Coronary Syndromes
- STEMI

Rationale for New a Trial of Bivalirudin in ACS

- Value of early invasive strategy
- Need for upstream use of IIb/IIIa inhibitors
- Role of pre-treatment with 600 mg of clopidogrel
- Recent evidence on adjunct antithrombotic therapy

ISAR-COOL Trial

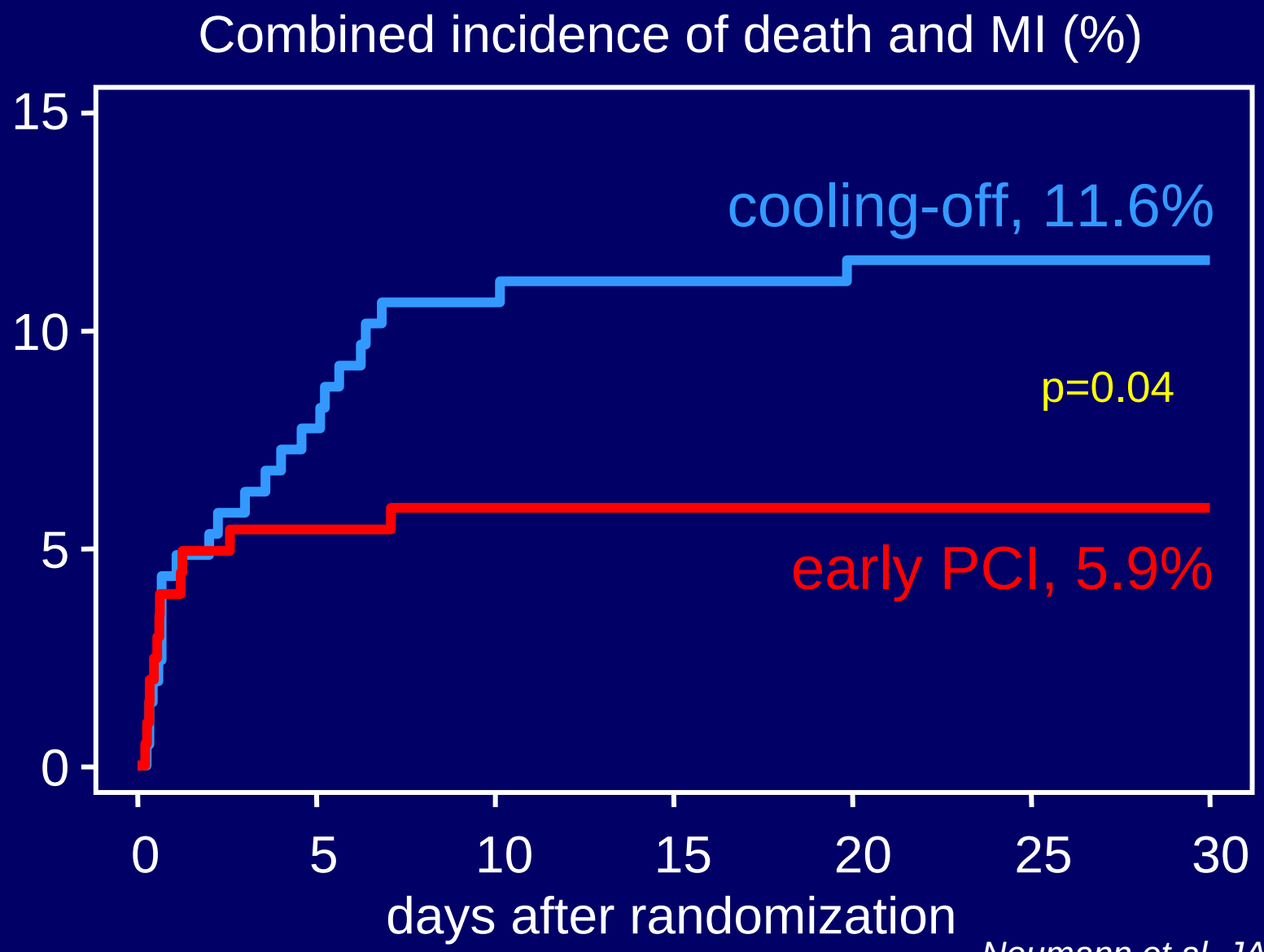
410 patients with ACS

207 Pts
Cooling-off
antithrombotic
pretreatment
for 72 - 120 h

203 Pts
Early PCI
antithrombotic pretreatment
for < 6 h

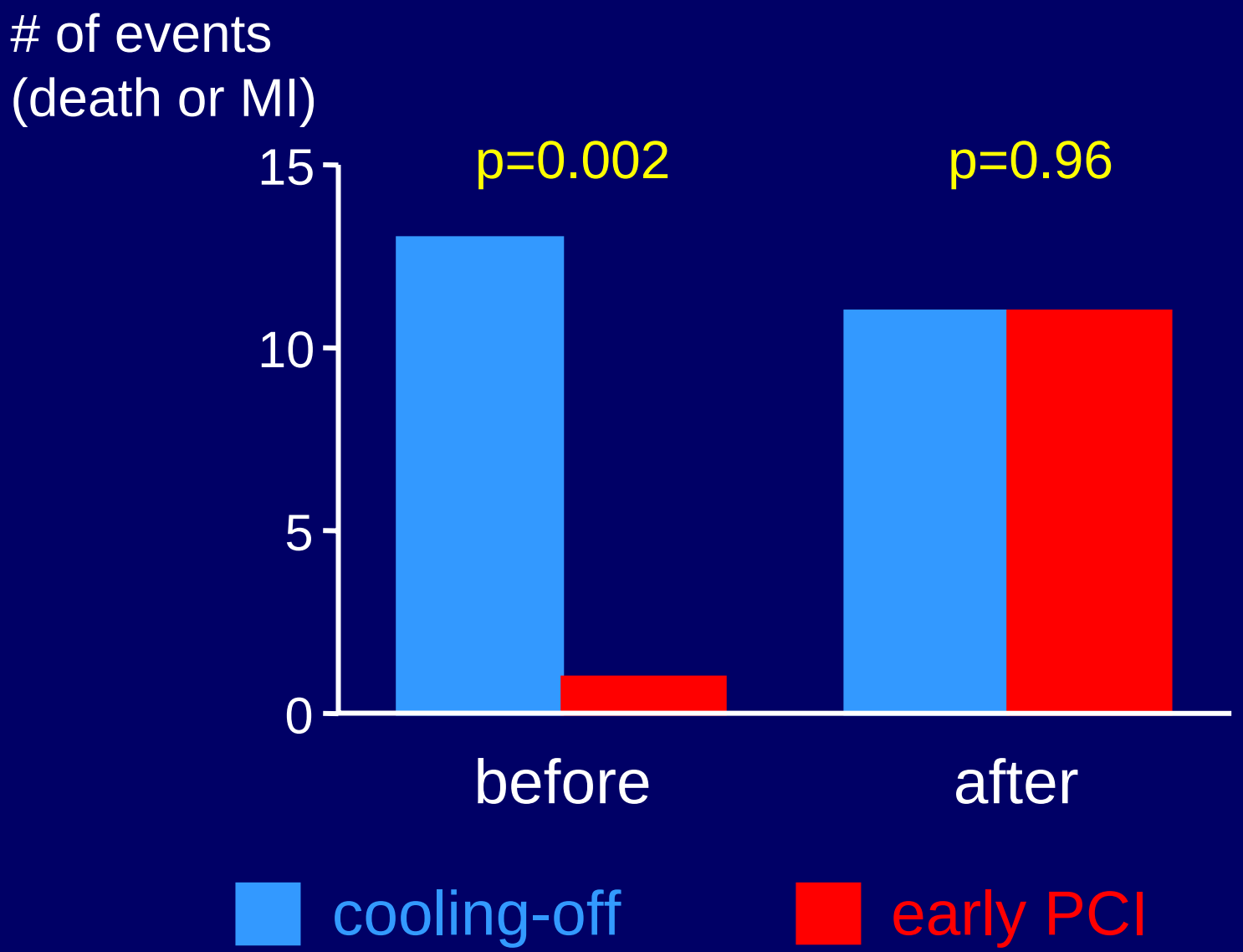
Neumann et al. JAMA 2003

ISAR-COOL: Primary Endpoint



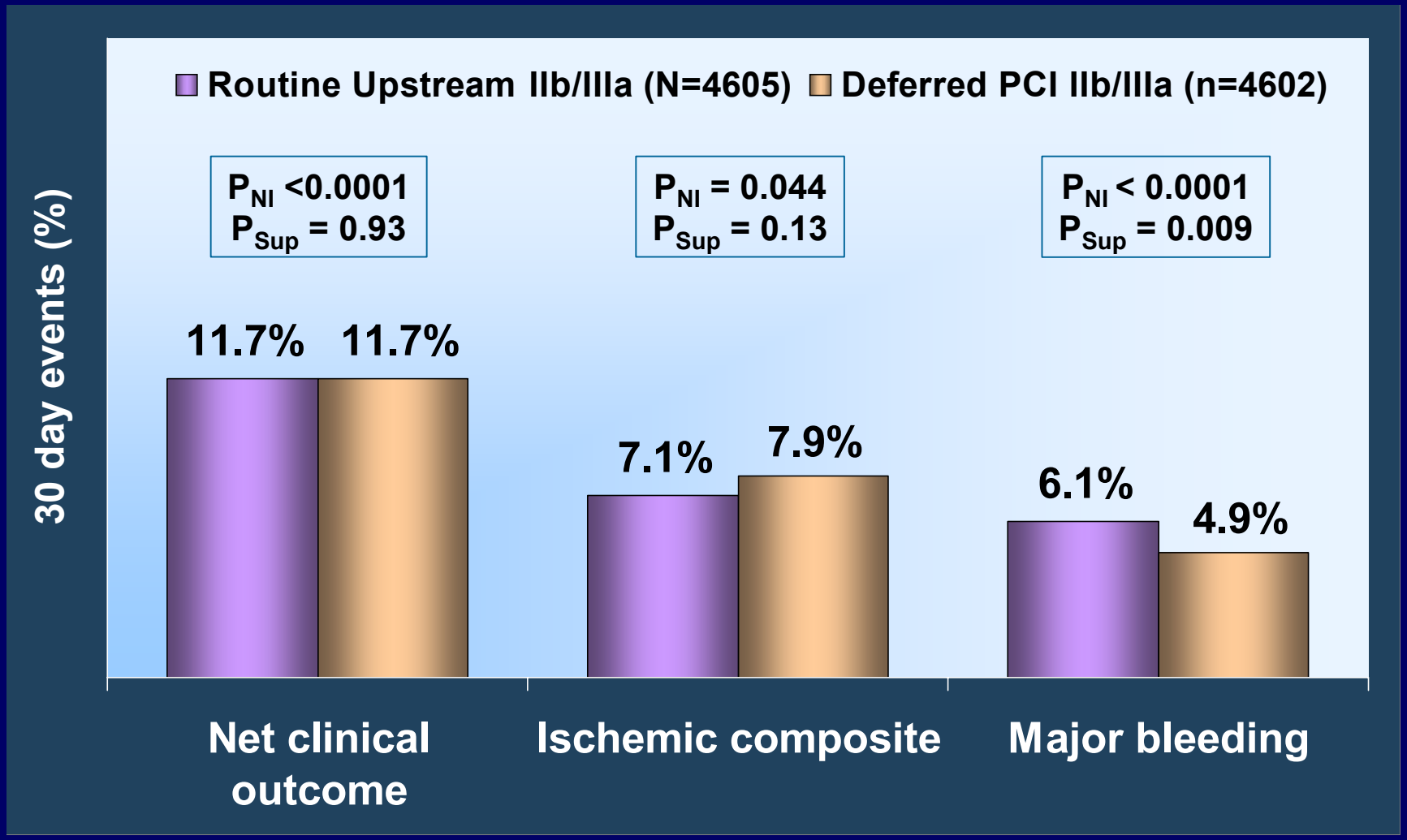
Neumann et al. JAMA 2003

Primary Endpoint Before and After Catheterization



Need for Upstream Use of IIb/IIIa Inhibitors - ACUITY Timing Trial -

Routine Upstream IIb/IIIa vs. Deferred PCI IIb/IIIa



ACUITY Timing ACC 2006

In ACS patients, data support early invasive treatment without the need for upstream use of IIb/IIIa inhibitors.

Does pre-treatment with 600 mg of clopidogrel obviate the need for IIb/IIIa inhibitors in ACS patients undergoing PCI such as it did for elective PCI patients?

ISAR–REACT 2 Trial

2022 patients with high-risk ACS

Pre-treated with 600 mg clopidogrel

Abciximab

Placebo

Double-blind

1010 Pts

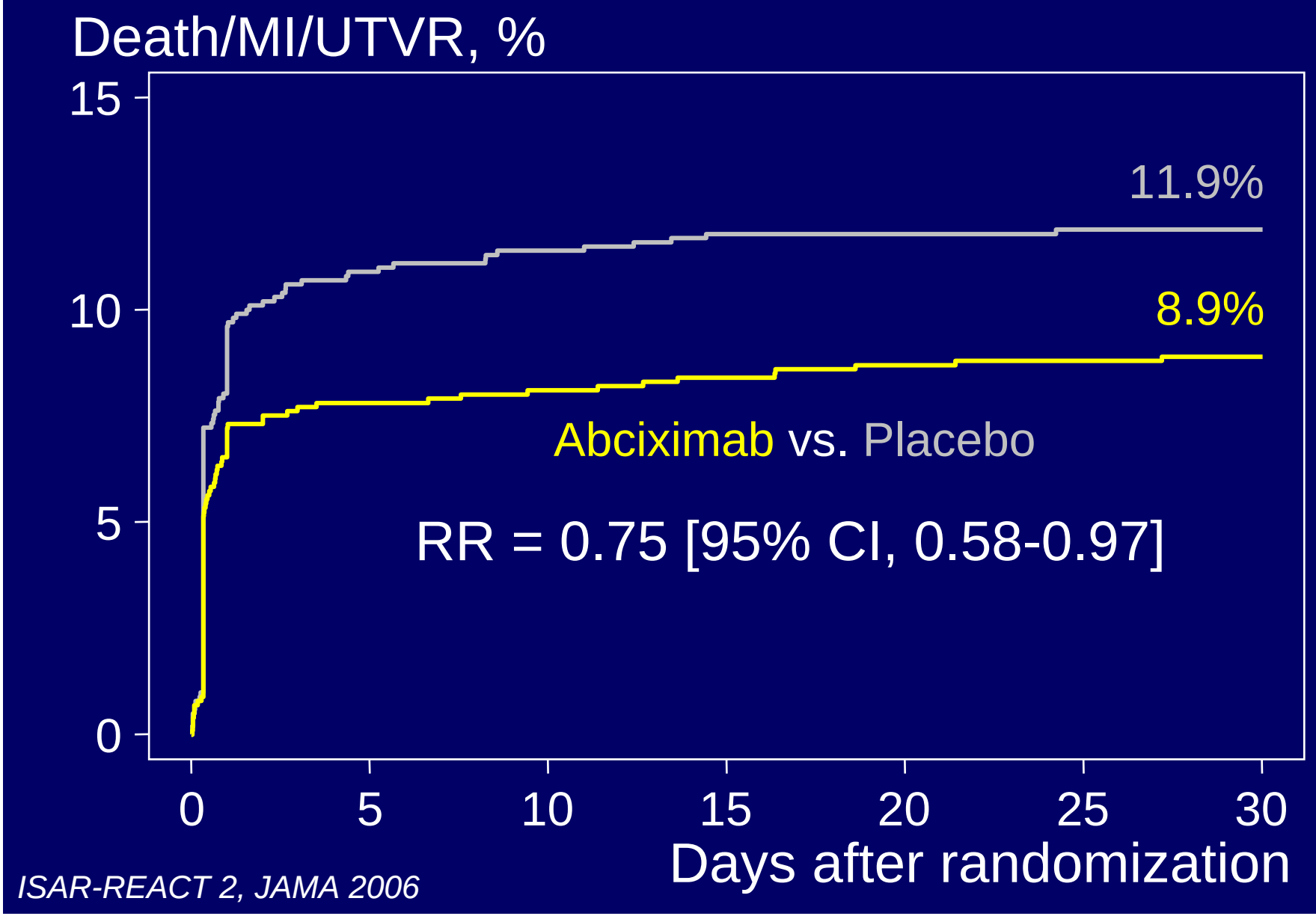
1012 Pts

PCI

30-day outcome

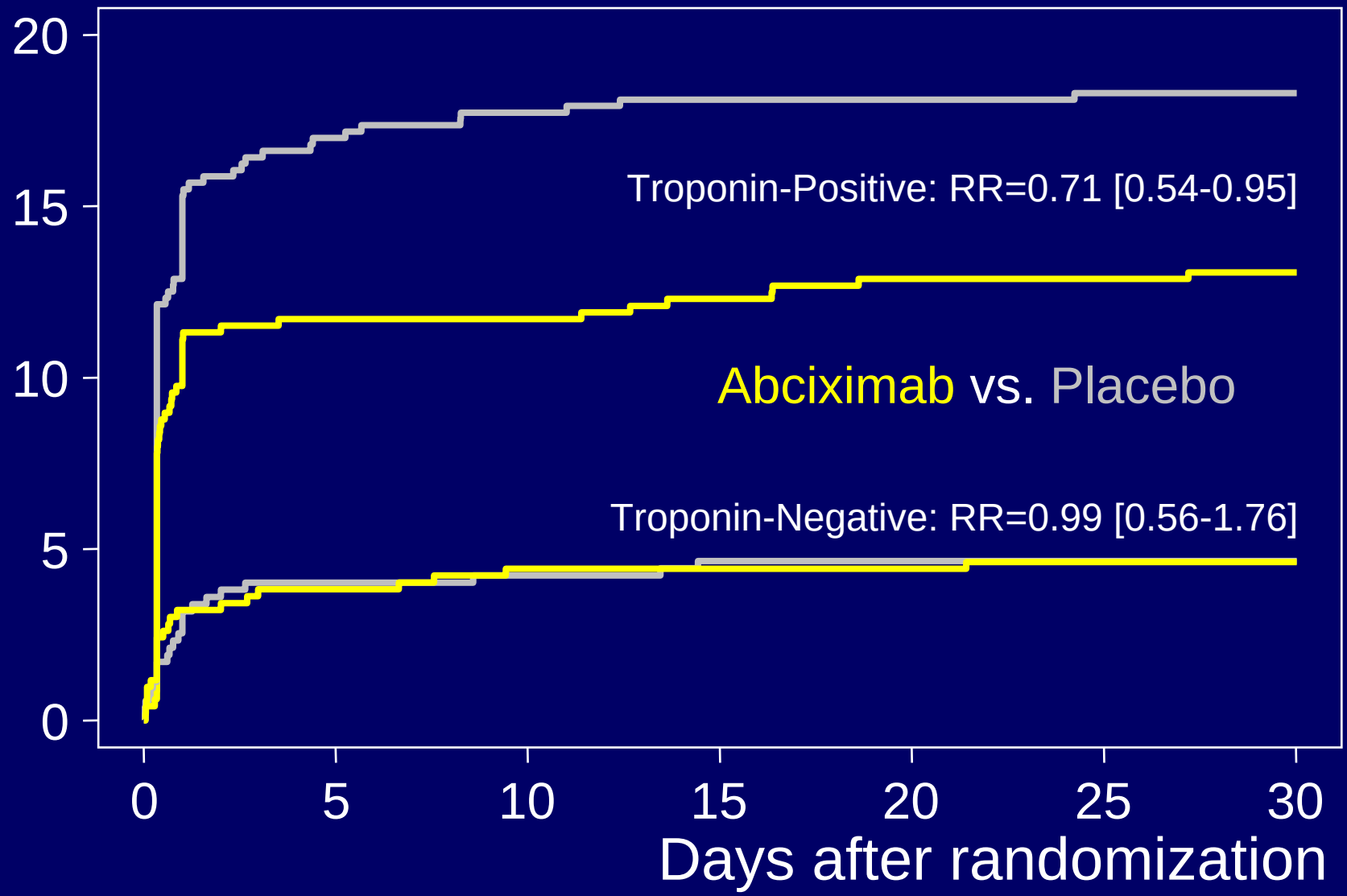
ISAR-REACT 2, JAMA 2006

ISAR–REACT 2: Primary End Point

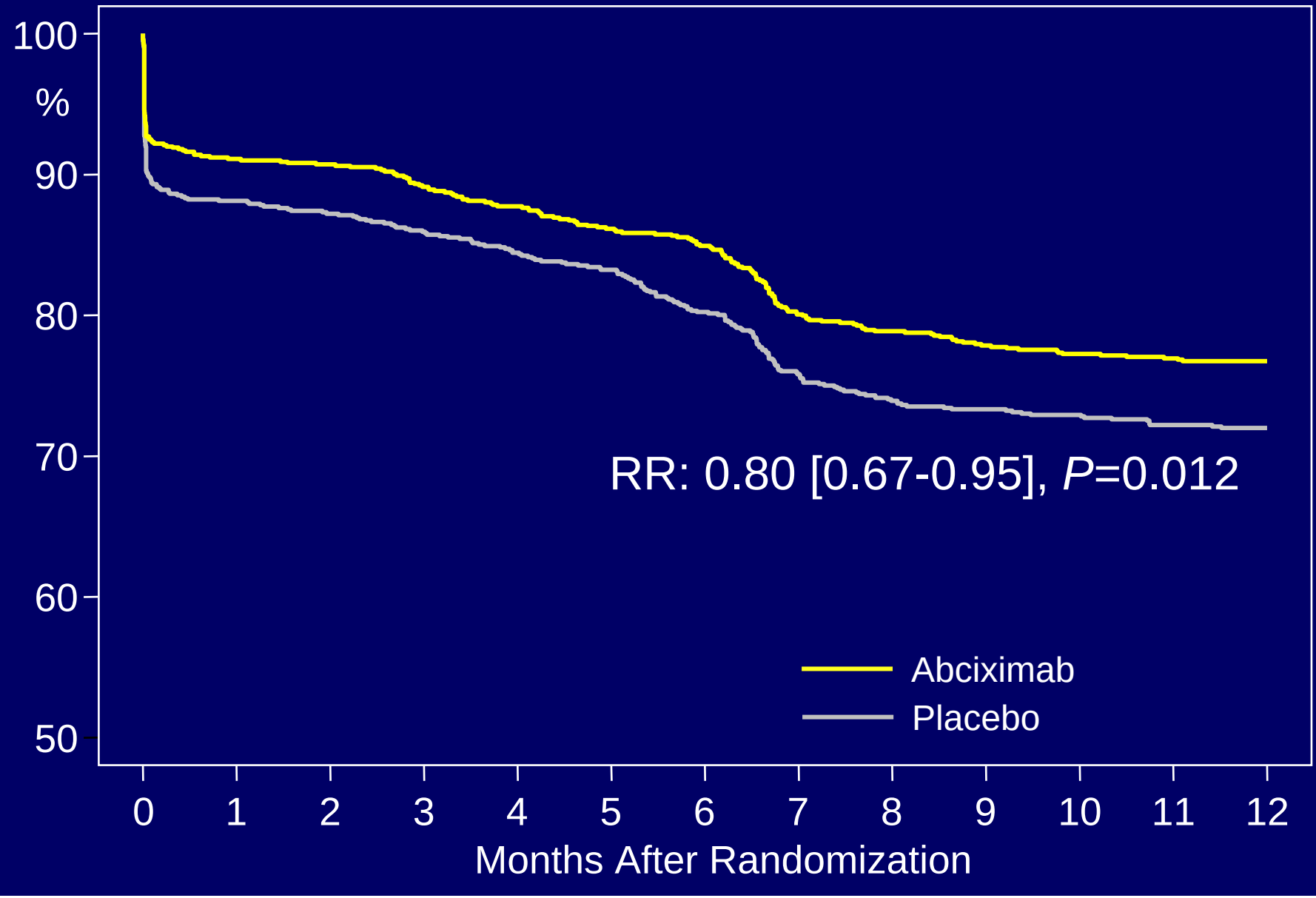


ISAR-REACT 2, JAMA 2006

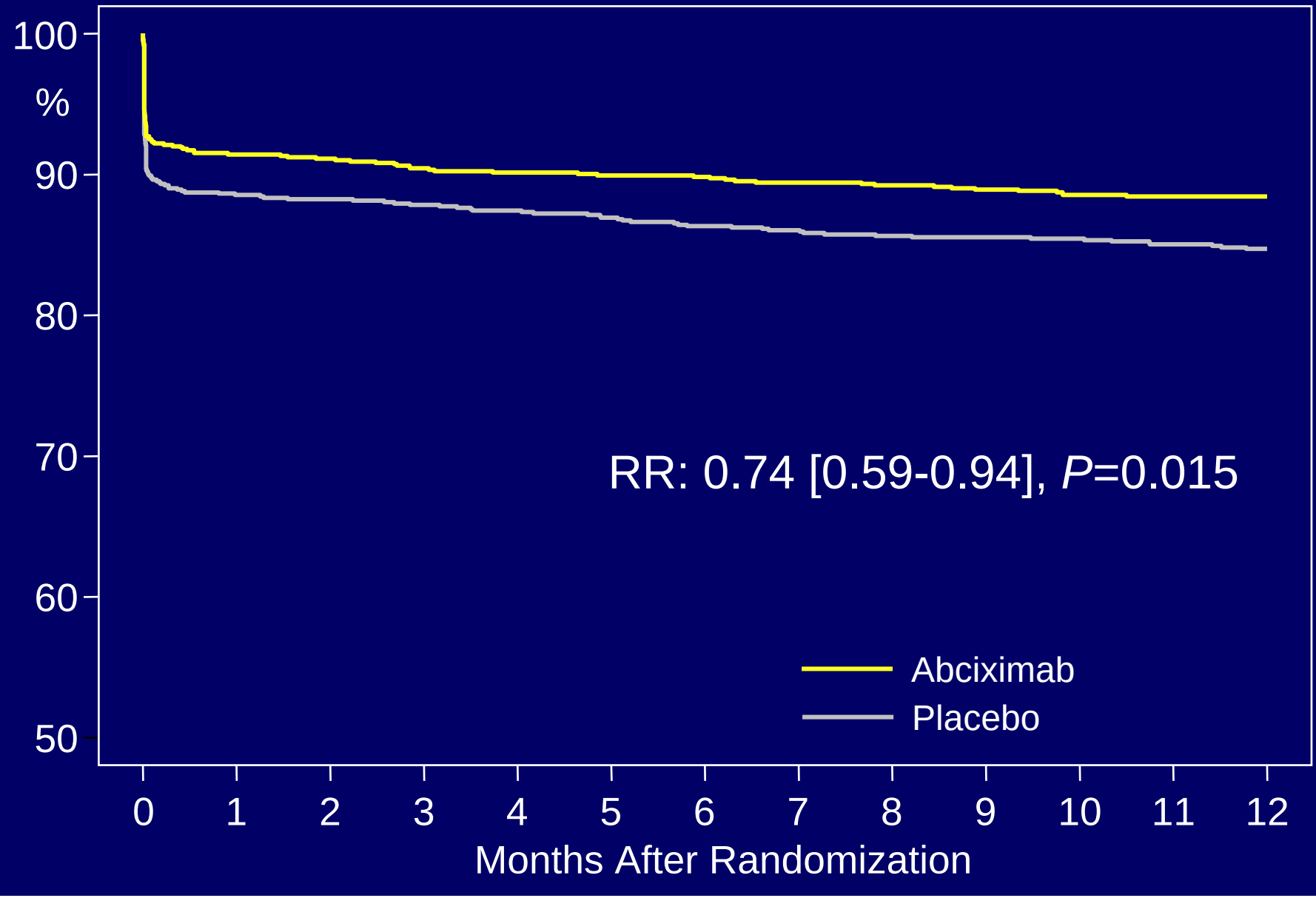
Troponin Level and Benefit With Abciximab



One-Year Survival Free of MACE

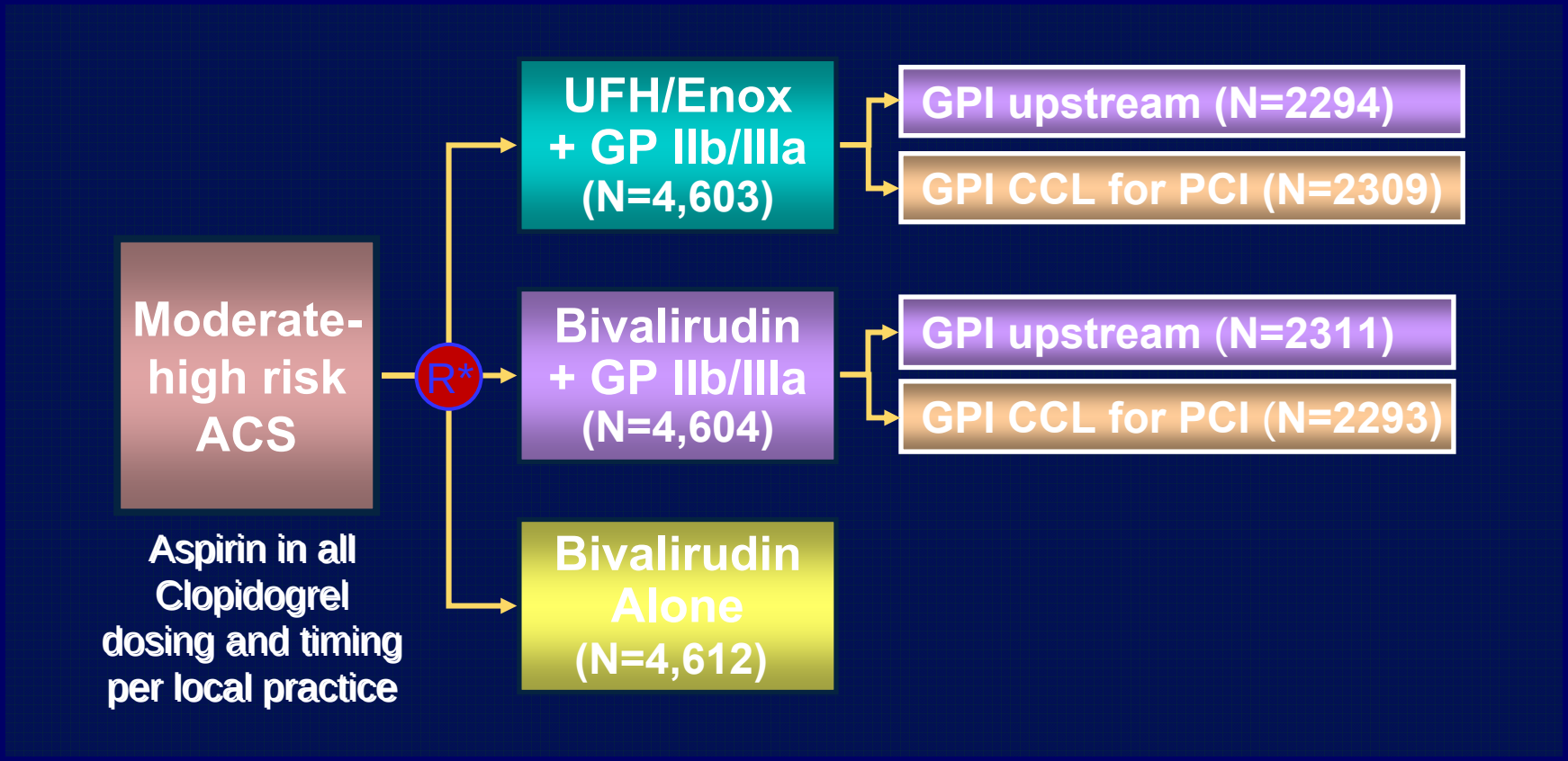


One-Year Survival Free of MI



Bivalirudin in ACS
- ACUITY -

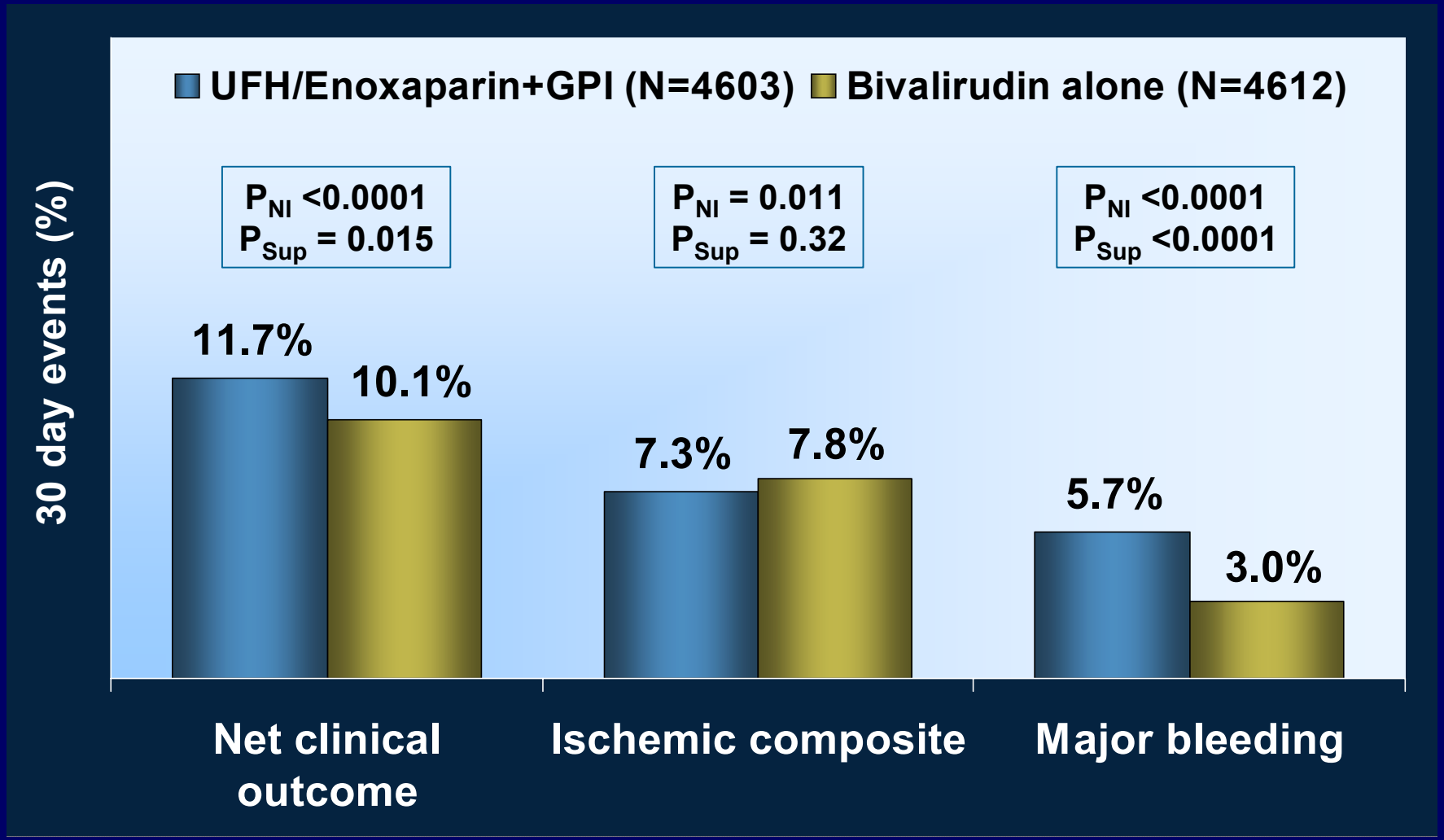
13,819 Pts



ACUITY, ACC 2006

ACUITY
- Primary End Point -

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



Issues With ACUITY
- Design -

- Open-label trial
- ACUITY did not address specifically Trop+ pts
- Major bleeding definition

▪ Non CABG related bleeding

- Intracranial bleeding or intraocular bleeding

- Retroperitoneal bleeding

-Access site bleed requiring intervention/surgery

- Hematoma ≥5 cm

- Hgb ⇓≥3g/dL with an overt source or ⇓≥4g/dL w/o overt source

- Blood product transfusion

▪ Reoperation for bleeding

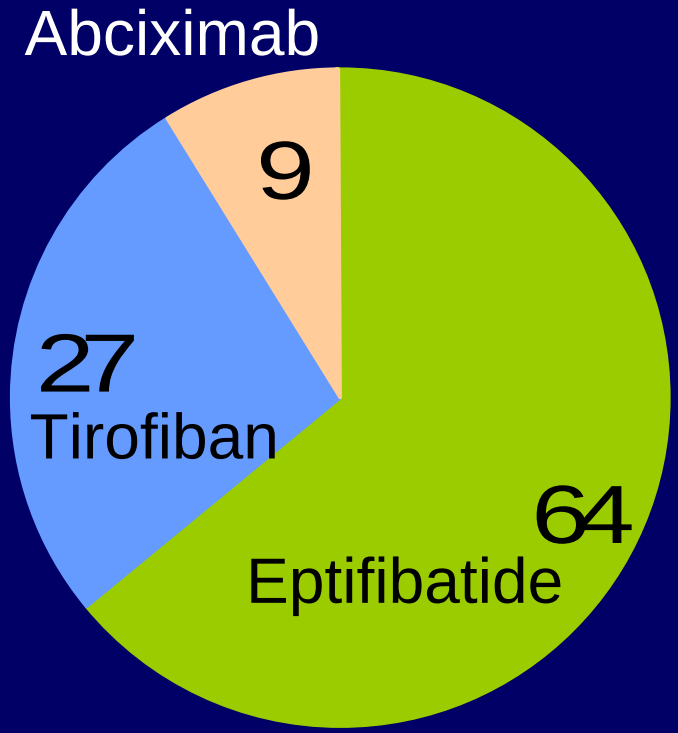
Issues With ACUITY
- Invasive Strategy -

	UFH/Enoxaparin + GP IIb/IIIa (N=4,603)	Bivalirudin + GP IIb/IIIa (N=4,604)	Bivalirudin alone (N=4,612)
Angiography	99.2%	98.8%	98.9%
Adm. to angio (h)	19.7 (7.0-29.3)	19.5 (7.0-28.2)	19.8 (7.3-29.0)
Drug to angio/interv (h)	5.6 (1.6-22.5)	5.0 (1.4-21.4)	5.2 (1.5-22.5)
Actual procedure			
PCI	55.6%	56.7%	56.8%
CABG	11.9%	10.8%	10.6%
Medical therapy	32.4%	32.5%	32.6%

Issues With ACUITY
- Control Group Therapy -

Control group:

A mixture of UFH and Enoxaparin



Unresolved Issue

Is bivalirudin inferior to abciximab+UFH in patients with NSTEMI undergoing PCI?

ISAR–REACT 4 Trial

1700 patients with NSTEMI

Pre-treated with 300-600 mg of clopidogrel

Double-blind

Bivalirudin

Abciximab+UFH

PCI

30-day Outcome

ISAR-REACT 4: Inclusion Criteria

- Patients with rest angina between 18 and 80 years
- Positive cardiac biomarkers (troponin or CK-MB)

ISAR-REACT 4
Major Exclusion Criteria

- Acute STEMI
- Hemodynamic instability
- Suspected aortic dissection, pericarditis
- Increased risk of bleeding, malignancies
- Relevant hematologic deviations
- Known allergic reaction to the study medication

Primary Quadruple End Point

A composite of death,
MI (Q-wave or 5xCK-MB elevation),
urgent target vessel revascularization
within the first 30 days after PCI or
in-hospital major bleeding
(intracranial, intraocular or retroperitoneal hemorrhage or any decrease in hemoglobin of more than 40 g/L associated with either overt source of bleeding or need for transfusion of 2 or more units)

Study Hypothesis:

30% reduction of the primary end point with abcicimab from 15.3% to 10.7%

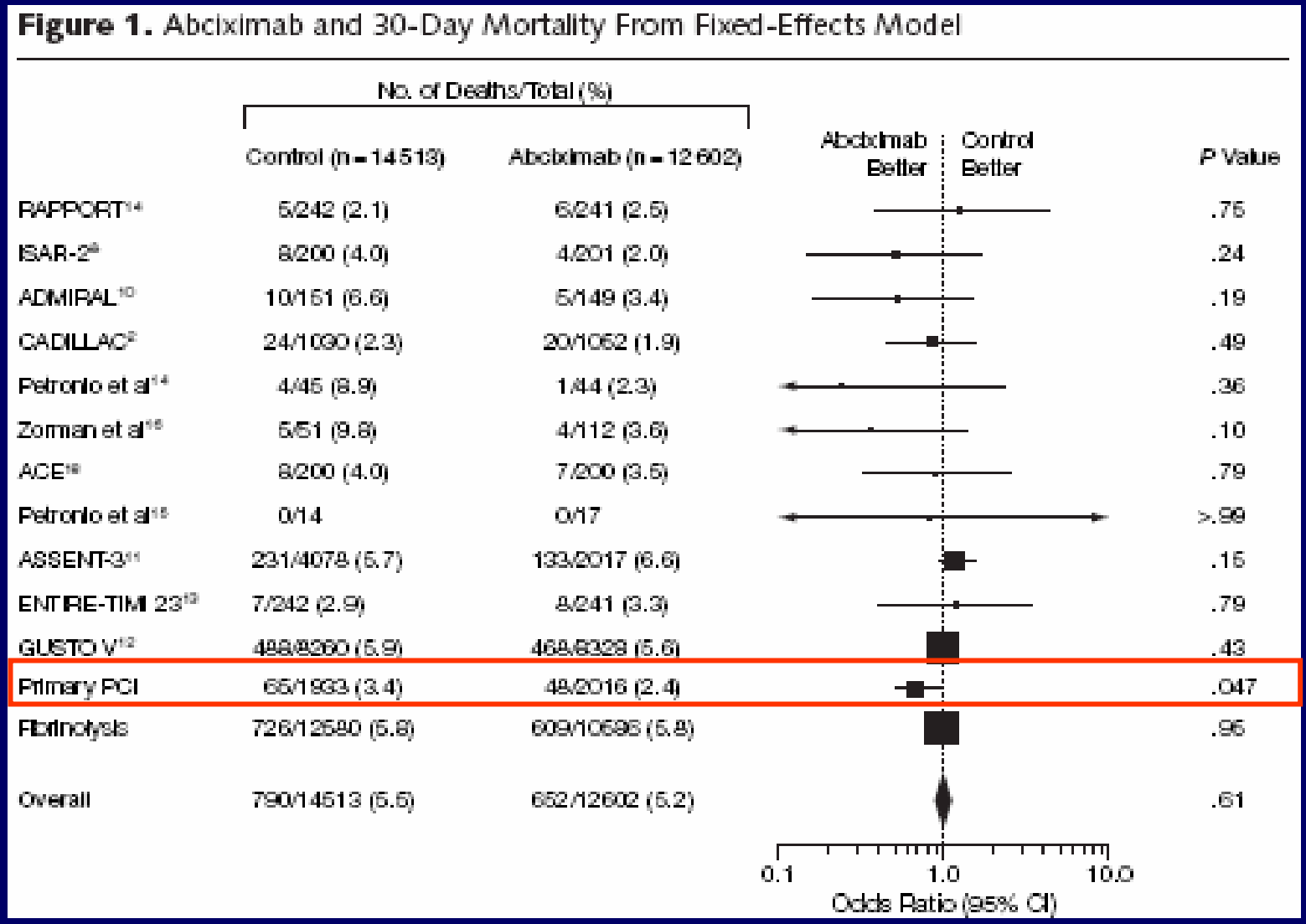
ISAR-REACT 4: Status

~250 Patients Included to Date

Rationale for a new trial of bivalirudin and DES in patients with acute STEMI undergoing PCI

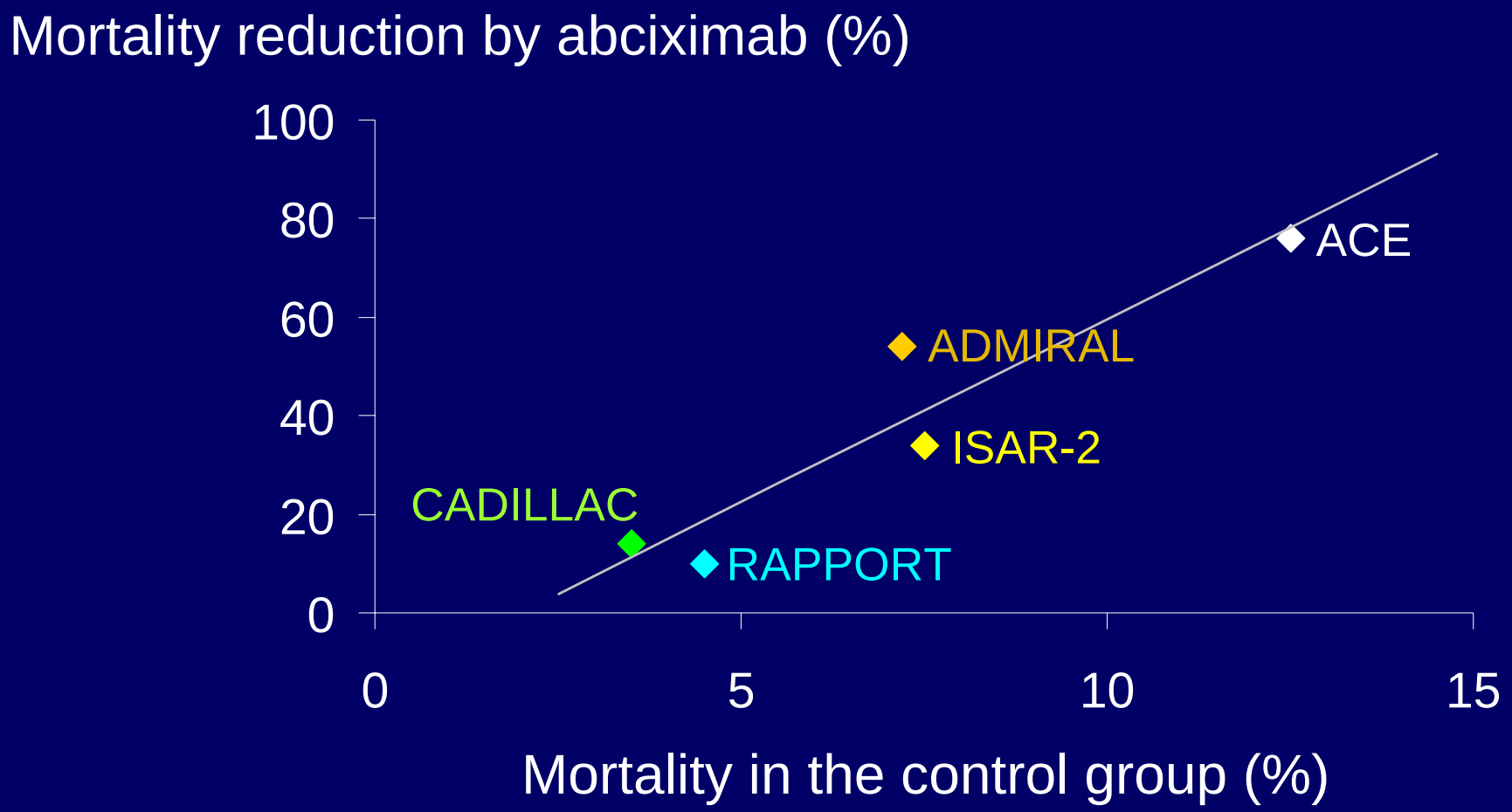
IIb/IIIa Inhibitors During PCI in AMI

Figure 1. Abciximab and 30-Day Mortality From Fixed-Effects Model



De Luca et al, Metaanalysis, JAMA 2005

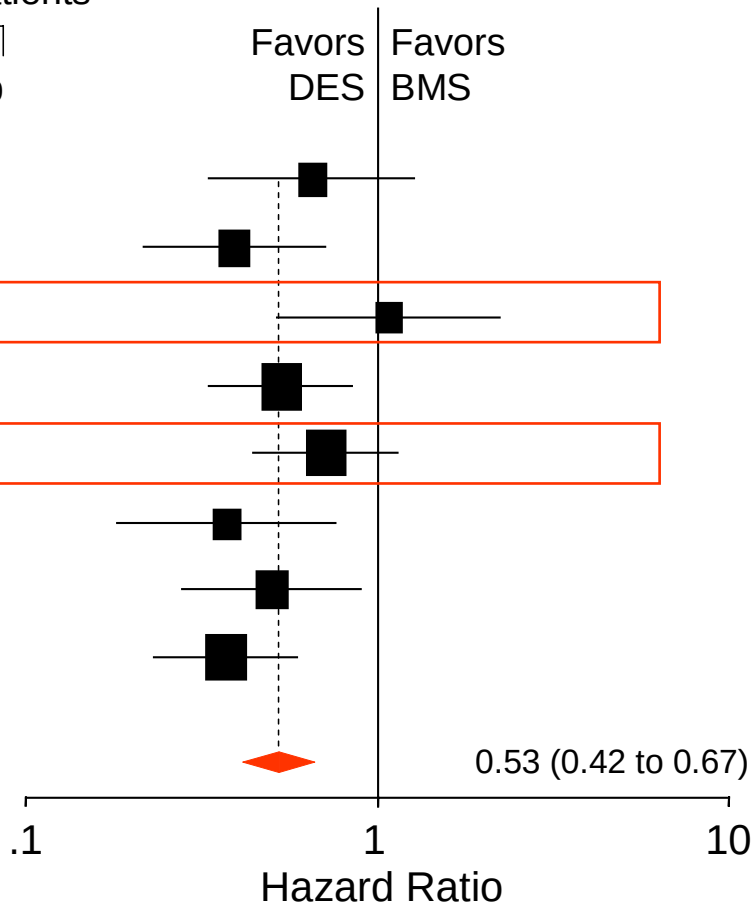
IIb/IIIa Inhibitors During PCI in AMI



IIb/IIIa Inhibitors are currently strongly recommended during primary PCI.
Data on the value of bivalirudin during primary PCI are lacking.

DES in AMI and Risk of MACE

Trial	No. of events / Total No. of patients: DES group	BMS group
BASKET-AMI	20/142	15/74
Di Lorenzo	20/180	24/90
HAAMU-STENT	15/82	14/82
MISSION	22/158	40/152
PASSION	29/310	40/309
SESAMI	11/160	26/160
STRATEGY	17/87	31/88
TYPHOON	24/355	62/357
Overall	158/1474	252/1312



$P_{(Heterogeneity)} = 0.22$

$I^2 = 26\%$

$P_{(Overall\ Effect)} < 0.001$

Experience with DES in AMI is still limited, especially in the case of the Taxus stent. It is not known whether it safely reduces the need for reintervention

HORIZONS AMI Trial

- 3400 randomized patients undergoing primary PCI -

Anti-thrombotic therapy
Randomize 1:1

- UFH + IIb/IIIa inhibitor
- Bivalirudin + bail-out IIb/IIIa

Hypothesis: Bivalirudin compared to UFH + routine IIb/IIIa will reduce the composite rate of death, reinfarction, TVR, stroke and major bleeding at 30-days.

Target vessel stenting
Randomize 3:1

- TAXUS stent
- Bare metal Express stent

Hypothesis: Use of the polymer-based slow-release paclitaxel-eluting TAXUS stent will safely reduce the 1-year rate of ischemia-driven TLR. 1° clinical end-point at 12 mo; 2° angio endpoint at 13 mo.

Sponsor: The Cardiovascular Research Foundation (PI: Gregg W. Stone), with unrestricted grant support from: Boston Scientific & The Medicine's Co.

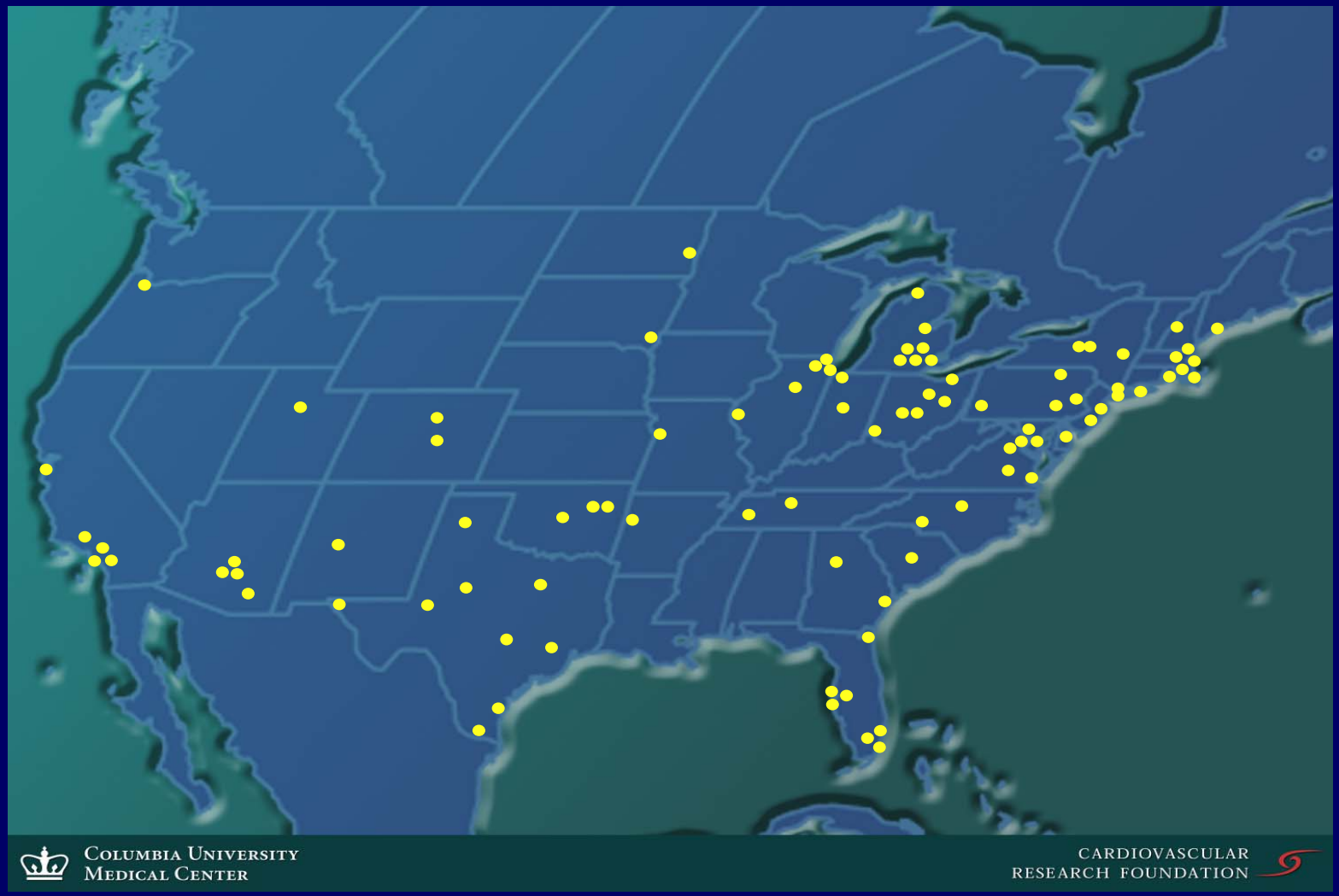
HORIZONS AMI

New Enrollment Target / Timeline

- Assumption: stent eligible subjects (estimate ~88% = 3000)
- Current enrollment: stent eligible subjects (Actual ~83%)

- Therefore, 3600 total patients randomized to the drug arm are needed to enroll 3000 subjects randomized to the drug and stent arm.

US HORIZONS Sites
- 50 sites currently active/enrolling-



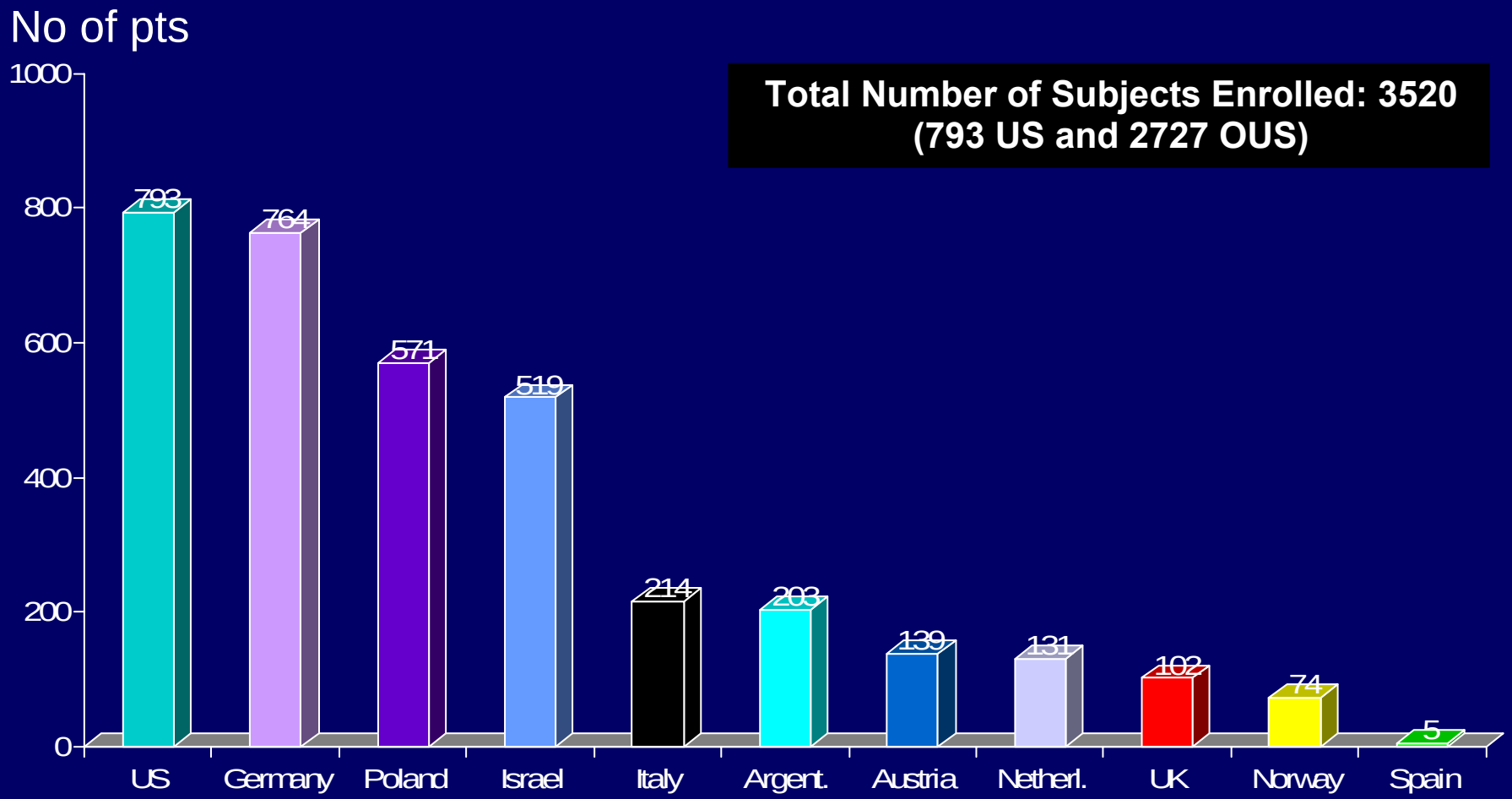
Courtesy of Gregg Stone

OUS HORIZONS Sites
- 71 sites currently active/enrolling-

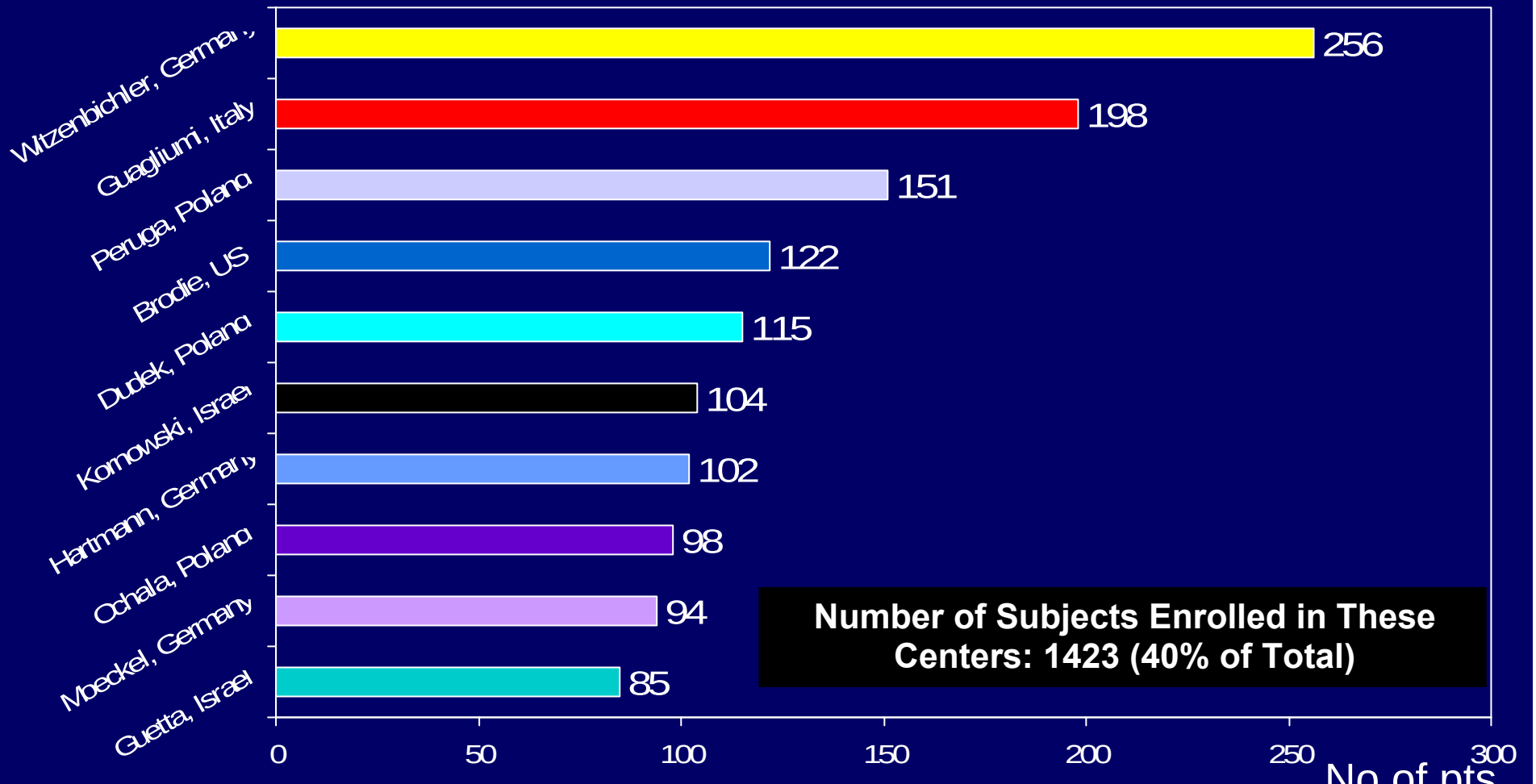
Courtesy of Gregg Stone

HORIZONS Enrollment Status
April 24, 2007

Total Number of Subjects Enrolled: 3520
(793 US and 2727 OUS)



Top 10 Enrolling Sites in HORIZONS



HORIZONS

Enrollment

114 Study Sites enrolled 3520 patients by April 24, ’07

On target for May, ’07 enrollment completion