Davos, 14th February 2012

Dual vs. Single Antiplatelet Therapy

The GLOBAL LEADERS Study

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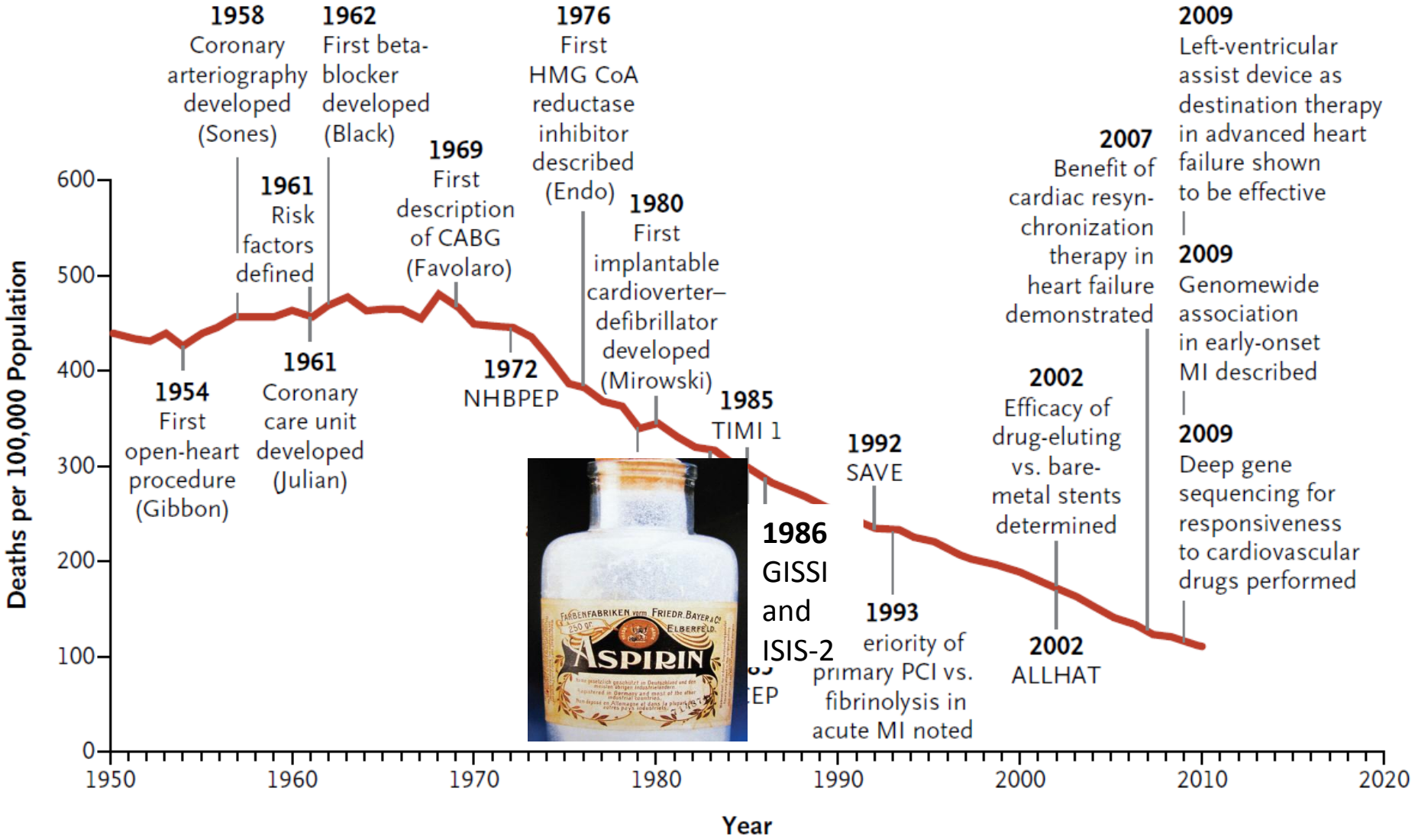
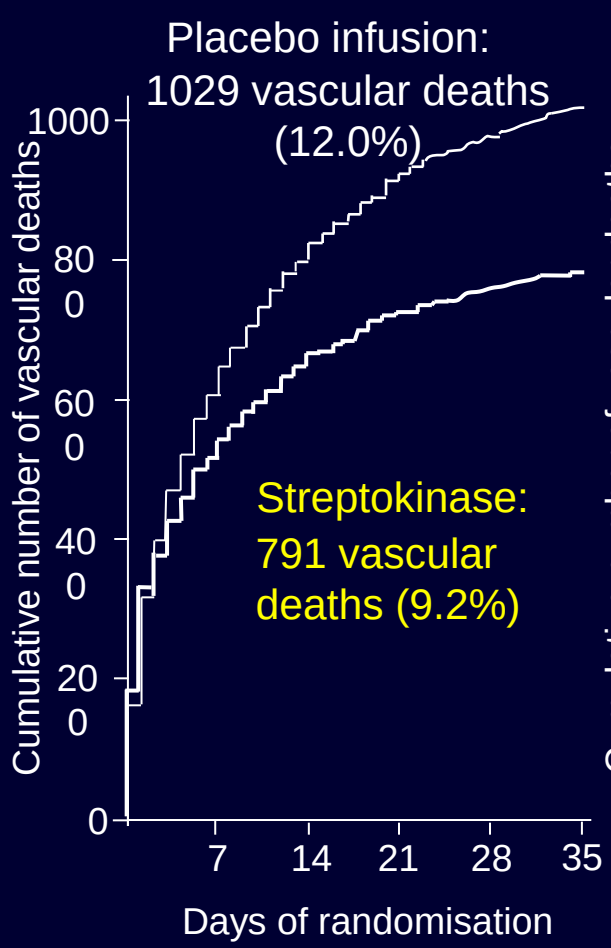
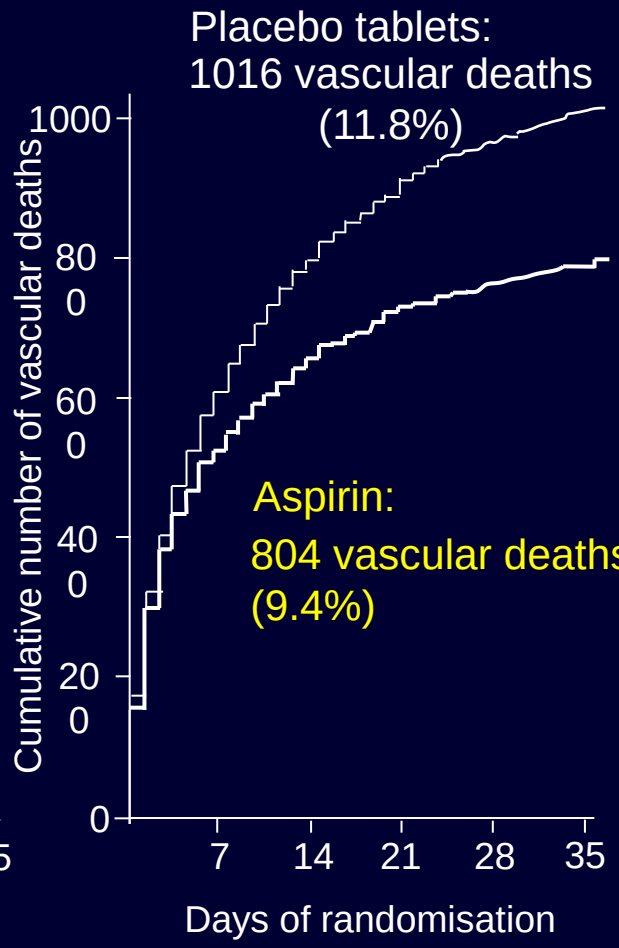
Scientific Advances and Cardiovascular Mortality

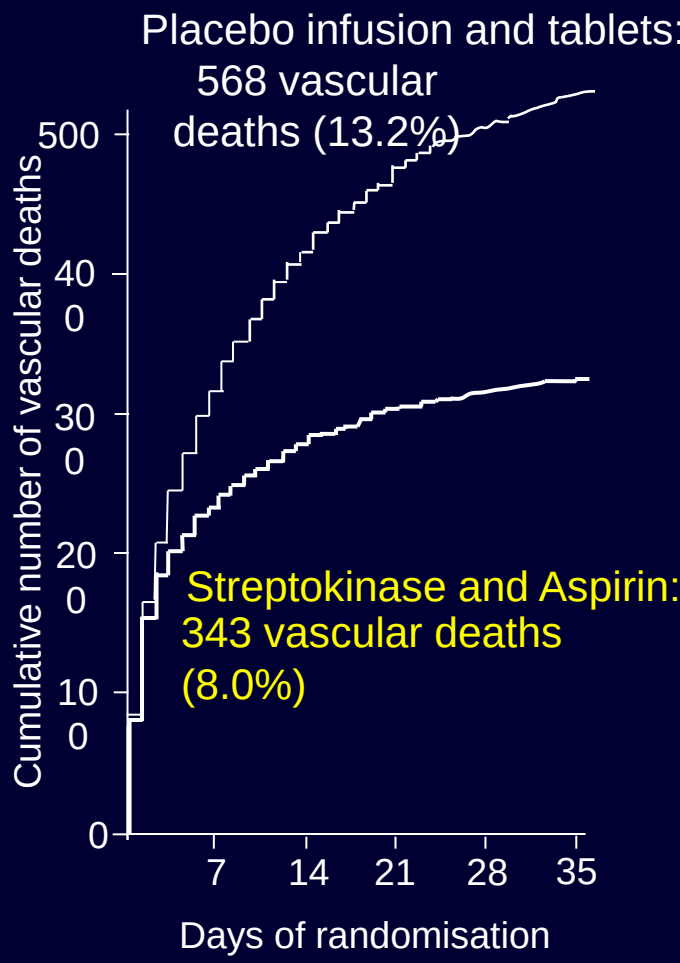
Nabel and Braunwald. *N Engl J Med* 2012;366:54-63



Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither among 17187 Cases of Suspected Acute Myocardial Infarction: ISIS-2



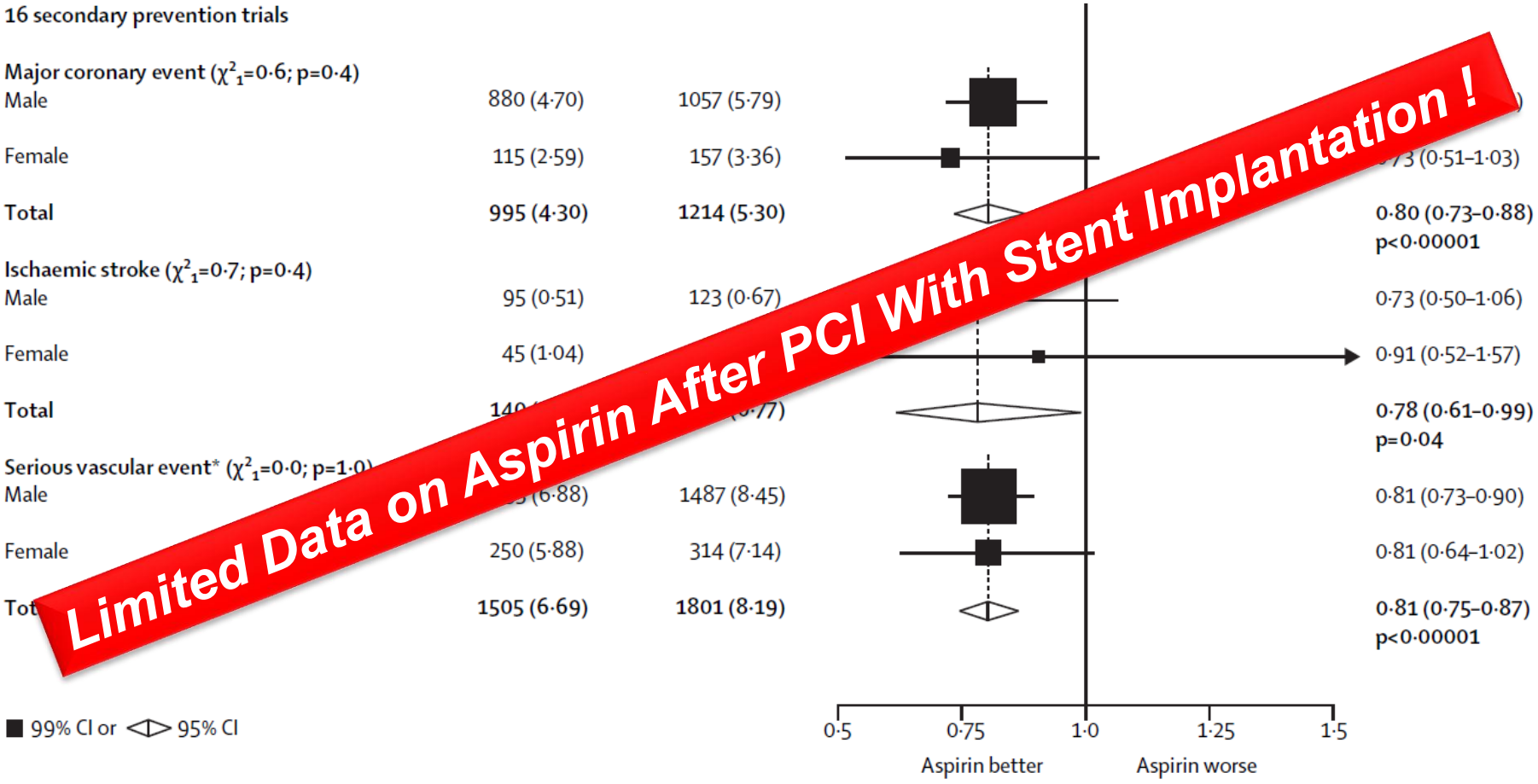




ISIS-2 Collaborative Group, Lancet 1988; II:349-360

Aspirin in Secondary Prevention

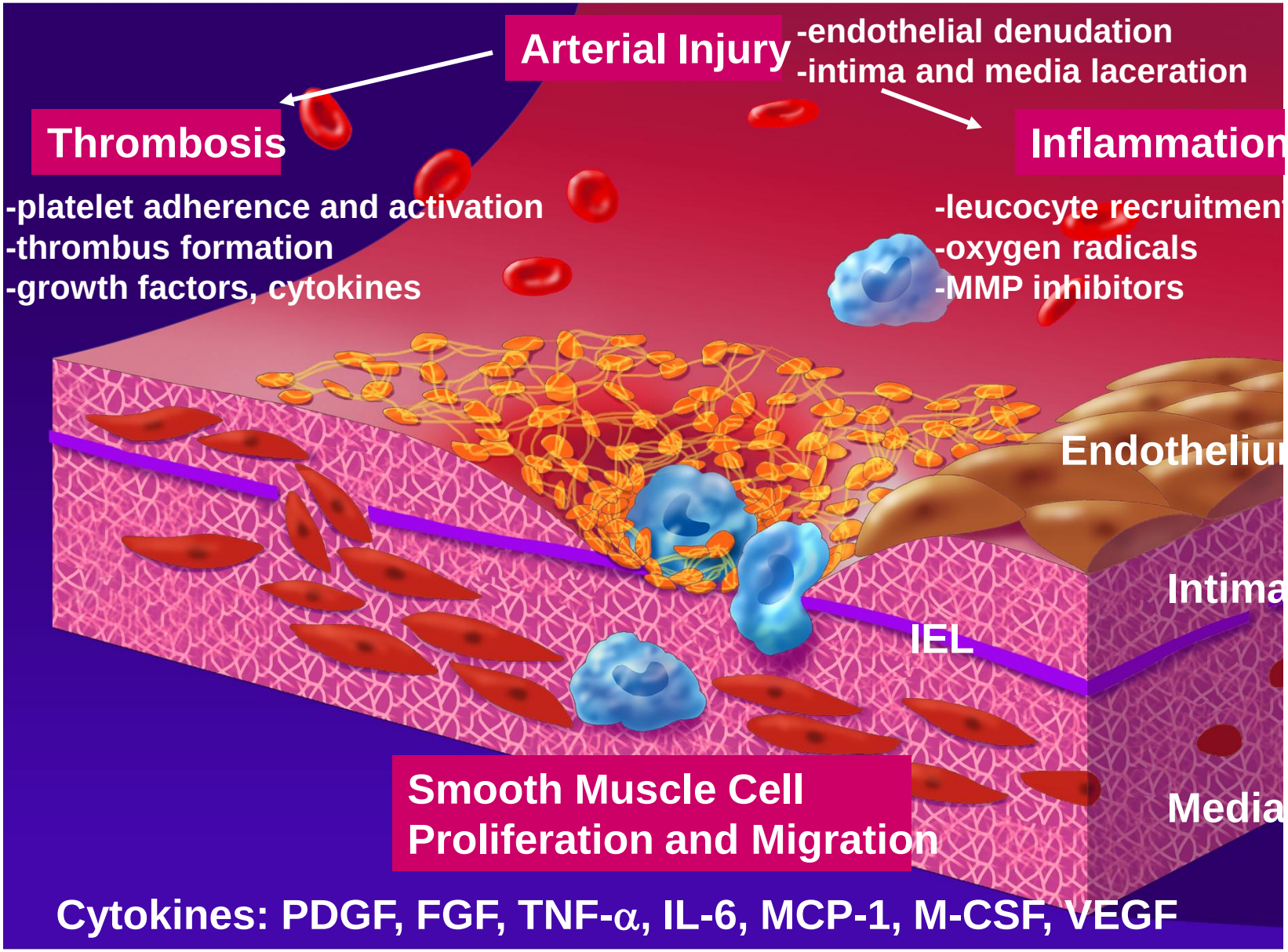
Antithrombotic Trialists Collaboration. *Lancet* 2009; 373:1849–60



Limited Data on Aspirin After PCI With Stent Implantation !

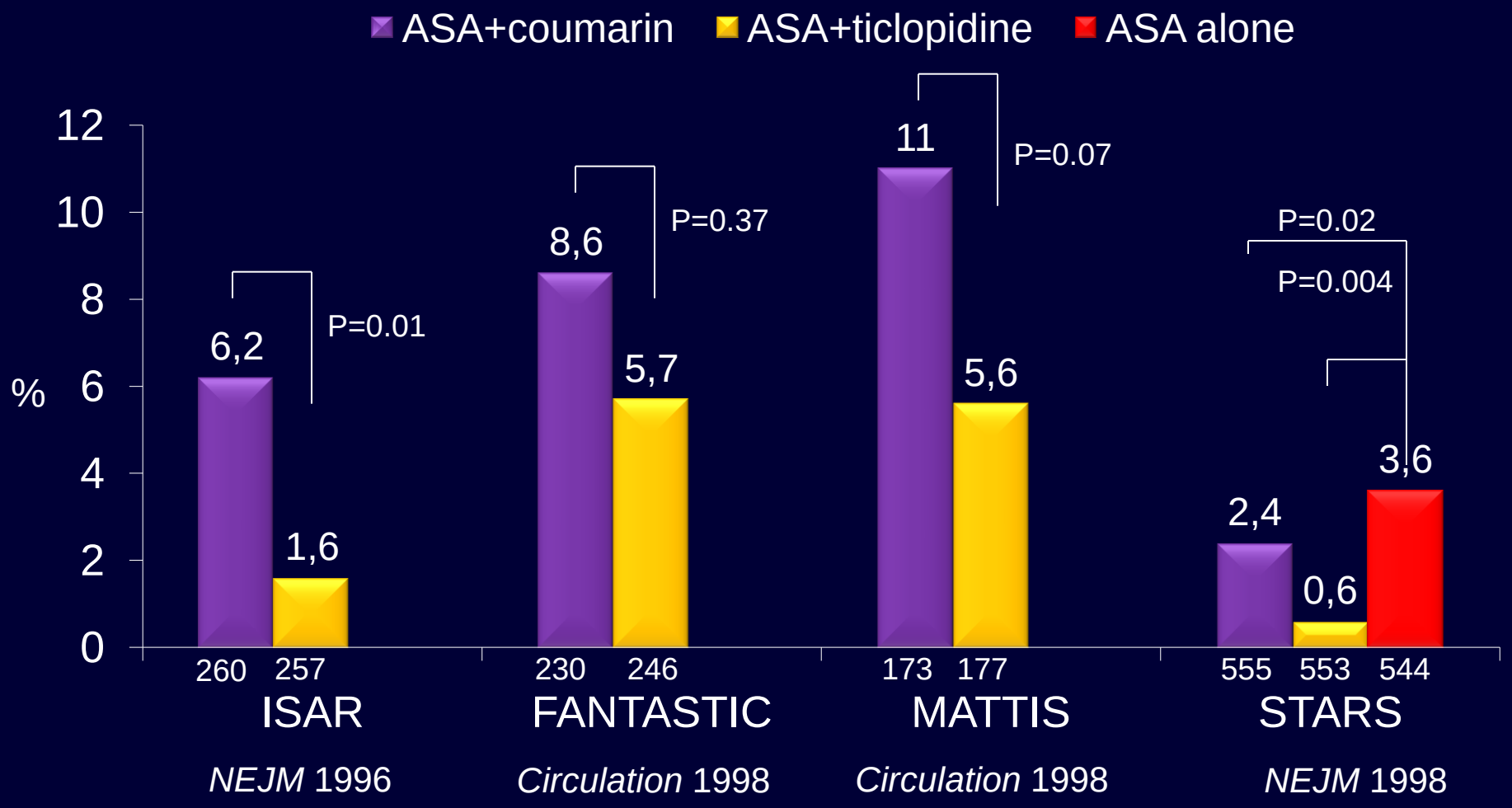
16 Secondary Prevention Trials – 43,000 Patient-Years

Stent-Mediated Arterial Injury

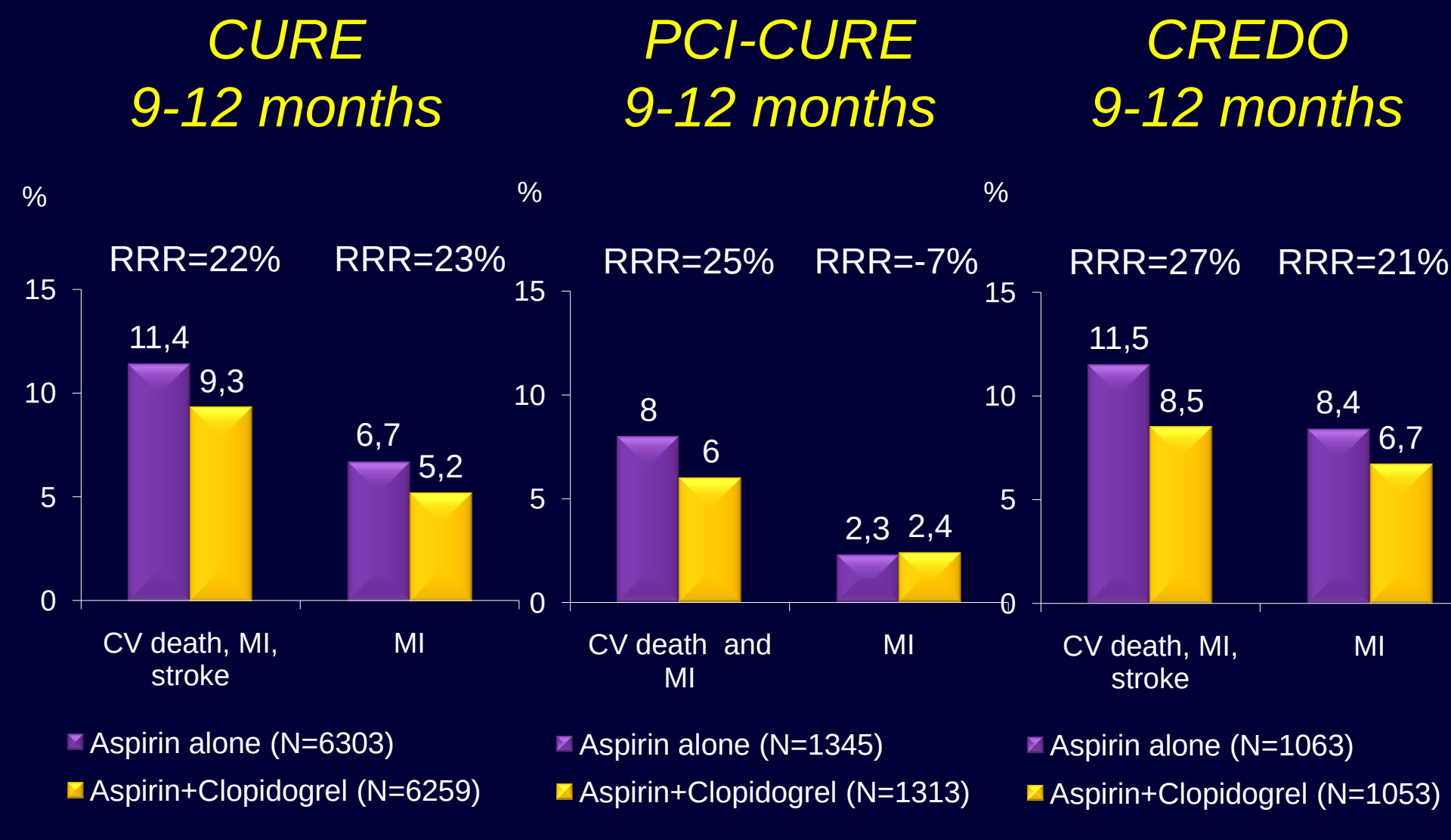


Rationale for DAPT Among Patients Undergoing PCI With Stents

Death, MI, or Revascularization at 30 Days



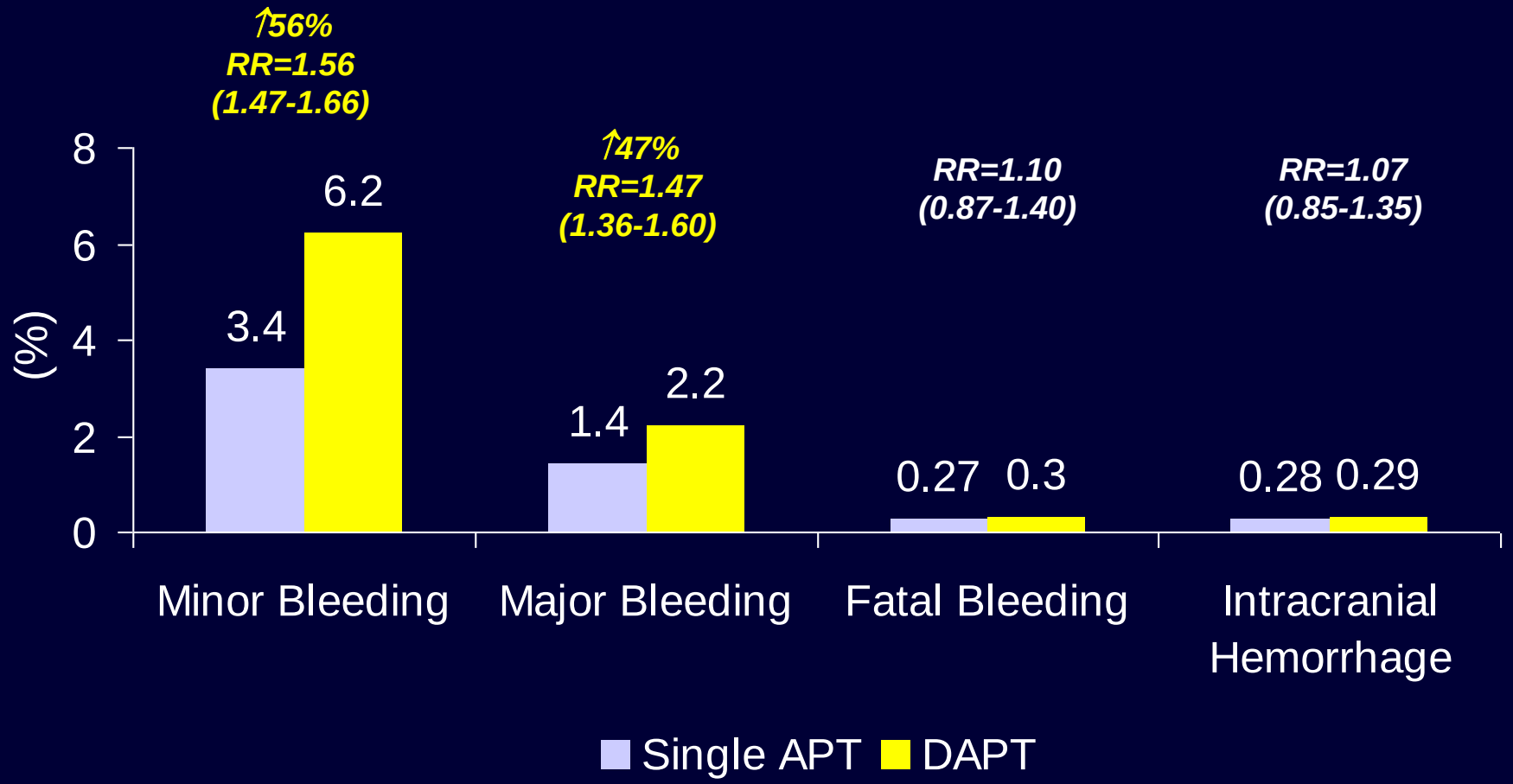
Dual Antiplatelet Therapy



Risk of Bleeding With DAPT

Serebruany VL et al. *Fund & Clin Pharmacology* 2008;22:315-21

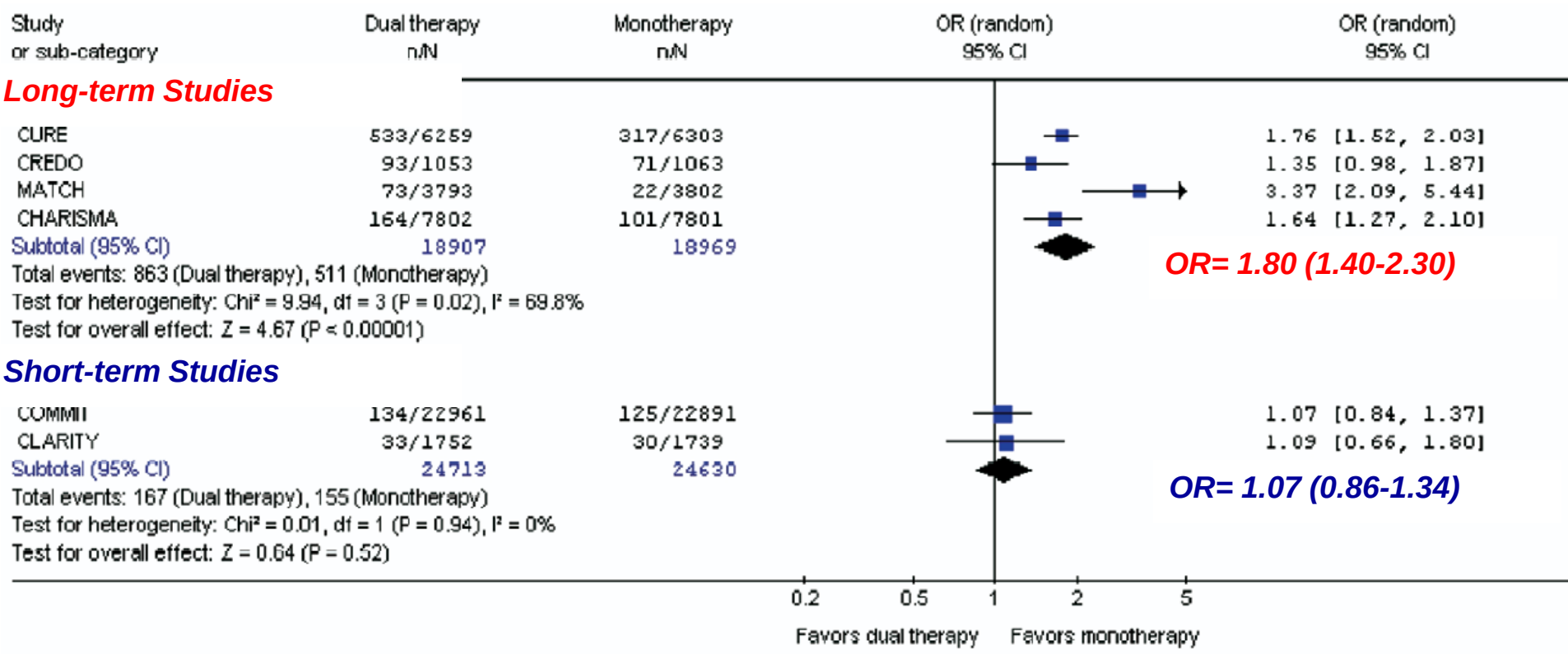
18 RCTs With 129,314 Patients Comparing Single versus Dual Antiplatelet Therapy

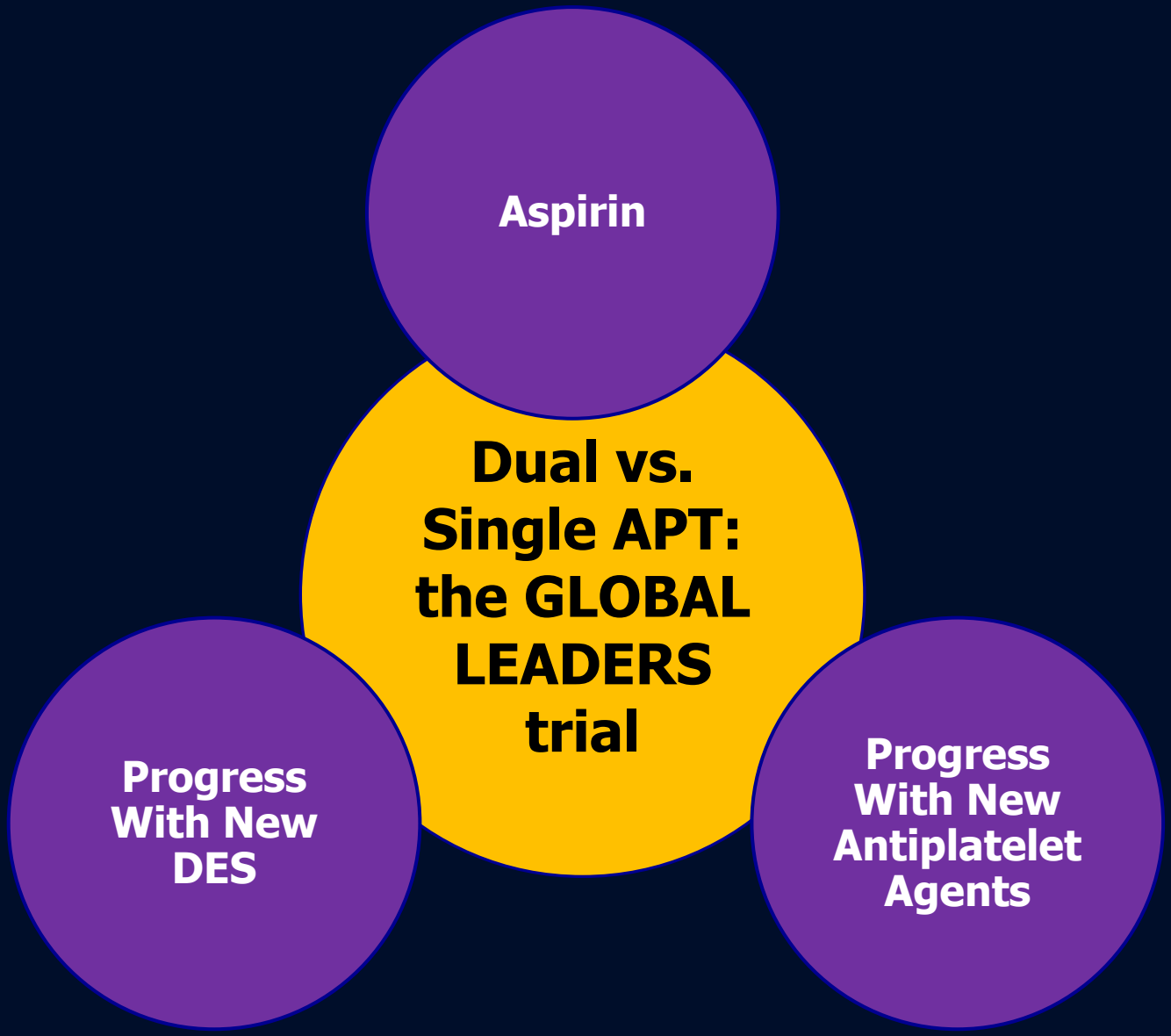


Risk of Bleeding With DAPT in Long- versus Short-term Studies

Bowry DK et al. *Am J Card* 2008;101:960-66

8 RCTs With 91,744 Patients Comparing Single versus Dual Antiplatelet Therapy



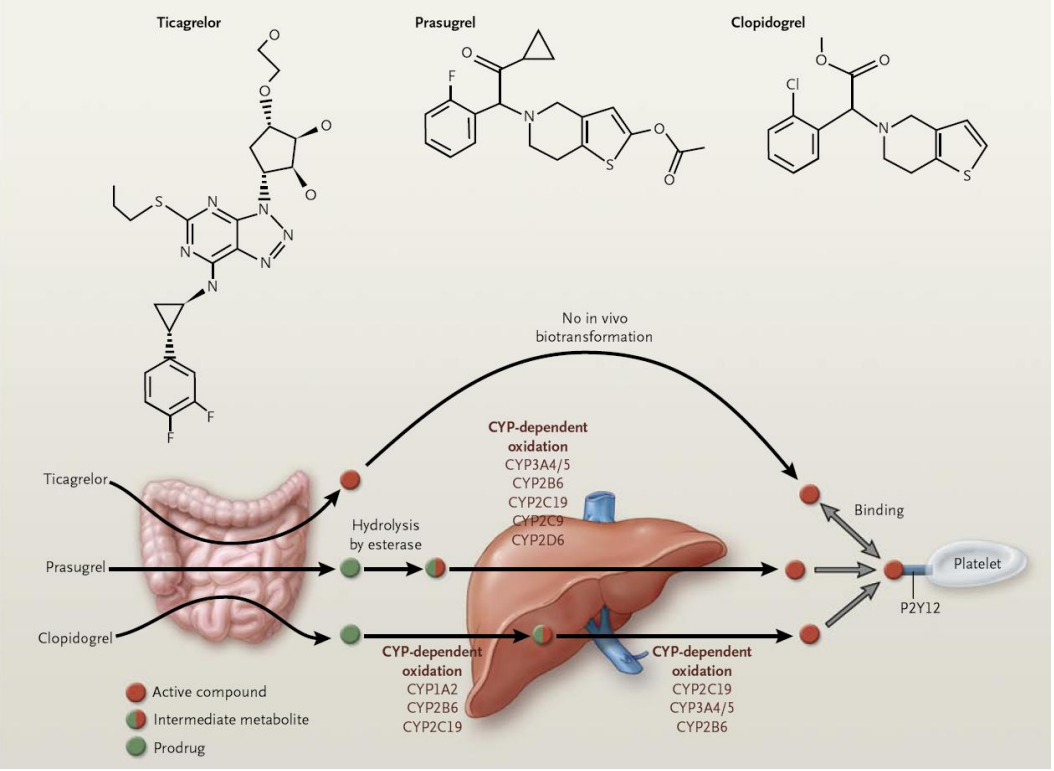

Aspirin
Dual vs. Single APT: the GLOBAL LEADERS trial
Progress With New DES
Progress With New Antiplatelet Agents

Mode of Action of $P2Y_{12}$ Inhibitors: Clopidogrel, Prasugrel, Ticagrelor

Schömig A. *N Engl J Med* 2009;361:1108-1111

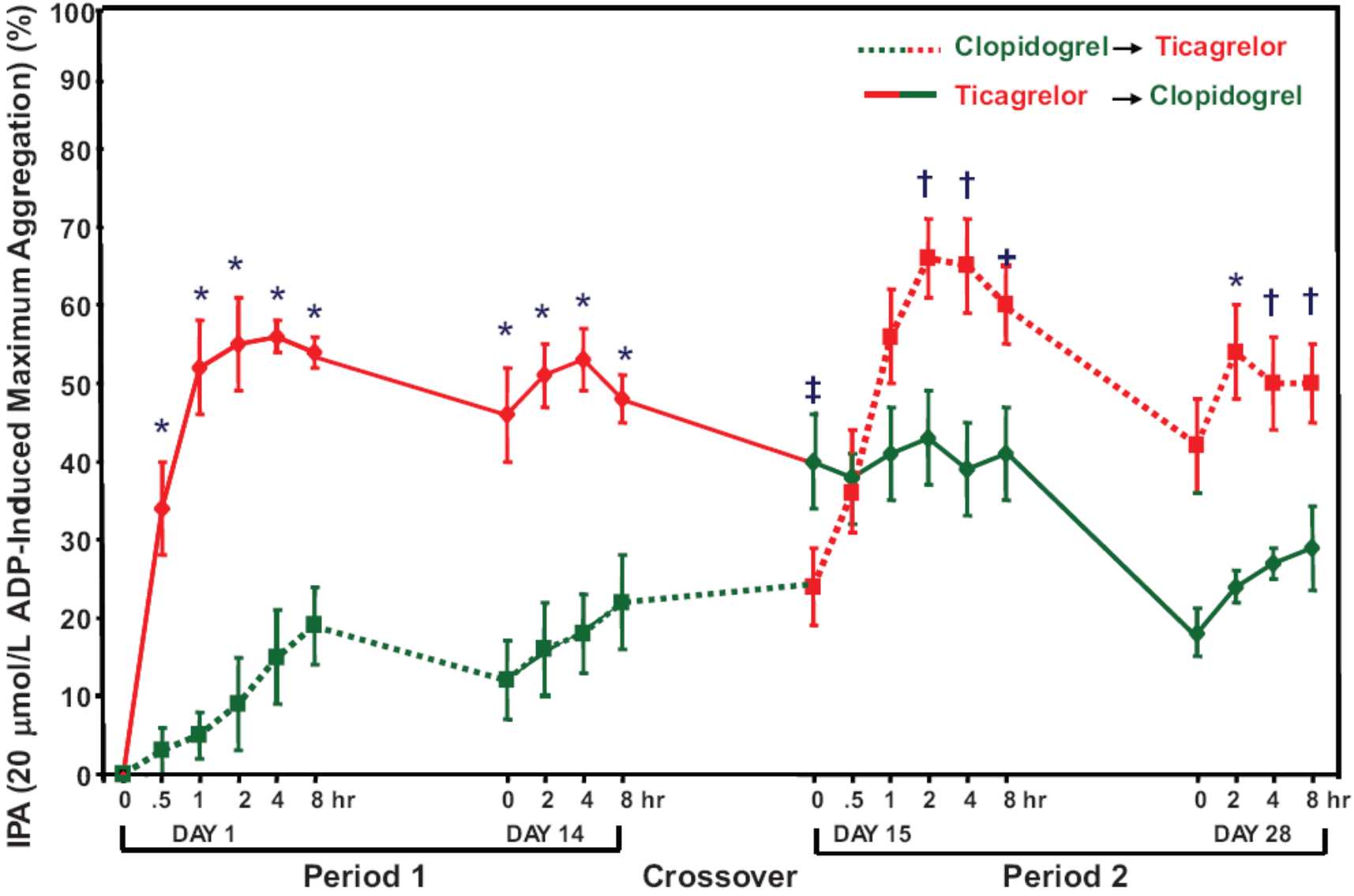
Limitations of Clopidogrel

1. Delayed onset of action
2. Large interindividual variability in platelet response
3. Irreversibility of inhibitory action



Ticagrelor and Inhibition of Platelet Aggregation in Clopidogrel-Nonresponsive Patients

Gurbel PA et al. *Circulation* 2010;121:1188-99



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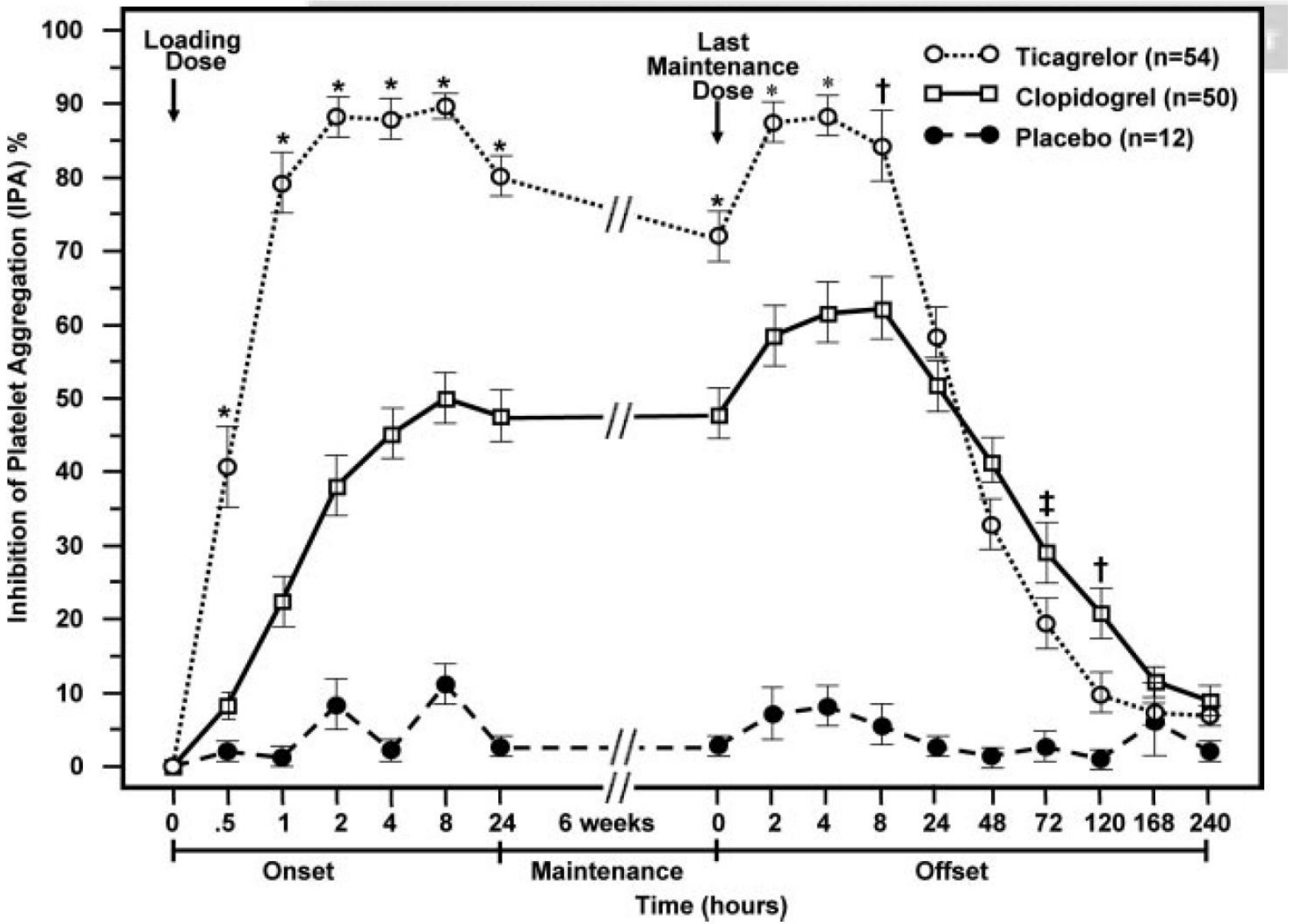
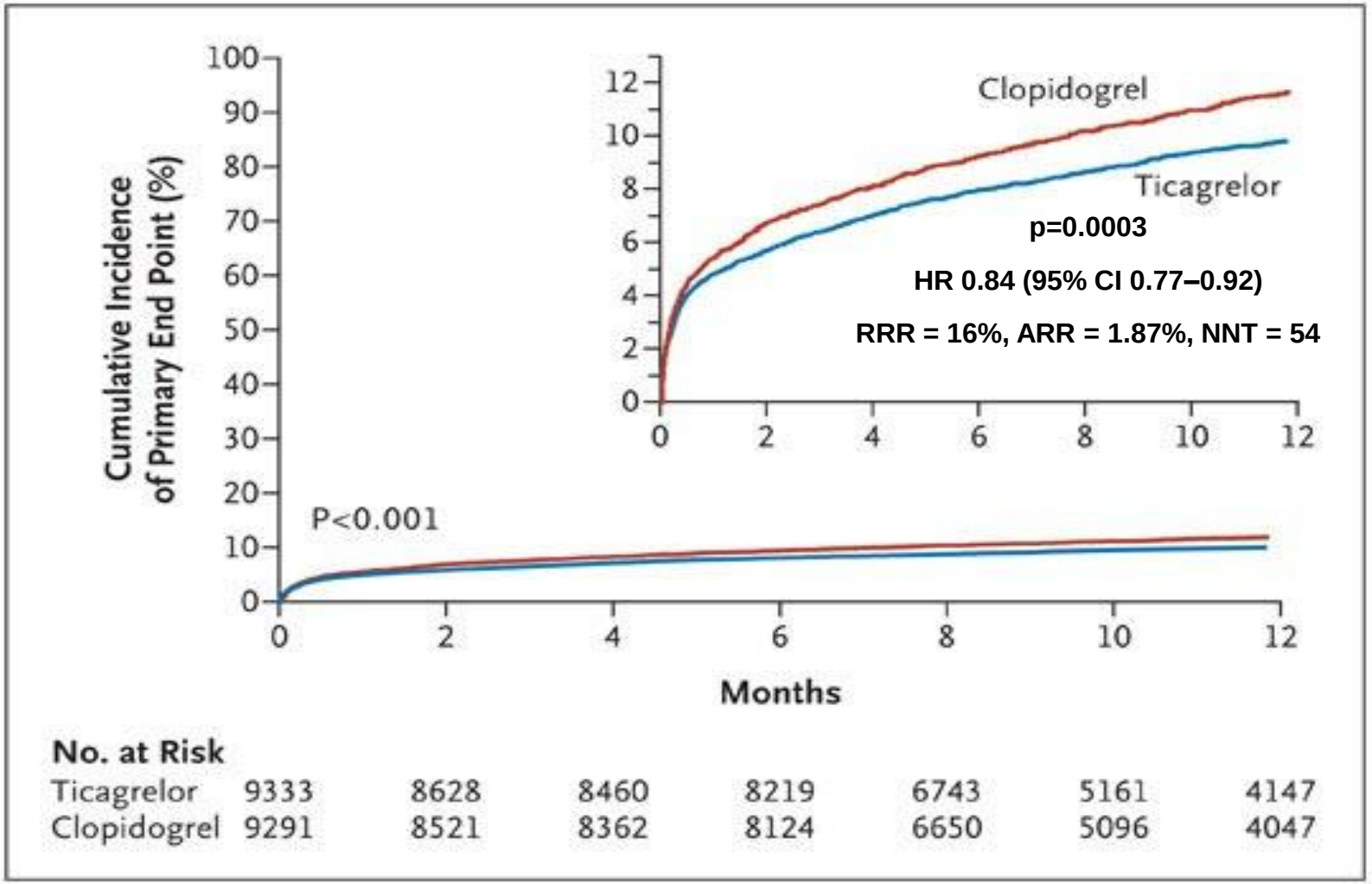


PLATO - Ticagrelor versus Clopidogrel in ACS

Wallentin L al. *N Engl J Med* 2009;361:1045-57

Primary Endpoint: CV Death, MI or Stroke



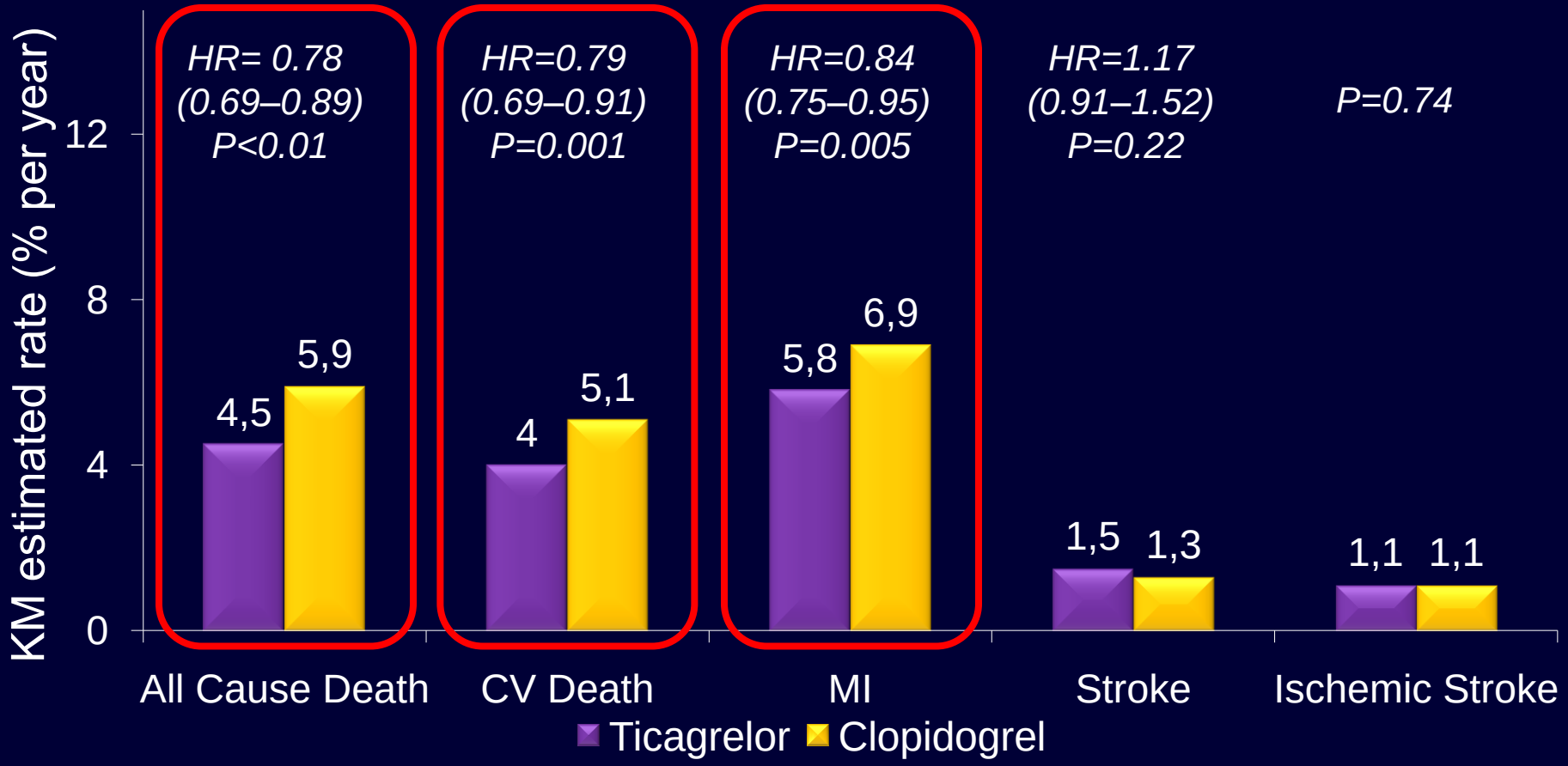
11.7%

9.8%

Ticagrelor versus Clopidogrel in ACS

Wallentin L al. *N Engl J Med* 2009;361:1045-57

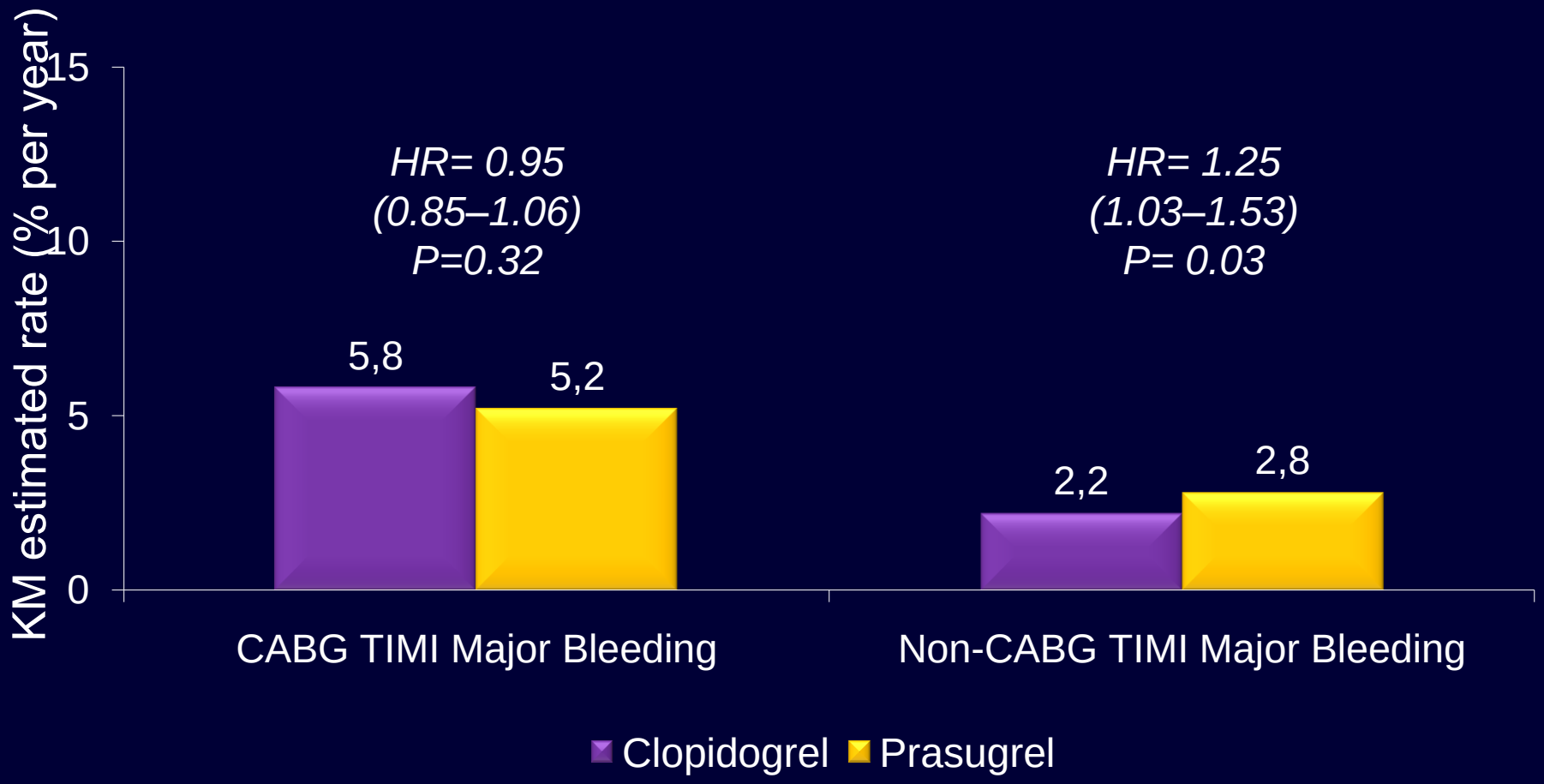
Individual Ischemic Endpoints



PLATO – Ticagrelor vs. Clopidogrel

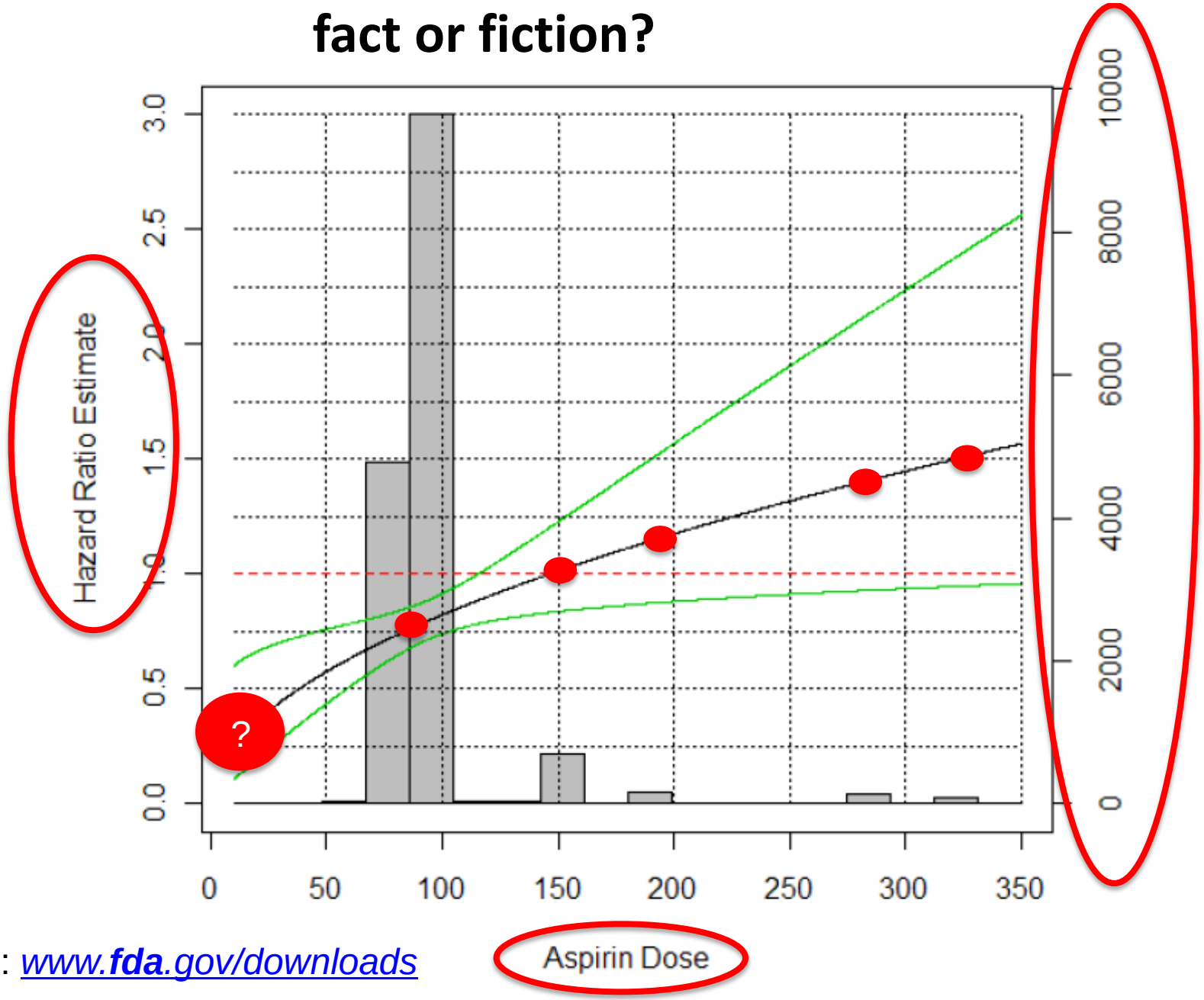
Wallentin L al. *N Engl J Med* 2009;361:1045-57

CABG and Non-CABG Related Bleeding



Aspirin dose and ticagrelor benefit in PLATO: fact or fiction?

GLOBAL LEADERS



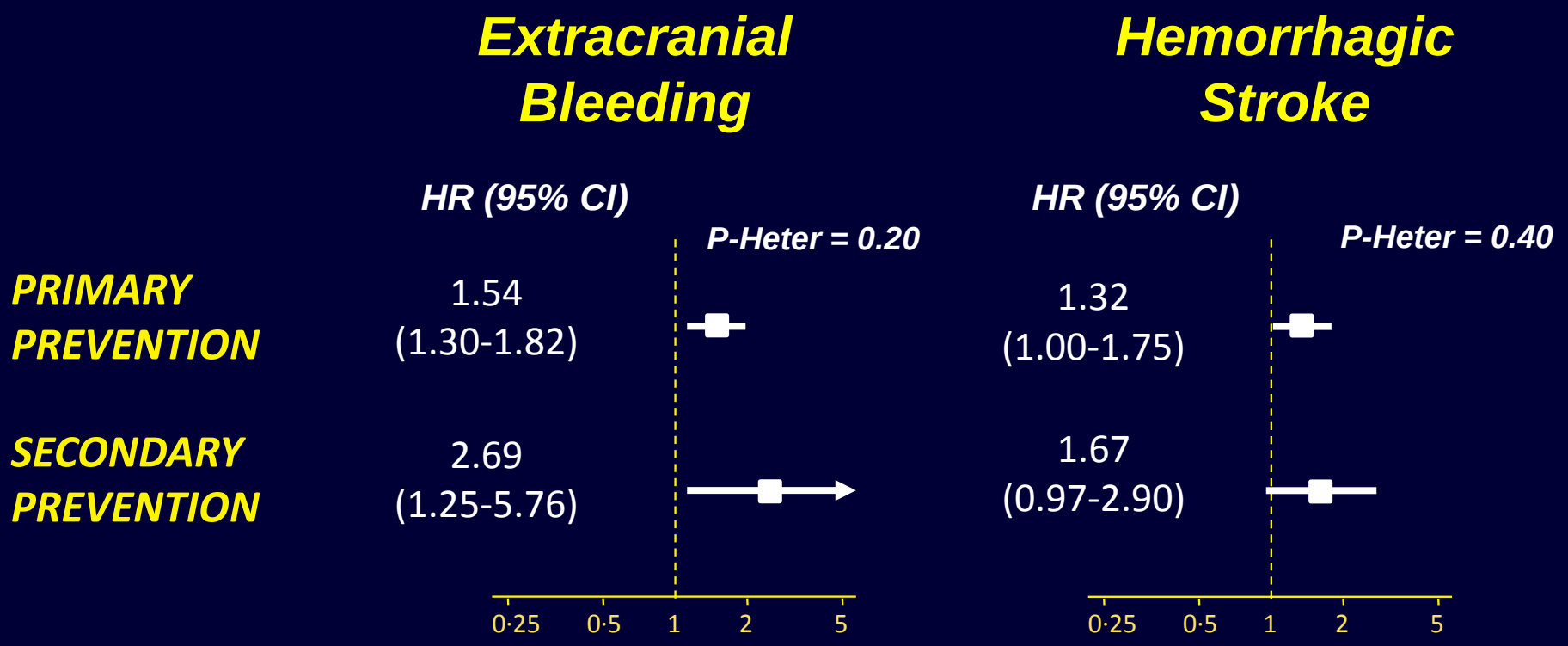
Source: www.fda.gov/downloads

Clinical Issues With Aspirin

- **Treatment Failure** (“Aspirin Resistance“)
  - Aspirin preparation (ie, enteric coated formulations)
  - Drug-drug interactions (ie, NSAIDs)
  - COX-1 related pathways
  - Medication noncompliance
  - Premature discontinuation
- **Irreversible platelet inhibition**
- **Bleeding risk**
- **Gastrotoxicity**

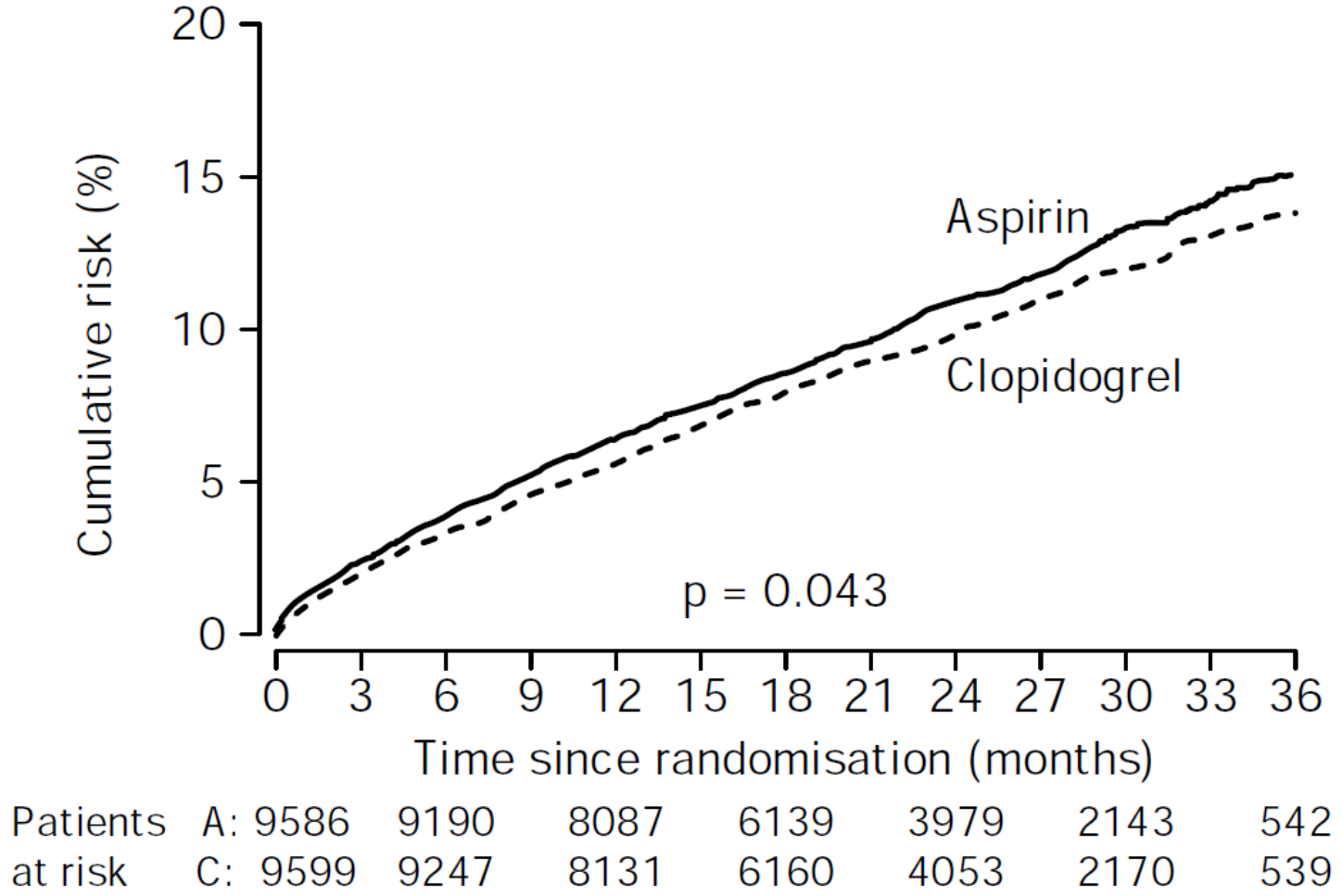
Risk of Bleeding With Aspirin

Antithrombotic Trialists Collaboration. *Lancet* 2009; 373:1849–60



Clopidogrel versus Aspirin in Patients with Atherosclerotic Disease – the CAPRIE trial

CAPRIE Steering Committee, *Lancet* 1996; 348: 1329–39



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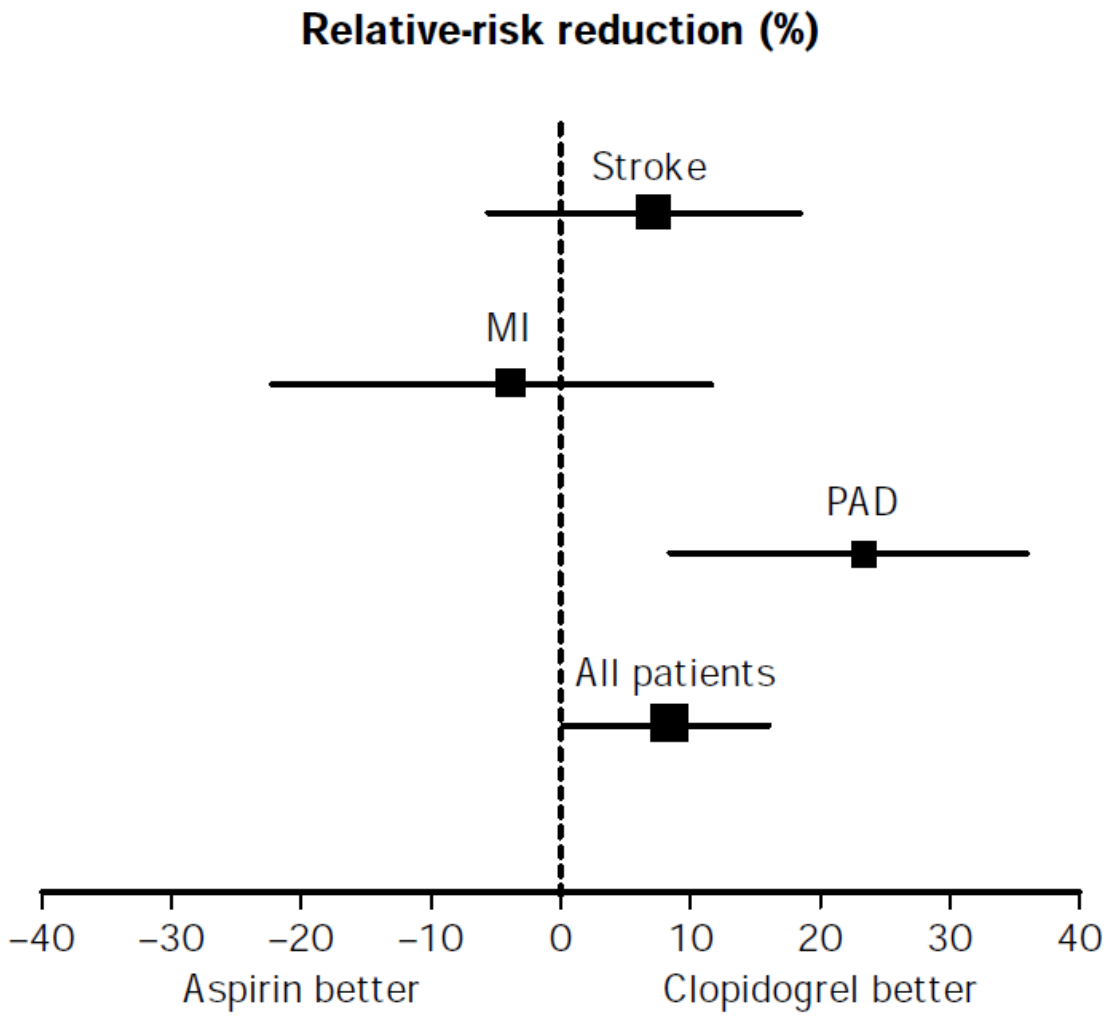
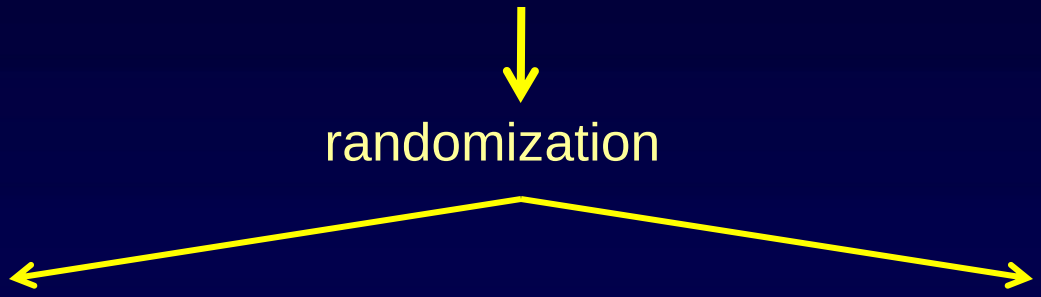


WOEST trial

573 patients on OAC undergoing stent (DES/BMS) implantation



randomization

oral anticoagulants*
+
clopidogrel 75 mg qd**
+
aspirin 80 mg qd

oral anticoagulants*
+
clopidogrel 75 mg qd**

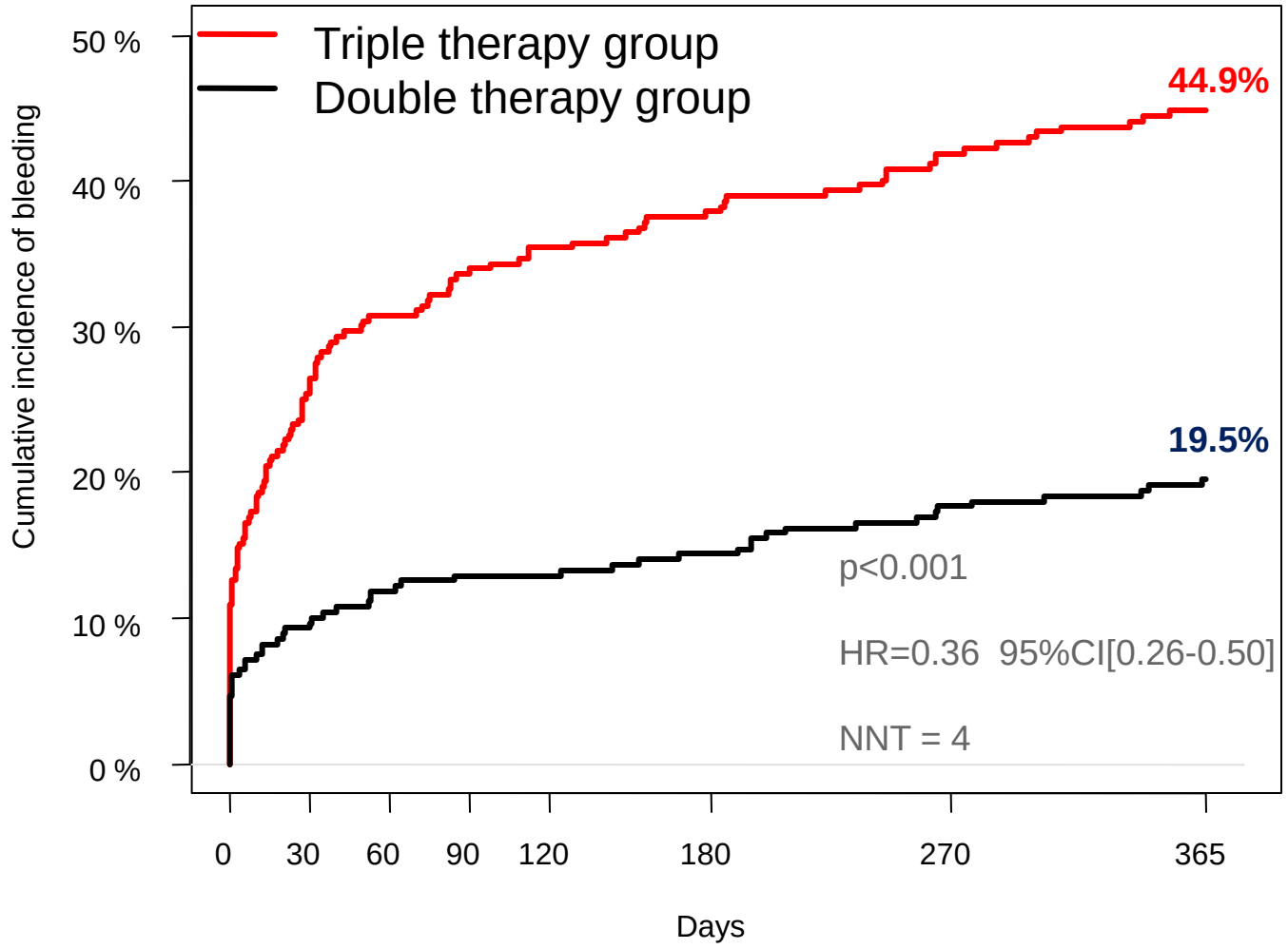
Follow-up:	1 year
Primary endpoint:	any bleeding
Secondary endpoint:	ischemic events

* INR as originally indicated

** BMS 1 month
DES and/or ACS 1 year

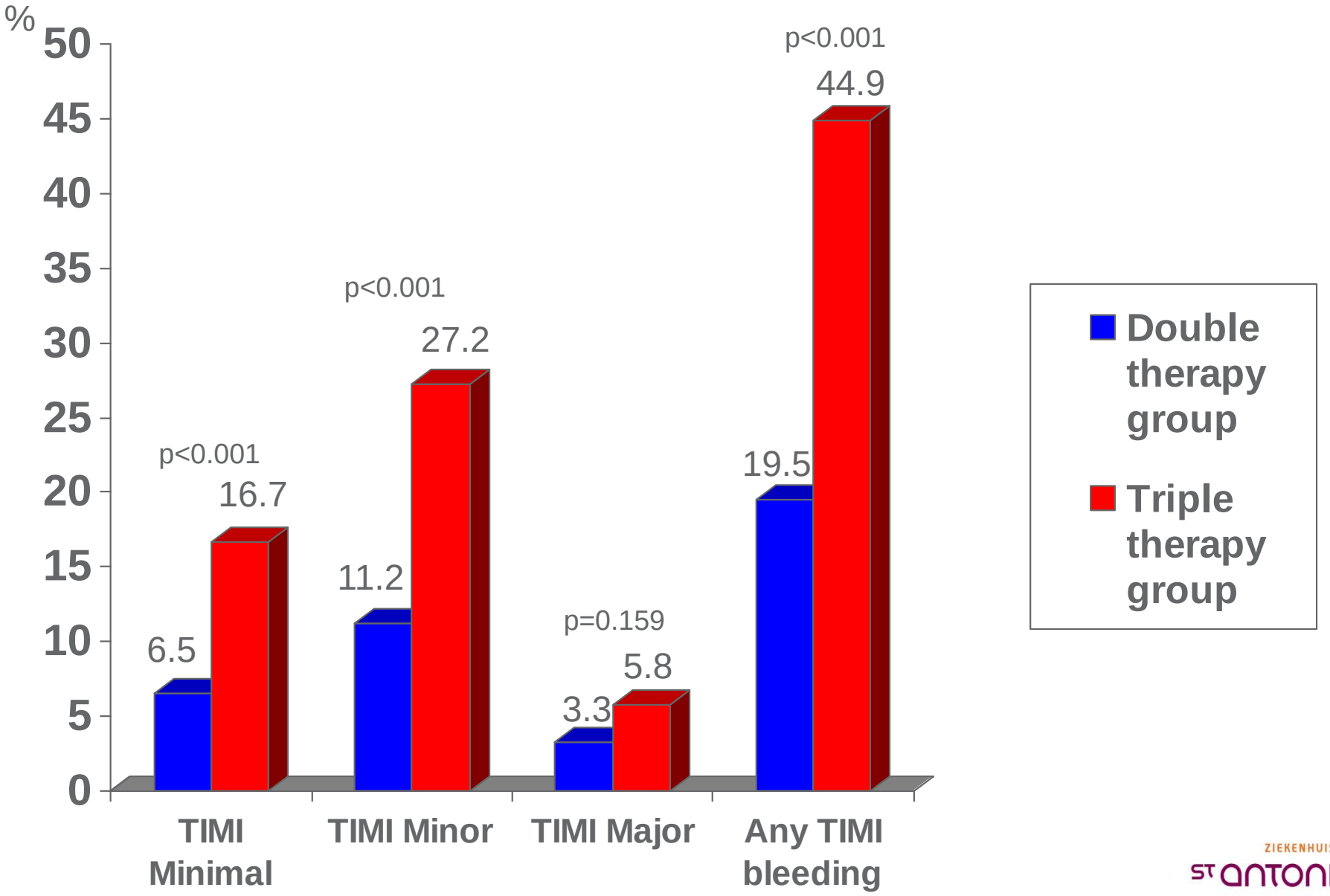
Dewilde W, Ten Berg JM. Am Heart J 2009;158:713-718

Primary Endpoint: Total number of bleeding events



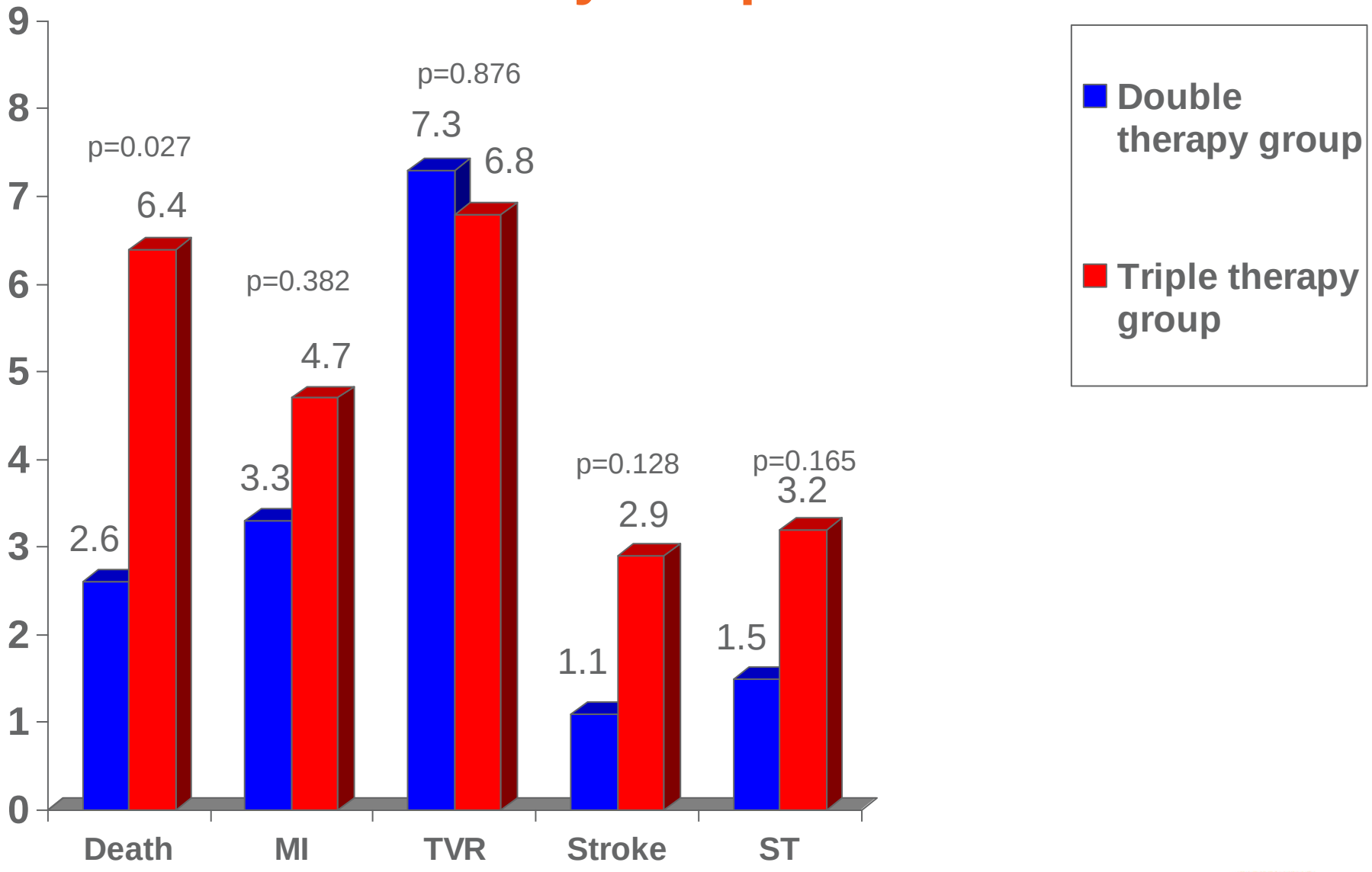
Lancet 2013 in press

Primary Endpoint: Bleeding events TIMI classification

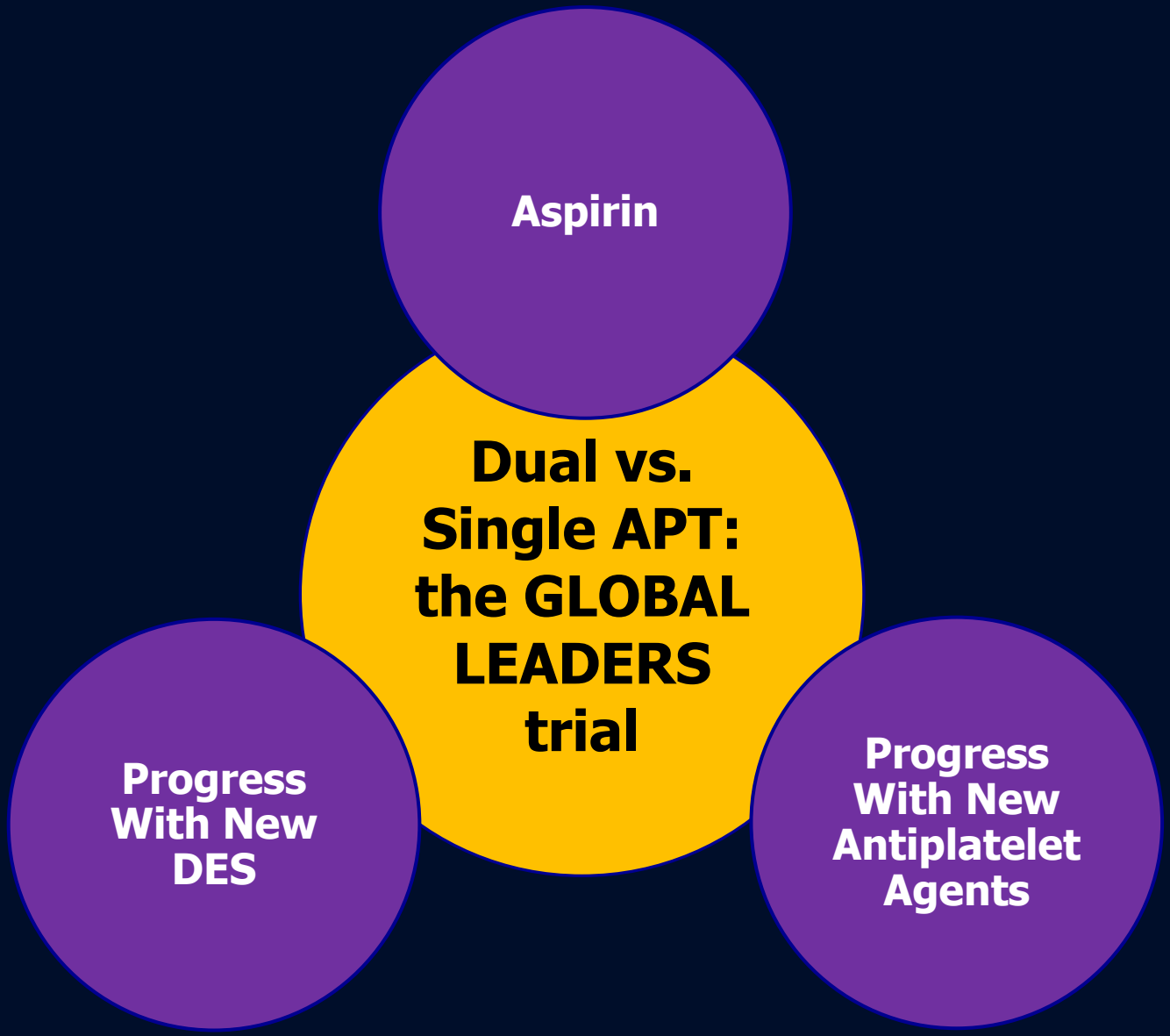


Lancet 2013 in press

Secondary Endpoint

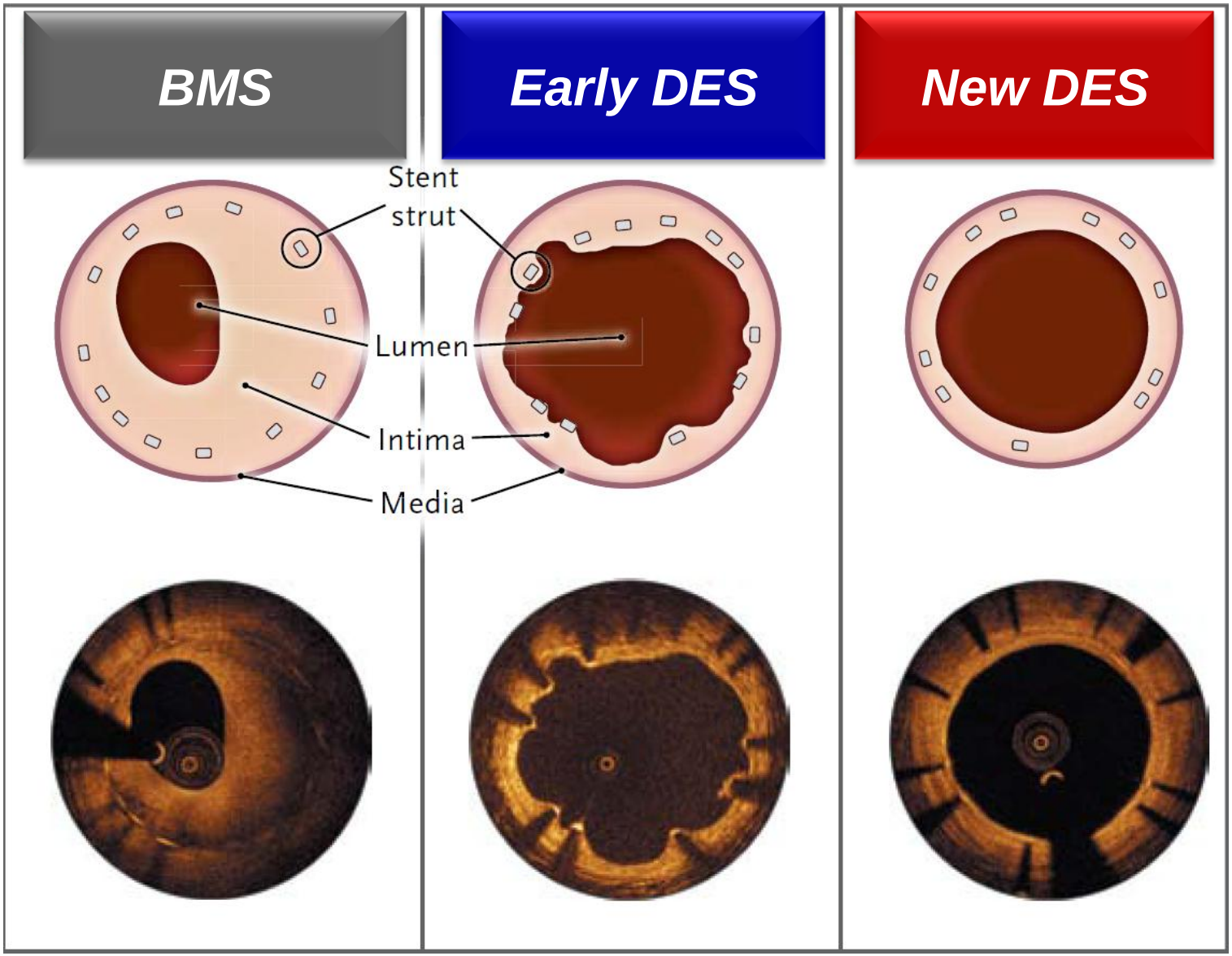


MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis


Aspirin
Dual vs. Single APT: the GLOBAL LEADERS trial
Progress With New DES
Progress With New Antiplatelet Agents

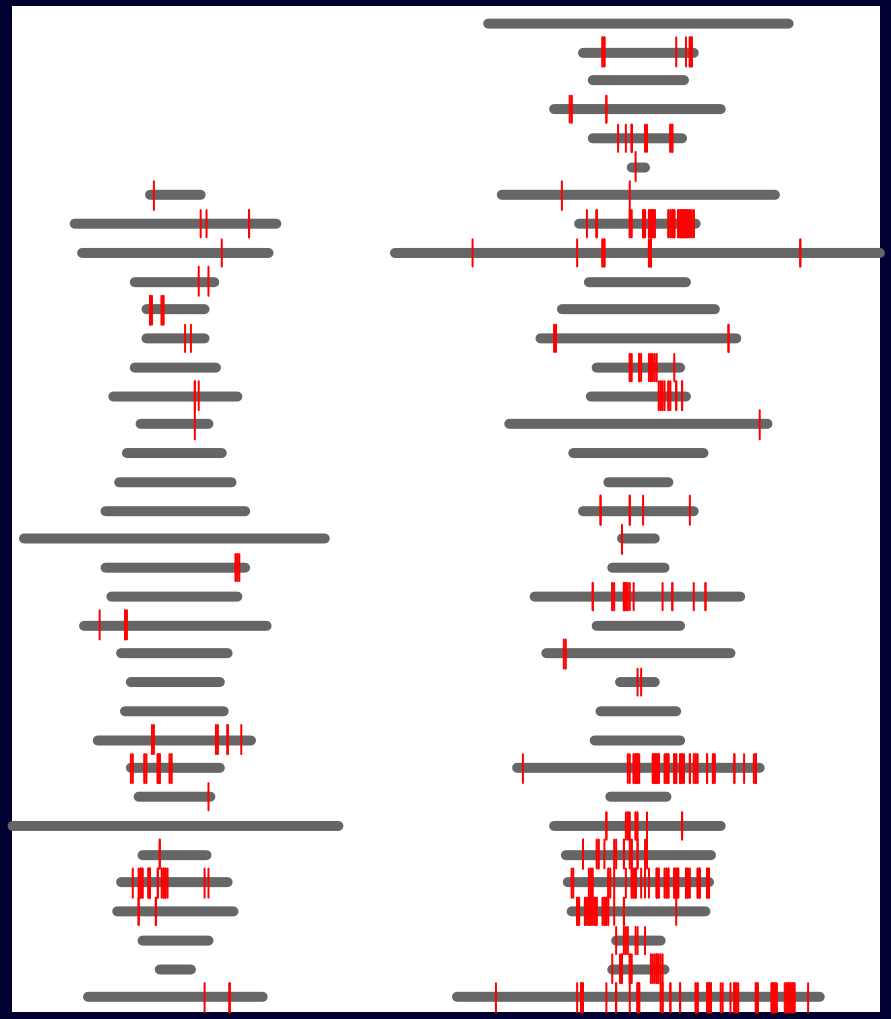
Arterial Healing After Coronary Stents Implantation

Stefanini G, Holmes D. *N Eng J Med* 2013;368:254-65



Biolimus Eluted from Biodegradable Polymer versus Sirolimus Eluted from Durable Polymer

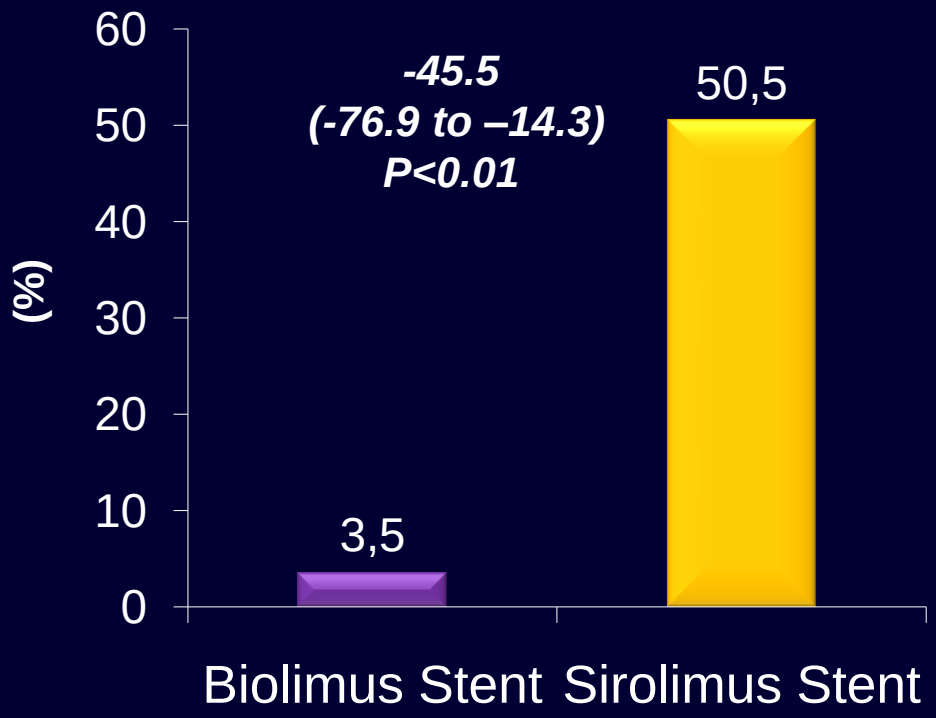
Barlis P et al. *Eur Heart J* 2010



Biolimus
N=29

Sirolimus
N=35

Lesions With At Least 5% Uncovered Struts



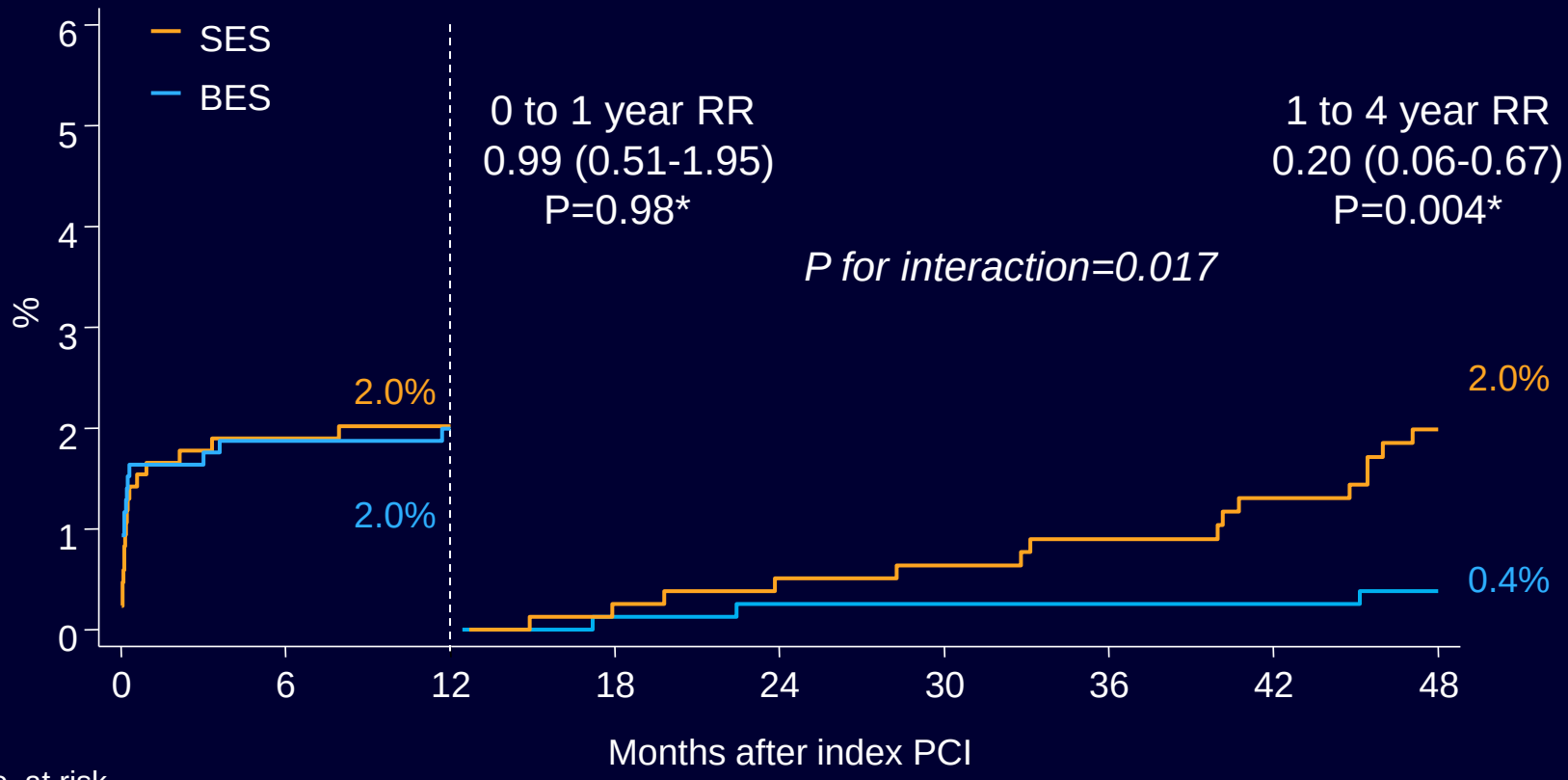
29 Lesions

35 Lesions

Biodegradable Polymer Biolimus-Eluting Stents vs Durable Polymer Sirolimus-Eluting Stents

Stefanini G et al. *Lancet* 2011;378:1940-8

Definite ST - Landmark Analysis @ 1 Year



No. at risk

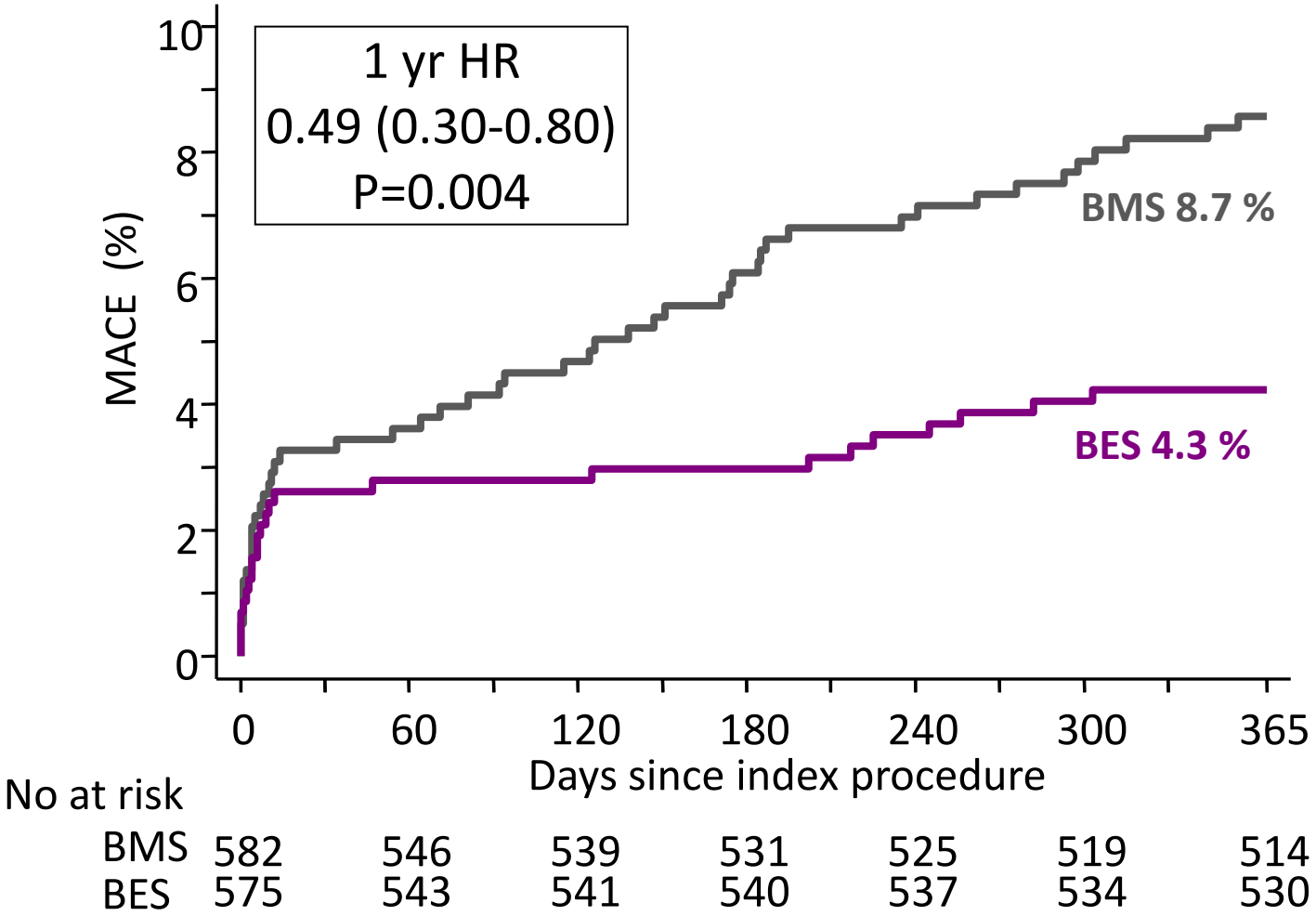
SES	850	817	801	787	776	759	750	730	714
BES	857	821	804	792	787	780	774	757	746

* P values for superiority

Biodegradable Polymer BES versus Bare Metal Stents in STEMI – COMFORTABLE AMI

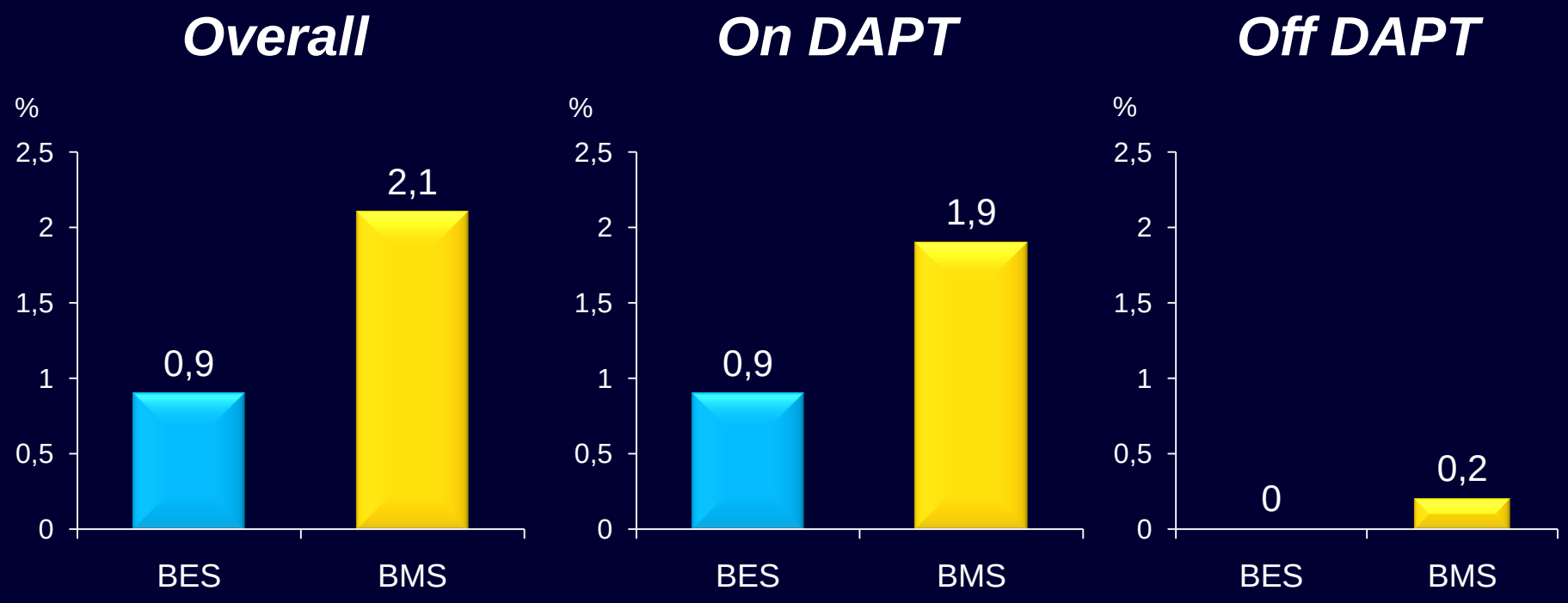
Räber L et al. *JAMA* 2012;308:777-87

1° EP – Cardiac Death, TV-MI or ci-TLR @ 1 Year



Definite ST According to Discontinuation of DAPT in the COMFORTABLE-AMI Trial

Räber L et al. *JAMA 2012;*308:777-87



GLOBAL LEADERS

The purpose of Global LEADERS is to compare:

Standard 12 months of DAPT following PCI

(and subsequent maintenance [12 month] antiplatelet therapy with ASA)

with

A new regimen involving 30 days of DAPT with ASA + ticagrelor

(and subsequent maintenance [23 month] therapy with ticagrelor)

In an <u>all-comers</u> population undergoing PCI with unrestricted biolimus eluting stent (BES) use

Comparative Effectiveness of 2 Pharmaco-Intervention Strategies

GLOBAL LEADERS

All-Comers PCI population
ACS and Elective/Stable patients
80 centres, 10+ countries, (n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 randomization

Study Treatment Strategy

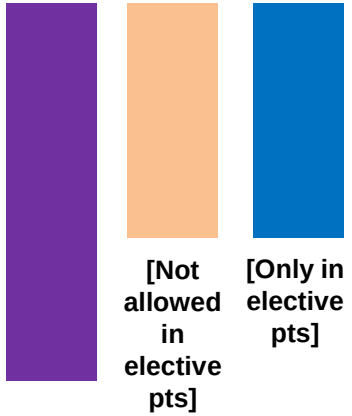
1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

12-months
monotherapy ASA



Primary Endpoint
Study treatment strategy superior to reference treatment strategy on cumulative **2 years composite of all-cause mortality and new Q-wave MI**

GLOBAL LEADERS

Study Design Considerations

- **Statistical Considerations**
  - event rate estimated to be 5% at 2 years based on the biolimus eluting stent (BES) arm in the LEADERS Trial, in order to detect a 22.5% relative risk reduction
  - 8000 patients per treatment arm are required to obtain a power >90%
- **Primary Outcome**
  - study treatment strategy **superior** to reference treatment strategy on cumulative **2 years composite of all cause mortality and new Q-wave MI**
- **Key Safety Secondary Endpoint**
  - A composite of BARC 3 or BARC 5 bleeding up to 2 years

GLOBAL LEADERS

Global Leaders Vision

1. Avoid the higher risk of bleeding potentially associated with adding ASA (even low dose) to Ticagrelor
2. Maintain the clinical benefits of potent platelet inhibition after PCI, beyond the initial period of high stent thrombosis risk (30 days)
3. More potent antiplatelet therapy with Ticagrelor may be a better foundation for long term antiplatelet therapy compared to ASA in at-risk patients
4. May pave the way for future studies of Ticagrelor as a single foundation therapy