Bivalirudin on Trial: Rationale and Status of ISAR-REACT 3 & 4

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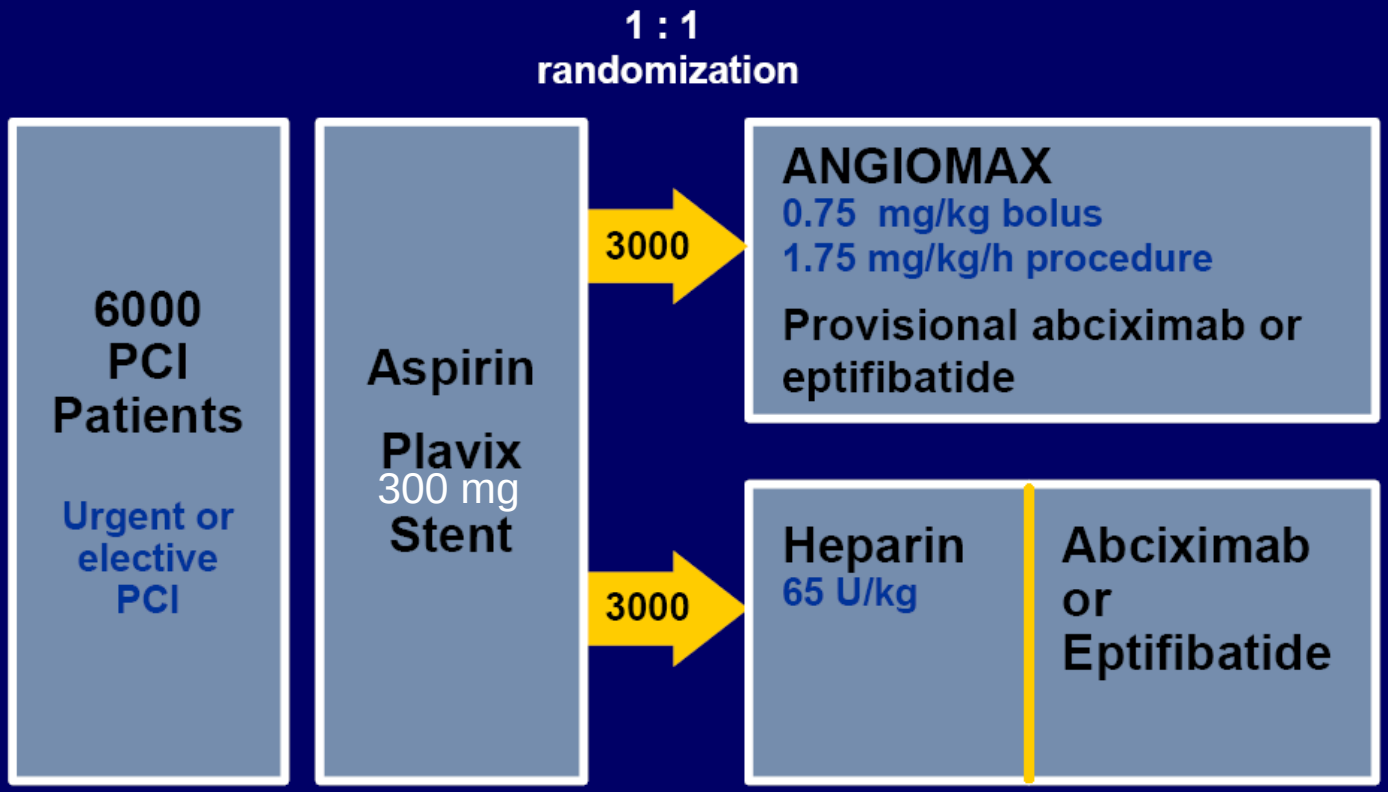
Periprocedural Antithrombotic Therapy

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

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

Bivalirudin in Patients With Stable/Unstable Angina Undergoing PCI

REPLACE 2: Study Design



Endpoints

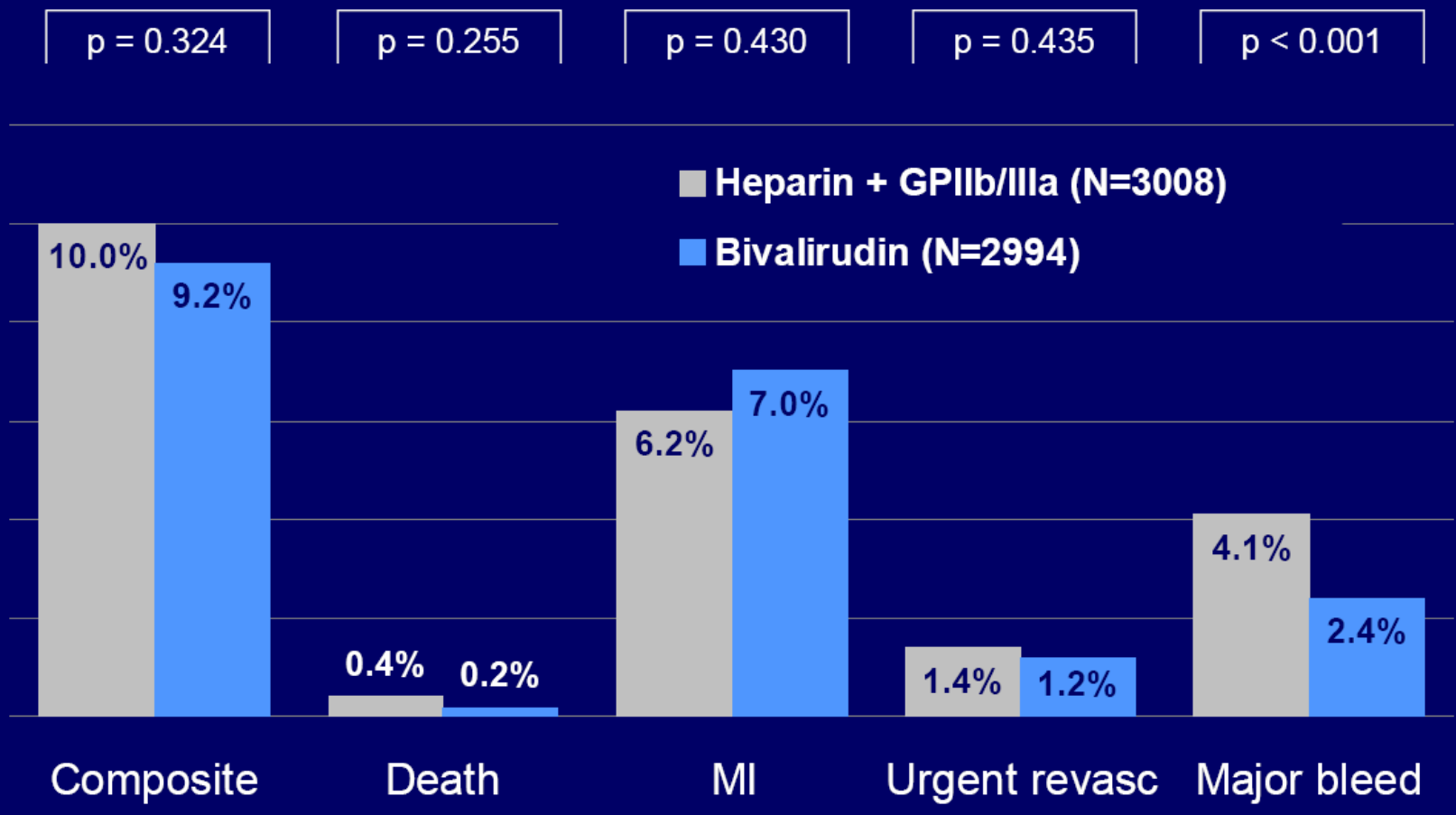
30-day
- Death
- MI
- Revasc
- Hemorrhage

Economics

1-year follow-up

~15% with unstable angina

REPLACE 2: 30-Day Results

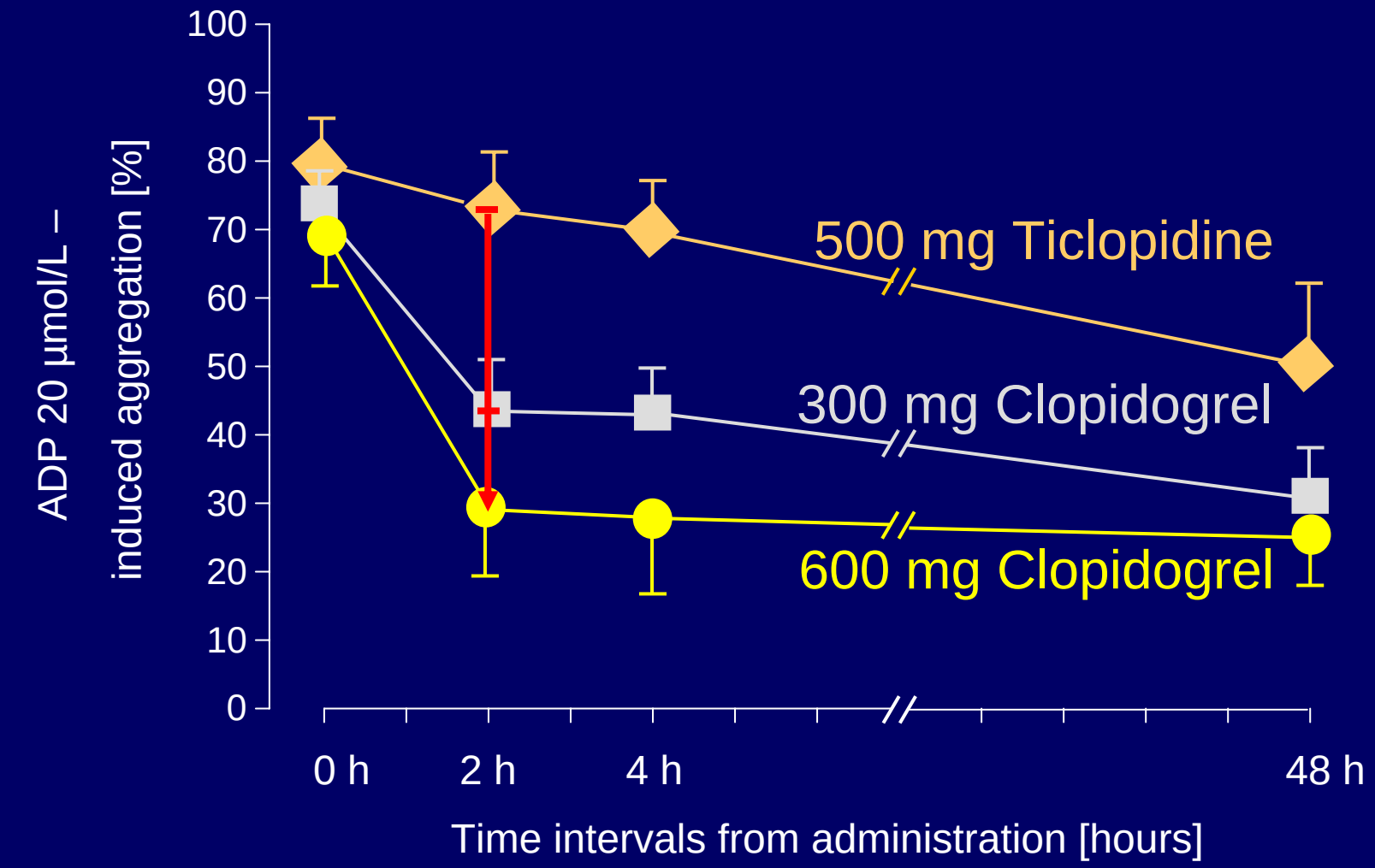


REPLACE 2, JAMA 2003

REPLACE 2: Limitations

- No Pretreatment With 600 mg of Clopidogrel
- No Direct Comparison With Heparin

The Advantage of 600 mg of Clopidogrel



Müller et al, Heart 2001

ISAR–REACT Trial

2159 stable patients

Pre-treated with 600 mg clopidogrel

Abciximab

Placebo

Double-blind

1079 Pts

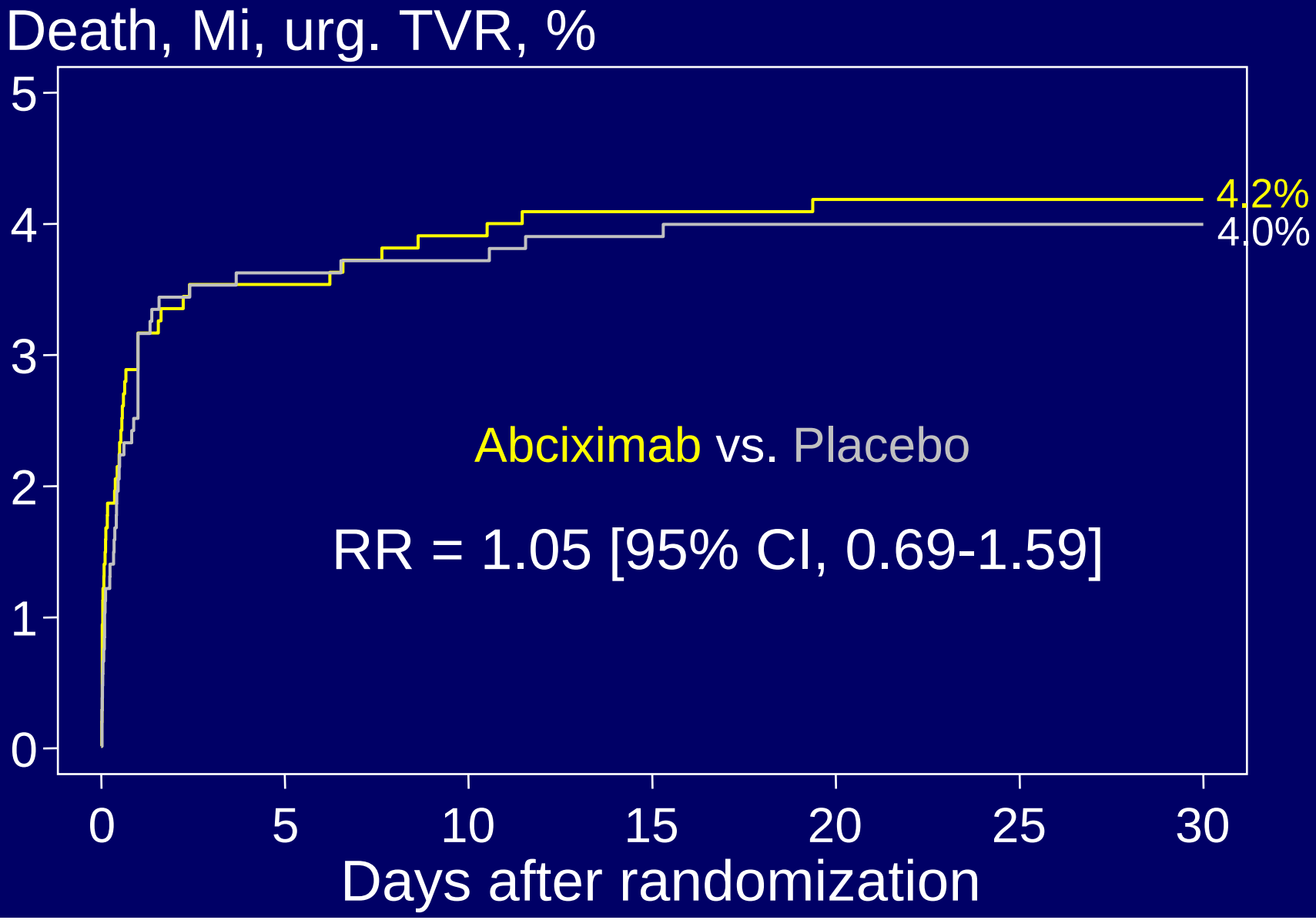
1080 Pts

PCI

30-day FU

ISAR-REACT, NEJM 2004

ISAR-REACT: Primary End Point



Unresolved Issue

Is Bivalirudin Superior to UFH in Patients with Stable or Unstable Angina Undergoing PCI After Pre-treatment With 600 mg of Clopidogrel?

ISAR–REACT 3 Trial

4500 patients without STEMI/NSTEMI

Pre-treated with 600 mg clopidogrel

Double-blind

Bivalirudin

UFH

PCI

30-day Outcome

ISAR-REACT 3: Inclusion Criteria

- Patients with stable or unstable angina >18-year old
- Pretreatment with 600 mg of clopidogrel >2 hours prior to PCI

ISAR-REACT 3: Major Exclusion Criteria

- Acute MI, STEMI or NSTEMI (Trop >.03 μg/L)
- 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 2xCK-MB elevation),
urgent target vessel revascularization
within the first 30 days after PCI or
in-hospital major bleeding (REPLACE 2 definition)

Study Hypothesis:

27.5% reduction of the primary end point with bivalirudin from 8% to 5.8%.

ISAR-REACT 3: Status

3200 Patients Included to Date

Bivalirudin in Patients With Acute Coronary Syndromes Undergoing PCI

ISAR–REACT 2 Trial

2022 patients with high-risk ACS

Pre-treated with 600 mg clopidogrel

Abciximab

Placebo

Double-blind

1010 Pts

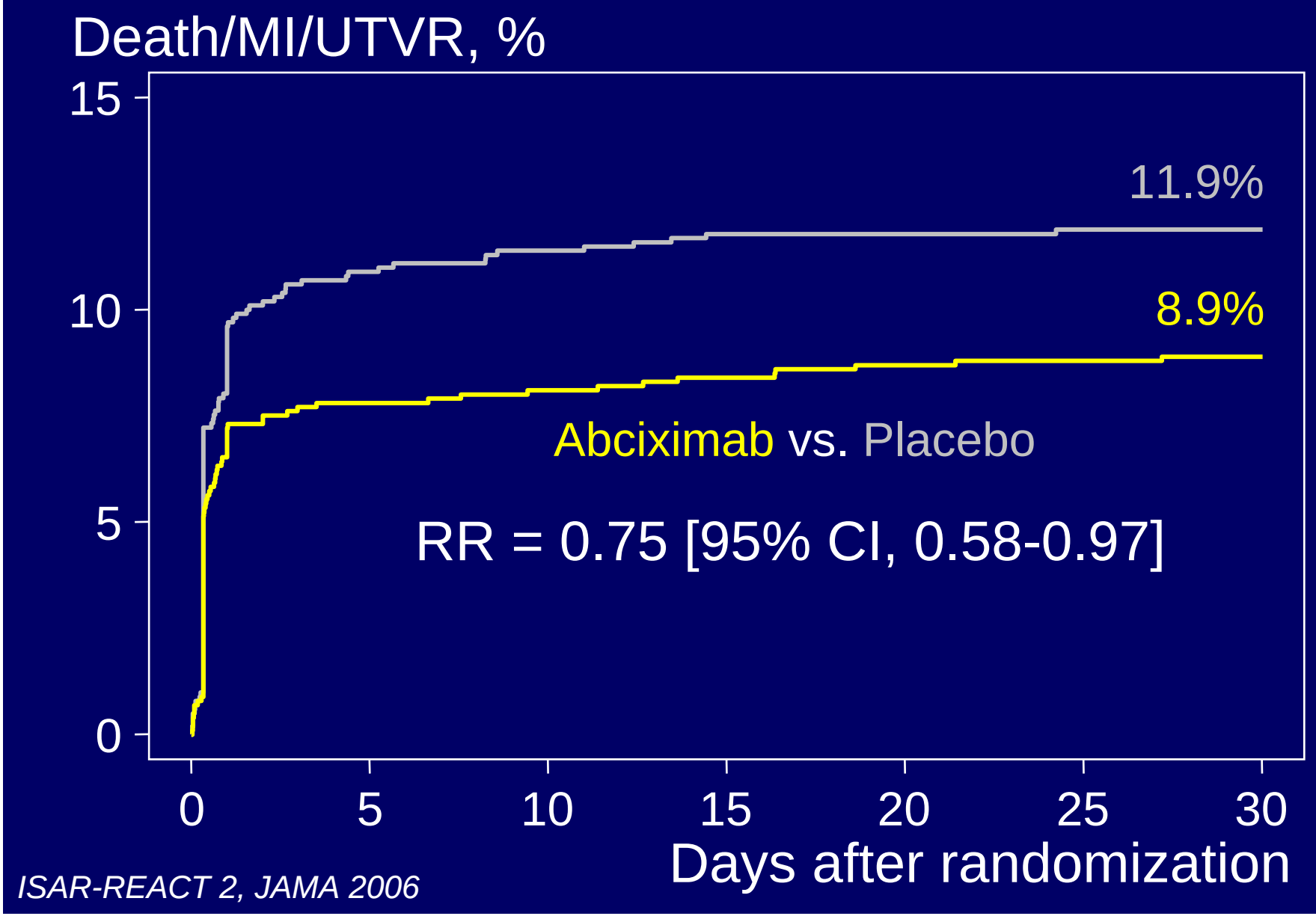
1012 Pts

PCI

30-day outcome

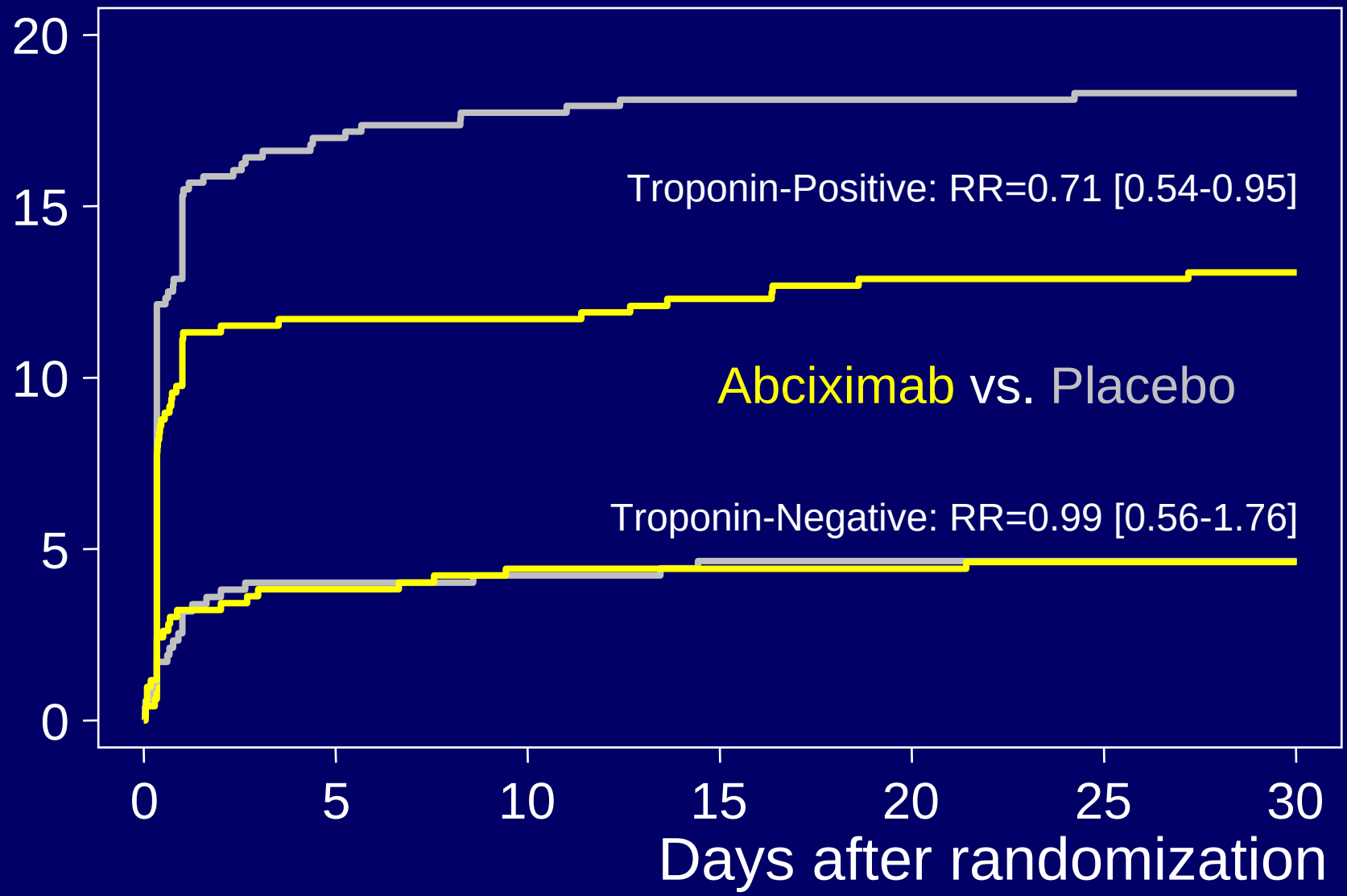
ISAR-REACT 2, JAMA 2006

ISAR–REACT 2: Primary End Point

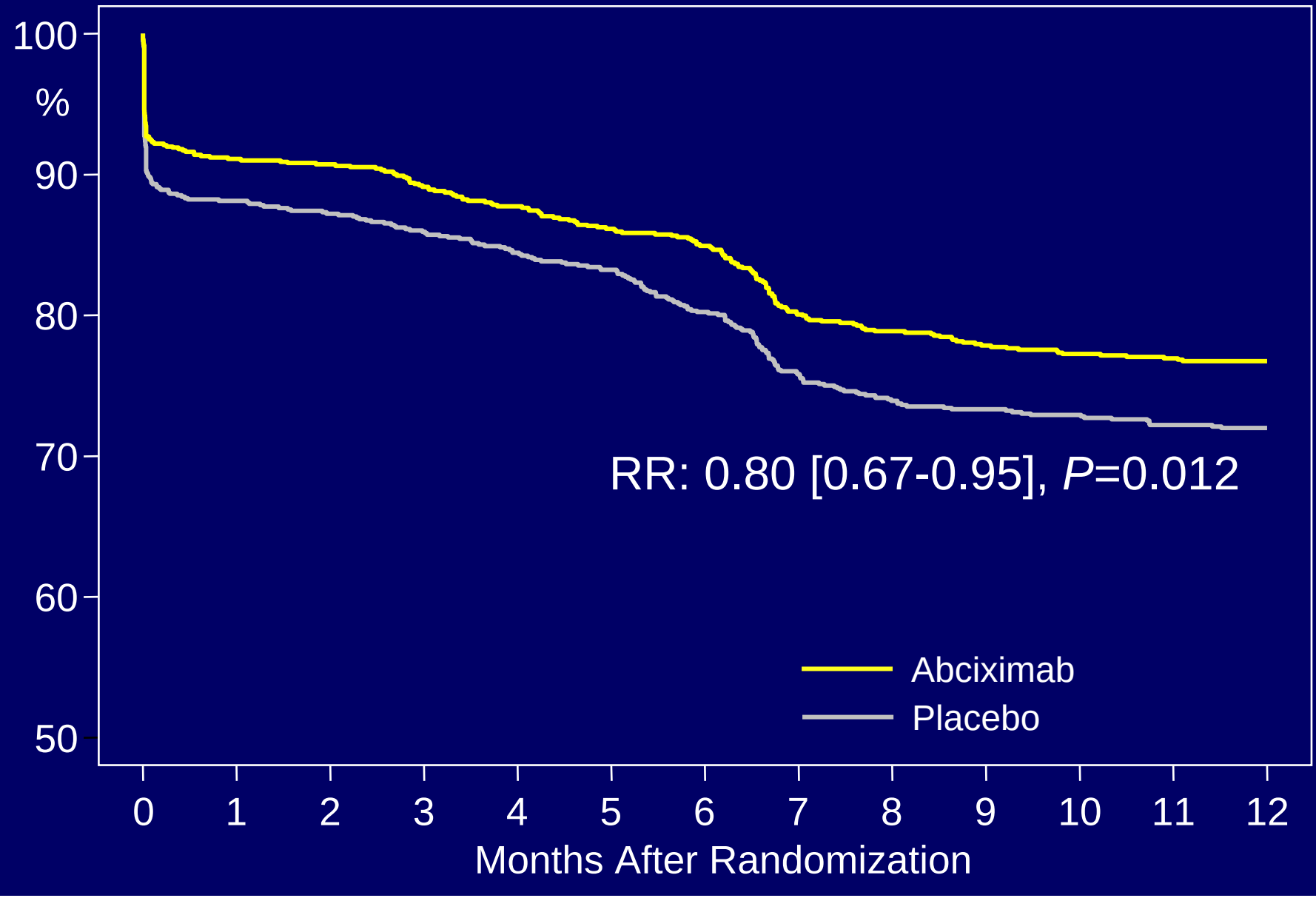


ISAR-REACT 2, JAMA 2006

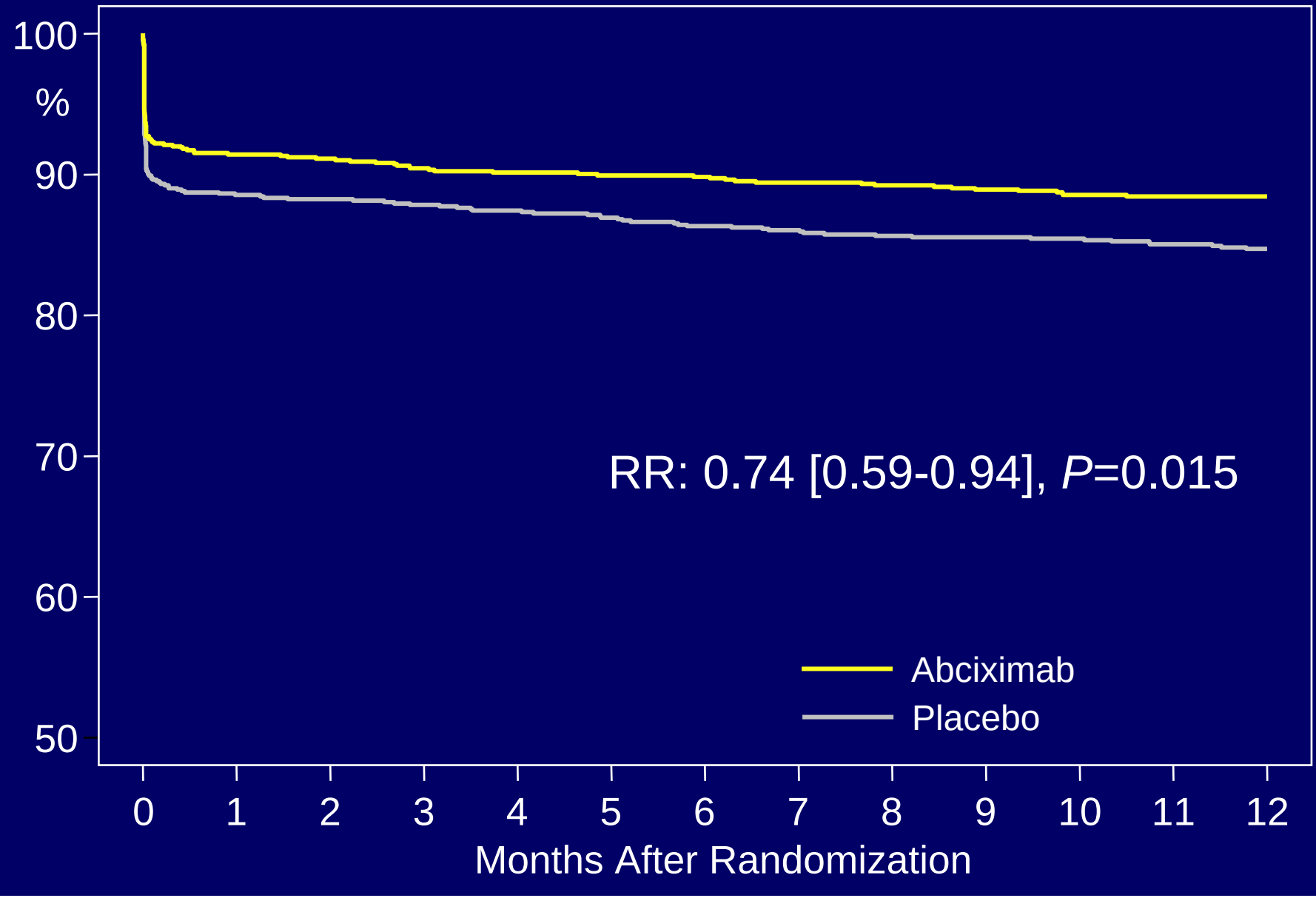
Troponin Level and Benefit With Abciximab



One-Year Survival Free of MACE

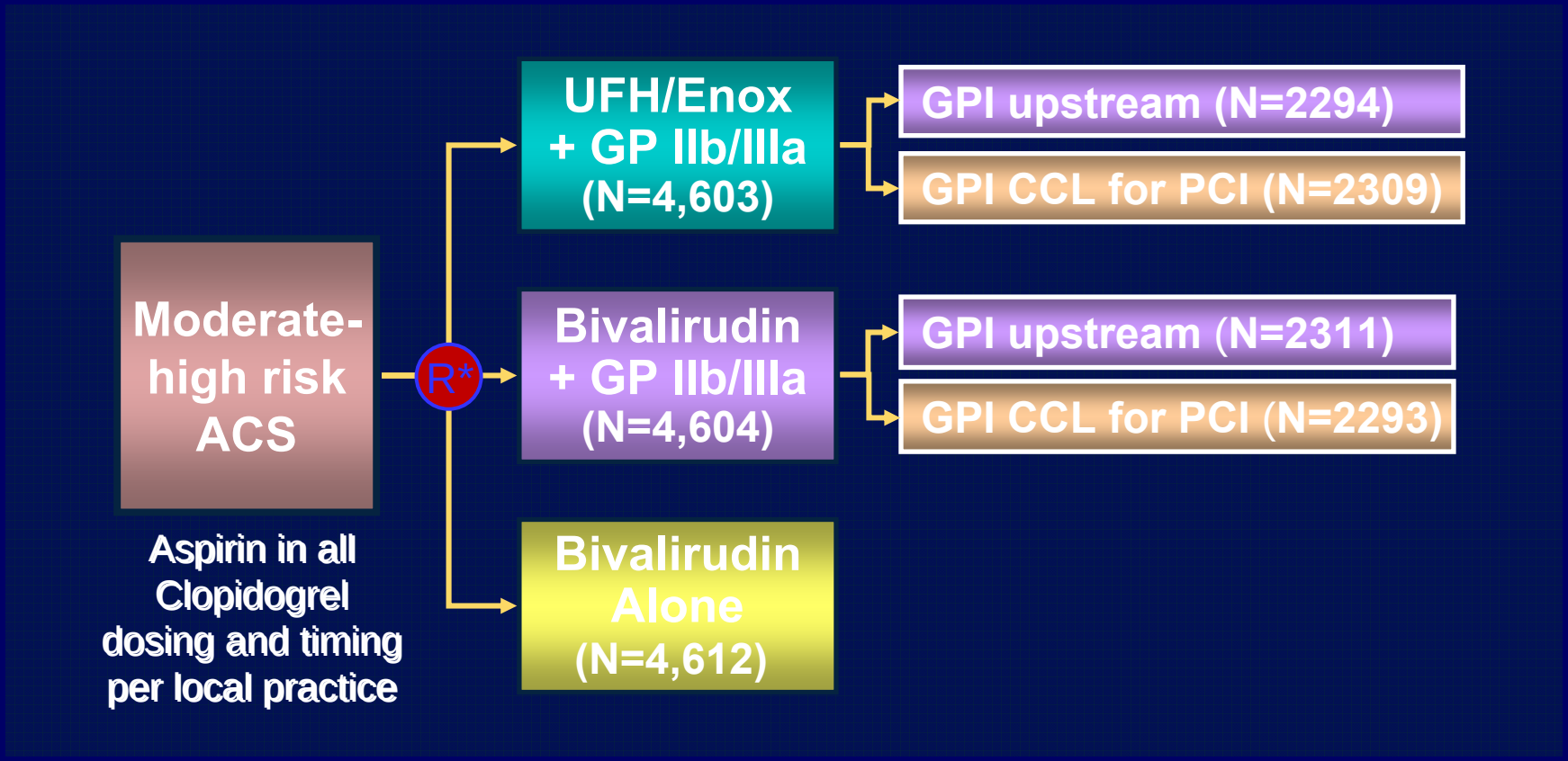


One-Year Survival Free of MI



Bivalirudin in ACS
- ACUITY -

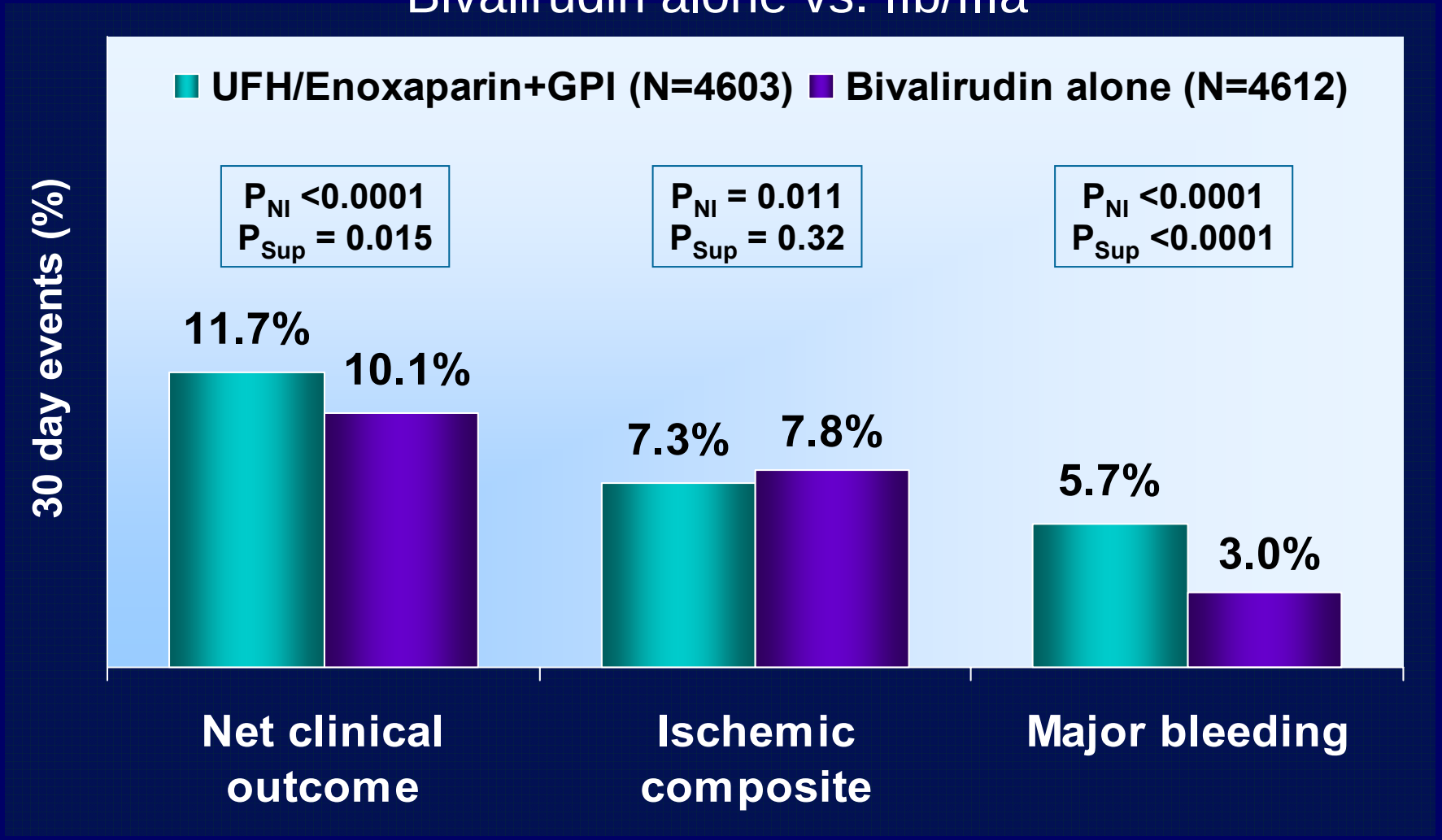
13,819 Pts



ACUITY, ACC 2006

ACUITY
- Primary End Point -

Bivalirudin alone vs. IIb/IIIa



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

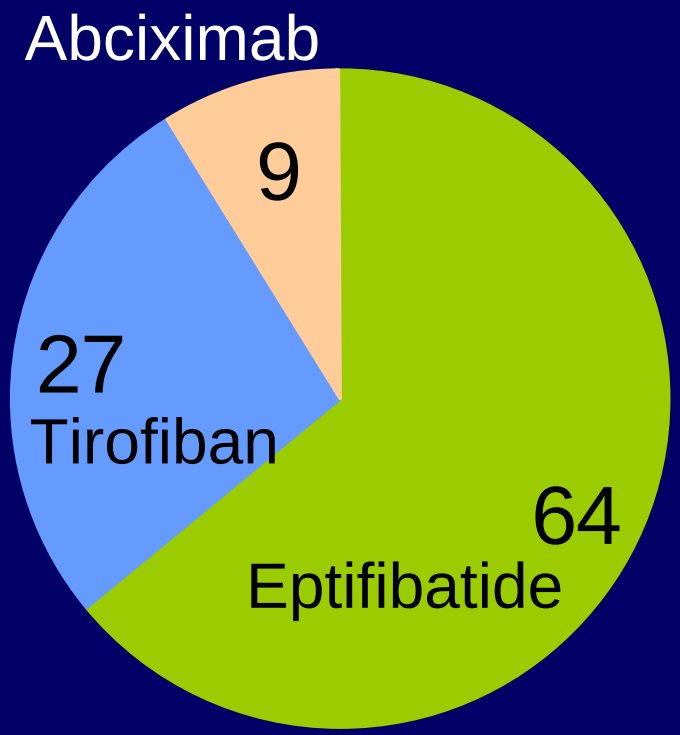
- Blood product transfusion

▪ 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
- Type of IIb/IIIa Inhibitors -



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 abciximab from 15.3% to 10.7%

ISAR-REACT 4: Status

~250 Patients Included to Date

Unique Features of ISAR-REACT 3 and 4

More liberal definition of ischemic and bleeding complications (lower threshold) for stable patients included in ISAR-REACT 3.

More conservative definition of ischemic and bleeding complications (higher threshold) for NSTEMI patients included in ISAR-REACT 4.