State of the art in hospital management of non-ST-elevation myocardial infarction (NSTEMI) / unstable angina

Professor Bernhard Meier
(Switzerland)

GlaxoSmithKline

State of the Art in Hospital Management of NSTEMI / Unstable Angina

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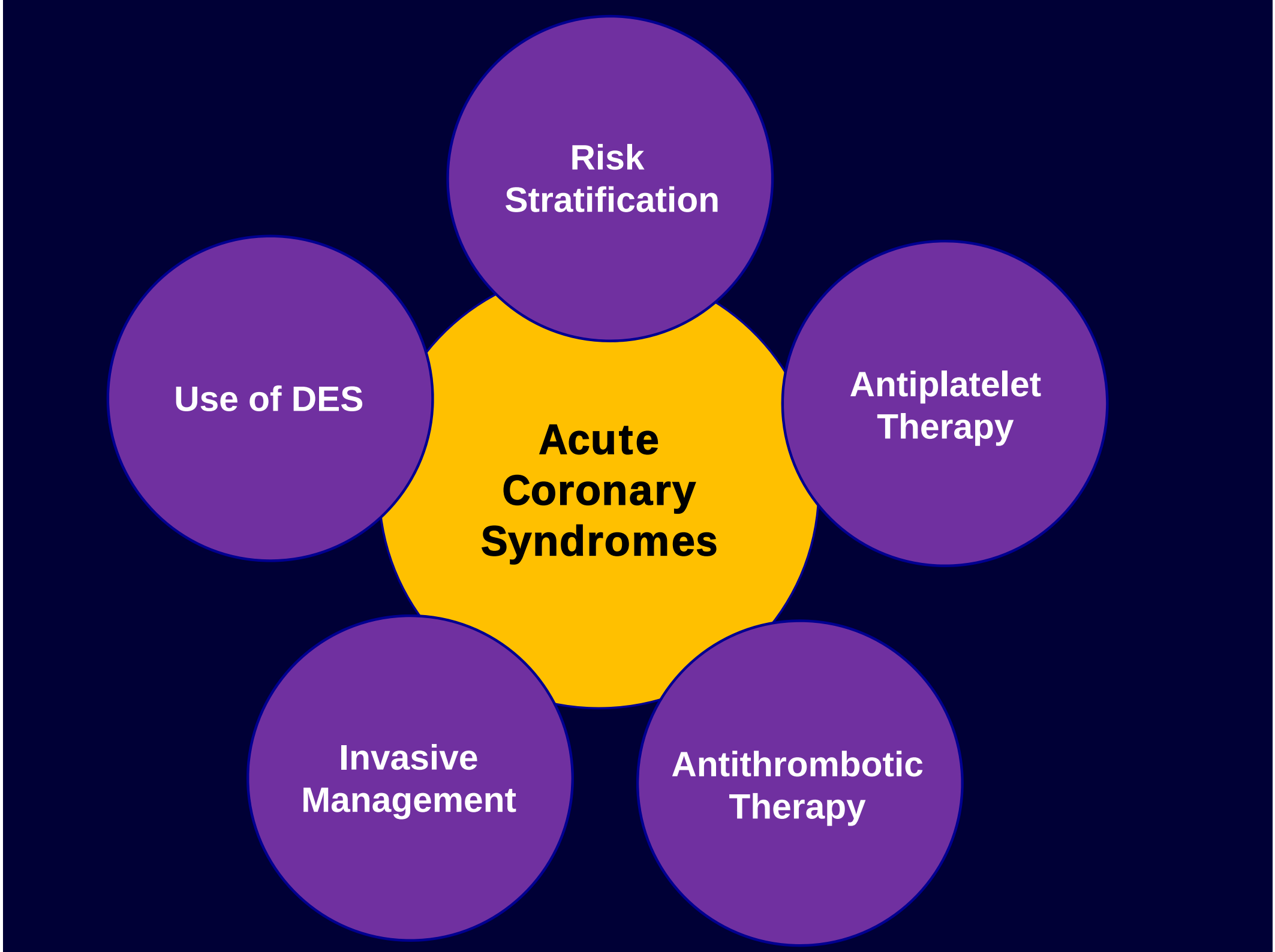
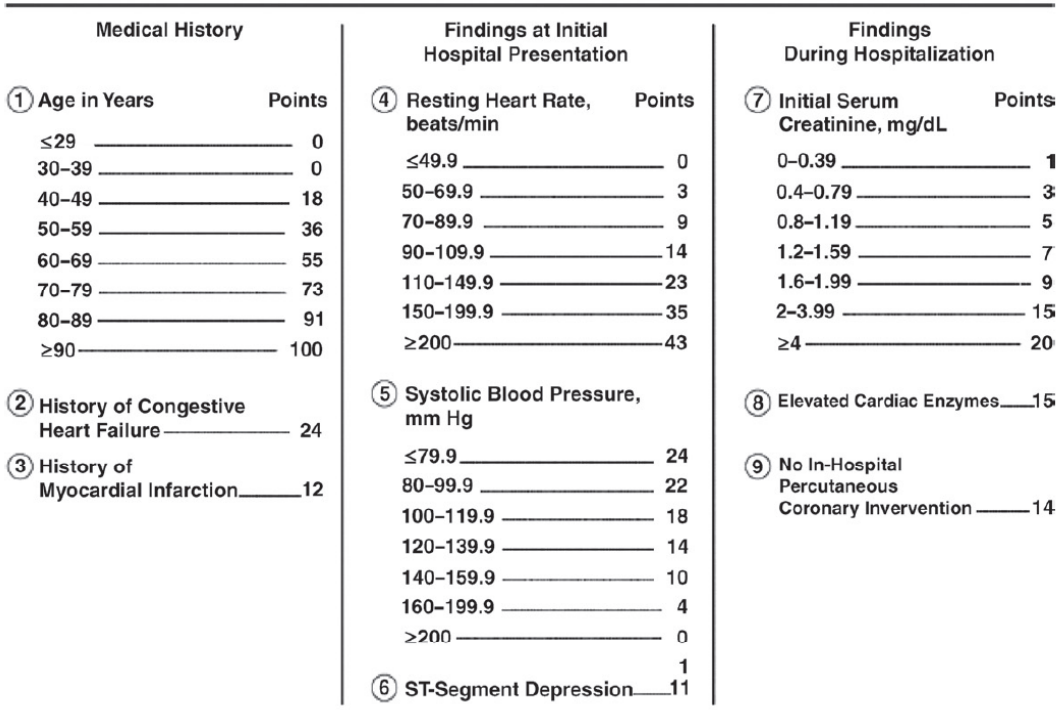

Risk Stratification
Use of DES
Acute Coronary Syndromes
Antiplatelet Therapy
Invasive Management
Antithrombotic Therapy

GRACE Risk Score
Mortality, In-Hospital and at 6 Months



Medical History

① Age in Years	Points
≤29	0
30–39	0
40–49	18
50–59	36
60–69	55
70–79	73
80–89	91
≥90	100

② History of Congestive Heart Failure	24
③ History of Myocardial Infarction	12

Findings at Initial Hospital Presentation

④ Resting Heart Rate, beats/min	Points
≤49.9	0
50–69.9	3
70–89.9	9
90–109.9	14
110–149.9	23
150–199.9	35
≥200	43

⑤ Systolic Blood Pressure, mm Hg	
≤79.9	24
80–99.9	22
100–119.9	18
120–139.9	14
140–159.9	10
160–199.9	4
≥200	0

⑥ ST-Segment Depression	1 11

Findings During Hospitalization

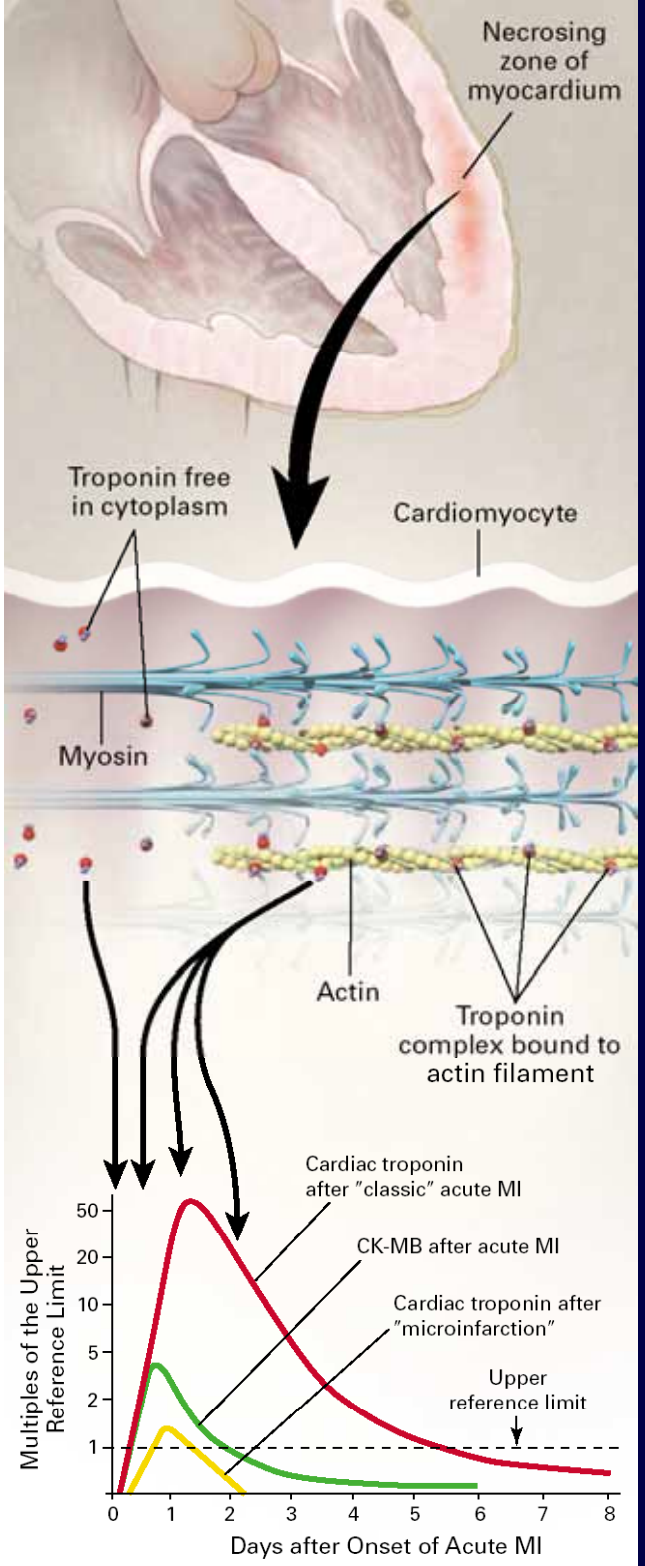
⑦ Initial Serum Creatinine, mg/dL	Points
0–0.39	1
0.4–0.79	3
0.8–1.19	5
1.2–1.59	7
1.6–1.99	9
2–3.99	15
≥4	20

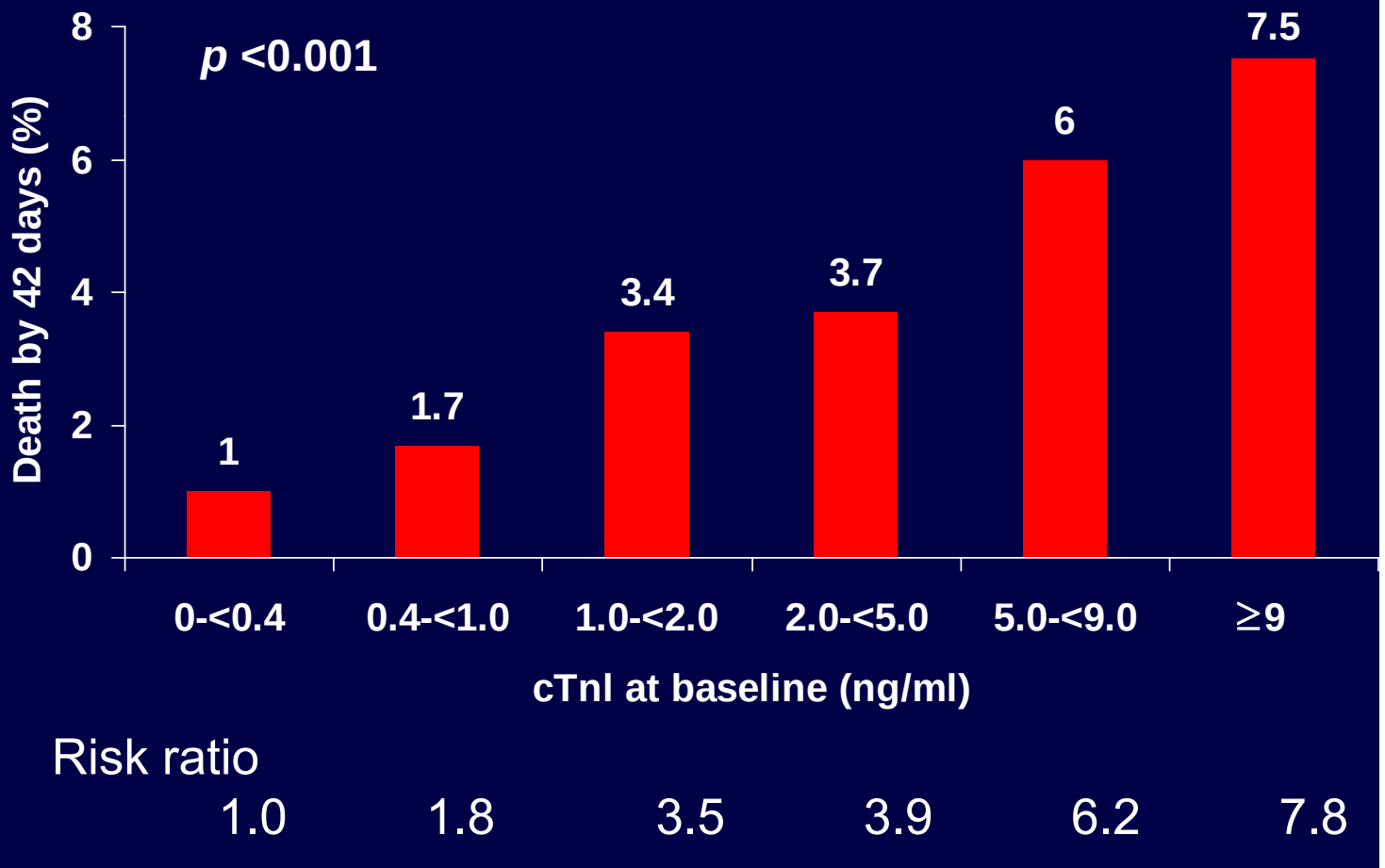
⑧ Elevated Cardiac Enzymes	15
⑨ No In-Hospital Percutaneous Coronary Invervention	14

Risk category (tertile)	GRACE risk score	In-hospital death (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertile)	**GRACE risk score**	**Post-discharge to 6-month death (%)**
Low	≤88	<3
Intermediate	89–118	3-8
High	>118	>8

Relationship of Troponin Level to Early Mortality in ACS

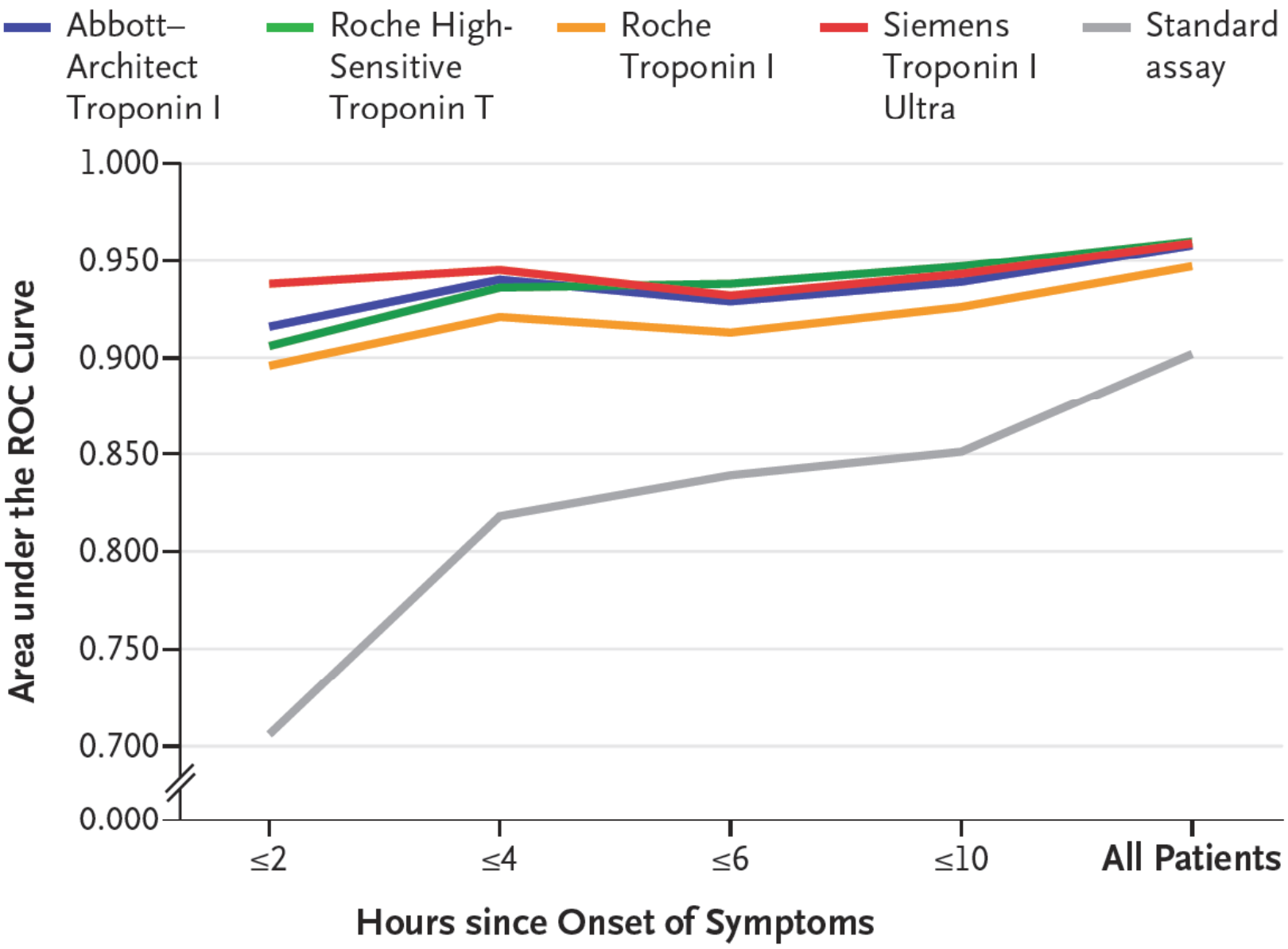
Antman EM et al. *NEJM* 1996;335:1342-49





Accuracy of Cardiac Troponin Assays According to Time of Onset of Chest Pain

Reichlin T et al, *N Engl J Med* 2009;361:858-67



Differential Diagnosis

Non-Cardiac Causes of Troponin Elevation

Hamm C et al. *Eur Heart J* 2001

- **Chronic or acute renal dysfunction**
- Severe congestive **heart failure** – acute and chronic
- **Hypertensive crisis**
- **Tachy- or bradyarrhythmias**
- **Pulmonary embolism**, severe pulmonary hypertension
- Inflammatory diseases, e.g. **myocarditis**
- Acute neurological disease, including **stroke**, or subarachnoid haemorrhage
- Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
- Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
- Hypothyroidism
- Apical ballooning syndrome (Tako-Tsubo cardiomyopathy)
- Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, sclerodermia
- Drug toxicity, e.g. adriamycin, 5-fluorouracil, herceptin, snake venoms
- Burns, if affecting >30% of body surface area
- Rhabdomyolysis
- Critically ill patients, especially with respiratory failure, or sepsis

High-Risk Indicators
Early Invasive Strategy Warranted

Class IA Indication for Early Invasive Strategy (ESC)

Primary

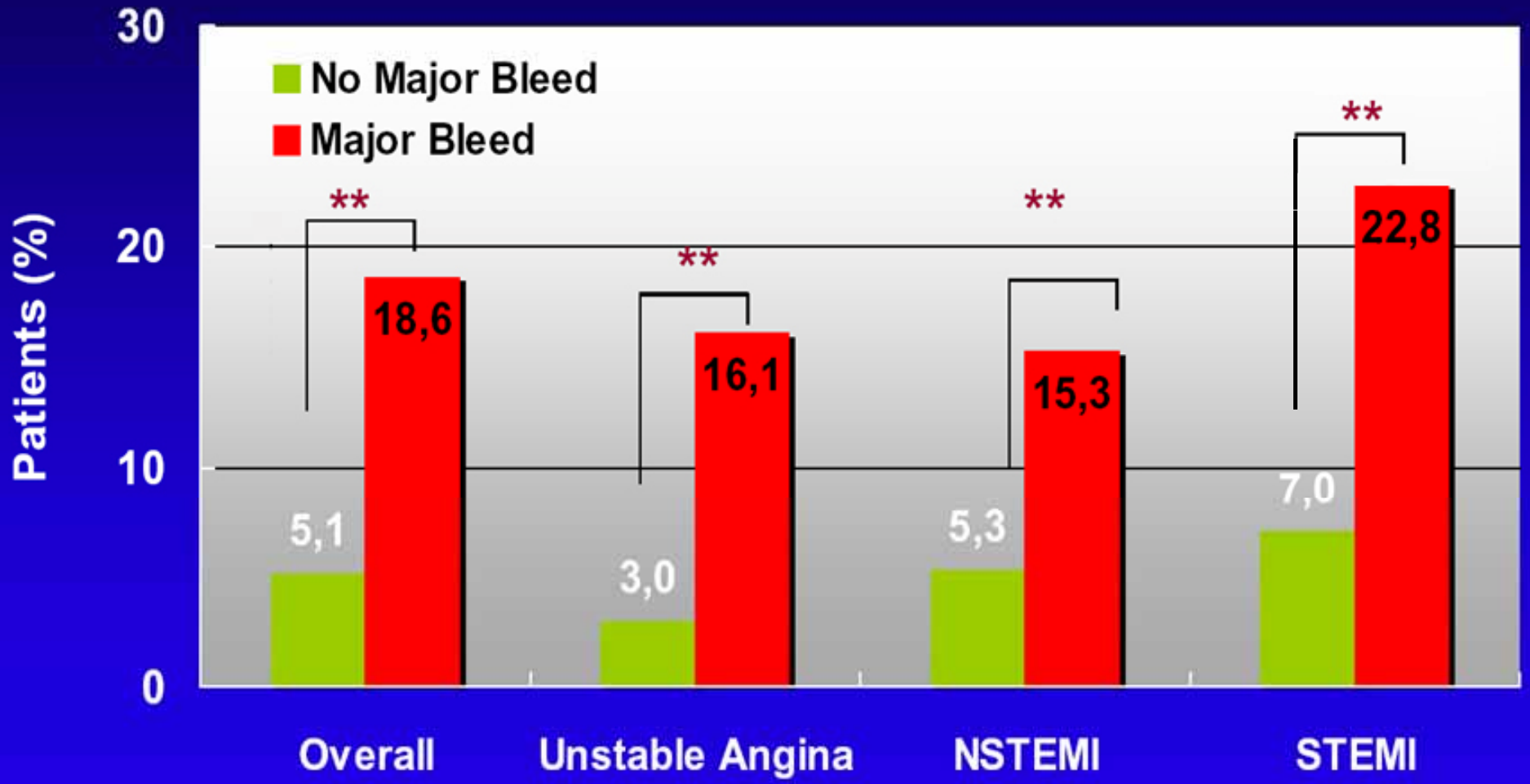
- Relevant rise or fall in troponin
- Dynamic ST- or T-wave changes

Secondary

- Diabetes mellitus
- Renal insufficiency (eGFR < 60 ml/min)
- Reduced LV function (LVEF <40%)
- Early post infarction angina
- Recent PCI
- Prior CABG
- Intermediate to high GRACE risk score

Bleeding and in-Hospital Mortality Rates in ACS

24,045 Patients



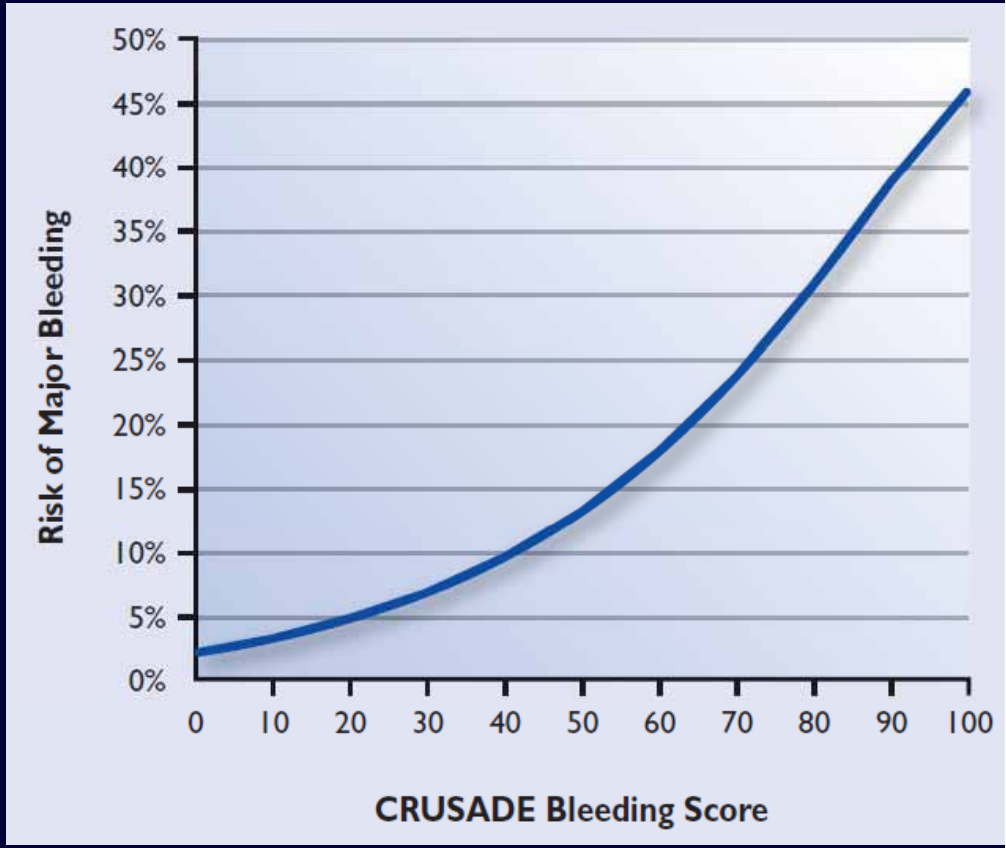
Major Bleeding: 3.9%
HR=1.64, 95% CI 1.2-2.3

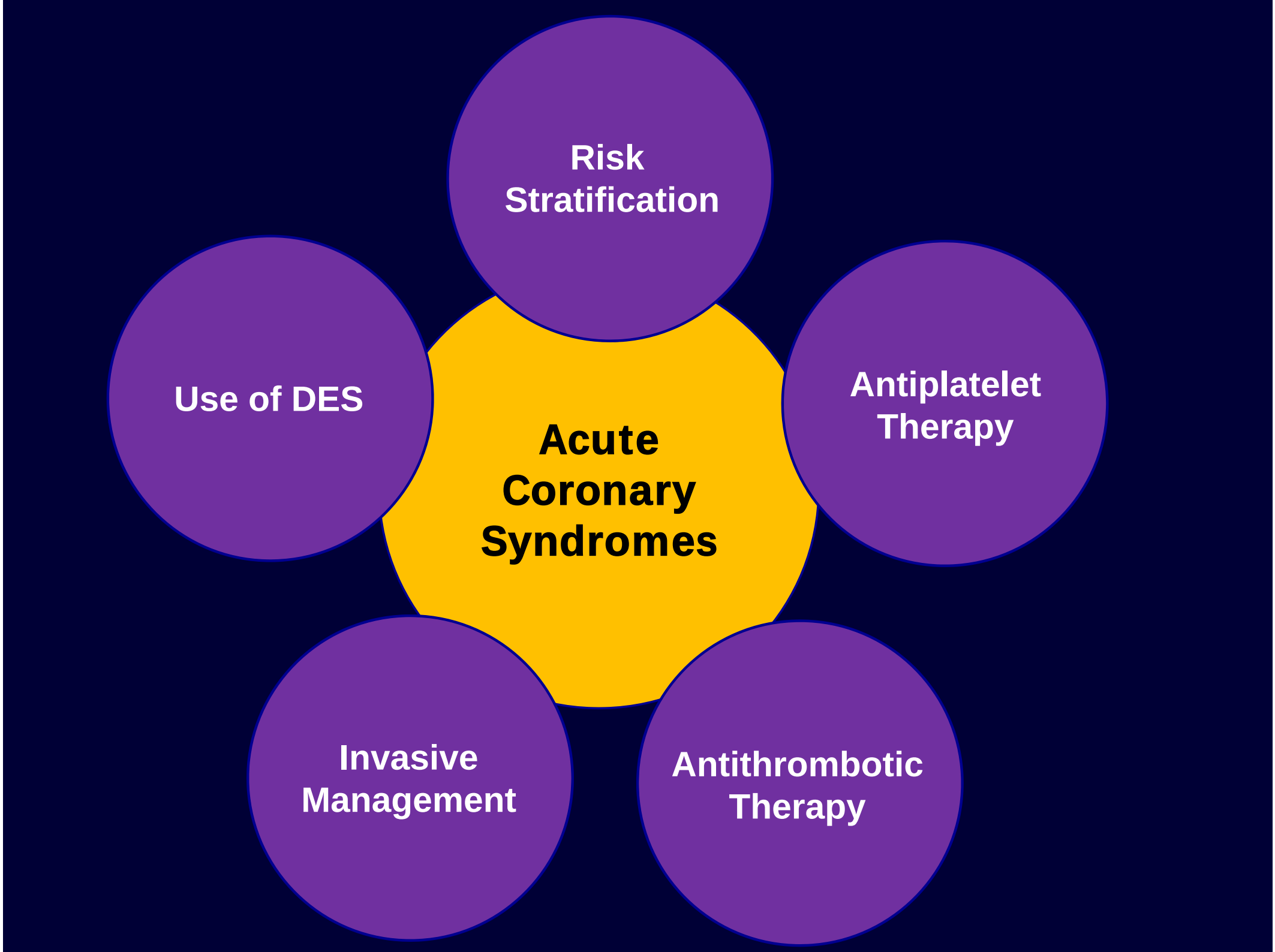
Moscucci M et al. ***Eur Heart J*** 2003;24:1815-23.

Assessment of Bleeding-Risk

Hamm C et al. ESC Guidelines UA/NSTEMI *Eur Heart J* 2011

- Age (>75y)
- Renal failure
- Low body weight (<60kg)
- Female gender
- Anemia
- High dose antithrombotic agents
- Duration of antithrombotic Rx
- Combination of several antithrombotic agents
- Change between various antithrombotic agents

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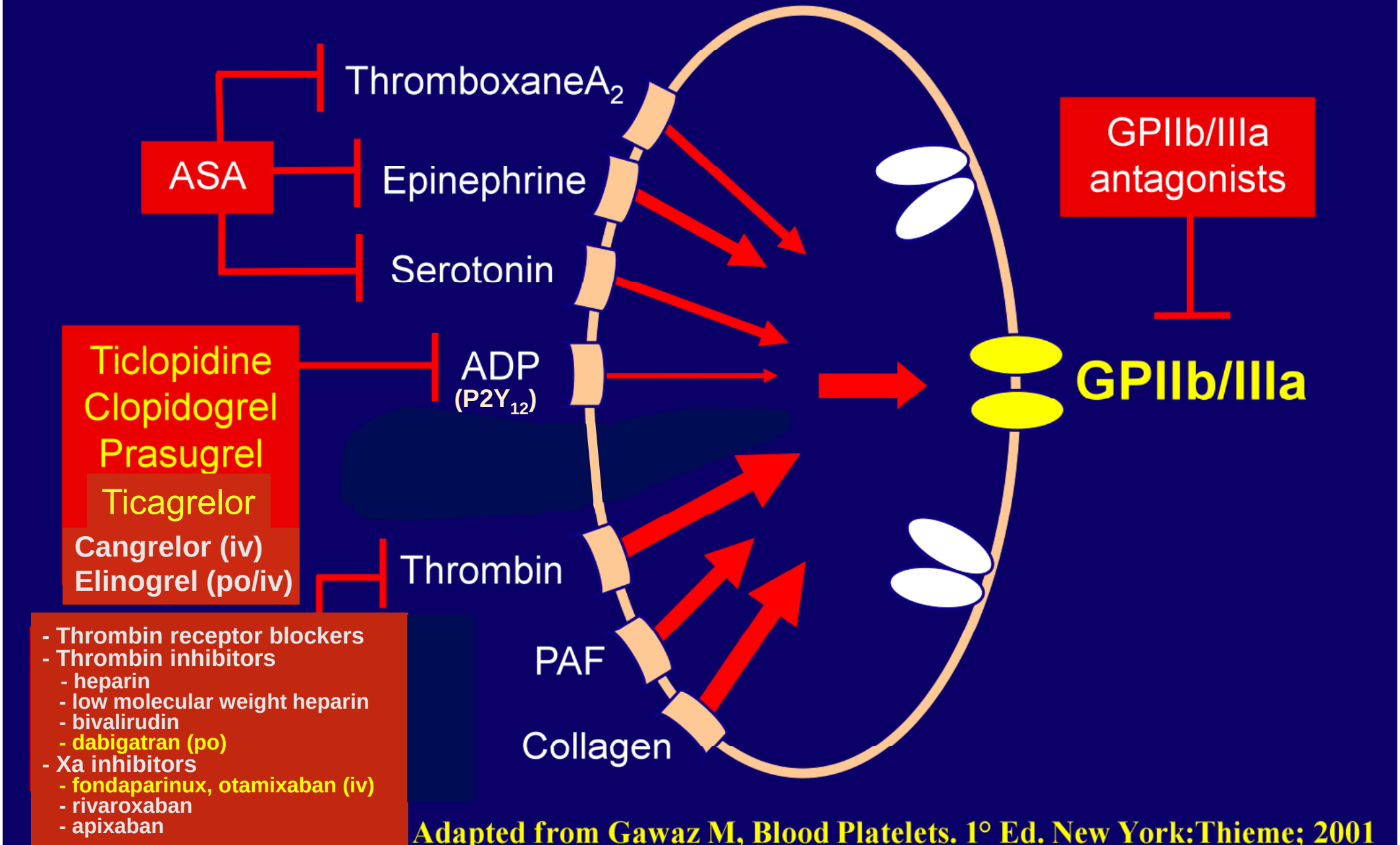
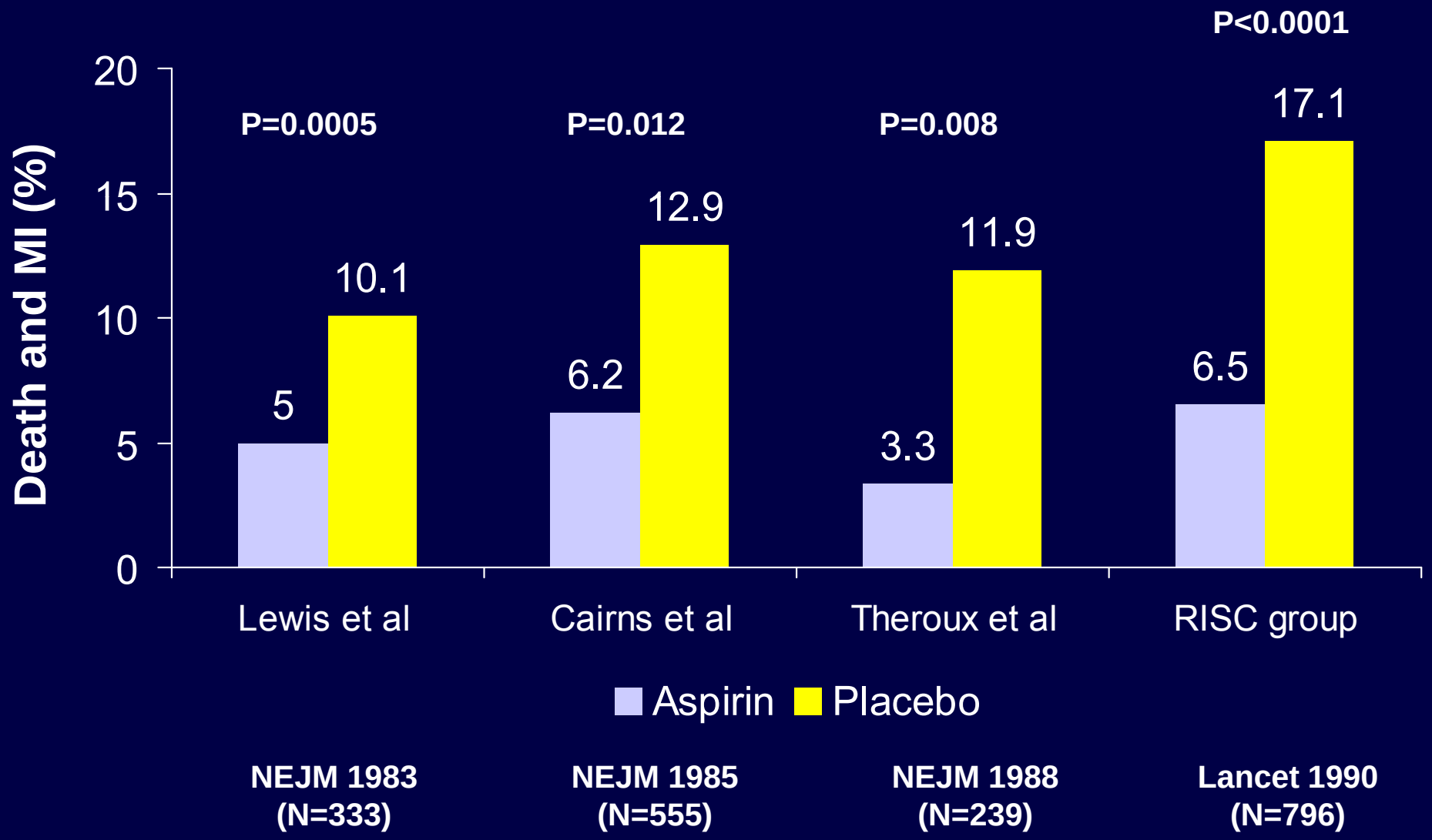
Platelet activating substances and targets for inhibition



Adapted from Gawaz M, Blood Platelets. 1° Ed. New York:Thieme; 2001

Benefit of Aspirin in Unstable Angina/NSTEMI: Four Randomized Trials



CURRENT OASIS 7 – Acute Coronary Syndromes
Aspirin "Double" Dosage

Mehta SR et al. *N Engl J Med* 2010;363:930-42

Primary outcome: CV death, MI or stroke at 30 days

High dose

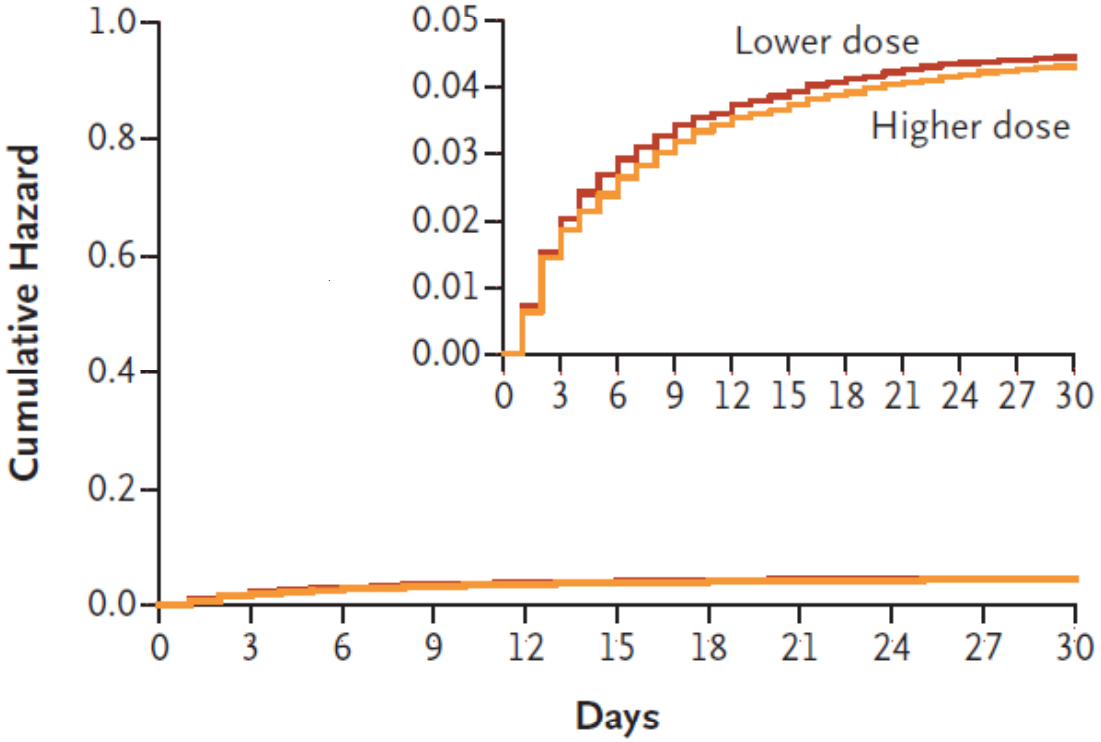
(300-325 mg)

versus

low dose

(75-100 mg)

Aspirin



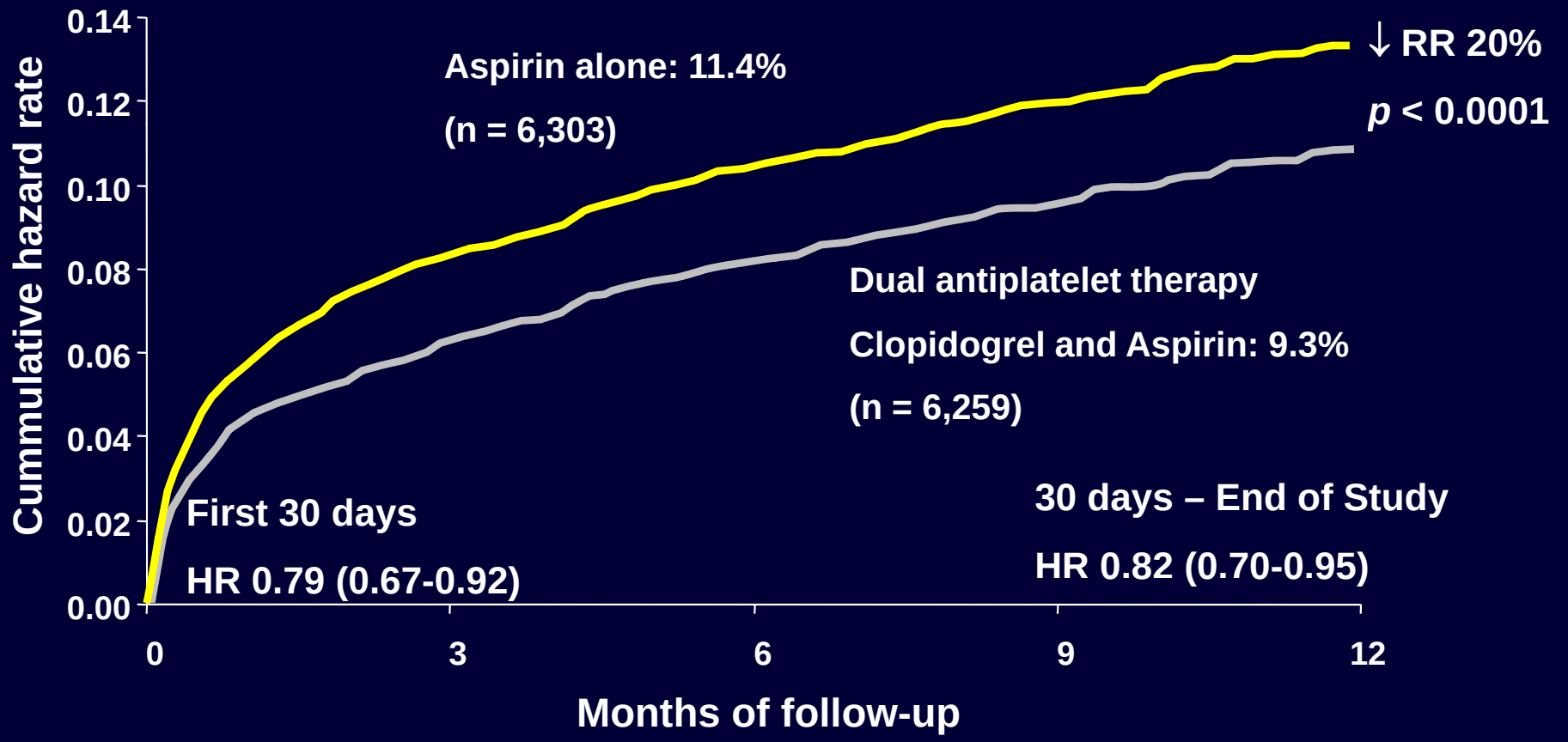
No. at Risk						
Higher dose	12,507	12,204	12,075	12,018	11,983	11,962
Lower dose	12,579	12,239	12,121	12,059	12,024	12,009

Major GI Bleeding: 0.4% (high dose) vs 0.2% (low dose), P=0.04

CURE: Early and Long-Term Benefits of Clopidogrel

The CURE Trial Investigators. *N Engl J Med* 2001;345:494–502

CV Death, Myocardial Infarction, or Stroke

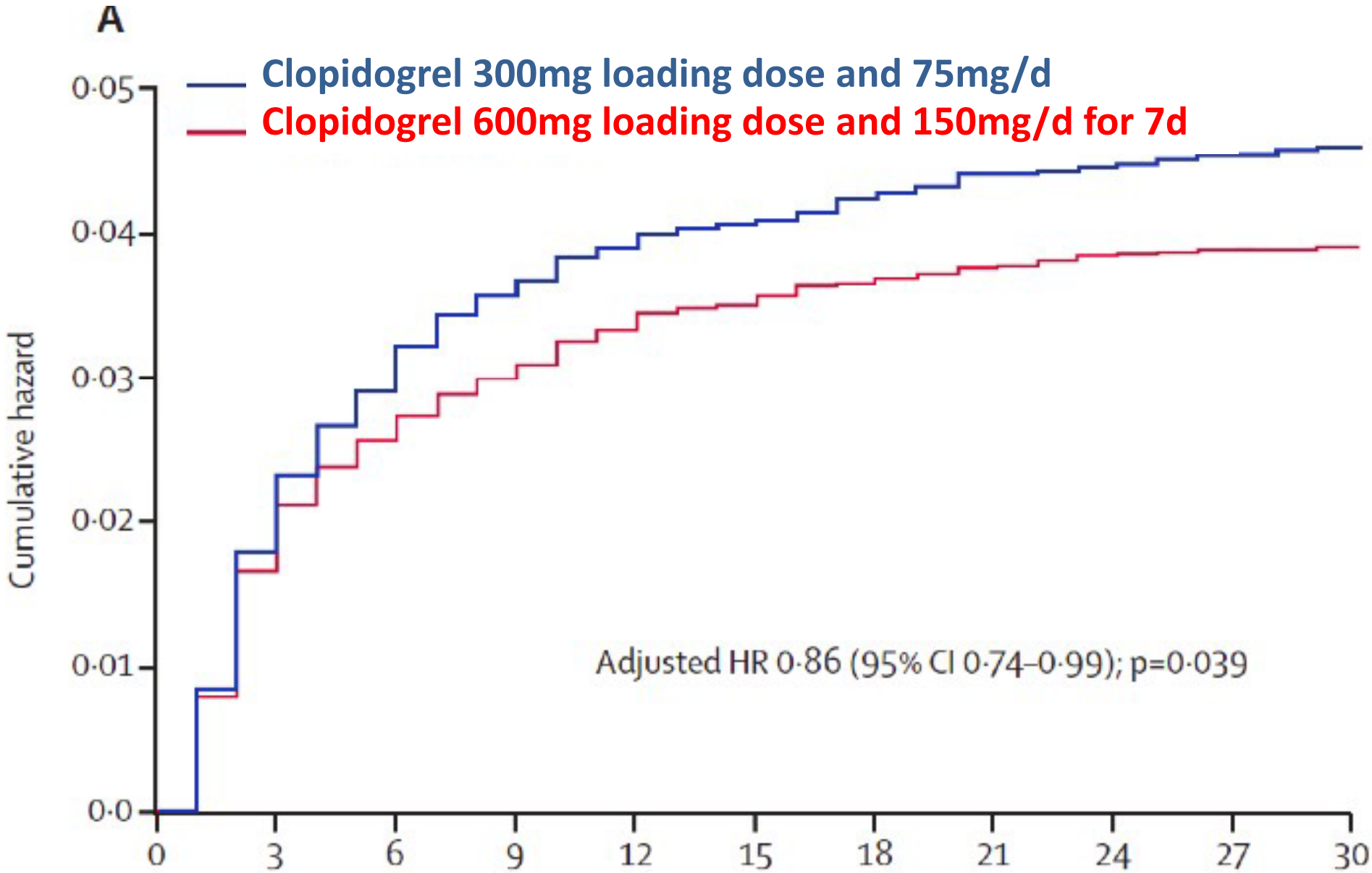


Clopidogrel loading dose: 300 mg in CURE

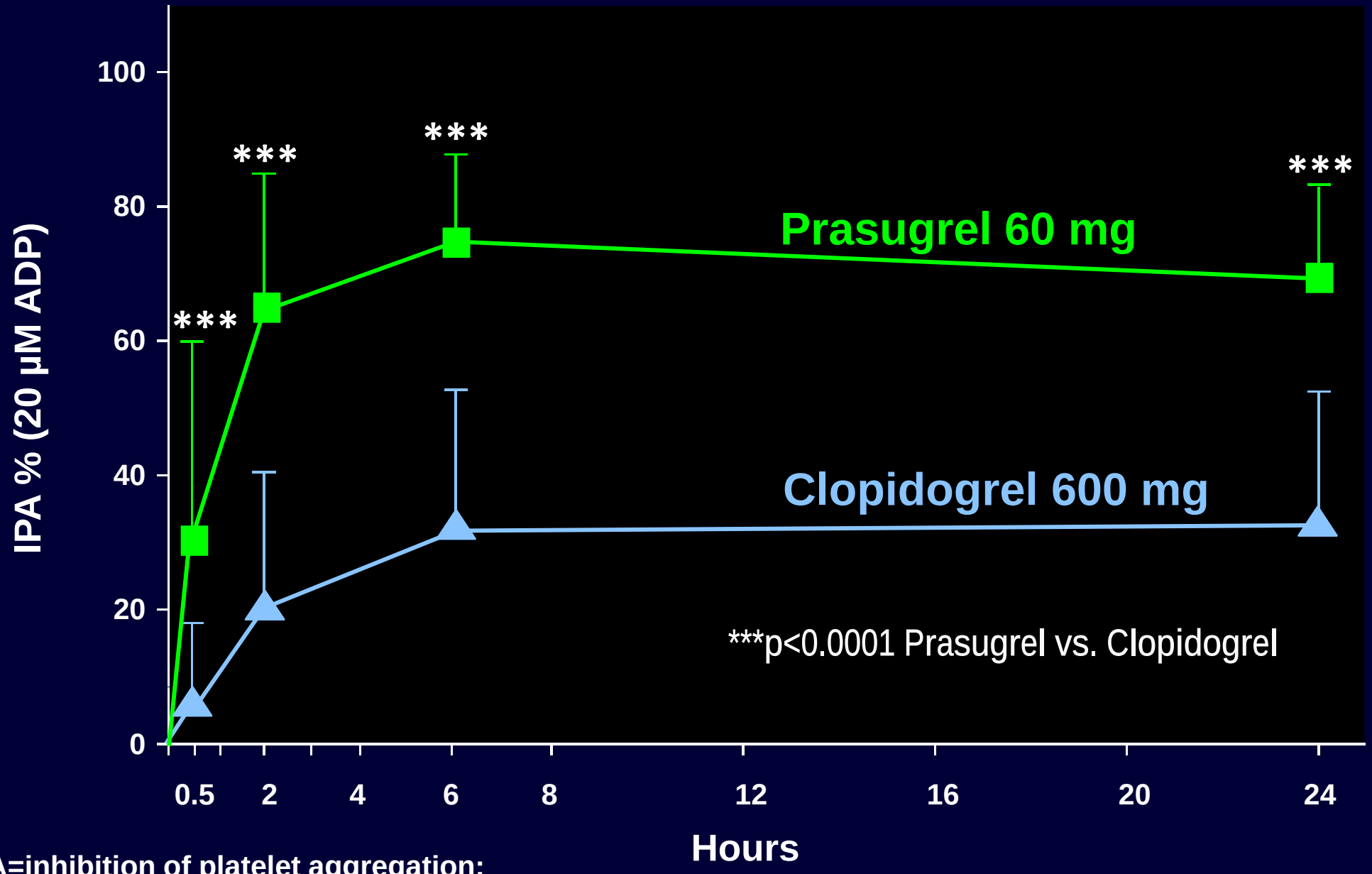
CURRENT OASIS 7 - PCI Population

Mehta SR et al Lancet 2010;376:1233-43

Primary outcome: CV death, MI or Stroke at 30 days



Inhibition of Platelet Aggregation After Loading Dose in Patients With Elective PCI

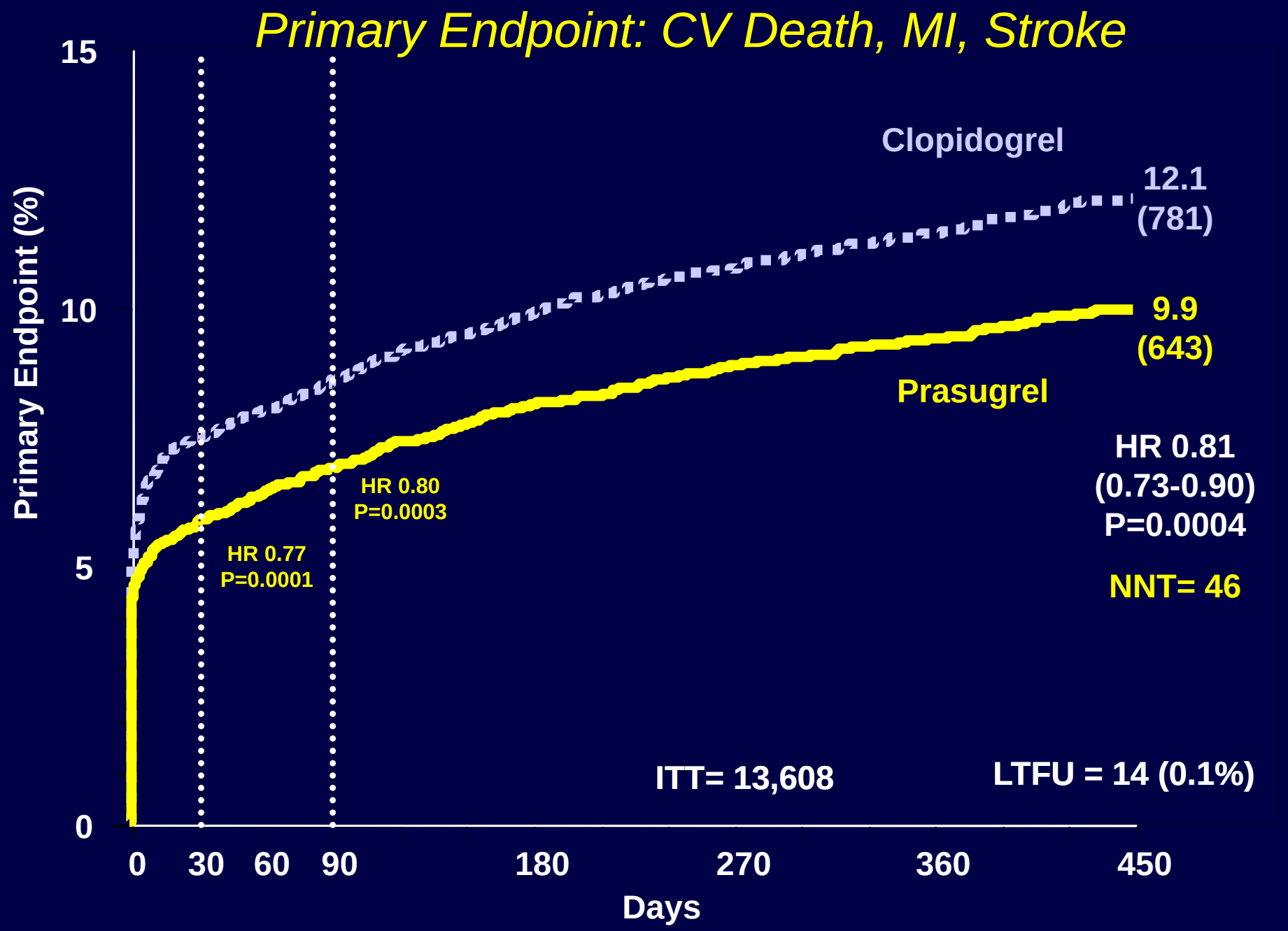


IPA=inhibition of platelet aggregation;
PCI=Percutaneous coronary intervention

Wiviott SD et al. *Circulation* 2007;116(25):2923-2932

Triton TIMI 38 – Prasugrel vs. Clopidogrel

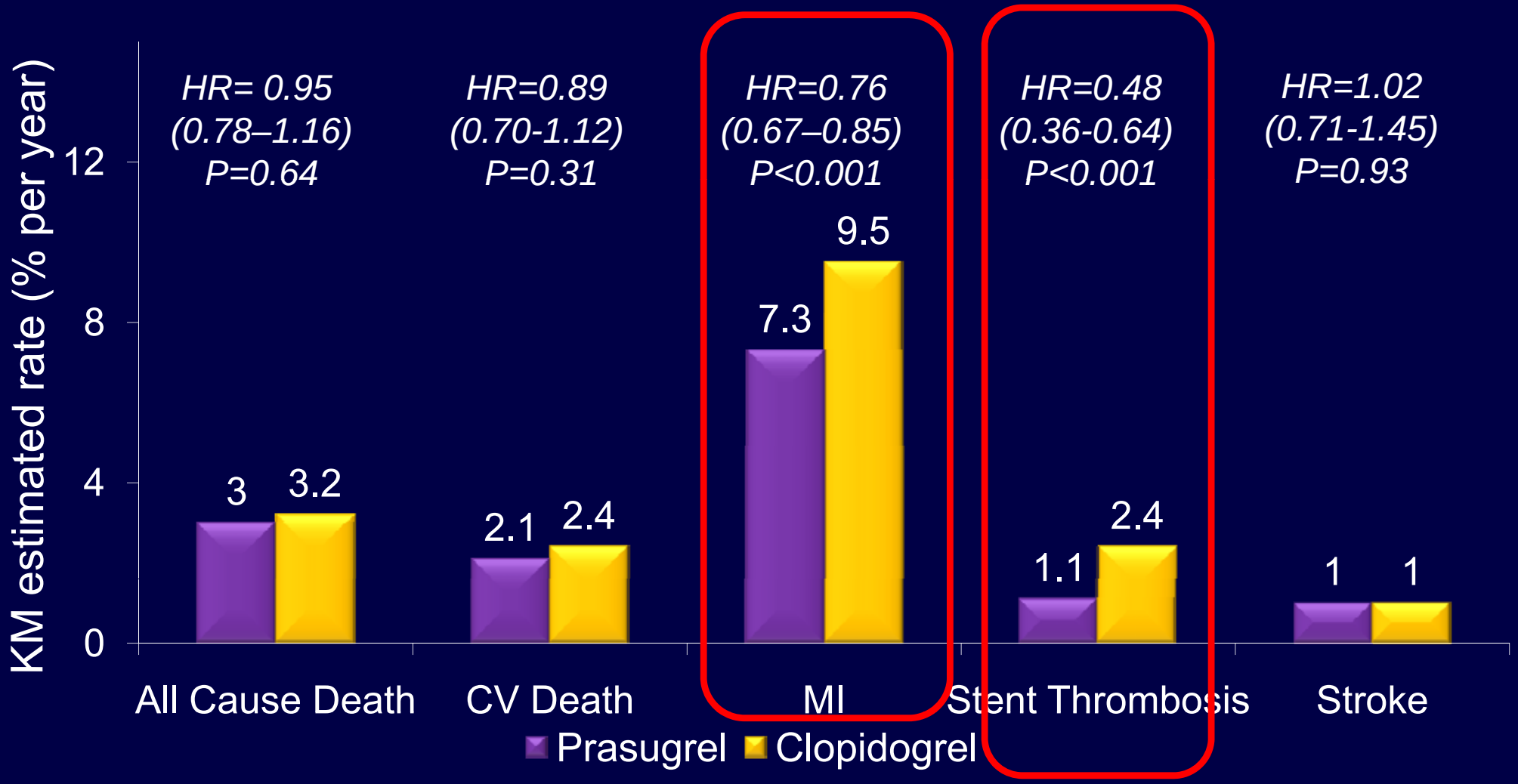
Wiviott SD et al. *N Engl J Med* 2007;357:2001-15



Triton TIMI 38 – Prasugrel vs. Clopidogrel

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15

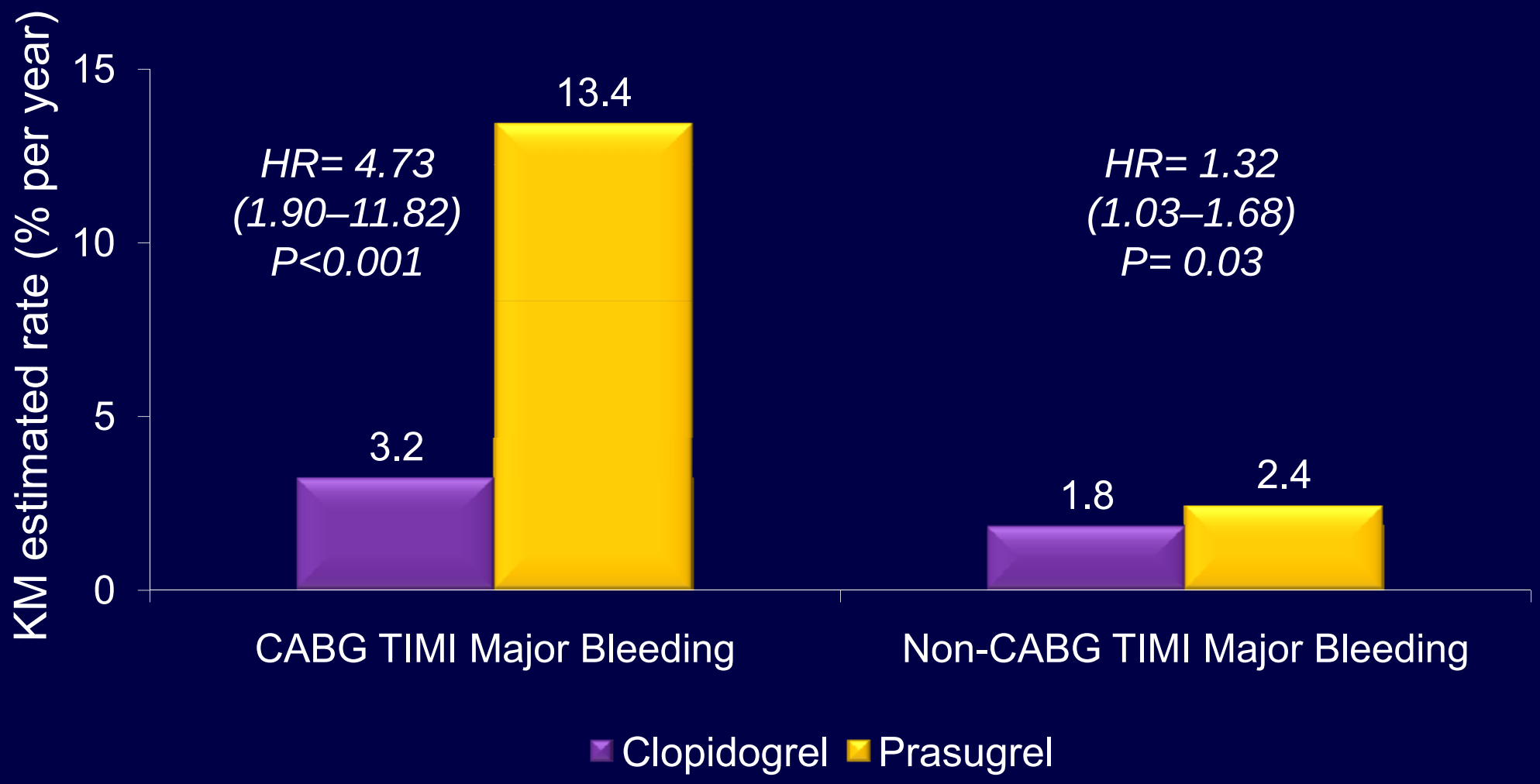
Individual Ischemic Endpoints



Triton TIMI 38 – Prasugrel vs. Clopidogrel

Wiviott SD et al. *N Engl J Med* 2007;357:2001-15

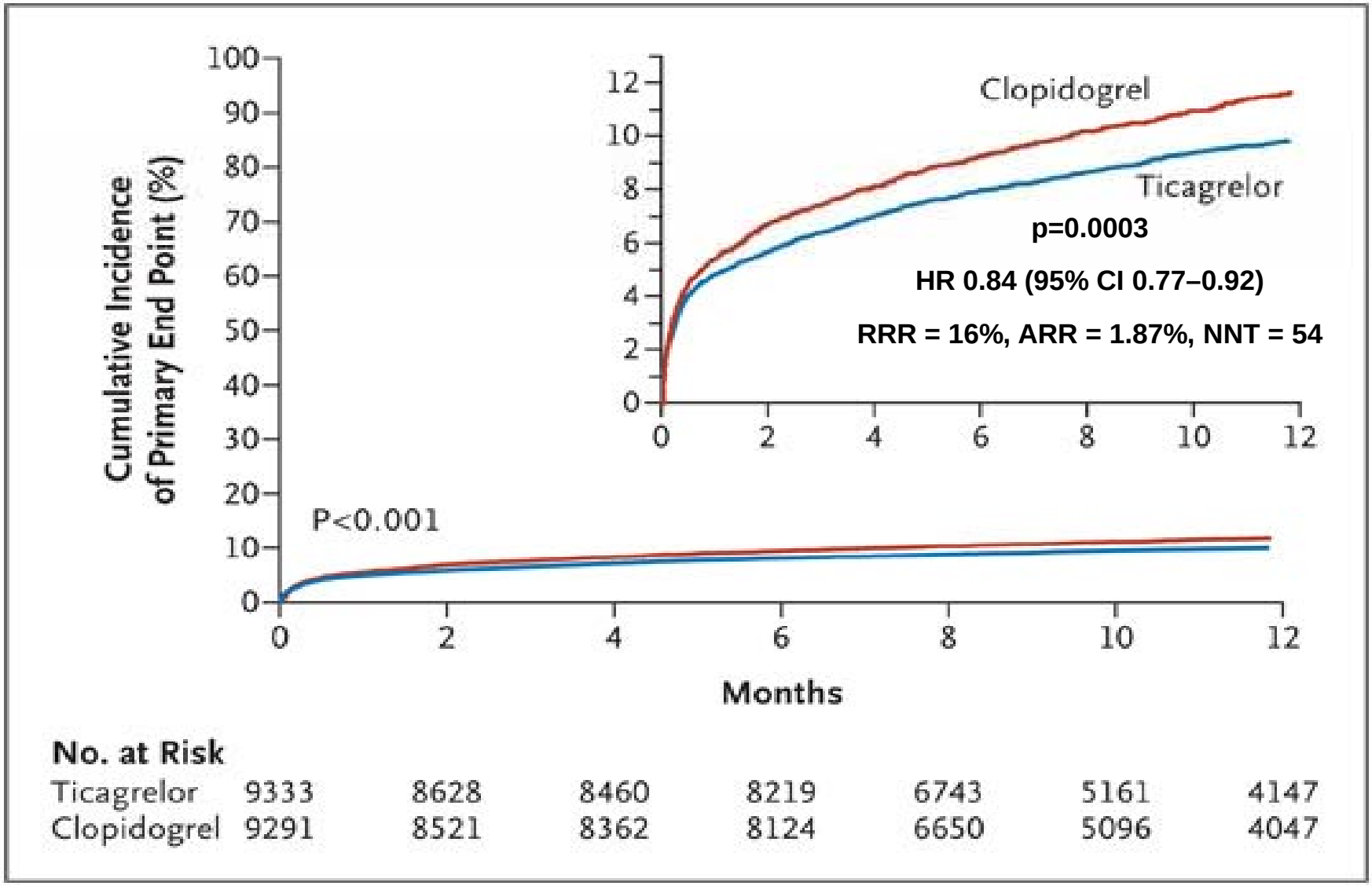
CABG and Non-CABG Related Bleeding



PLATO - Ticagrelor versus Clopidogrel in ACS

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

Primary Endpoint: CV Death, MI or Stroke



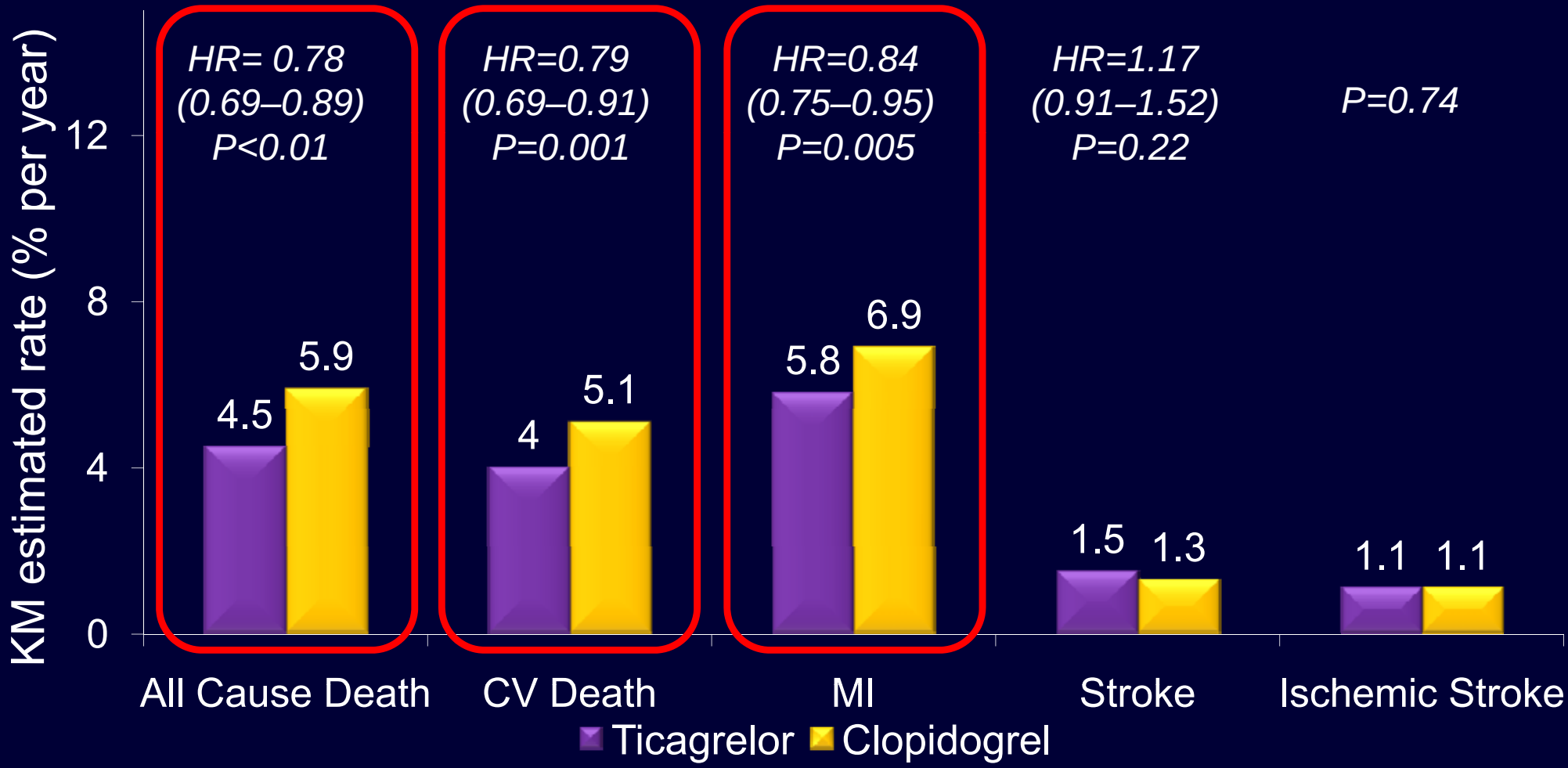
11.7%

9.8%

Ticagrelor versus Clopidogrel in ACS

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

Individual Ischemic Endpoints



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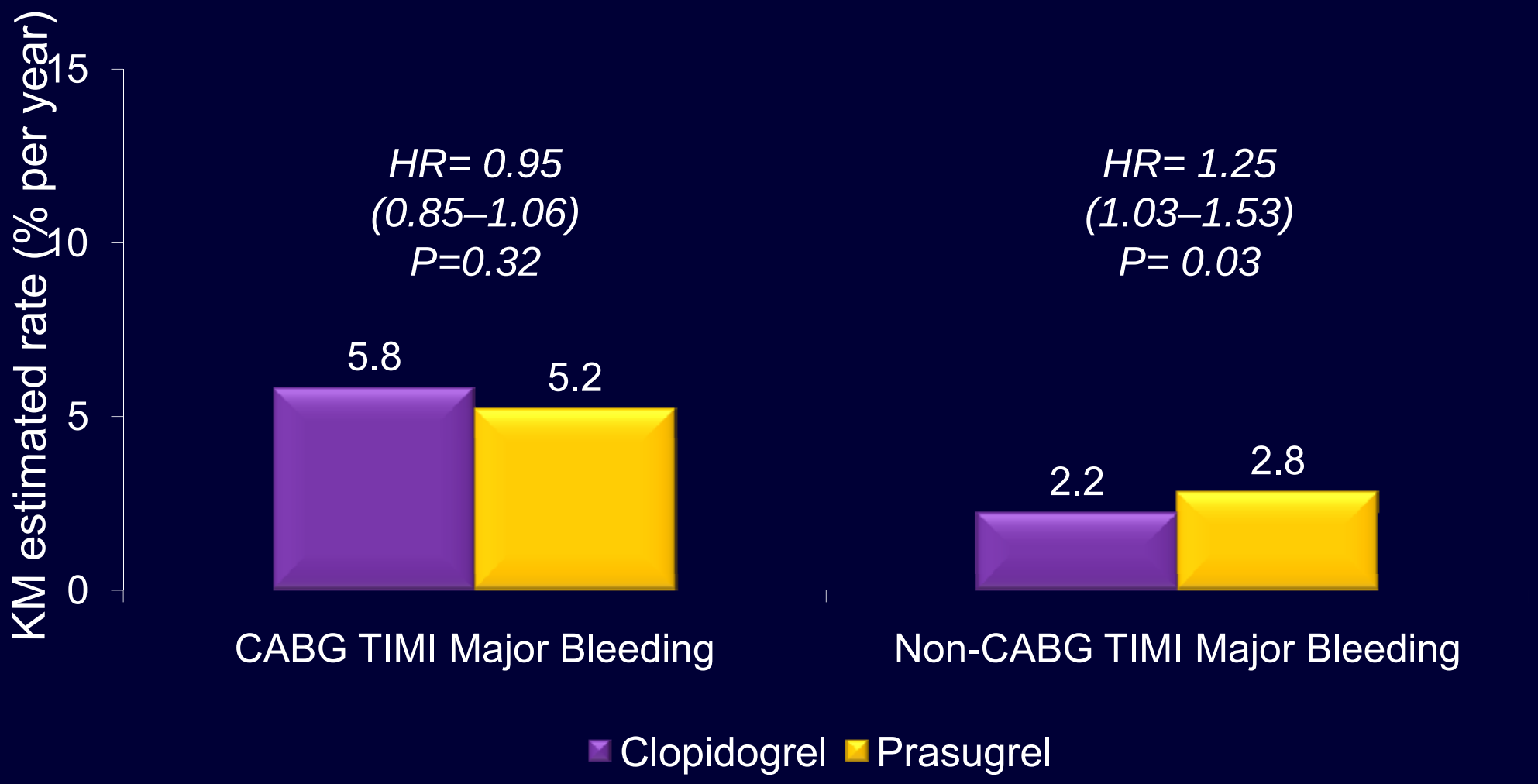
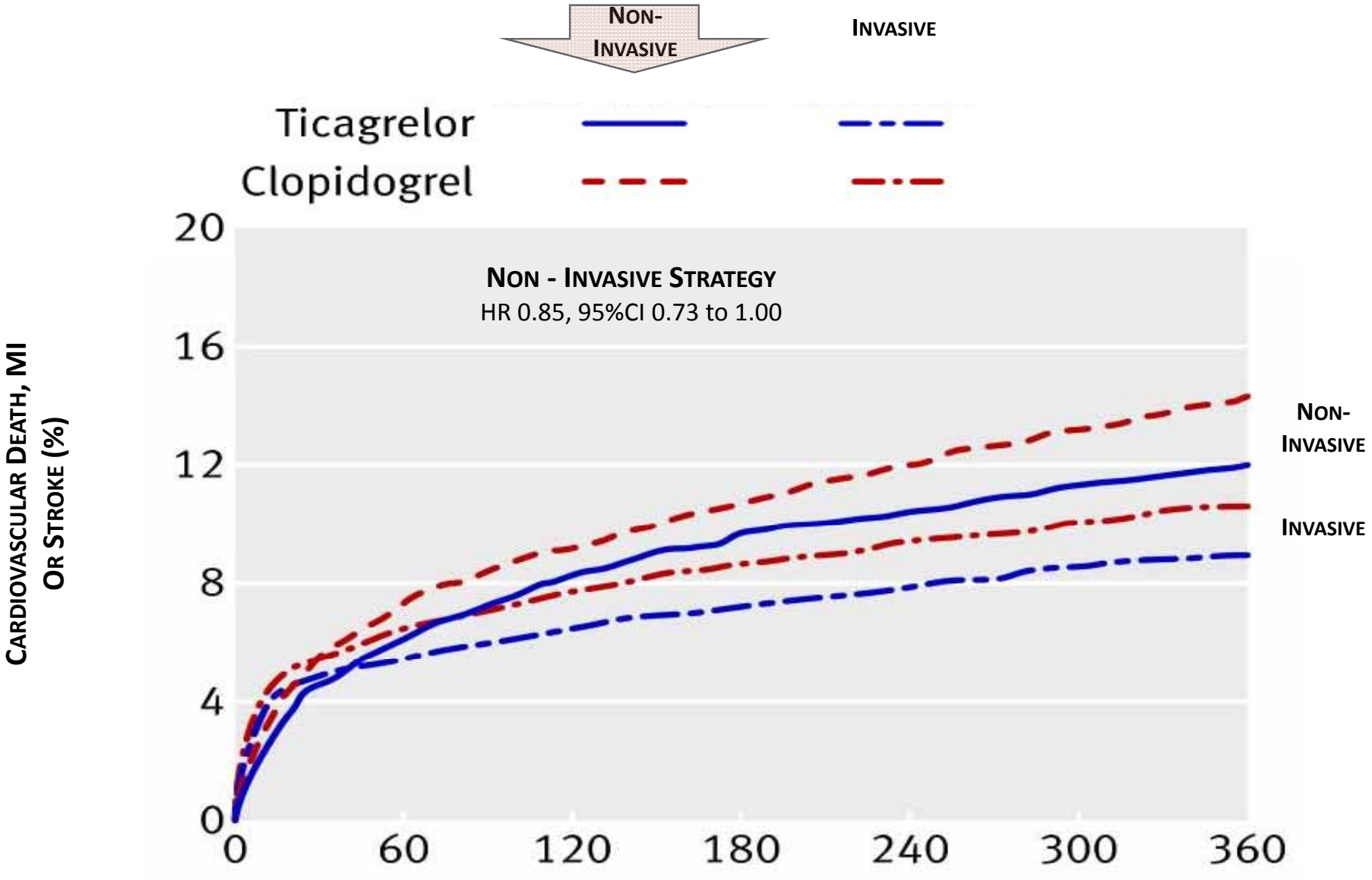


Ticagrelor vs. Clopidogrel for ACS in Patients Intended to Treat Non-Invasively

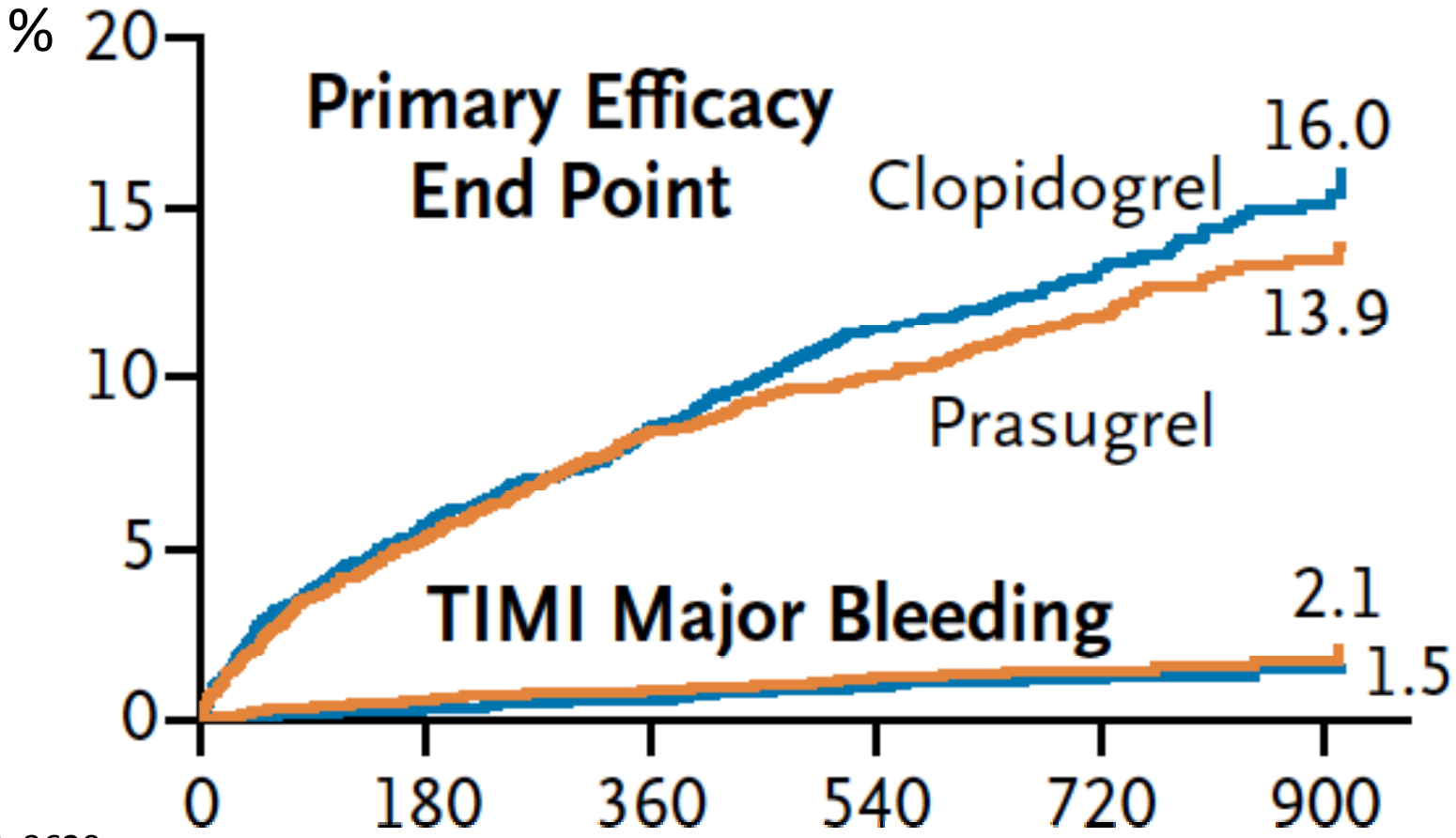
James SK et al. BMJ 2011, 342:d3527. doi: 10.1136/bmj.d3527



Prasugrel vs. Clopidogrel for ACS Without Revascularization – TRILOGY ACS

Roe MT et al. *N Eng J Med* 2012

Primary EP: CV Death, MI, or Stroke at 30 Months



HR 0.91 (0.79-1.05)

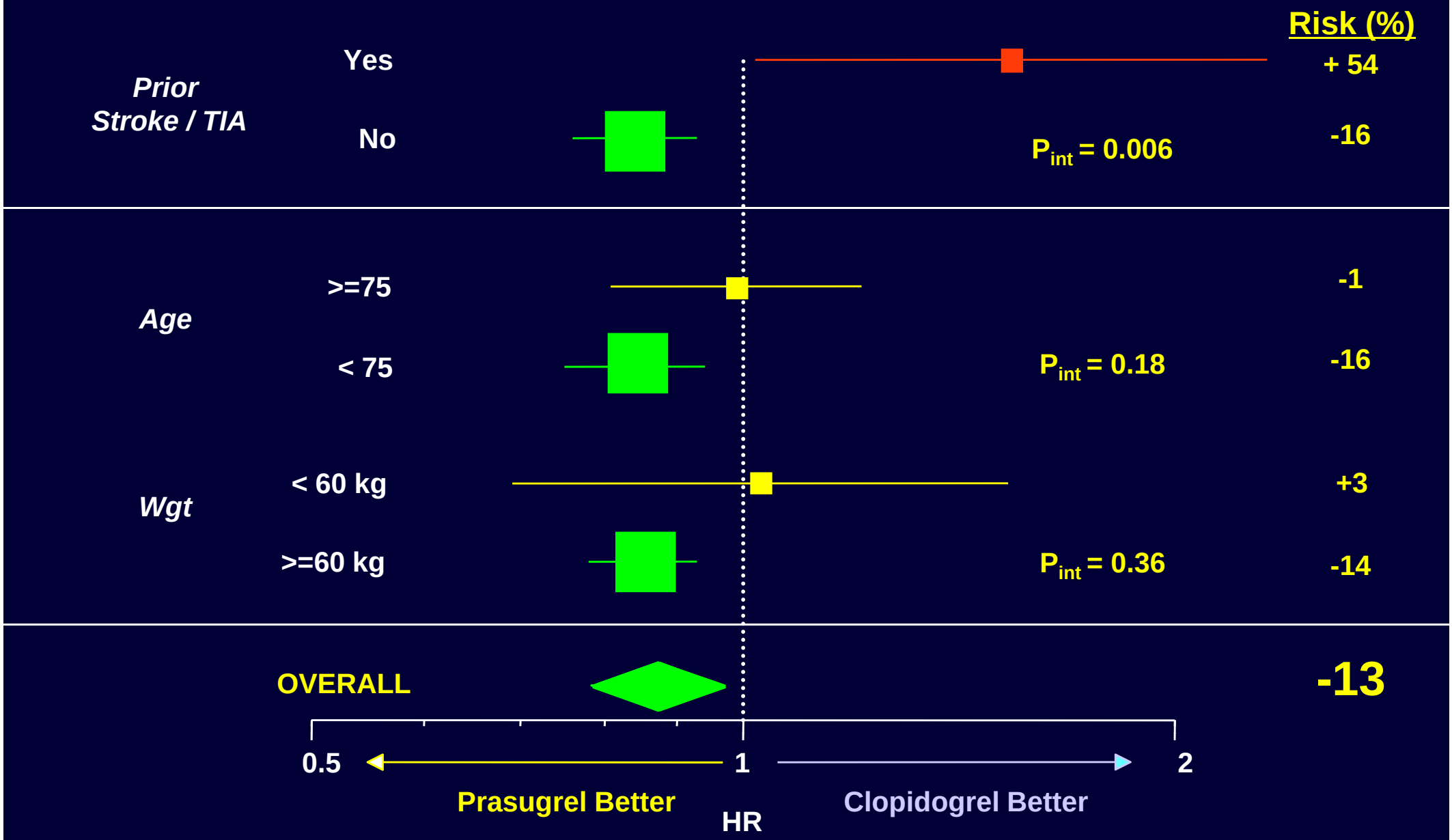
HR 1.31 (0.81-2.11)

Prasugrel N=3620

Clopidogrel N=3623

Net Clinical Benefit: Bleeding Risk Subgroups

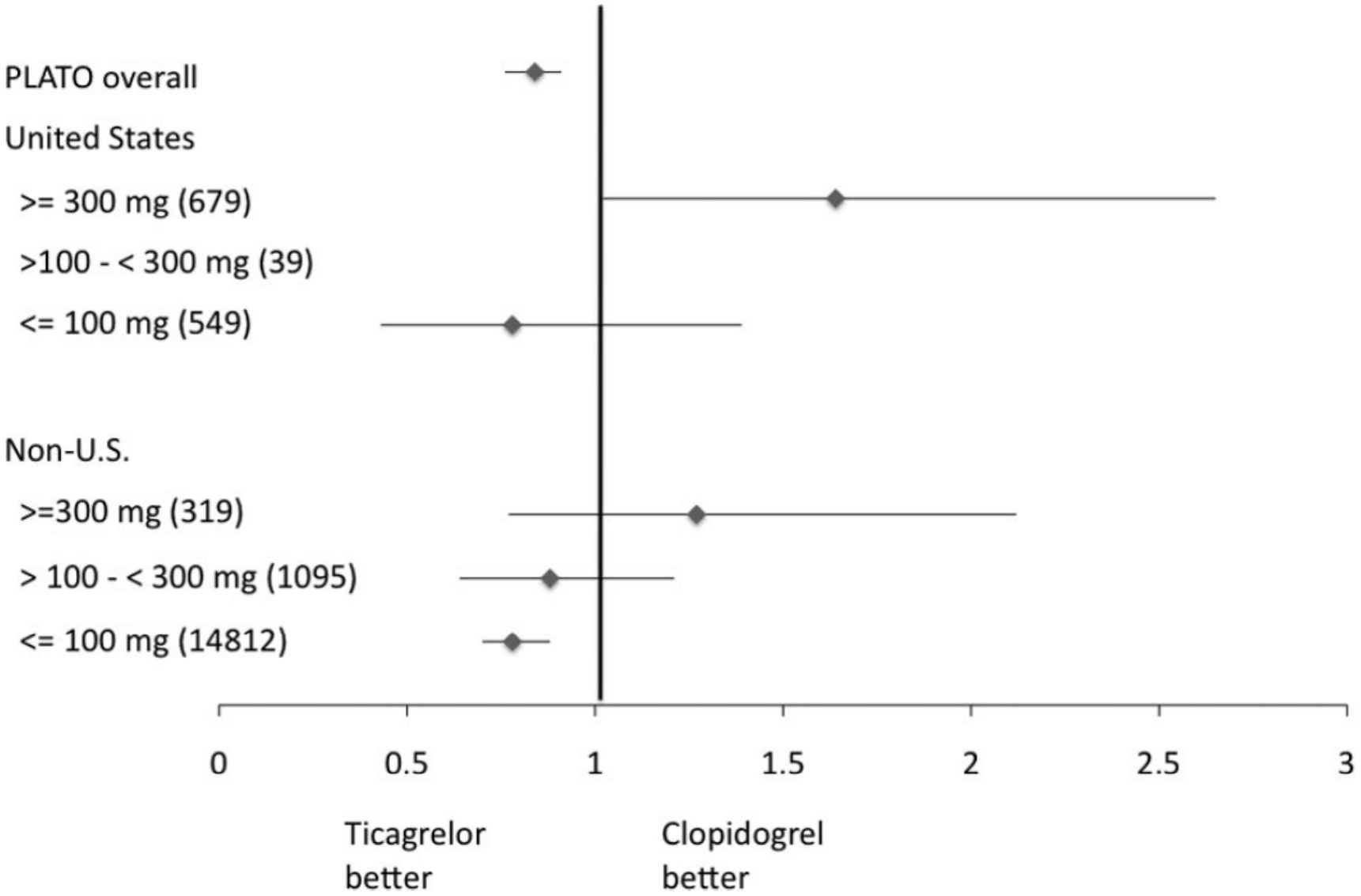
Post-hoc analysis



Ticagrelor versus Clopidogrel - PLATO

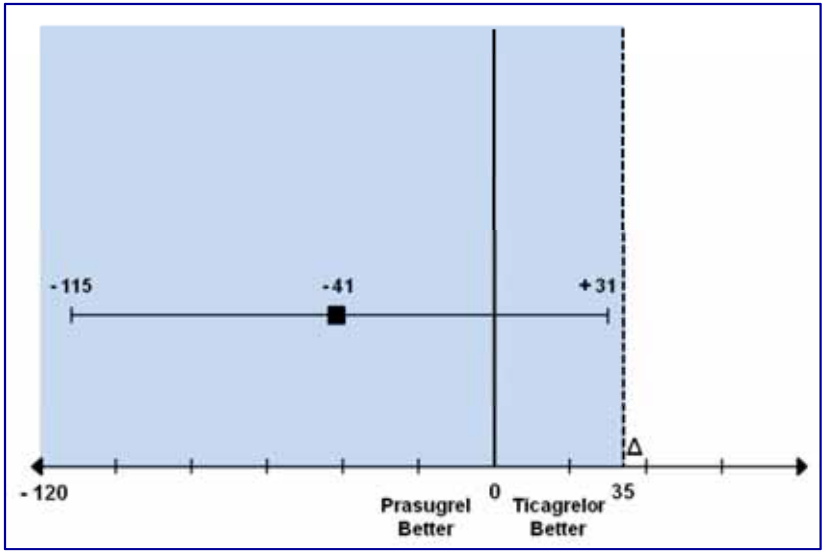
Wallentin L, et al. *N Engl J Med* 2009;361:1045-57

Outcomes by Geography and Aspirin Dose

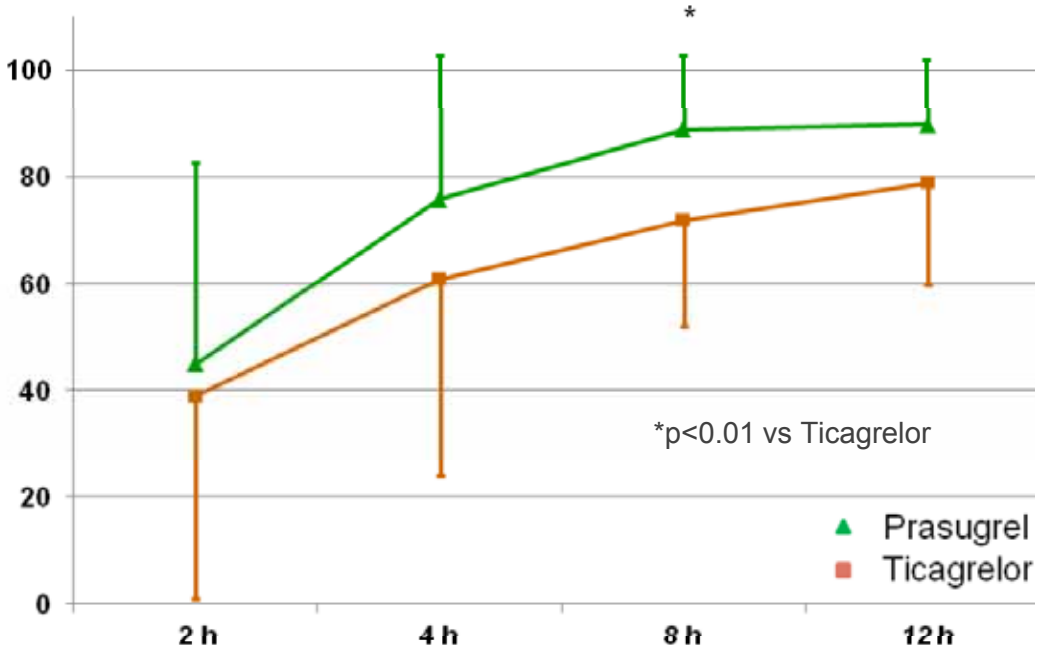


Prasugrel and Ticagrelor loading doses (LD) in PCI for STEMI (RAPID)

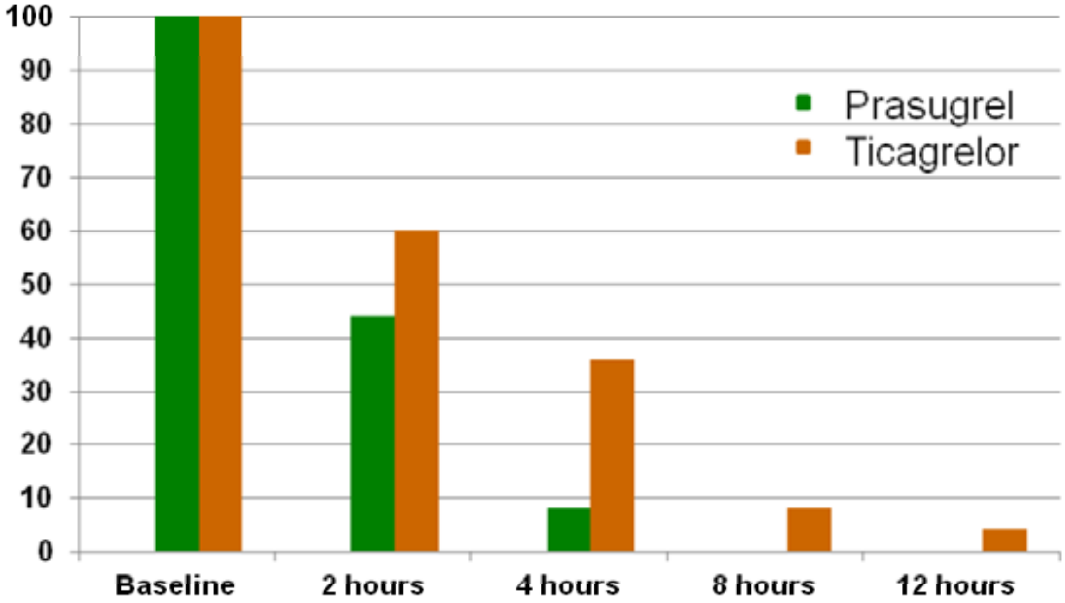
50 pts with PCI for STEMI (bivalirudin monotherapy)
- randomized to
  - 60 mg prasugrel LD
  - 180 mg ticagrelor LD
- platelet reactivity assessed by VerifyNow



Inhibition of Platelet Aggregation



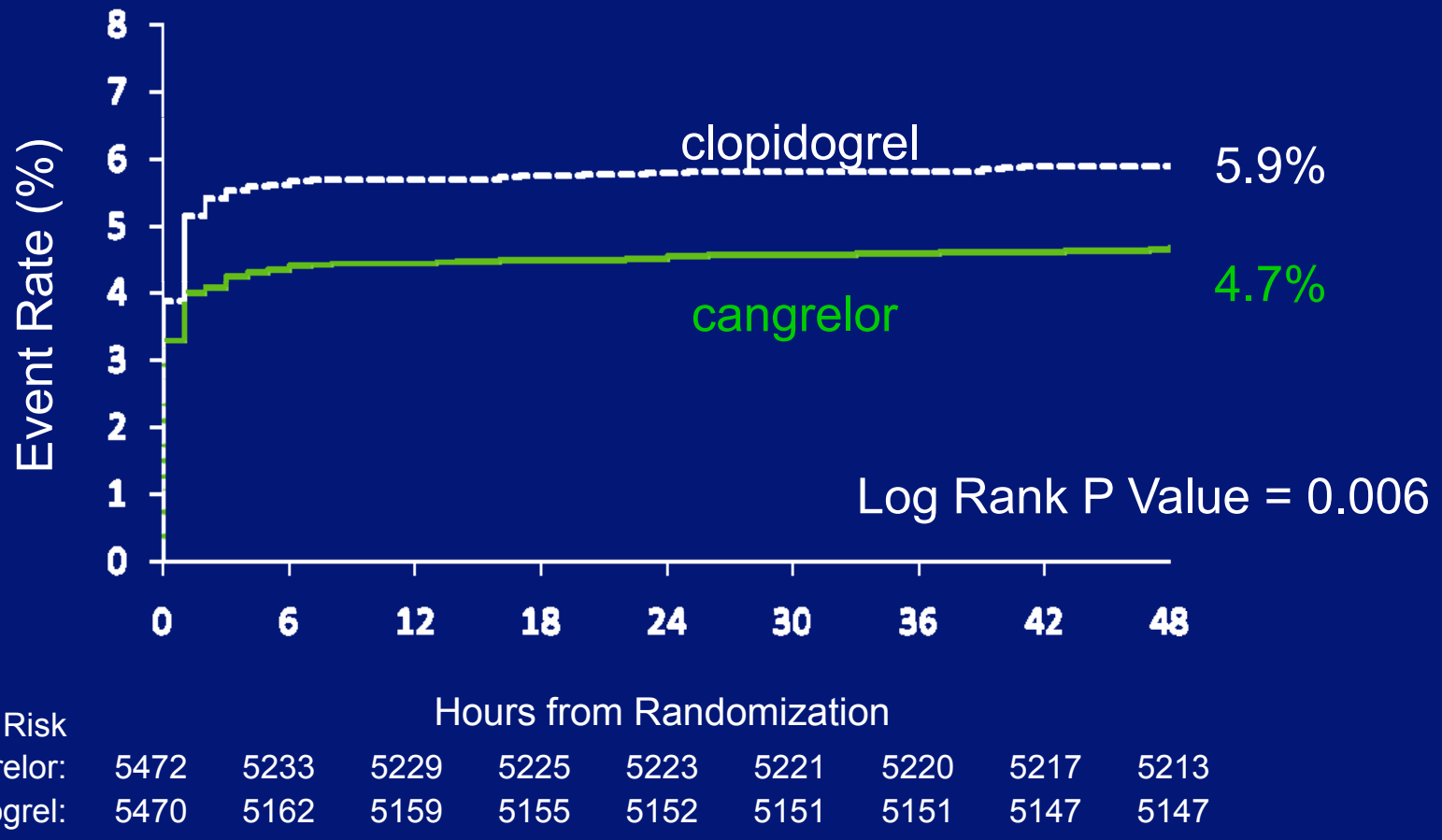
Percentage of High Residual Platelet Reactivity



Parodi G, Antoniucci D, J Am Coll Cardiol 2013;61:1601–6

Bhatt DL, N Engl J Med 2013;368:1303-13

Death / MI / ILR / Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

Vorapaxar (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

- Death (cardiovascular)
- MI
- Stroke

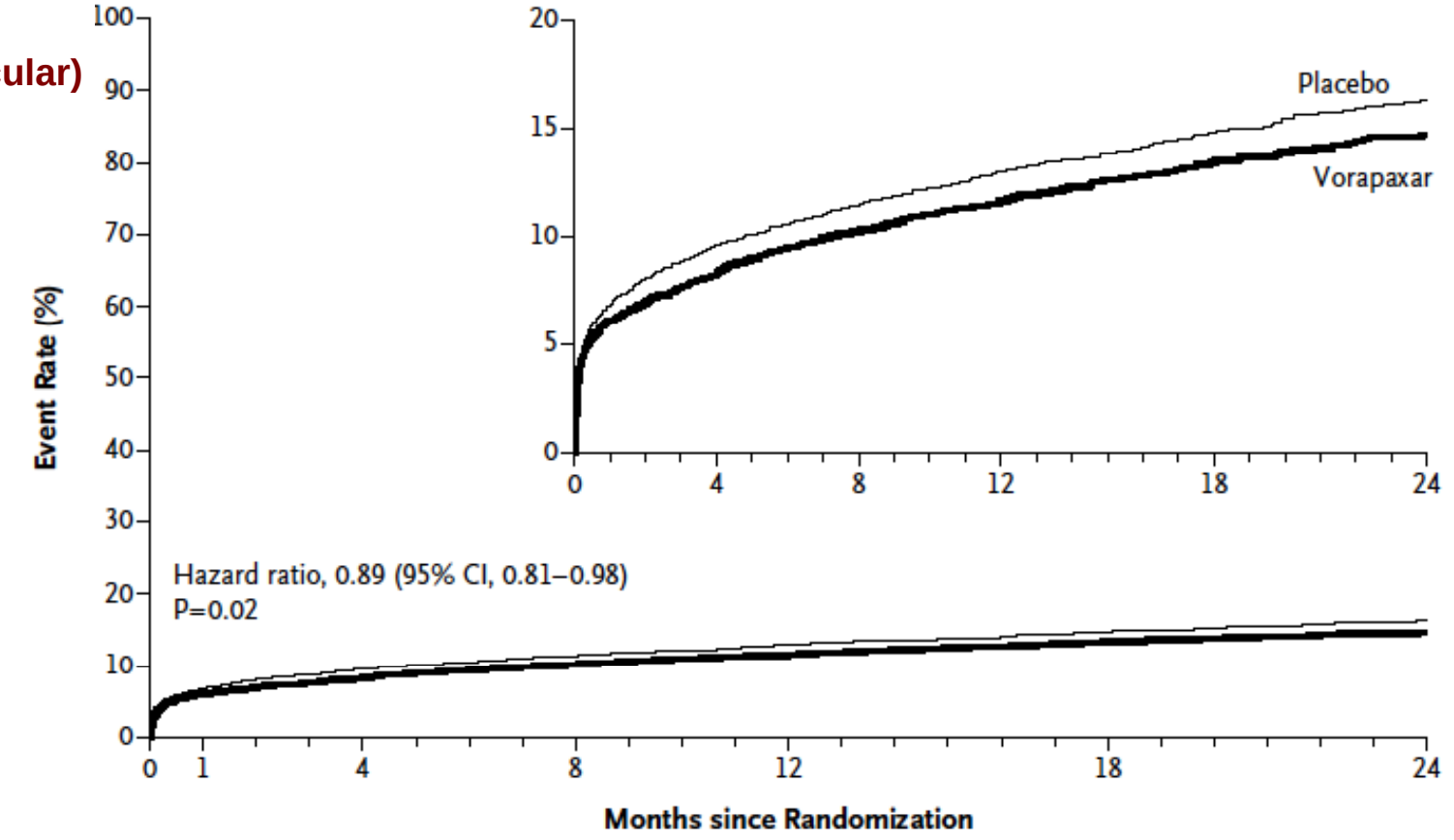


Figure 1. Study End Points.

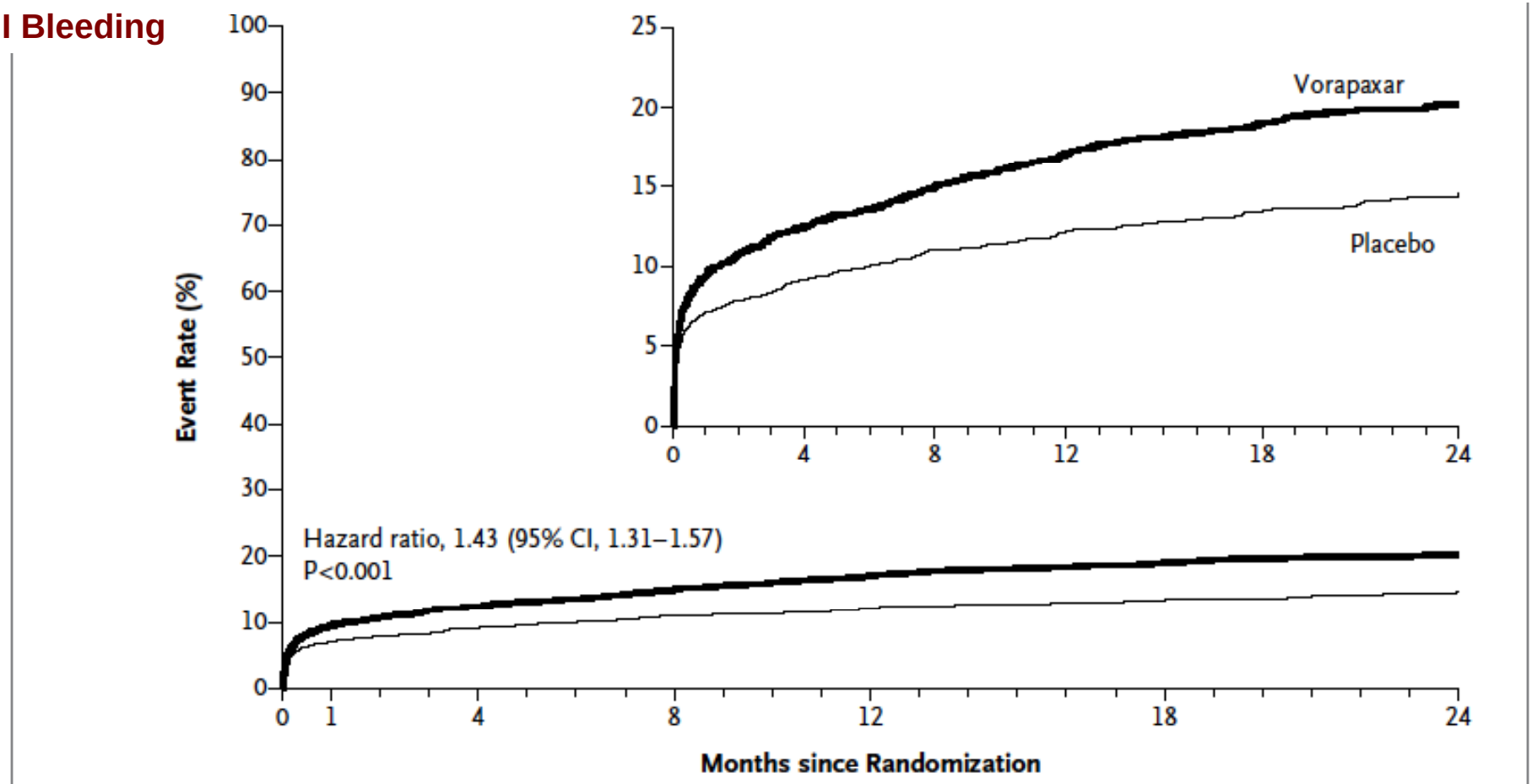
Shown are Kaplan–Meier event rates at 2 years in the two study groups for the primary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) (Panel A) and the key secondary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) (Panel B).

Merck (MSD)

Tricoci P, N Engl J Med 2012;366:20-33

Vorapaxar (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

TIMI Bleeding



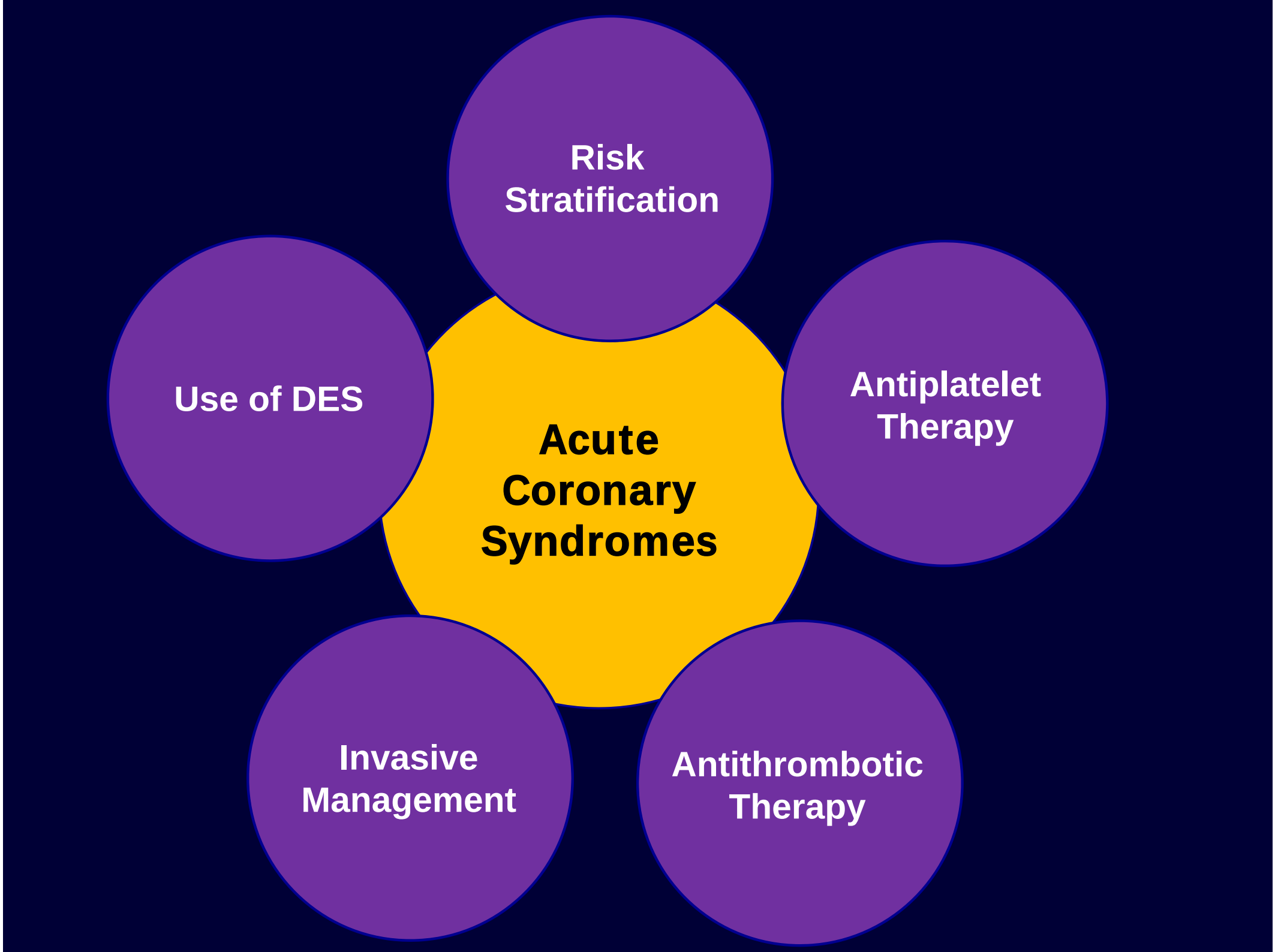
No. at Risk

Placebo	6441	5320	4877	4385	3147	1806	573
Vorapaxar	6446	5257	4772	4219	2950	1663	548

Figure 2. Risk of Bleeding.

Shown are Kaplan–Meier event rates at 2 years in the two study groups for Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for moderate or severe bleeding (Panel A) and for Thrombolysis in Myocardial Infarction (TIMI) criteria for clinically significant bleeding (Panel B).

Tricoci P, N Engl J Med 2012;366:20-33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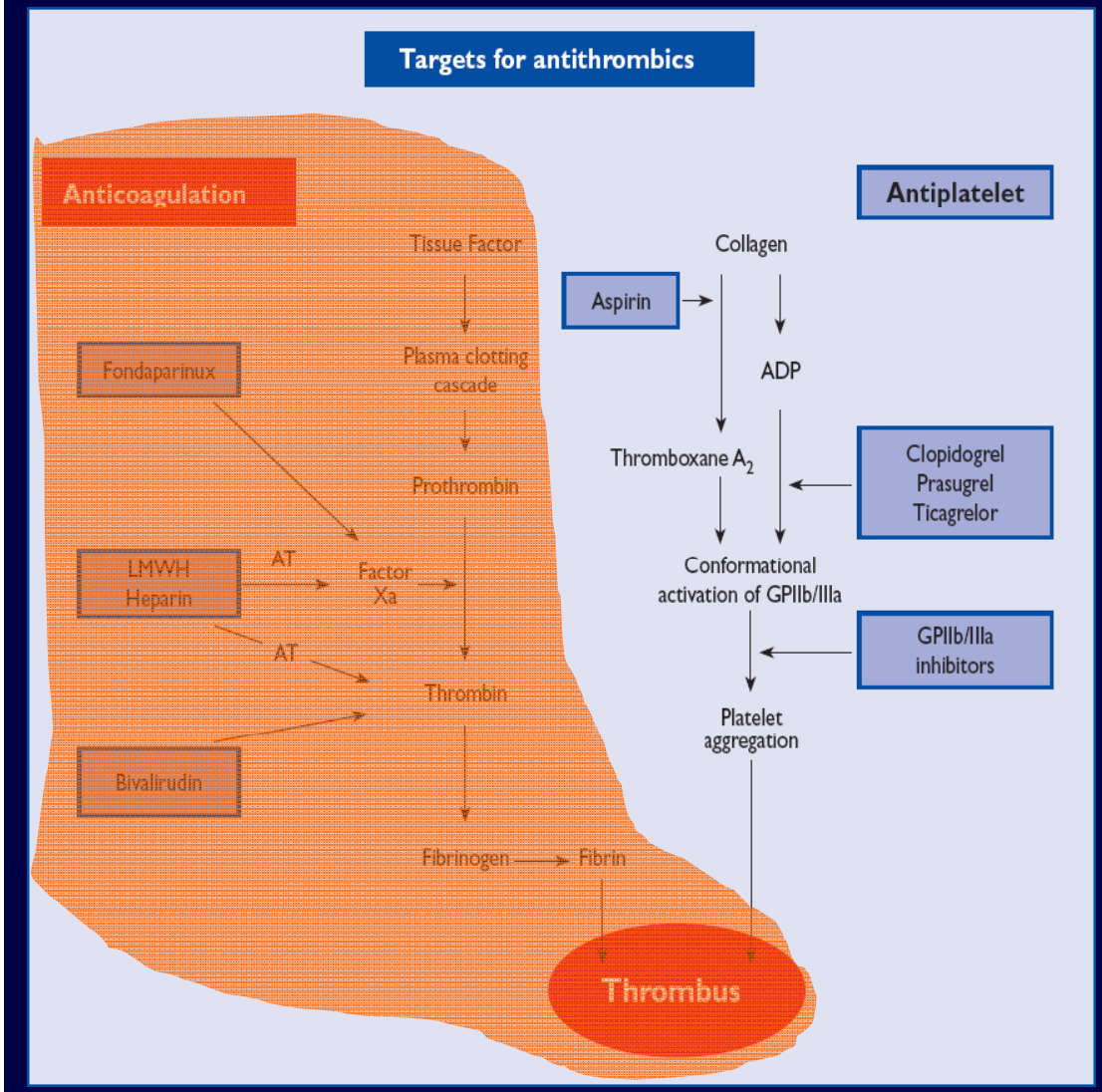
Antithrombin Agents in Acute Coronary Syndromes



UFH

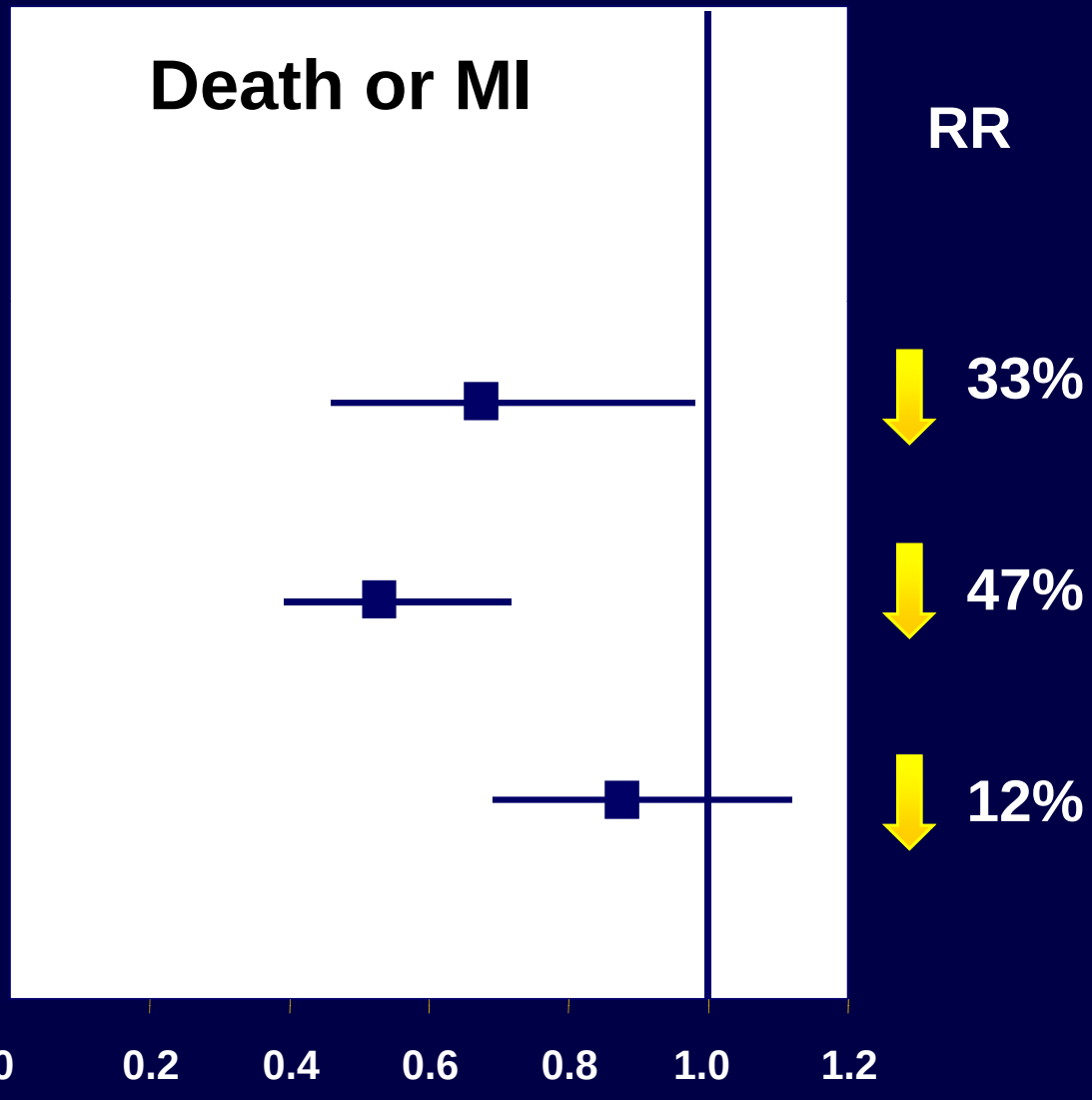
- Glycosaminoglycan MW 3000-30 000
- UFH inhibits factor II and Xa via binding AT III
- Unpredictable pharmacokinetics requiring monitoring of coagulation status
- Intravenous infusion

LMWH

- Short chain (18 saccharides) fragments MW 4000 – 6000
- Anti-factor Xa:factor IIa ratio: 1.9-3.8
- Predictable pharmacokinetic profile
- No monitoring of anticoagulation
- Ease of administration

Acute Non-ST Elevation Myocardial Infarction

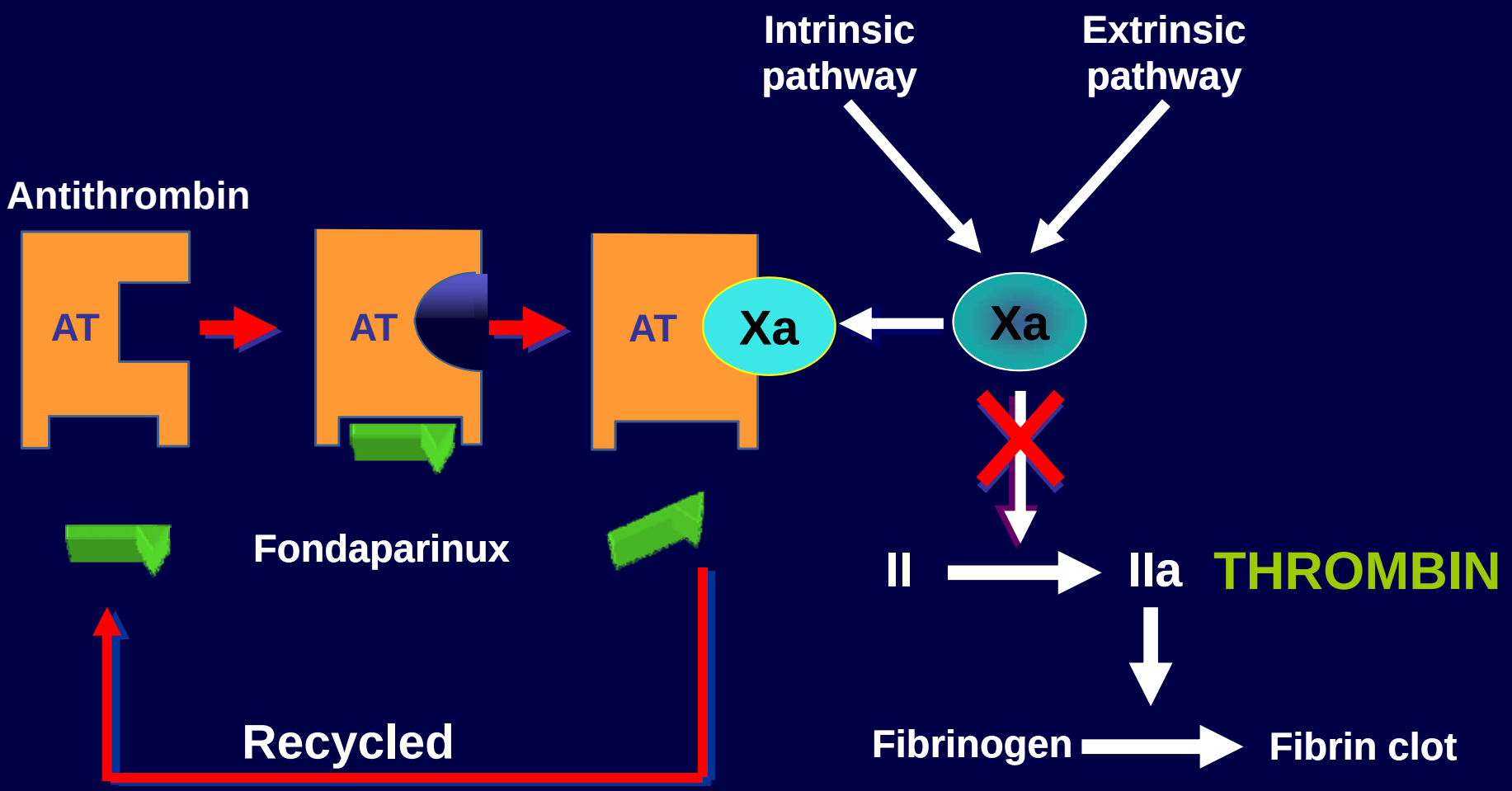
Unfractionated Heparin versus Low Molecular Weight Heparin



** JAMA 1996;276:811-5*
*** Lancet 2000;355:1936-1942*

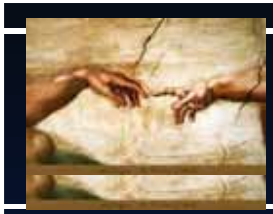
Fondaparinux

A Synthetic Inhibitor of Factor Xa, Mechanism of Action



Turpie AGG et al. N Engl J Med. 2001;344:619.

Antithrombotic Agents: Fondaparinux in the Treatment of UA/NSTEMI



Study Design: Randomized, Double Blind

Patients with NSTE ACS, Chest discomfort < 24 hours
2 of 3: Age>60, ST Segment Δ, ↑ cardiac markers

Exclude
Age < 21
Any contra-ind to Enox
Hem stroke< 12 mo.
Creat> 3 mg/dL/265 umol/L

ASA, Clop, GP IIb/IIIa, planned Cath/PCI as per local practice

Randomize

N=20,078

Fondaparinux
2.5 mg sc once daily

PCI <6 h: IV Fonda 2.5 mg without IIb/IIIa, 0 with IIb/IIIa
PCI> 6 h: IV Fonda 2.5 mg with and 5.0 mg without IIb/IIIa

Enoxaparin
1 mg/kg sc twice daily

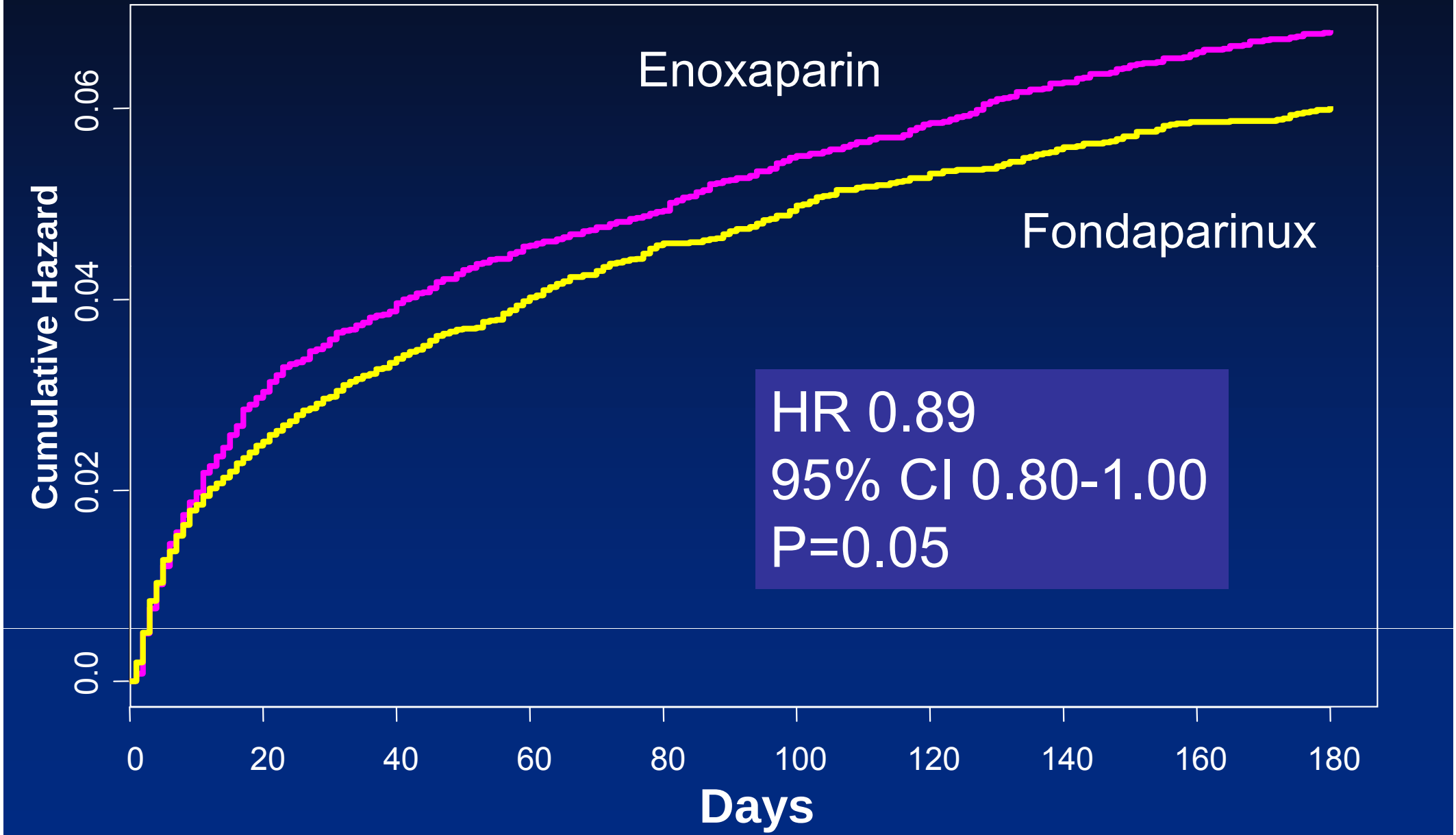
PCI< 6 h, No additional UFH
PCI >6 h, IV UFH
With IIb/IIIa 65 U/kg
Without IIb/IIIa 100 U/kg

Outcomes

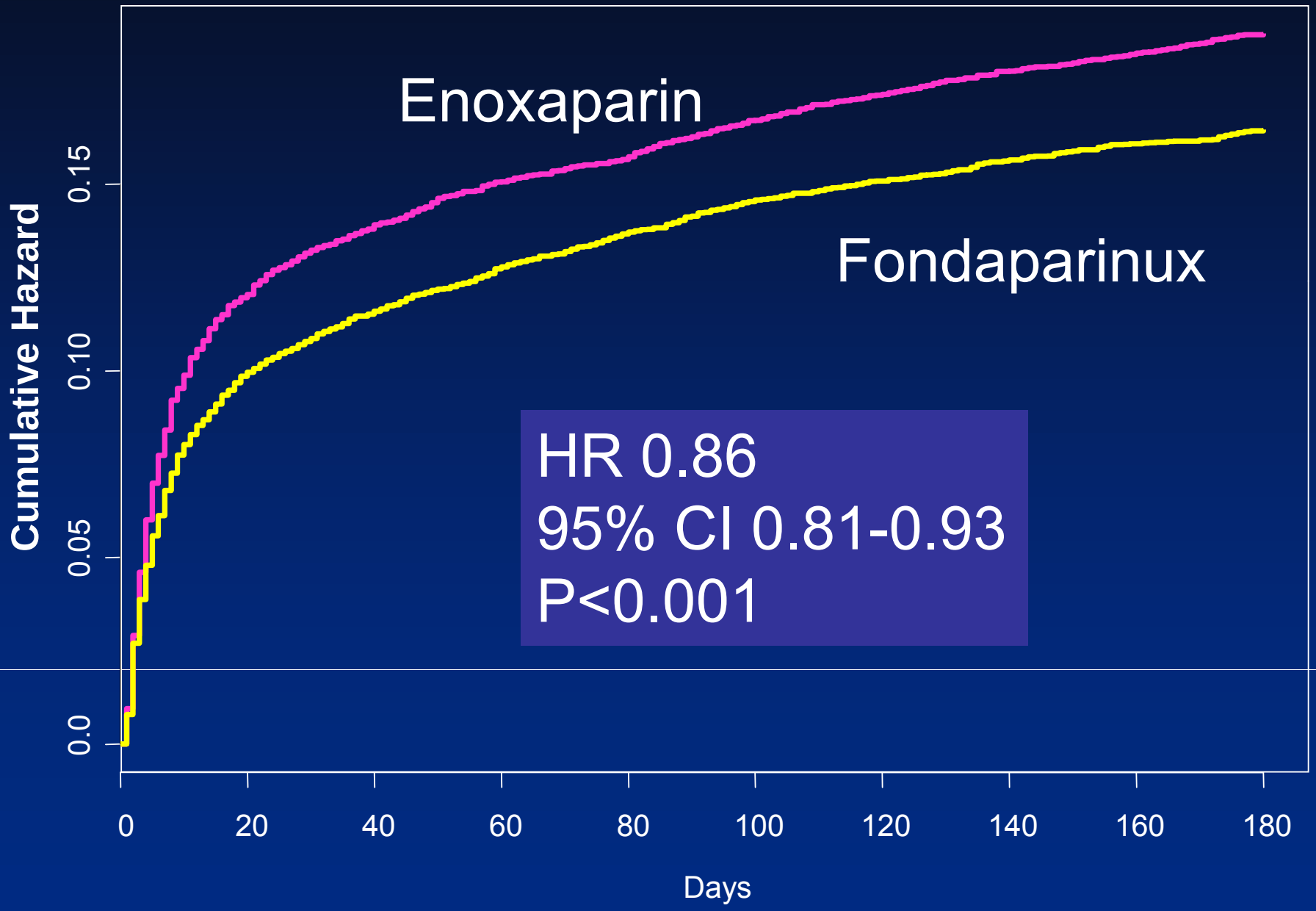
Primary: **Efficacy**: Death, MI, refractory ischemia at 9 days
Safety: Major bleeding at 9 days
Risk benefit: Death, MI, refractory ischemia, major bleeds 9 days
Secondary: Above & each component separately at day 30 & 6 months
Hypothesis: First test non-inferiority, then test superiority

Yusuf OASIS 5 *N Engl J Med* 2006;354.

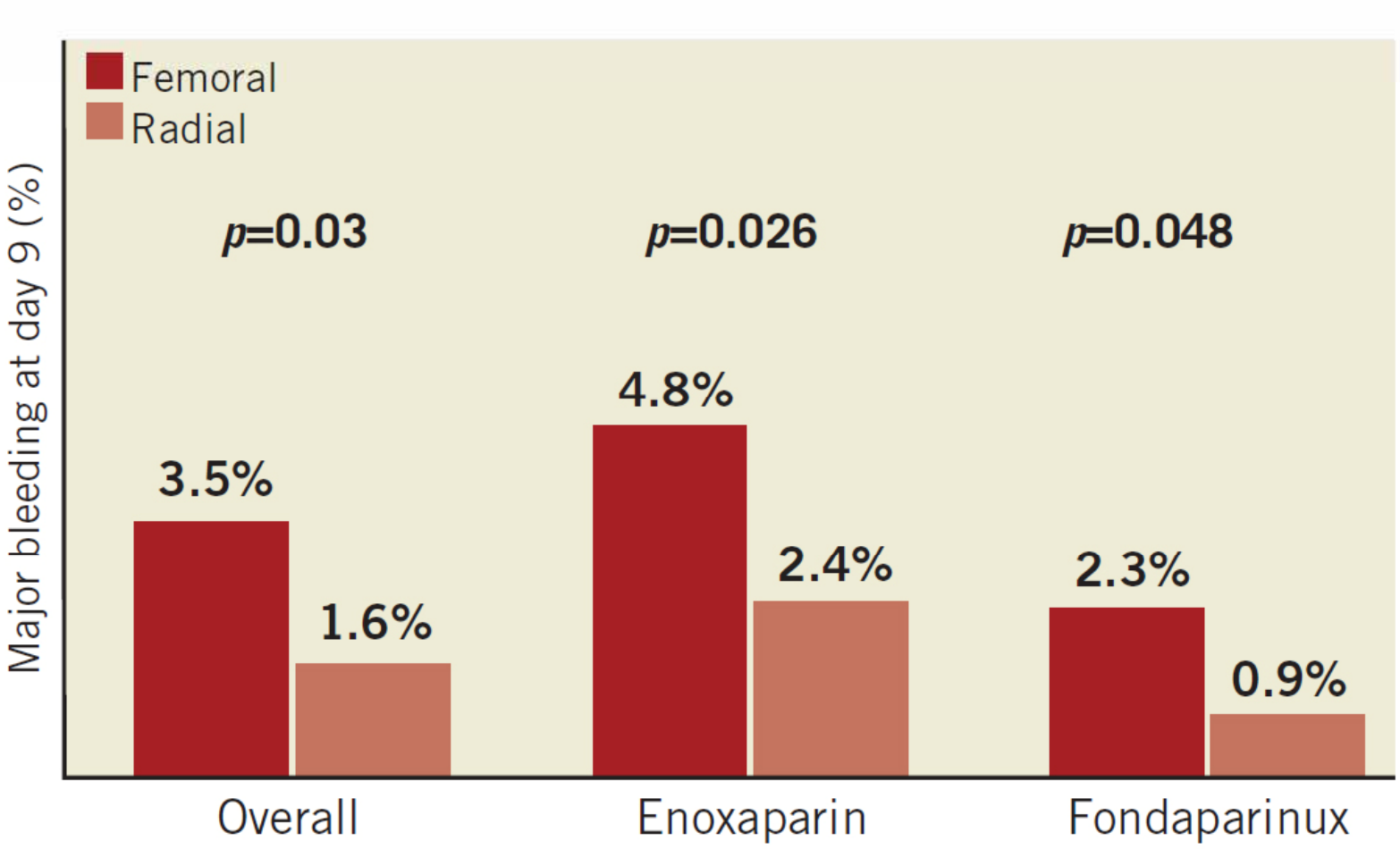
Mortality at 6 Months



Death, MI, RI, Major Bleeding at 6 Months



Bleeding Femoral vs. Radial Access



Major bleeding in PCI patients at day nine during blinded study drug administration

EuroIntervention 2011;7:**91-97**

Acuity Trial (Bivalirudin)

13,819 patients with moderate to high risk non-ST-segment-elevation ACS with invasive management

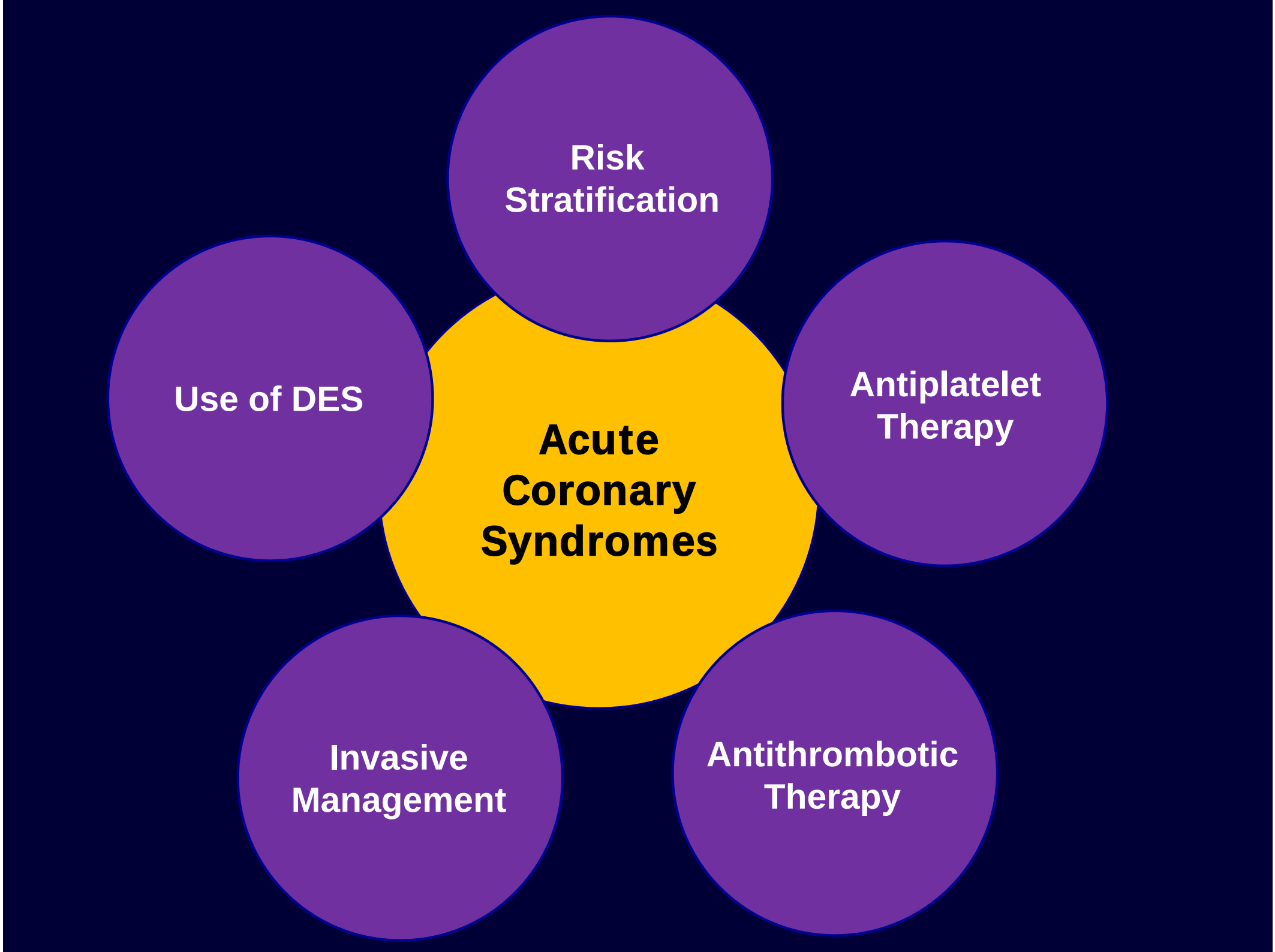
Endpoints (30 days)	**bivalirudin**	**UFH/enoxaparin + GP IIb/IIIa inhibitors**	**bivalirudin + GP IIb/IIIa inhibitors**	**significance**
Death (%)	1.6	1.3	1.5	ns
Myocardial infarction (%)	5.4	4.9	5.0	ns
Unplanned revascularisation (%)	2.4	2.3	2.7	ns
Major bleeding (%)	3.0*	5.7*	5.3	p* = 0.0001
Any of the above (%)	10.1**	11.7**	11.8	p** = 0.015

* Difference significant only pertaining to access site bleeding.

** Difference entirely due to bleeding in patients pretreated with clopidogrel, and with normal troponin and creatine kinase as well as low risk score at the outset.

UFH = unfractionated heparin; ns = no significant difference.

Meier B, Cardiovasc Med 2006;9:353–358

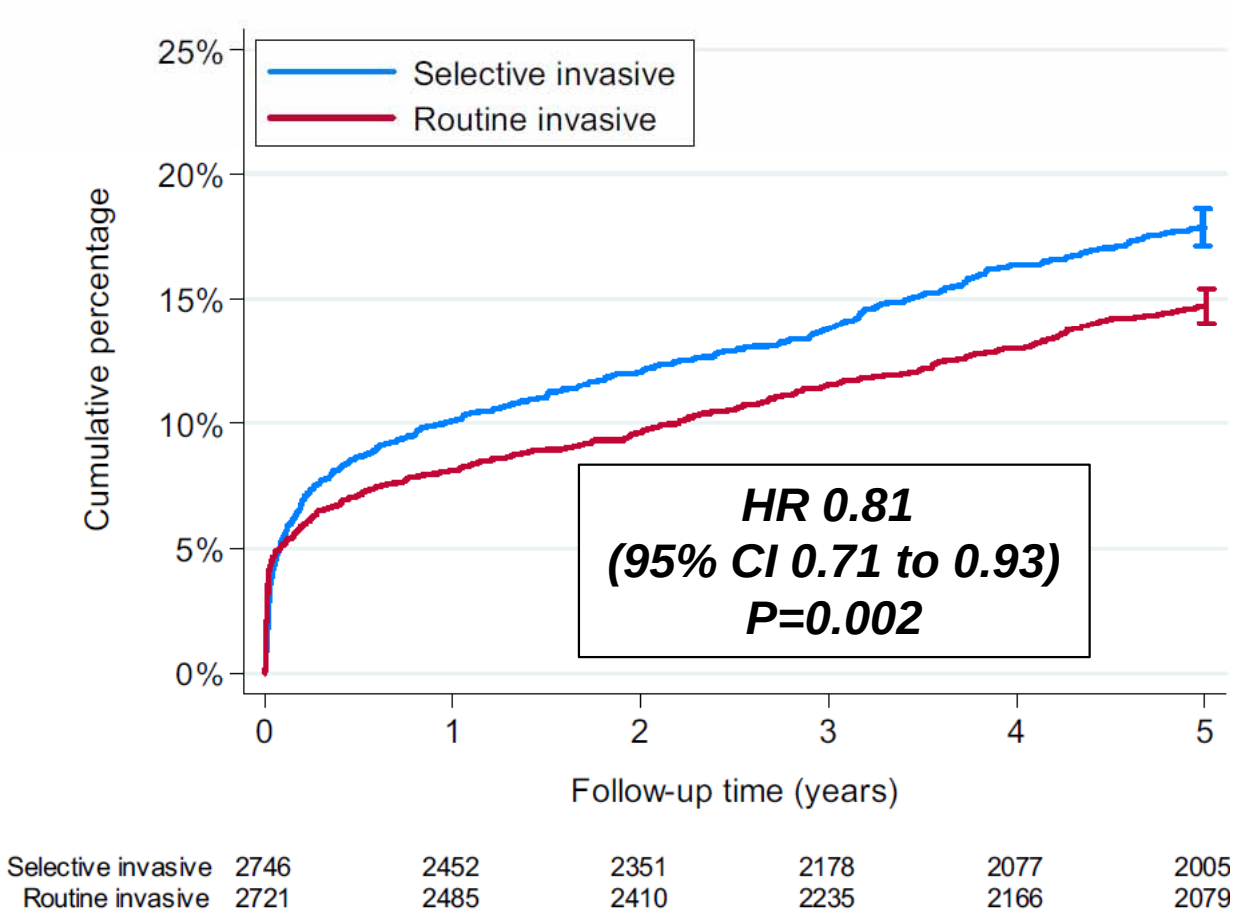

Risk Stratification
Use of DES
Acute Coronary Syndromes
Antiplatelet Therapy
Invasive Management
Antithrombotic Therapy

Routine vs Selective Invasive Strategy in Patients With NSTE-ACS

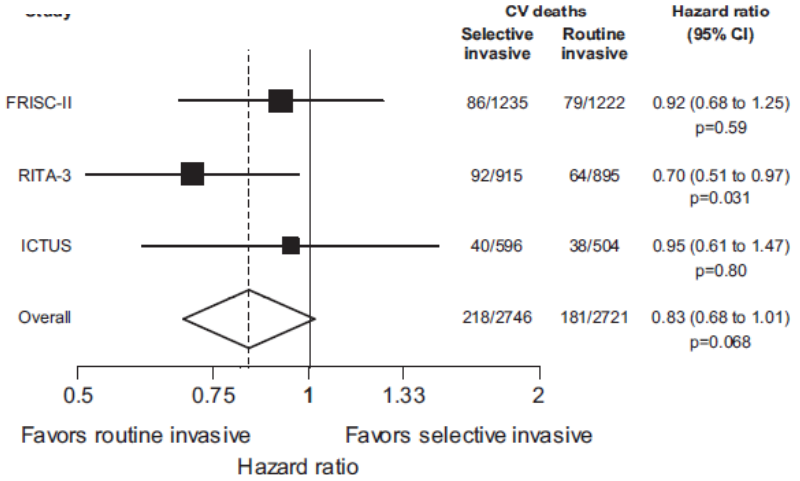
Fox K et al. *J Am Coll Cardiol* 2010

An IPD Meta-Analysis of FRISC-II, ICTUS, and RITA-3 Trials

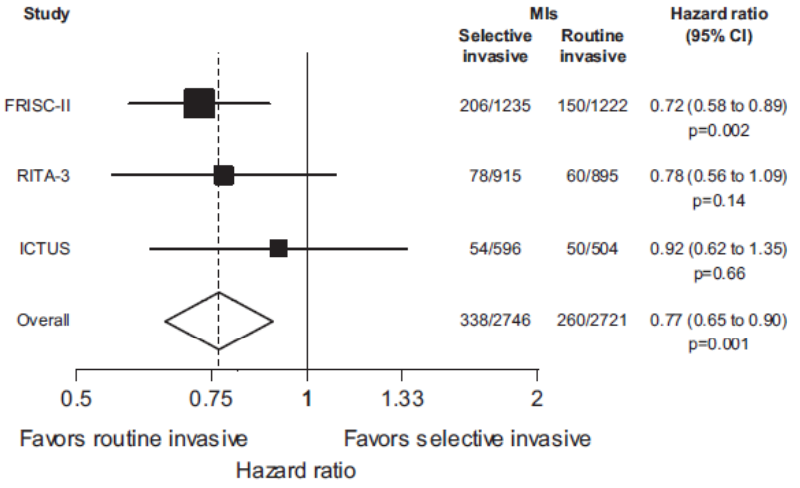
Cardiac Death or MI @ 5 Years

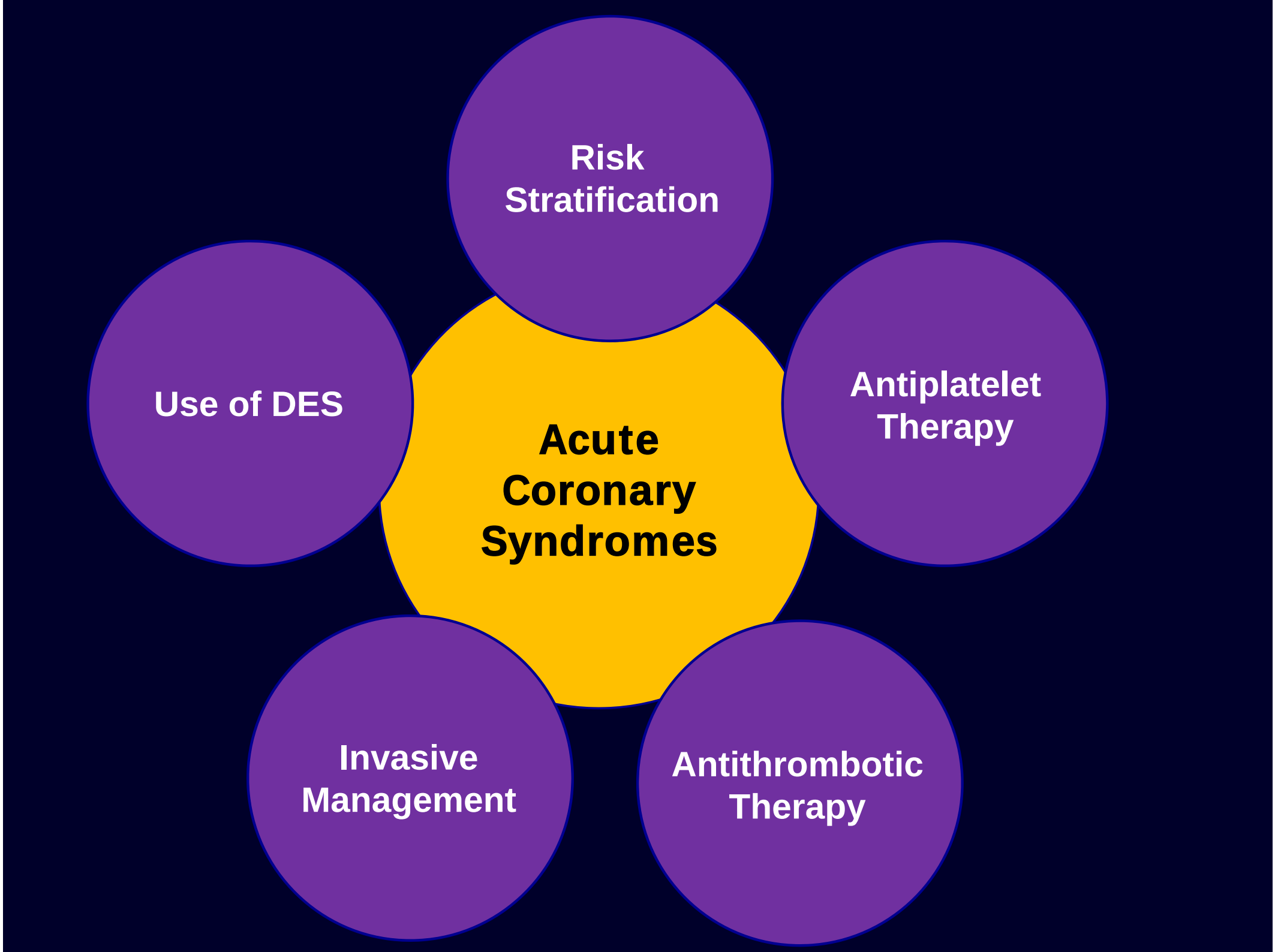


Cardiac Death



Myocardial Infarction




Risk Stratification
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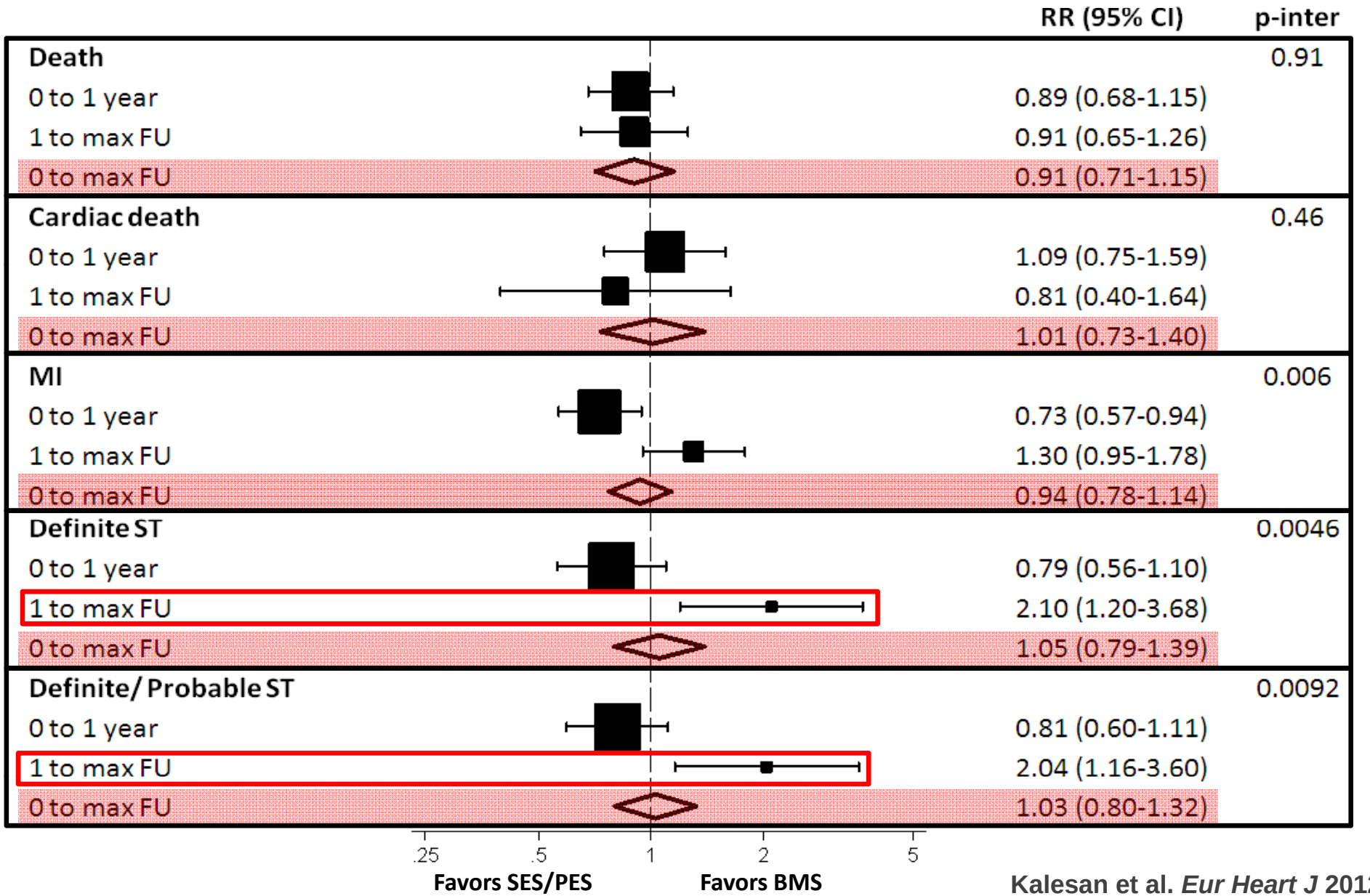
Risk of Ischemic Events and Stent Thrombosis Stratified According to Time and Stent Type (DES vs BMS) in STEMI

15 RCTs Comparing DES and BMS in 7,843 STEMI Patients



Kalesan et al. *Eur Heart J* 2012

Recommendations for the Use of DES in Acute Coronary Syndromes

- ***No safety concerns***
- ***Consistent reduction in repeat revascularization procedures with the use of DES***

NSTE-ACS Hamm C et al. *Eur Heart J* 2011

- **DES** are indicated based on an individual basis taking into account baseline characteristics, coronary anatomy, and bleeding risk **I A**