Anti-platelet Therapies in Cardiovascular Disease: From Stable CAD to ACS and Afib!

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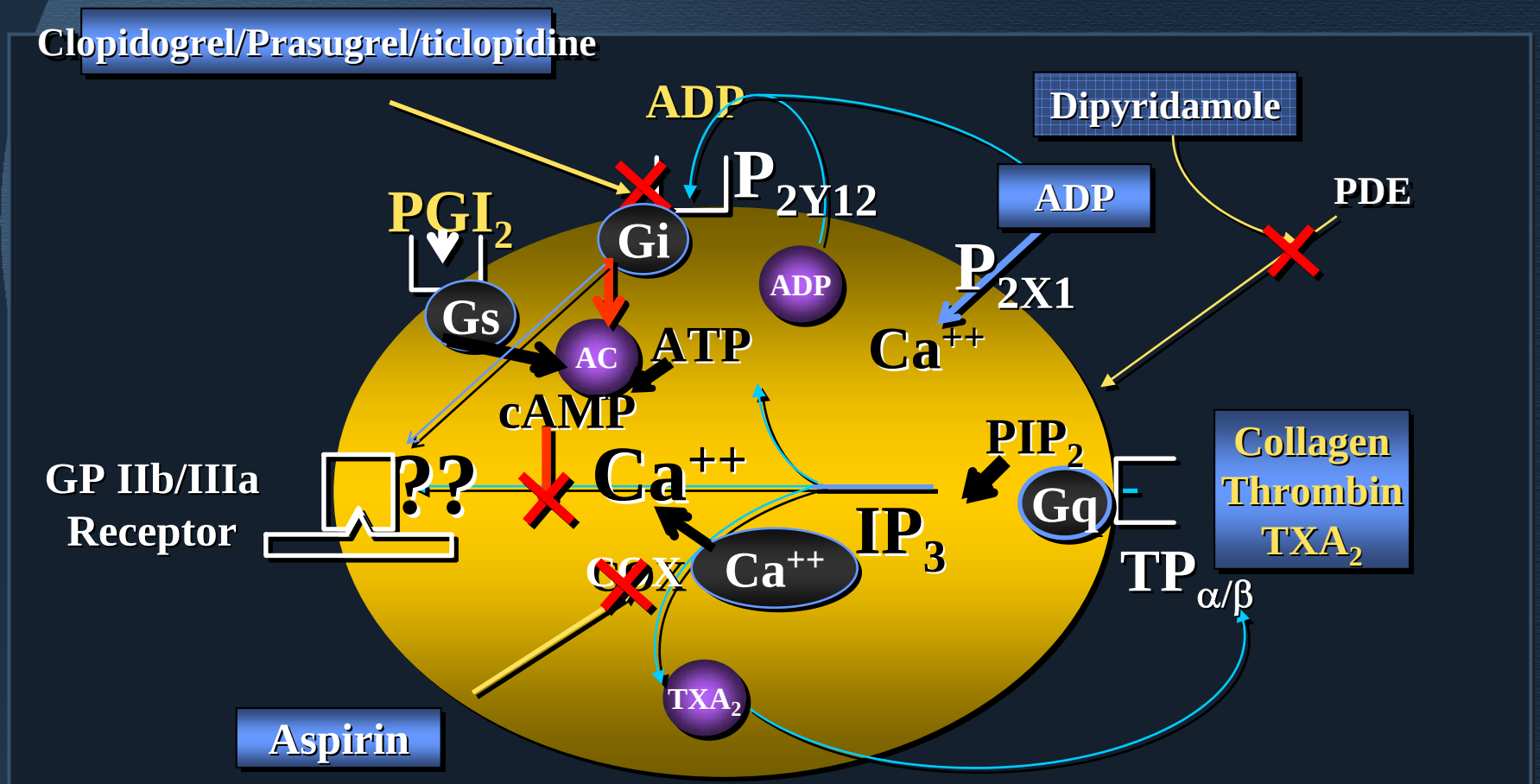
Disclosures

- Research support (significant) from: The Medicines Company, Boston Scientific, Cordis, Medtronic Vascular, Abbott Vascular, Sanofi/Aventis
- Consultant (Modest): Lilly/Diachi Sankyo, Medtronic Vascular, Abbott Vascular, Cordis, Bracco, The Medicines Company

ACC/AHA/SCAI Guidelines:

- Currently the ACC/AHA/SCAI guidelines and FDA recommendations state that patients should receive aspirin indefinitely and clopidogrel for a minimum of 3 or 6 months following implantation of Cypher or Taxus stents (now all approved DES) respectively, with the duration of dual antiplatelet therapy extended to at least 12 months in patients who are at low risk for bleeding

Inhibitors of Platelet Activation



Schafer AI. *Am J Med.* 1996;101:199–209 & Schrör K. *Vasc Med* 1998;3:247-51.

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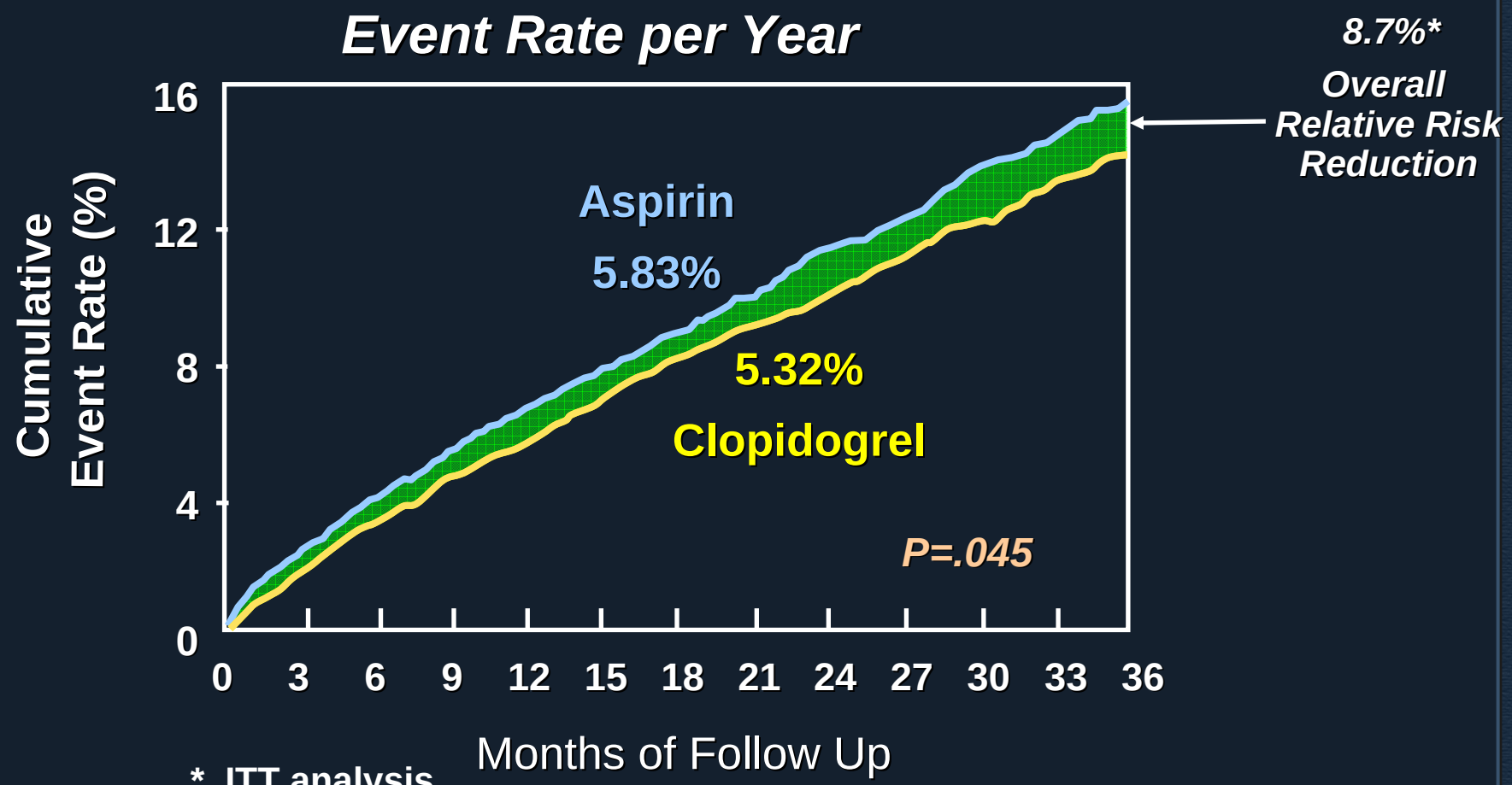
CAPRIE

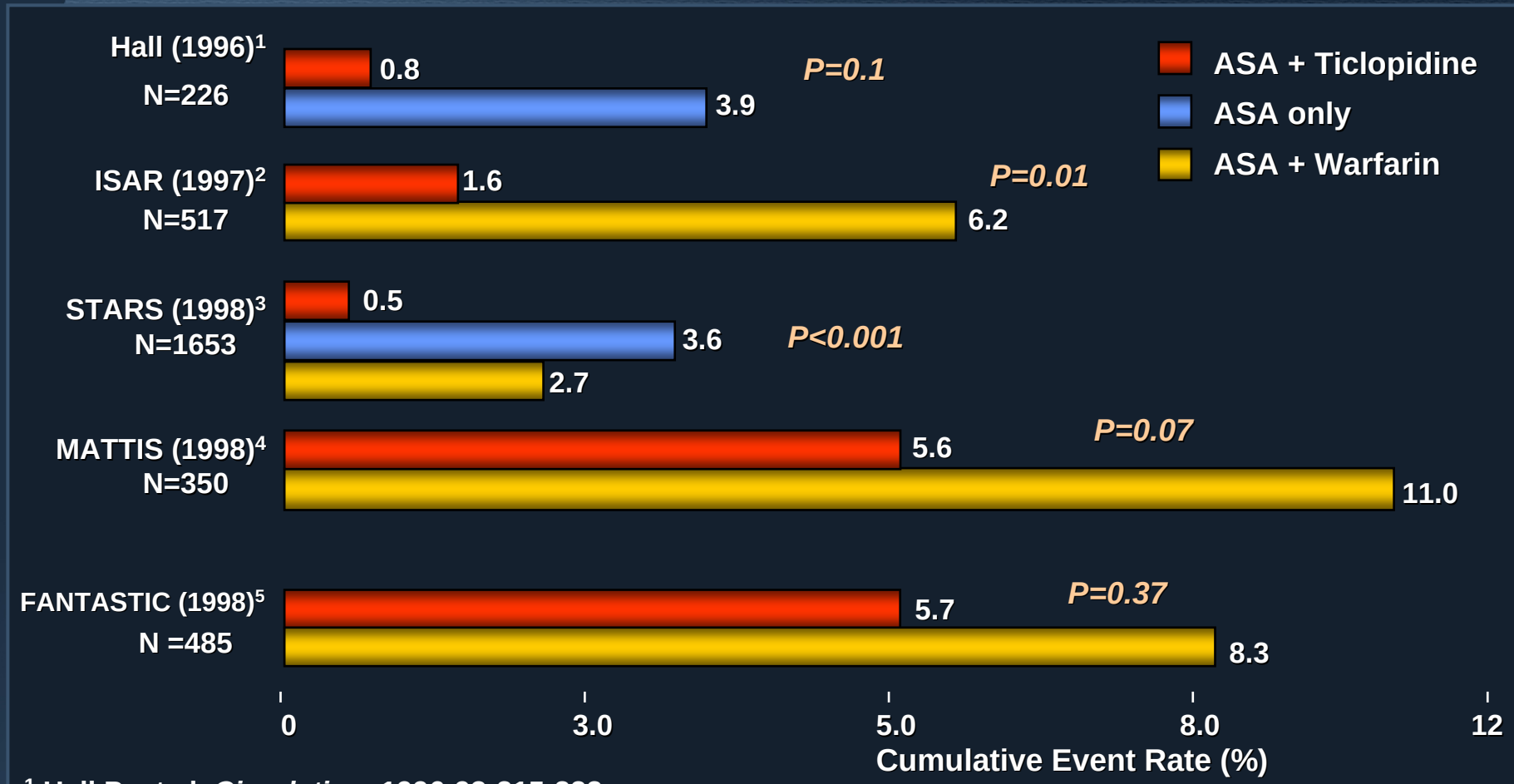
Efficacy of Clopidogrel vs Aspirin in MI, Ischemic Stroke, or Vascular Death (n=19,185)



* ITT analysis

CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.

Efficacy of Combination Antiplatelet Therapy in Reducing Coronary Events after Stenting

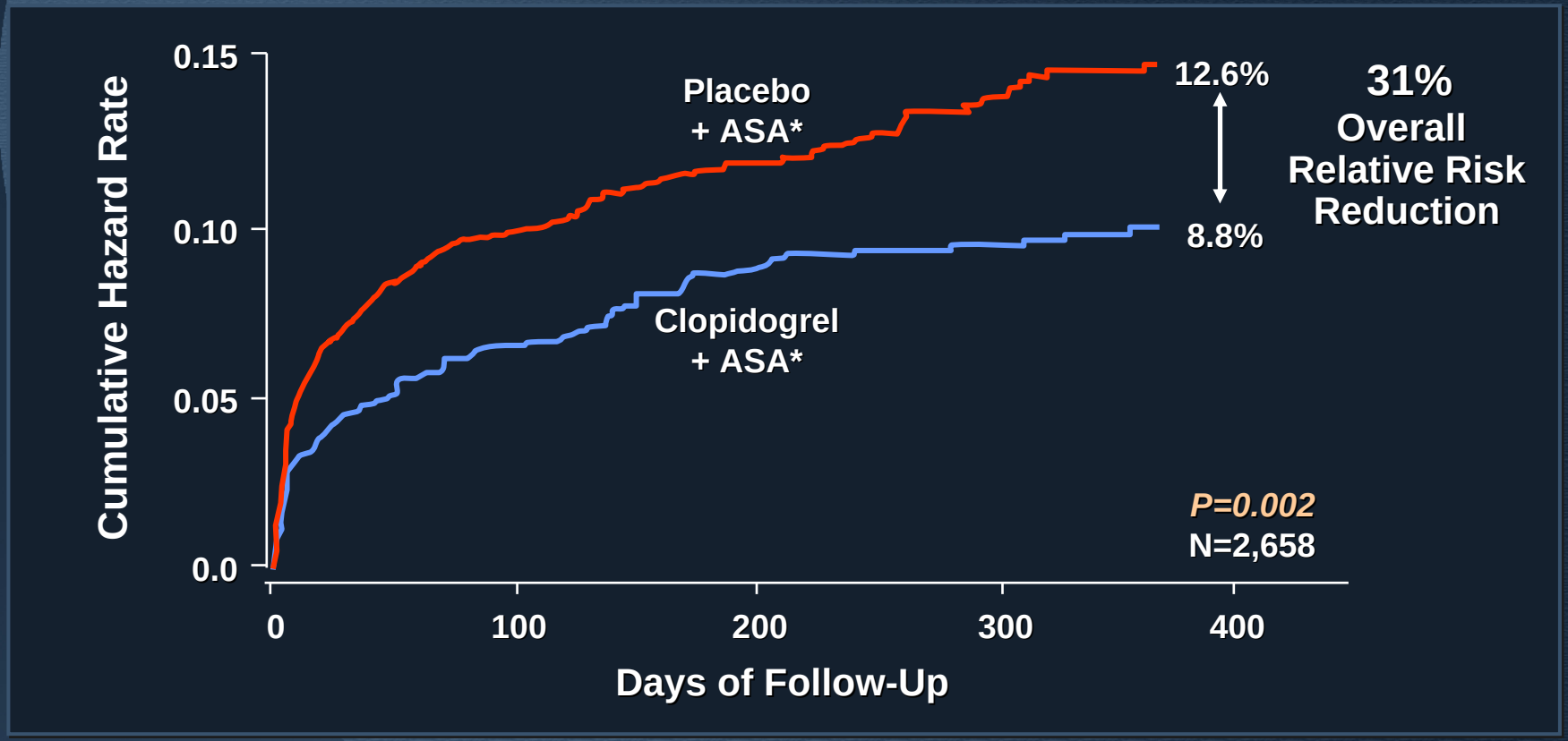


[1] Hall P, et al. *Circulation*. 1996;93:215-222.
[2] Schömig A, et al. *N Engl J Med*. 1996;335:1084-1089.
[3] Leon M, et al. *N Engl J Med*. 1998:339:1665-71.
[4] Urban P, et al. *Circulation*. 1998 98:2126-2132.
[5] Bertrand M, et al. *Circulation.* 1998;98:1597-1603. (Events include death, Q-wave or non-Q-wave MI).

PCI-CURE

Overall Long-Term Results

Composite of MI or Cardiovascular Death From Randomization to End of Follow-Up



* In addition to other standard therapies.

Mehta SR, et al, for the CURE Investigators. *Lancet.* 2001;358:527-533.

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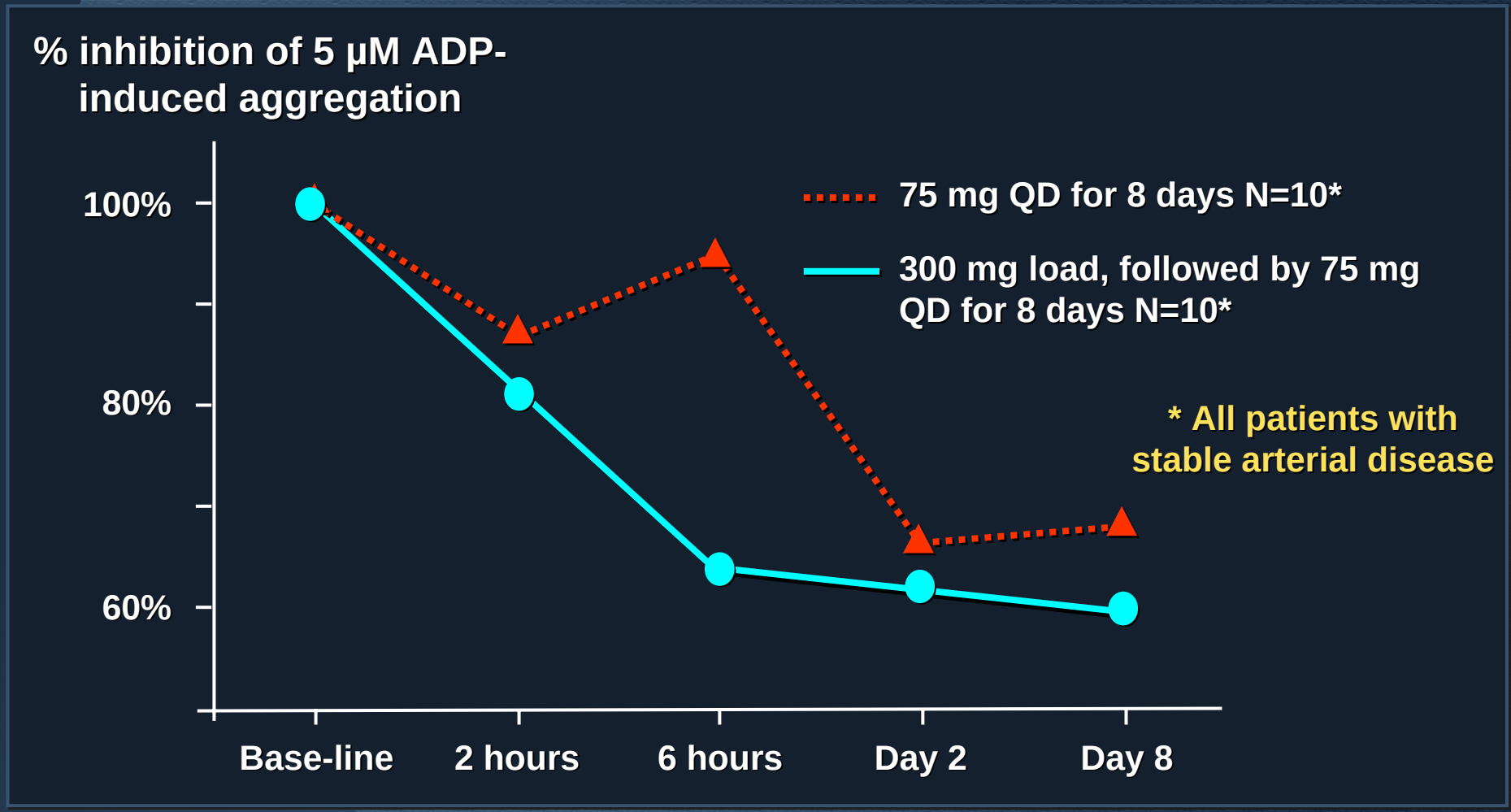
Clopidogrel Loading Dose: 300 mg vs. 75 mg



Helft G. Arterioscler Thromb Vasc Biol 2000;20:2316-21

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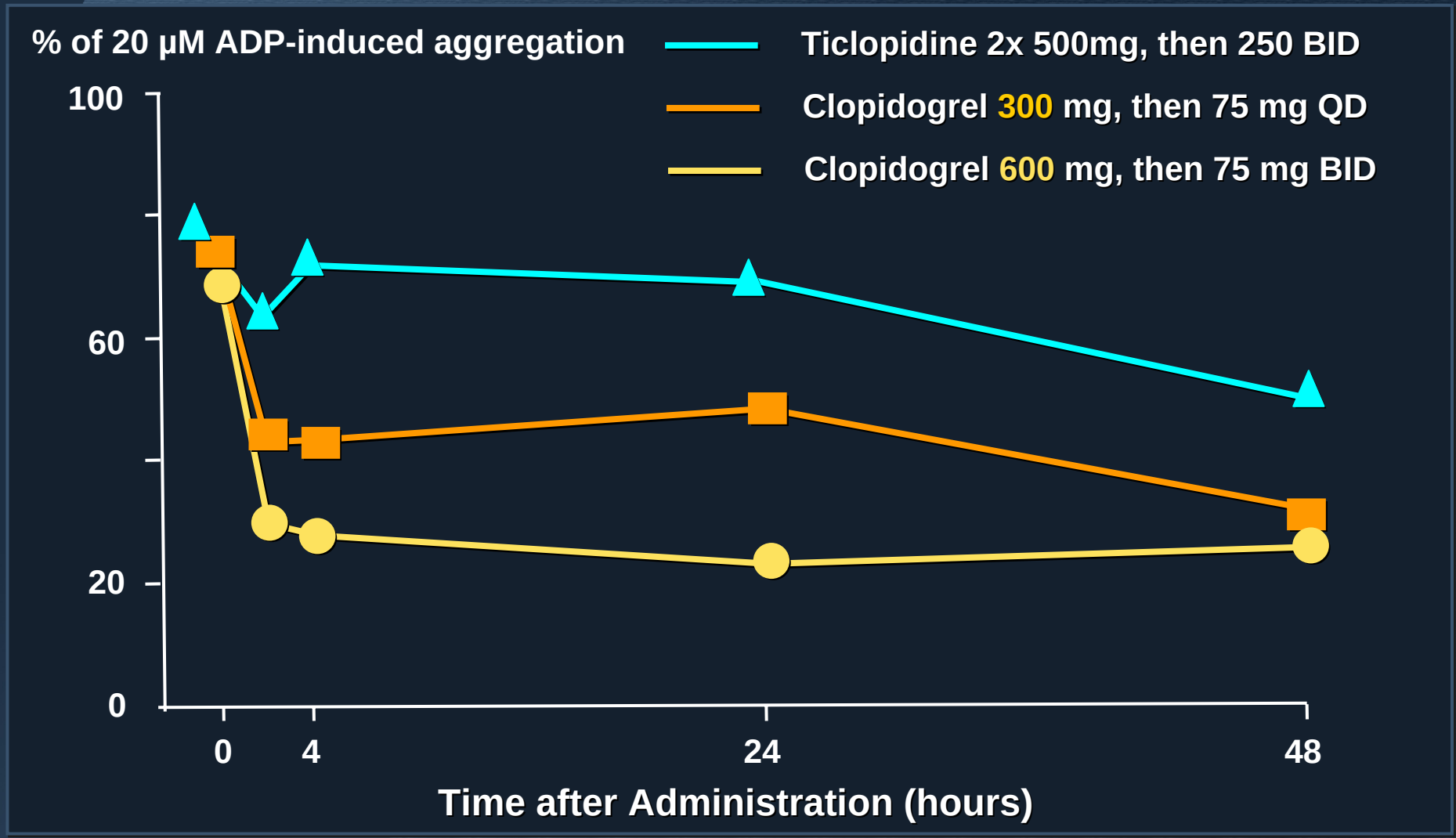
Clopidogrel LD: Is Higher Dosage Better?



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Muller I. *Heart* 2001;85:92-3

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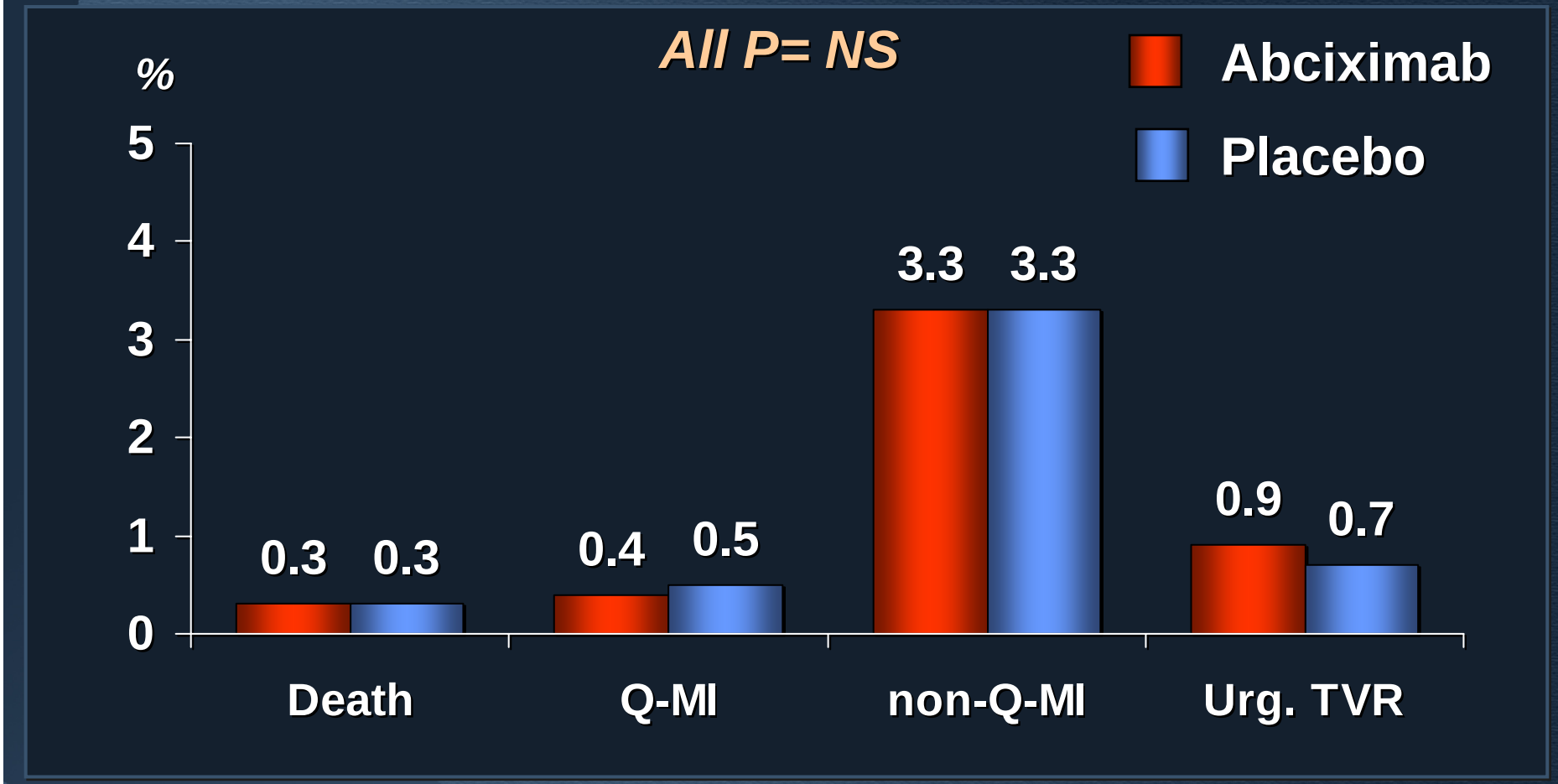
ISAR-REACT

Study Design

- Multicenter, Randomized, Double Blind, Placebo-Controlled Trial (Germany and Mayo Clinic)
- Patients undergoing elective PCI (no recent MI, no ACS, no diabetics)
- Pretreatment with 600 mg clopidogrel for at least 2 hours prior to the intervention; clopidogrel 2x75 mg/day until discharge; 75 mg for at least 4 weeks
- Heparin 70 U/kg bolus
- Patients randomized to abciximab or placebo

ISAR-REACT

Endpoint Components



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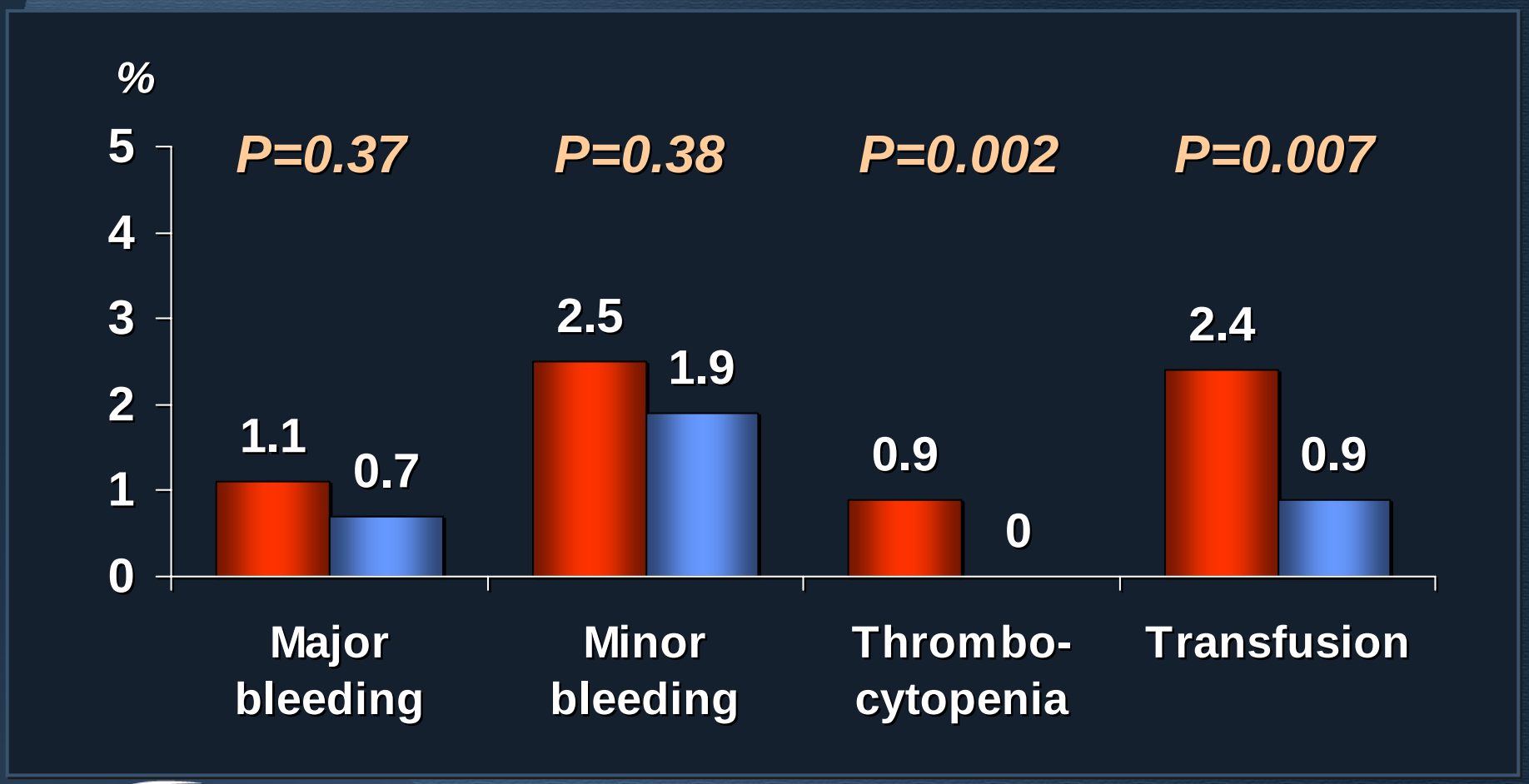
ISAR-REACT

Safety Analysis



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ISAR-REACT 2 Trial: Study Design

2022 patients with an episode of angina within the preceding 48 hours and an elevated troponin T level or new ST-segment depression of ≥0.1 mV or transient (<20 minutes) ST-segment elevation of ≥0.1 mV or new or presumed new bundle-branch block; significant angiographic lesions in a native coronary vessel or venous bypass graft amenable to and requiring a PCI

Placebo Controlled. Randomized. Blinded.

24% female, mean age 66 years, mean follow-up 30 days

↓

Pre-treatment with high dose (600mg) clopidogrel at least 2 hours pre-procedure

↙ ↘

Abciximab
(usual bolus or infusion dose)
n=1012

Placebo
n=1010

- **Primary Endpoint: Composite of death, MI, and urgent target vessel revascularization (TVR) due to myocardial ischemia within 30 days**
- **Secondary Endpoint: In-hospital major and minor bleeding**

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Kastrati A, et al. *JAMA* 2006;295:1531-1538

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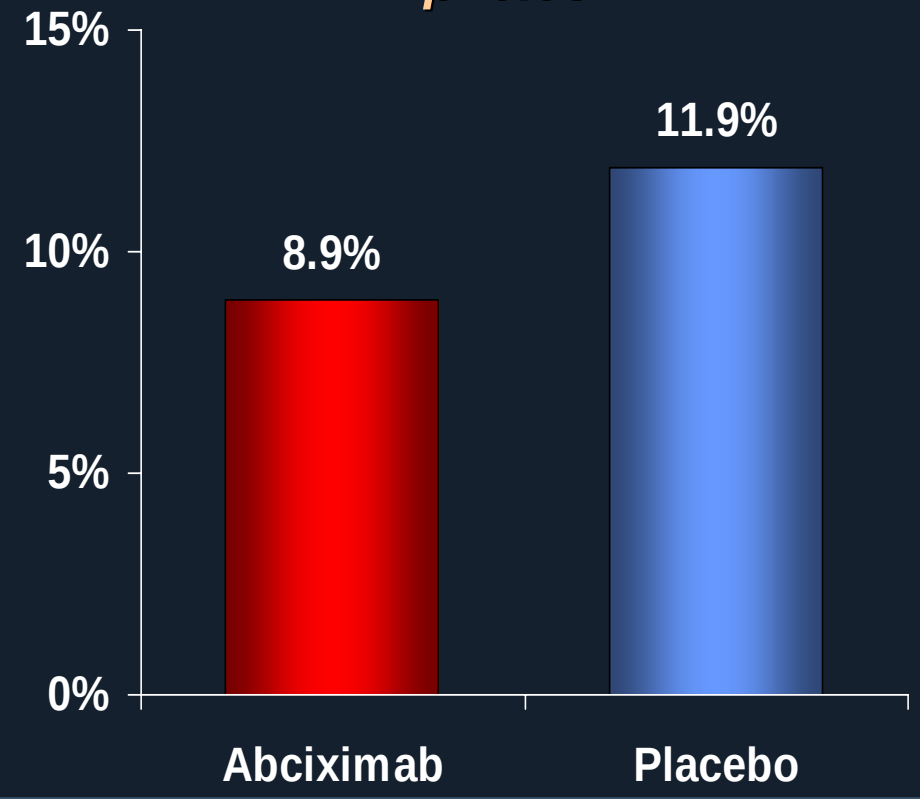
ISAR-REACT 2 Trial: Primary Composite Endpoint

Composite of death, MI, or urgent TVR due to Myocardial Ischemia within 30 days (%)

p=0.03



- **The primary composite endpoint occurred less frequently in the abciximab group compared to placebo (8.9% vs 11.9%; relative risk [RR] 0.75 p=0.03)**

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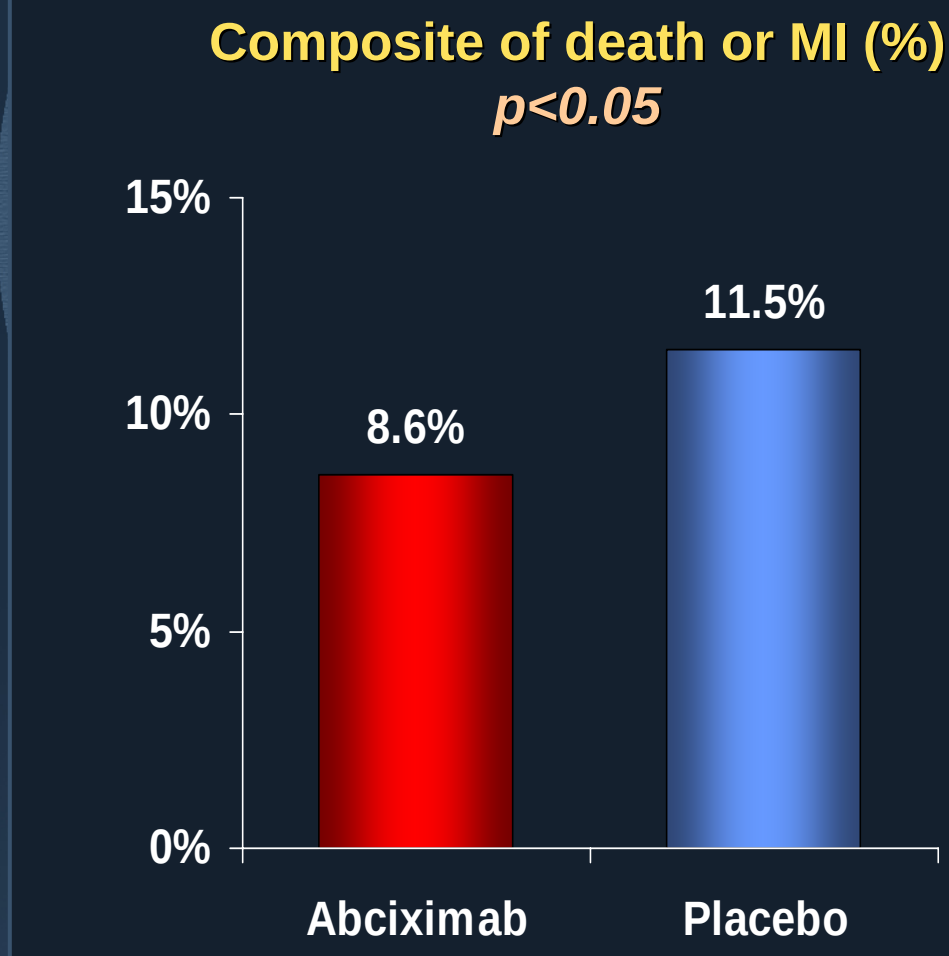
ISAR-REACT 2 Trial: Death or MI



- The composite endpoint of death or MI was also significantly reduced in the abciximab group compared to placebo (8.6% vs 11.5%; RR 0.75; *p<0.05*)

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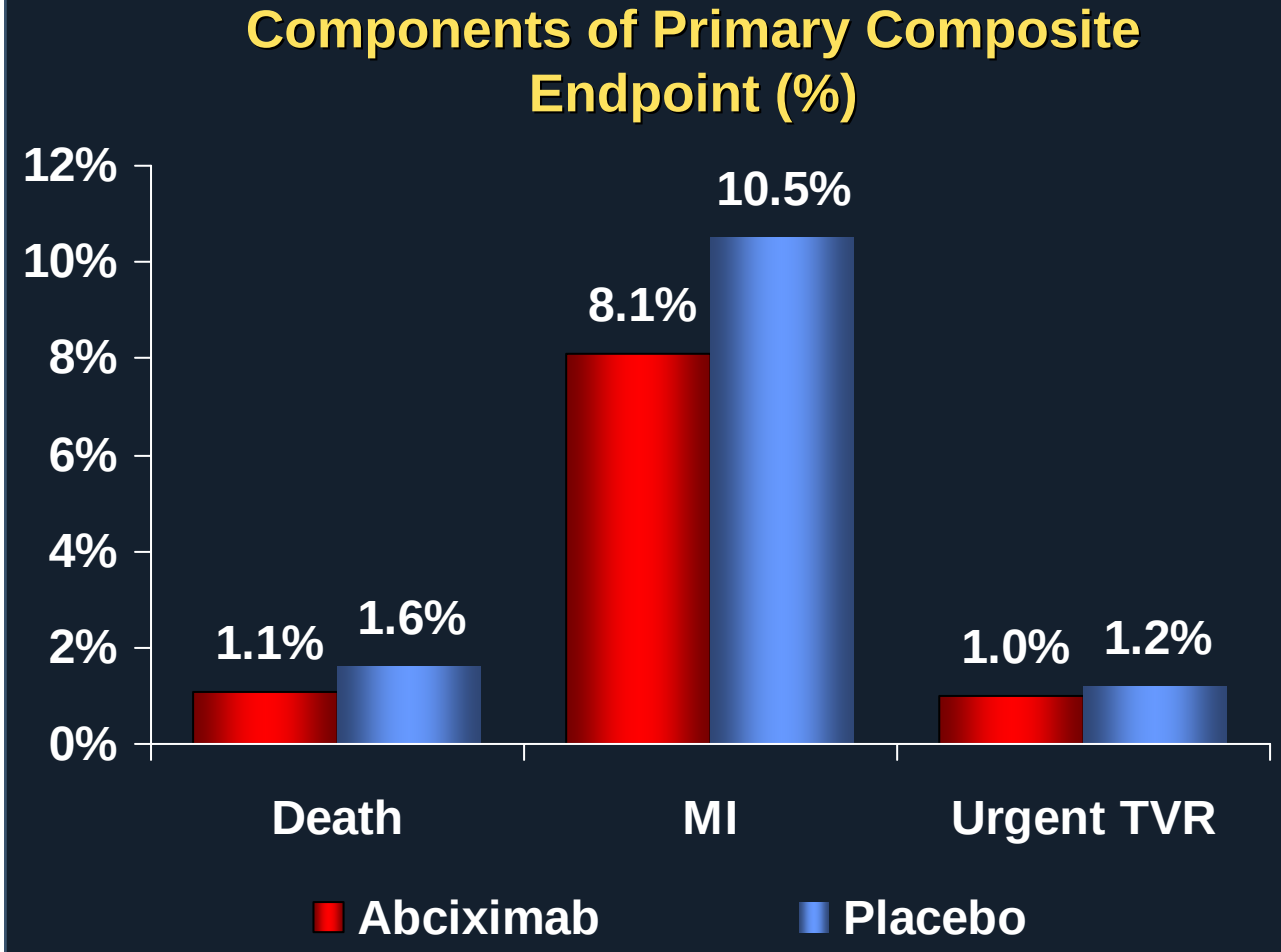
ISAR-REACT 2 Trial: Individual Endpoints



- The components of the primary composite endpoint were directionally lower in the abciximab group:
- Death (1.1% vs 1.6%; RR 0.69)
- MI (8.1% vs 10.5%; RR 0.77)
- Urgent TVR (1.0% vs 1.2%; RR 0.83)

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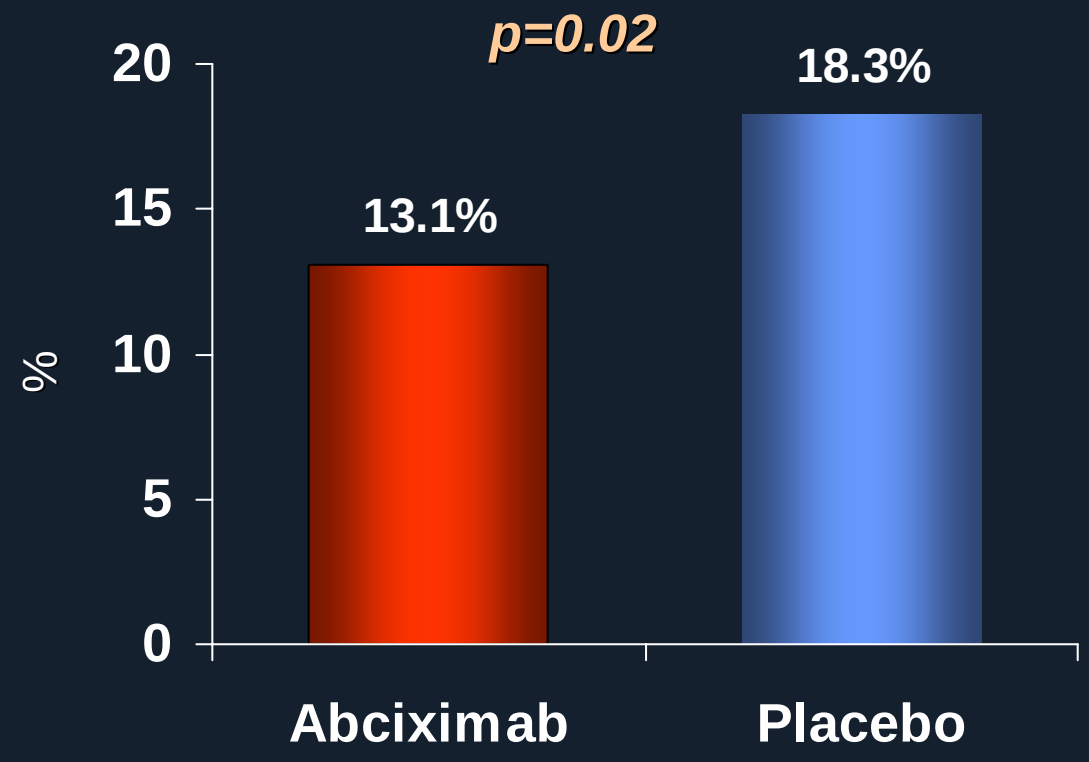
ISAR-REACT 2 Trial: Primary Endpoint (subgroup)

Primary endpoint in troponin positive patients (defined as >0.03 µg/L, n=1049)



- Abciximab therapy was associated with reductions in the primary endpoint among patients who were troponin positive at baseline (13.1% vs 18.3%; RR 0.71; p=0.02)

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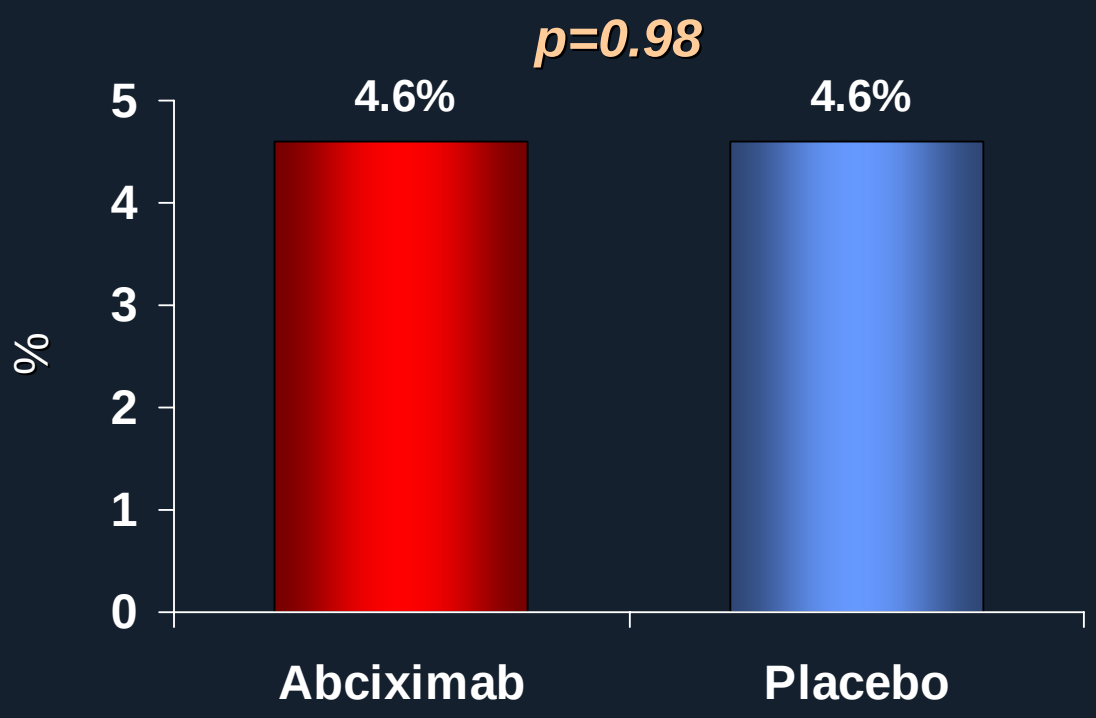
ISAR-REACT 2 Trial: Primary Endpoint (subgroup)

Primary endpoint in troponin negative patients (defined as <0.03µg/L, n=973)



- There was no difference seen in patients who were troponin negative at baseline (4.6% each; RR 0.99; p=0.98; interaction p=0.07)

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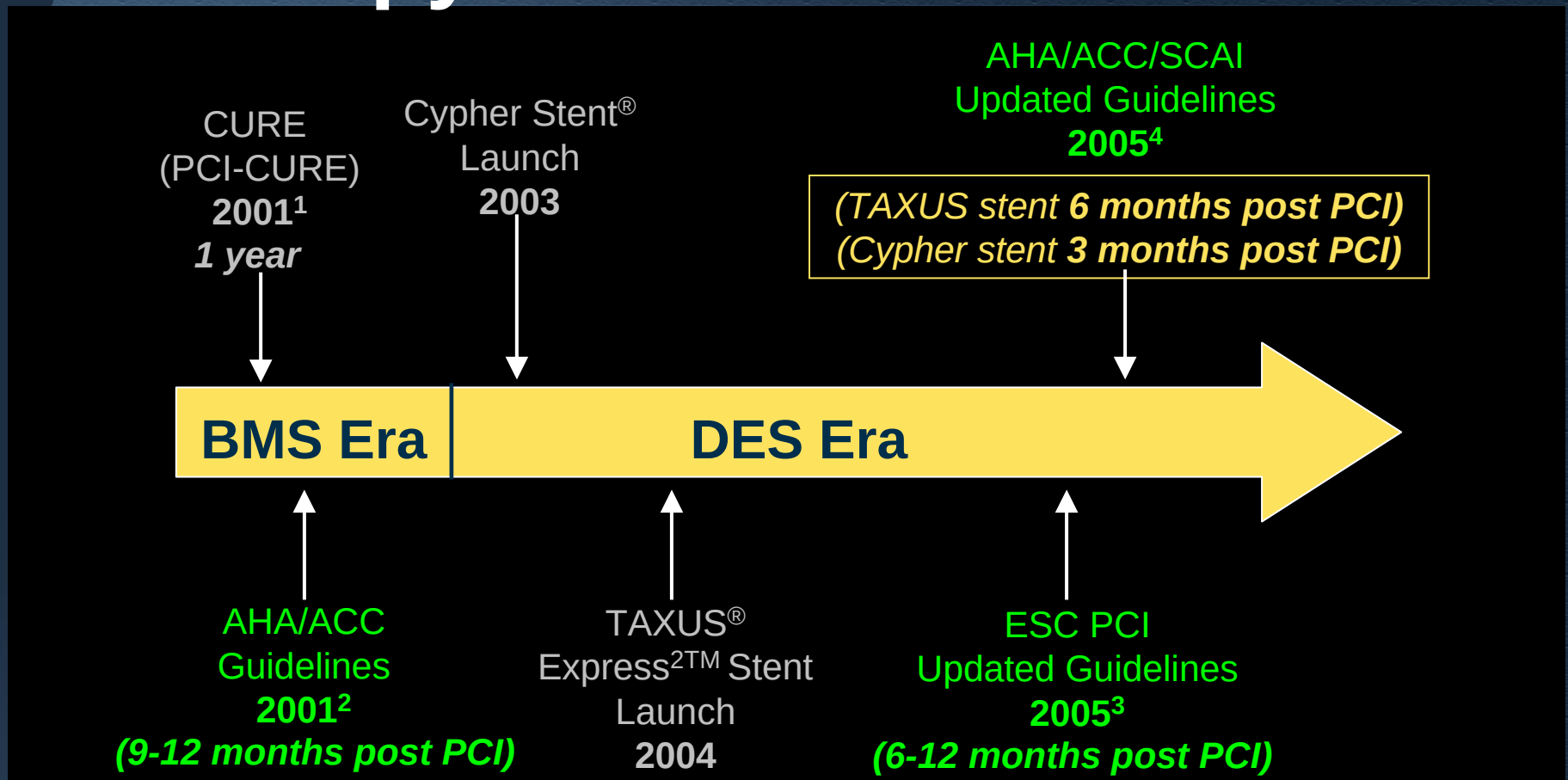
Scope of the Problem

- DES needs long-term combination antiplatelet therapy (ASA+clopidogrel for at least 1 year)
- Surgery has bleeding complications
  - Hence, surgeons are used to stop all anti-platelet and anti-thrombotic agents pre-op
- Premature stopping of anti-platelet Rx after DES may risk stent thrombosis
  - The cardiologist needs to know if anti-platelet Rx is to be altered in a patient with DES.
- Therefore, both specialties have to communicate provided that they know what this entails

Optimal Duration of Anti-platelet Therapy Post DES Still Unclear



PCI = percutaneous coronary intervention; AHA = American Heart Association; ACC = American College of Cardiology; SCAI = Society for Cardiac Angiography and Interventions.

1. Mehta et al. Lancet. 2001;358:537; 2. Smith et al. *JACC.* 2001;37:238ii; 3. Silber et al. *Eur Heart J.* 2005;26:2476;
4. Smith et al. *Circulation.* 2006;113:e166.

Bleeding *vs.* SAT Risk

- **Bleeding peri-op**
  - In certain surgeries more than others (e.g. intra-abdominal)
  - Increased length of stay
  - Transfusion
  - Wound complications
  - Life-threatening rarely
- **SAT peri-op**
  - Surgery is prothrombotic
    - Certain ones more than others (e.g. vascular etc)
  - Events relate to the total duration of antiplatelet interruption
    - Stopping 1 can be detrimental, but still better than stopping both
  - Can be fatal or debilitating (CHF)
  - Treatment can be very problematic peri-op
    - Anticoagulation restrictions
    - Decreased/unreliable p.o. intake
    - Comorbidities (e.g. infection, sepsis)
- **Therefore, the stakes clearly favor putting Heart First!**

FACT

Major bleeding (with or without blood product transfusions) has emerged as a powerful independent predictor of early and late mortality in pts with NSTEMI, STEMI and in those undergoing PCI

HORIZONS AMI

Question?

Should major bleeding be combined with major adverse ischemic events (MACE) in a composite endpoint to predict mortality?

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Should major bleeding be combined with major adverse ischemic events (MACE) in a composite endpoint to predict mortality?

The concept of NACE = Net Adverse Cardiovascular Events

HORIZONS AMI

ACTIVE A

Effects of Addition of Clopidogrel to Aspirin in Patients with Atrial Fibrillation who are Unsuitable for Vitamin K Antagonists

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Vitamin K Antagonists in AF

- Reduce stroke by 38%, compared to aspirin
- Recommended in high risk patients with AF
- Only 40-50% of ideal patients receive VKA in Western countries
  - Many patients considered unsuitable
  - Due to poor INR control, concern about bleeding
  - Patient preference

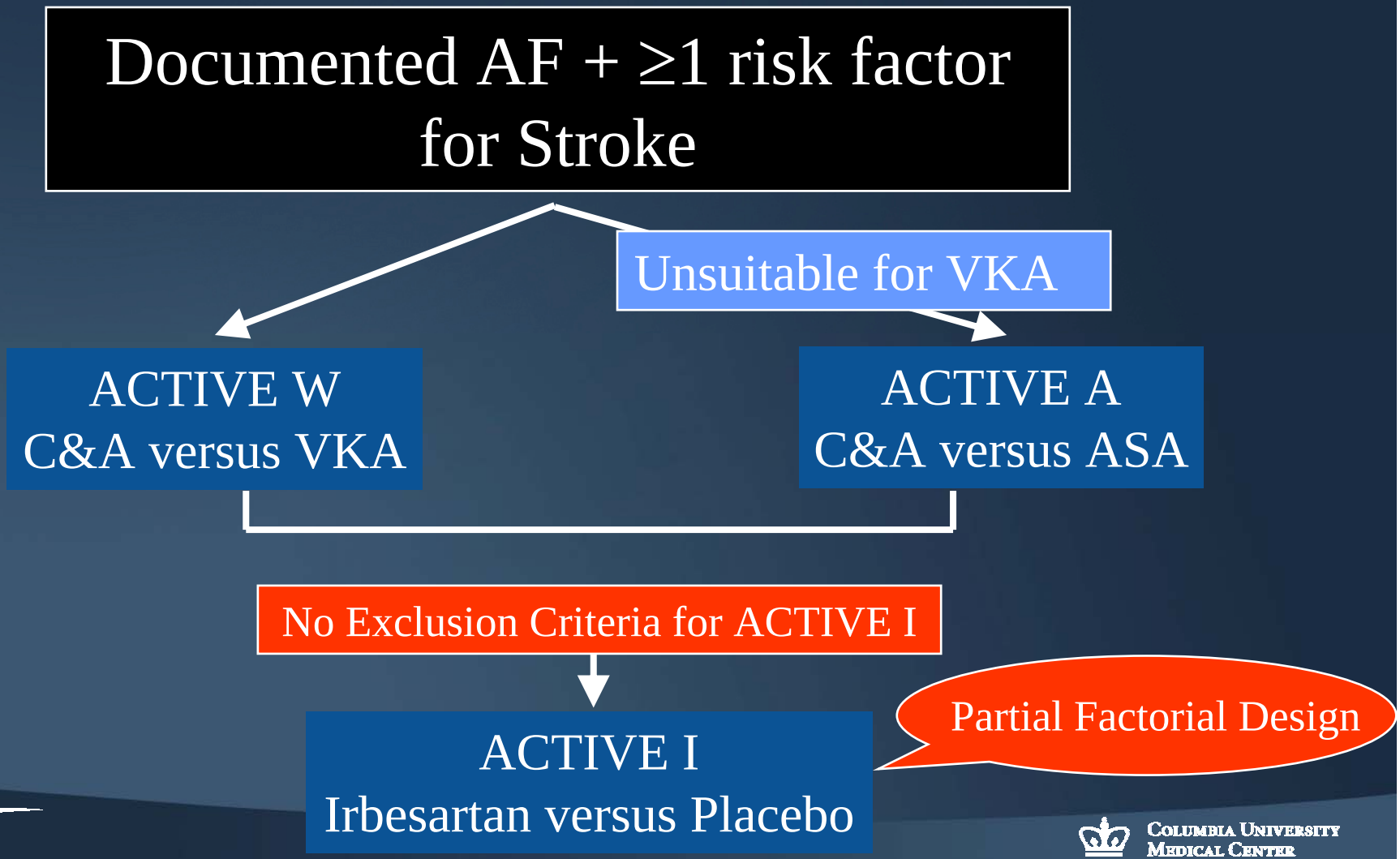
Antiplatelet Therapy in AF

- Increased platelet activation in AF
- Aspirin reduces stroke in AF by 22%
- Addition of clopidogrel to aspirin achieves greater suppression of platelet activity
- Addition of clopidogrel to aspirin reduces vascular events in ACS, with acceptable risk of bleeding

Hypothesis of ACTIVE A

In patients with AF, unsuitable for VKA therapy, addition of clopidogrel to aspirin will reduce the risk of major vascular events, at acceptable risk of major bleeding

Design of ACTIVE



Patient Eligibility

- Eligibility criteria for ACTIVE A and ACTIVE W were identical
  - Documented AF
  - One or more risk factors for stroke
  - Absence of major risk factor for bleeding

- Investigators selected patients for either study based on assessment of suitability for VKA

ACTIVE A Study Treatments

- All patients received aspirin at a recommended daily dose of 75-100 mgs
- Patients were randomized, double blind, to clopidogrel, 75 mg per day, or matching placebo

Outcomes and Statistical Power

- Primary outcome was a composite of major vascular events:
  - Stroke, myocardial infarction, non-CNS systemic embolism or vascular death
- Secondary outcomes
  - Stroke
  - Major hemorrhage
- 7500 patients planned to achieve 88% power to detect 15% reduction in primary outcome (1600 events)

Study Conduct

- 33 Countries, 580 centers
- 7554 patients enrolled between June 2003 and May 2006
- Final follow up in November 2008
  - Median follow up 3.6 years
  - Follow up was complete in 99.4% of patients

Reasons for Enrolment in ACTIVE A

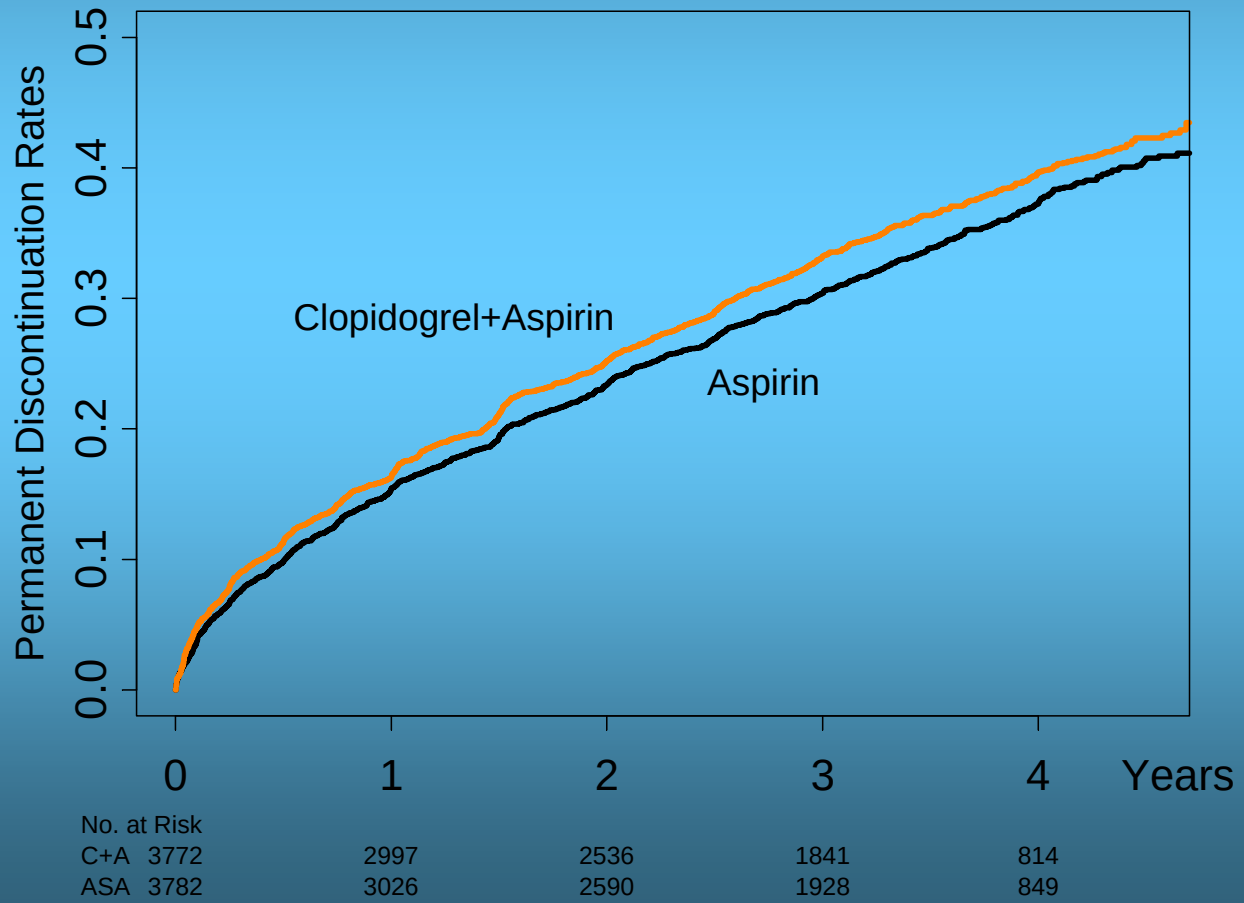
Relative risk factor for bleeding*	23%
Physician assessment that patient is inappropriate for VKA	**50%**
Patient Preference Only	**26%**

* Inability to comply with INR monitoring, predisposition to falling or head trauma, persistent BP >160/100, previous serious bleeding on VKA, severe alcohol abuse <2 years, peptic ulcer disease, thrombocytopenia, need for chronic NSAID

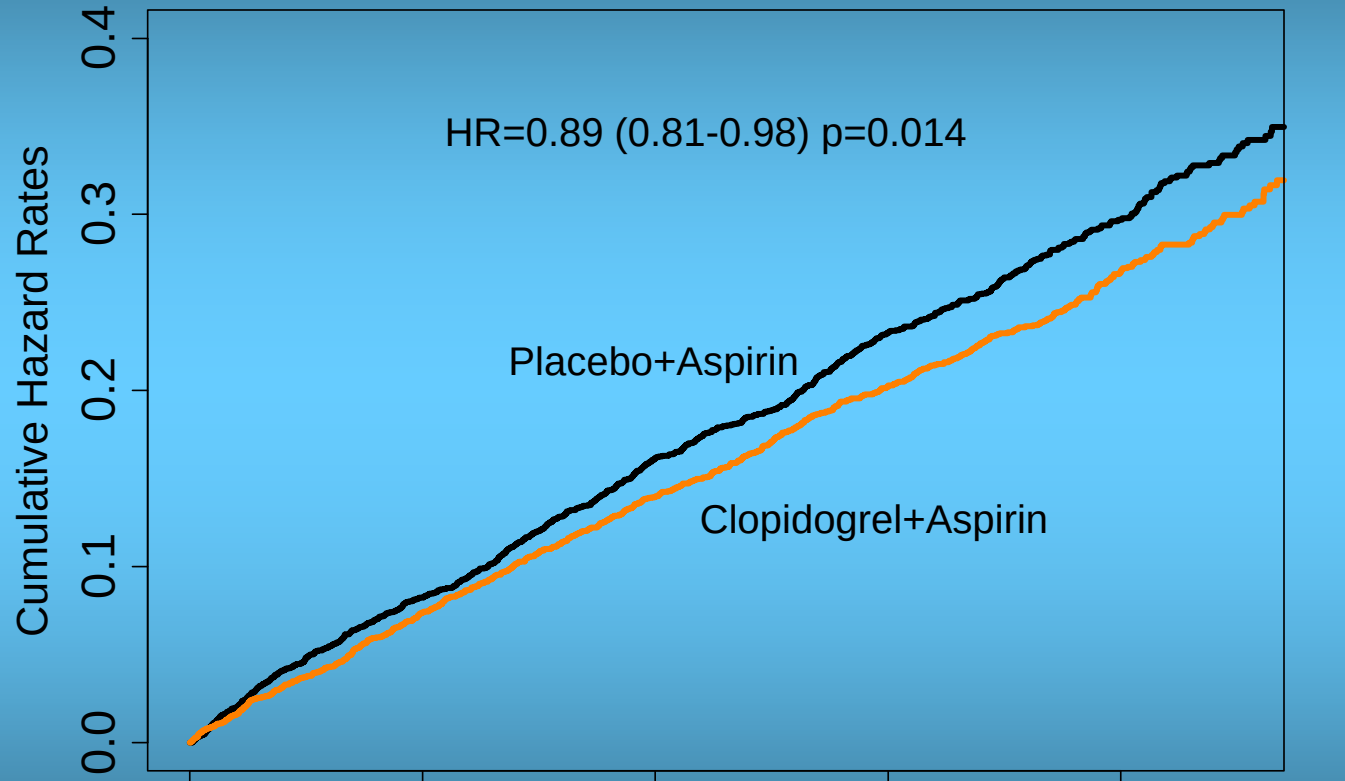
Baseline Demographics

	ACTIVE A	ACTIVE W
N	7554	6706
Mean age (years)	71 ± 10	70 ± 9
Male	58%	66%
Mean systolic BP (mmHg)	136 ± 19	133 ± 19
Permanent AF	64%	68%
Baseline VKA use	8.5%	77%
Baseline aspirin use	83%	26%
Prior MI	14%	18%
Prior stroke or TIA	13%	15%
Mean CHADS2 score	2.0 ± 1.1	2.0 ± 1.1

Permanent Study Medication Discontinuation



Primary Outcome (Stroke, MI, non-CNS Systemic Embolism, Vascular Death)



No. at Risk					
C+A	3772	3456	3180	2522	1179
ASA	3782	3426	3103	2460	1156

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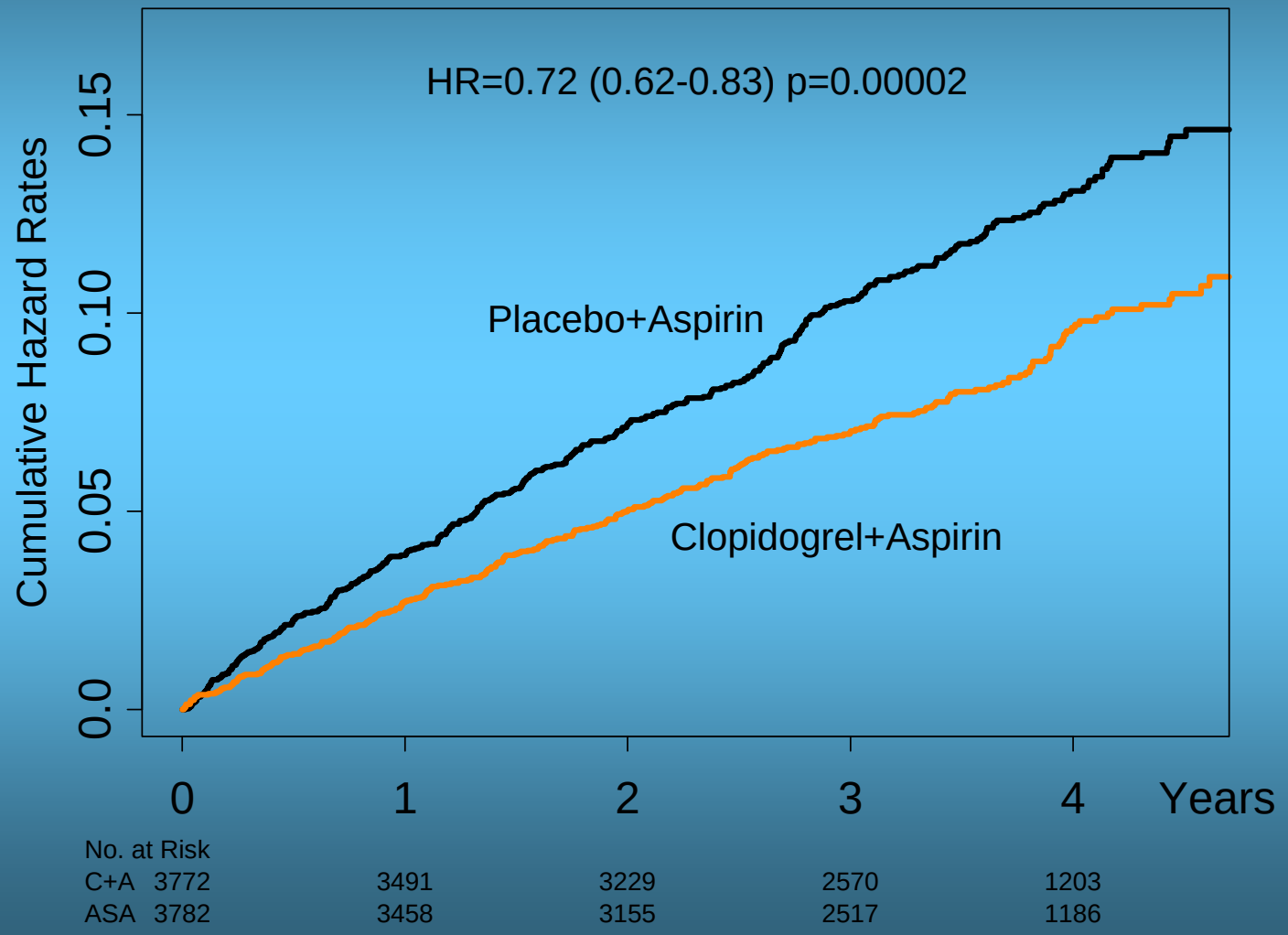
Stroke



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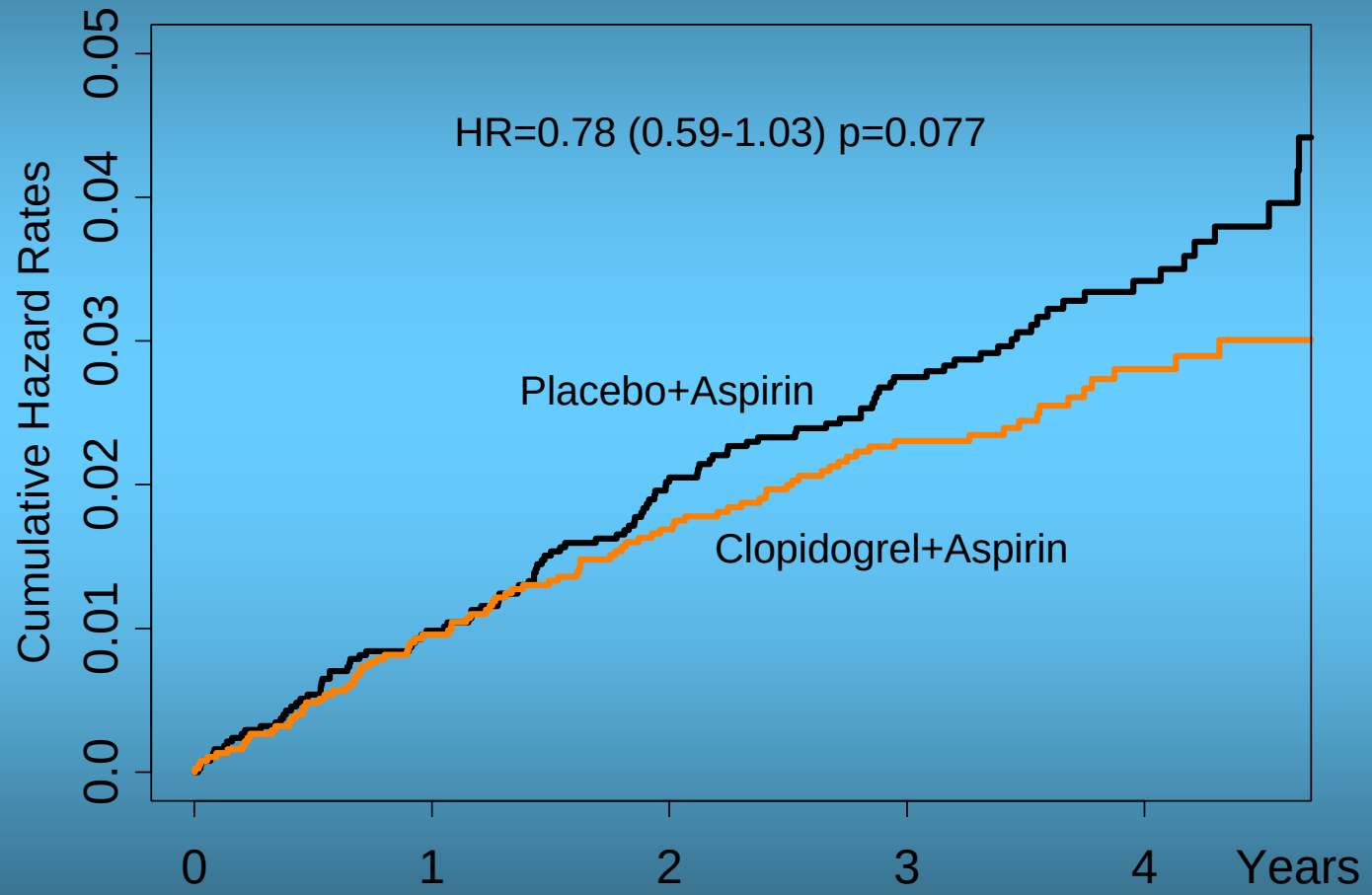
Myocardial Infarction



No. at Risk					
C+A	3772	3529	3297	2635	1264
ASA	3782	3521	3259	2632	1265

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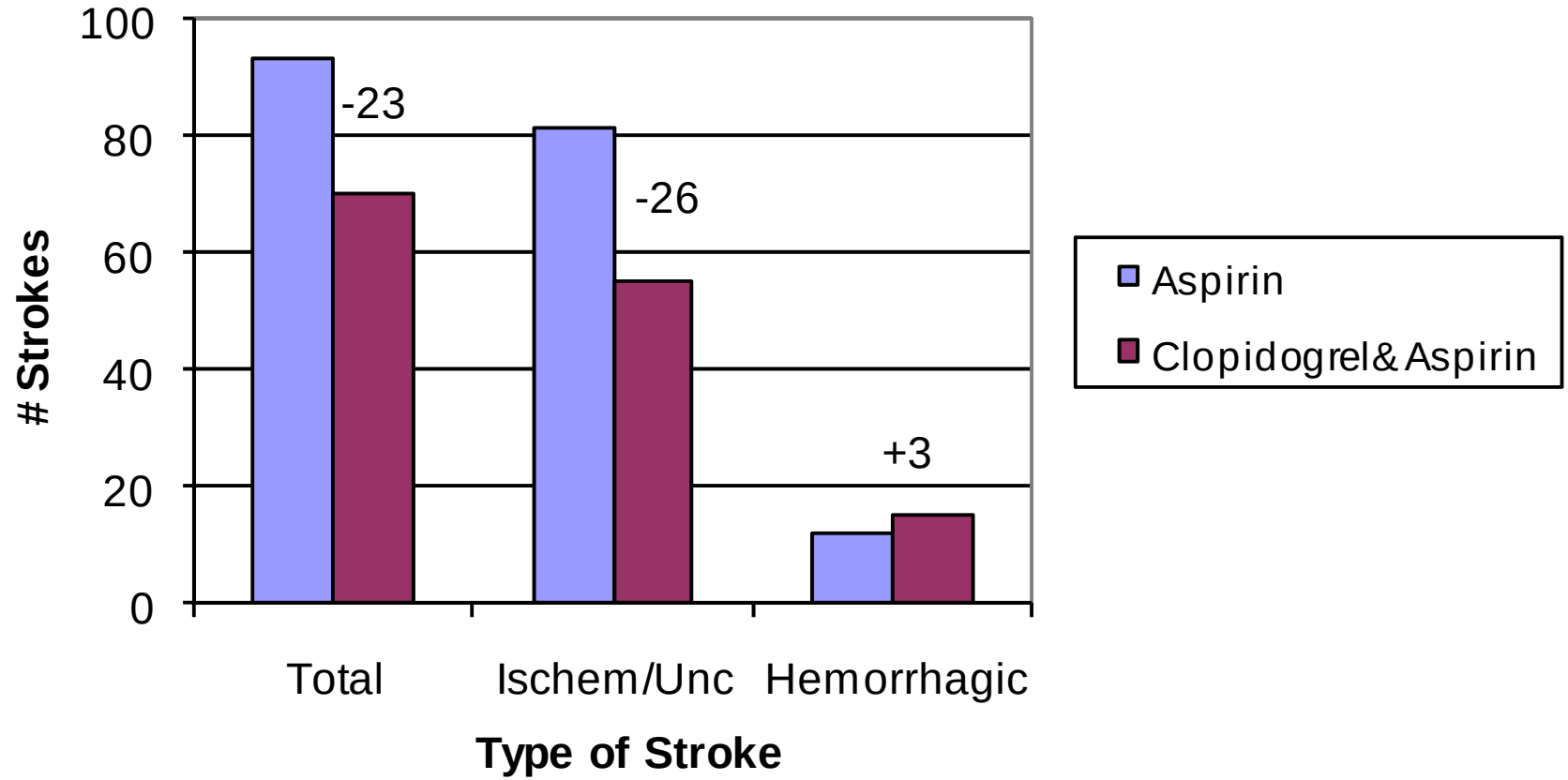
Numbers of Fatal Strokes Prevented



ACTIVE Bleeding Definitions

- **Major Bleed**
  - **an overt bleed requiring ≥2 unit transfusion**

    OR
  - **severe Bleed**
    - **drop in hemoglobin of ≥ 5.0 gm/dL**
    - **hypotension requiring inotropic agents**
    - **intraocular bleeding leading to substantial vision loss**
    - **requirement for surgical intervention**
    - **symptomatic intracranial**
    - **≥4 unit transfusion**
    - **fatal**

Benefits and Risks

1000 patients treated for 3 years

- Will prevent
  - 28 strokes (17 fatal or disabling)
  - 6 myocardial infarctions
- At a cost of 20 (non-stroke) major bleeds (3 fatal)

Conclusions

Addition of clopidogrel to aspirin in high risk AF patients, unsuitable for VKA:

- **Reduces major vascular events**
- **Primarily due to a reduction in stroke**
- **With an increase in major bleeding**

It provides an important benefit to many patients, at an acceptable risk

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