Guidelines and best practice in antithrombotic therapy: the view from Europe

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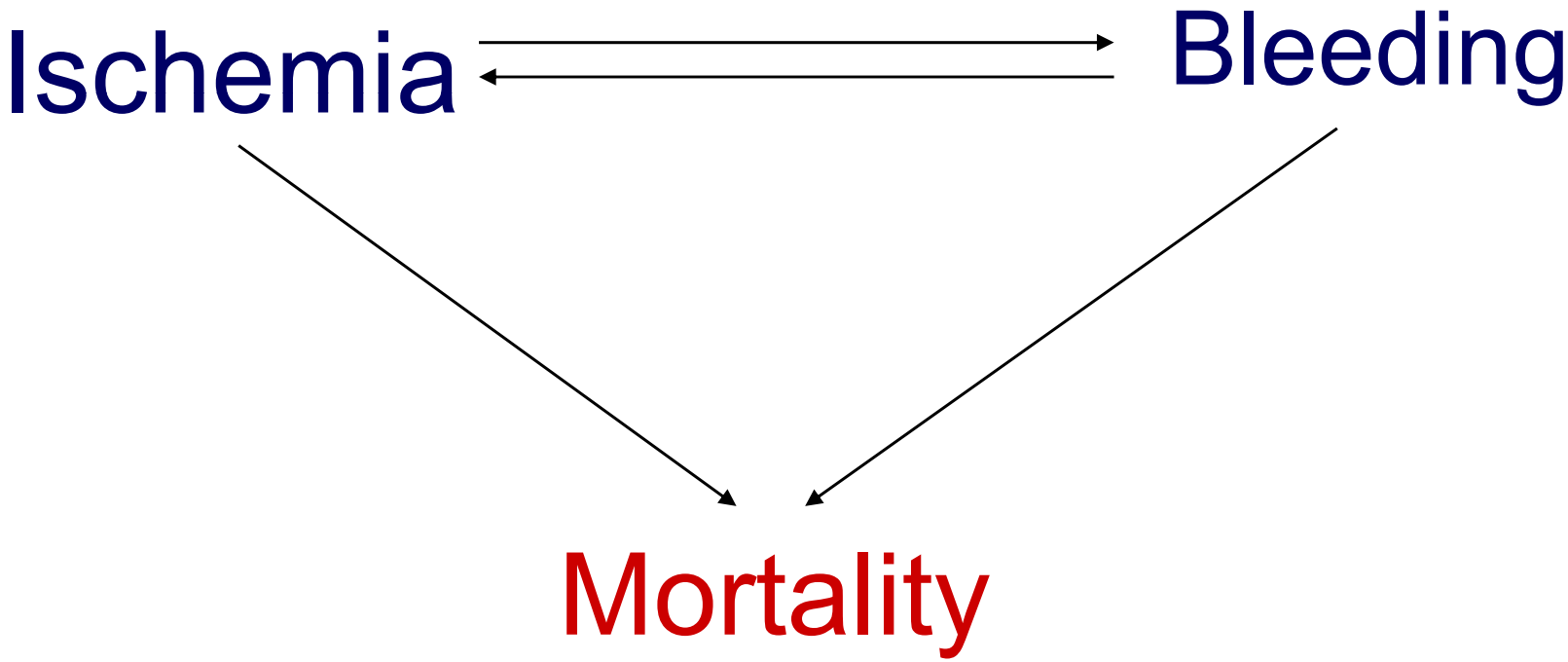
KliLu
Wir leben Medizin.

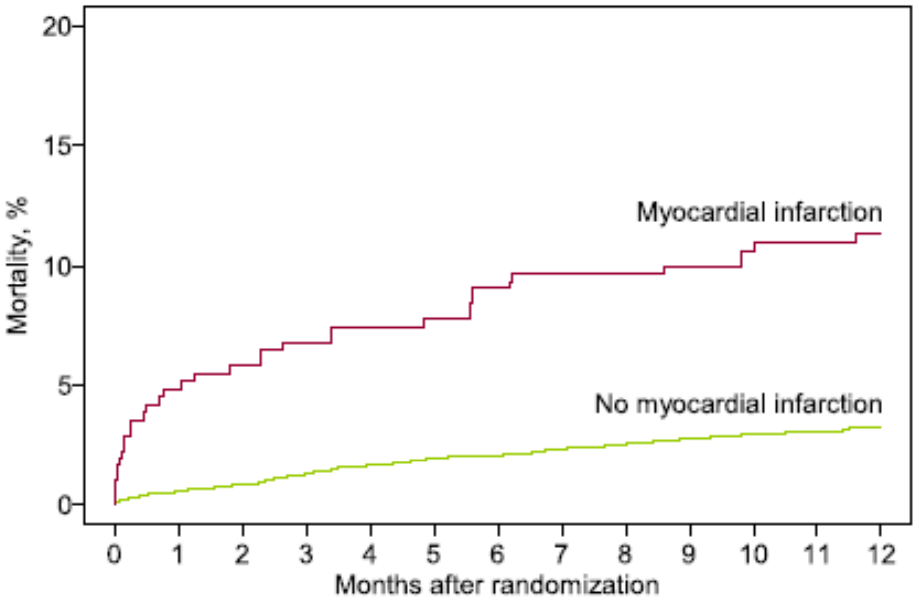
STIFTUNG IHF INSTITUT FÜR HERZINFARKT FORSCHUNG

Decoding antithrombotic therapies for Non-ST elevation ACS
Seoul 24.04.2013

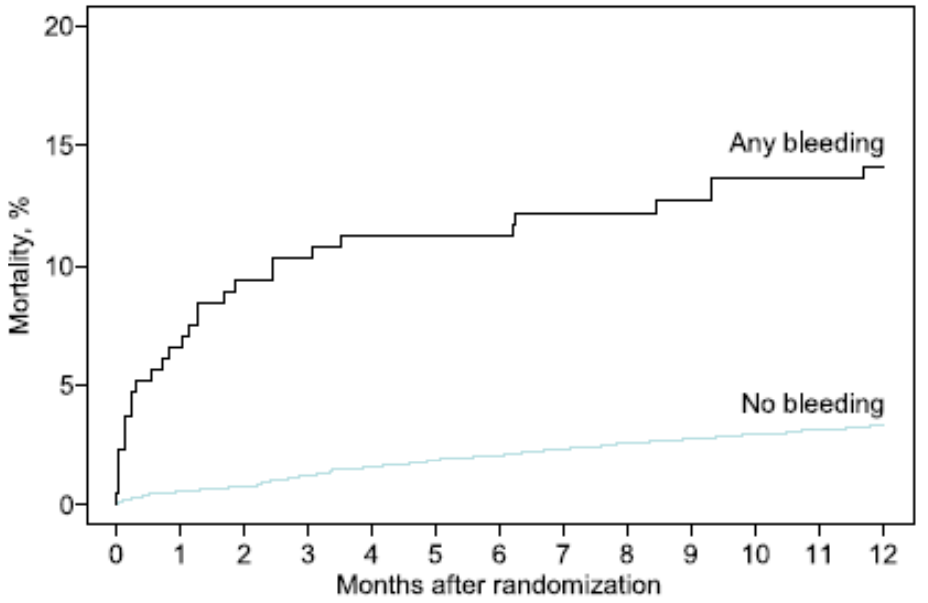
Antithrombotic Therapy 2013



Impact of bleeding and MI on 1 year mortality after PCI



Post-Procedural Myocardial Infraction and 1 year Mortality



Post-Procedural Bleeding and 1 year Mortality

Ndrepa set al. JACC 2008

European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).

ESC Committee for Practice Guidelines: Jeroen J. Bax (Chairperson) (The Netherlands), Angelo Auricchio (Switzerland), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Don Poldermans (The Netherlands), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

European Heart Journal
Advance Access published August 26, 2011

www.escardio.org

Antithrombotic therapy

- Antiplatelet therapy
  - Aspirin
  - ADP receptor blockers
  - GP IIb/IIIa inhibitors
- Anticoagulants
  - Heparins
  - Fondaparinux
  - Bivalirudin

$P2Y_{12}$ inhibitor recommendations 1

A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding

Class	Level
I	A

A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (H. pylori infection, age ≥65 years, concurrent use of anticoagulants or steroids)

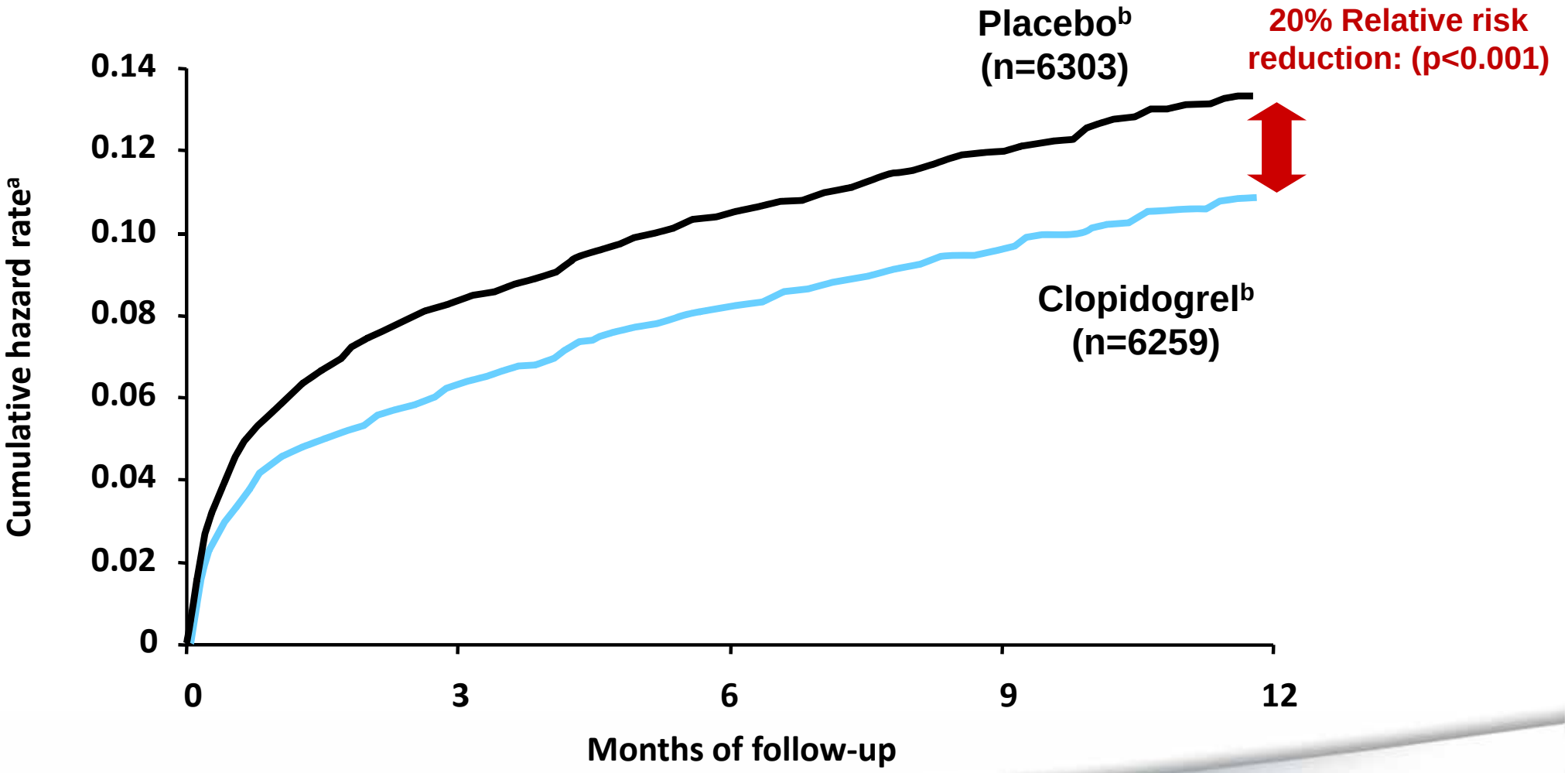
Class	Level
I	A

$P2Y_{12}$ inhibitor recommendations 2

Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated

Class	Level
I	C

CURE: Early and long-term benefits of clopidogrel in ACS Patients



[a]MI, stroke or cardiovascular death
[b]On a background of standard therapy including aspirin)

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

EUROPEAN SOCIETY OF CARDIOLOGY®

Limitations of Clopidogrel

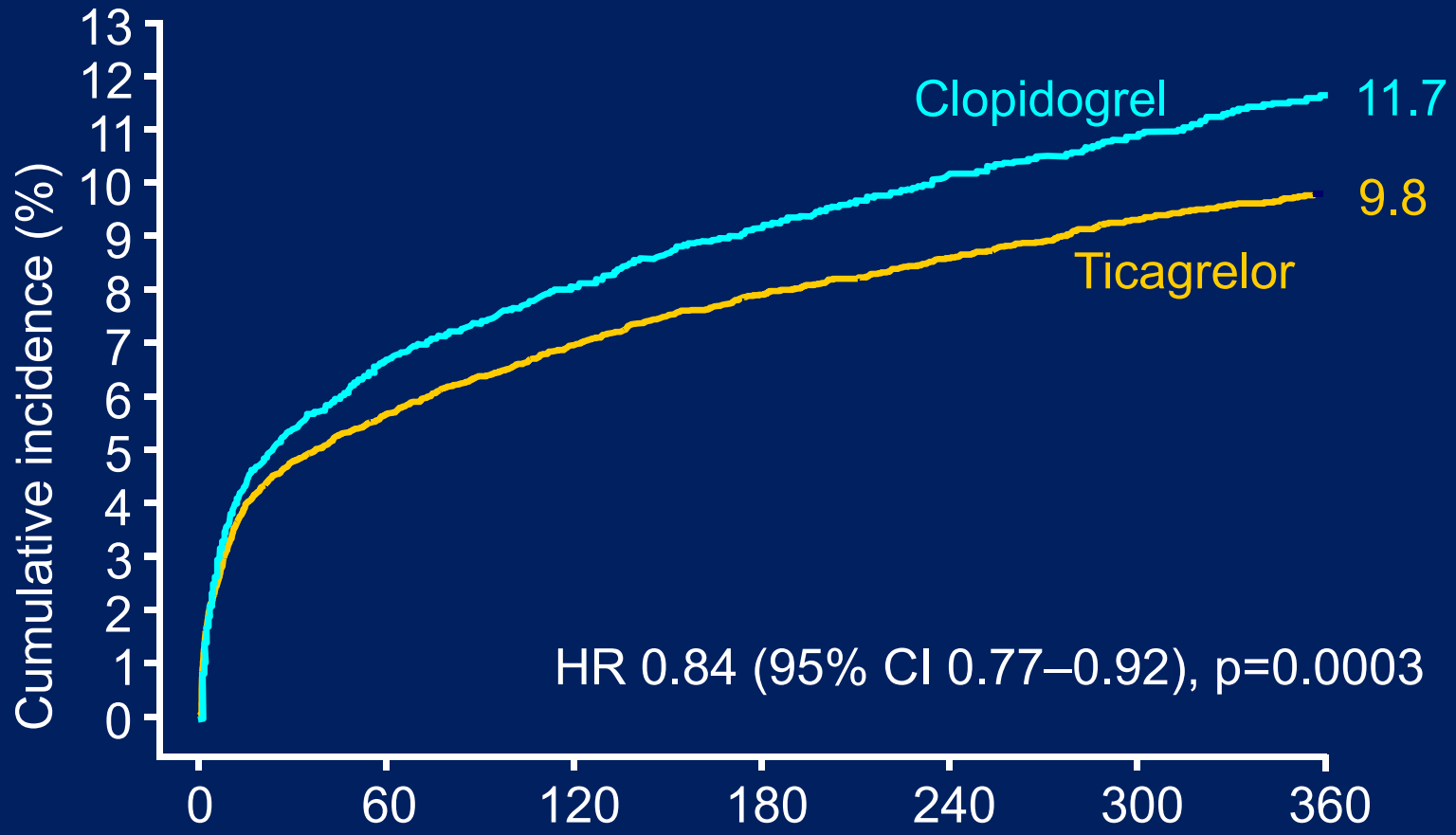
- Delayed onset of action
- Limited platelet inhibition
- Non-Responders (Non-Metabolisers)
- Drug-interactions (PPI, CCB)

$P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect	2-4 h	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

PLATO: time to first primary efficacy event (composite of CV death, MI or stroke)

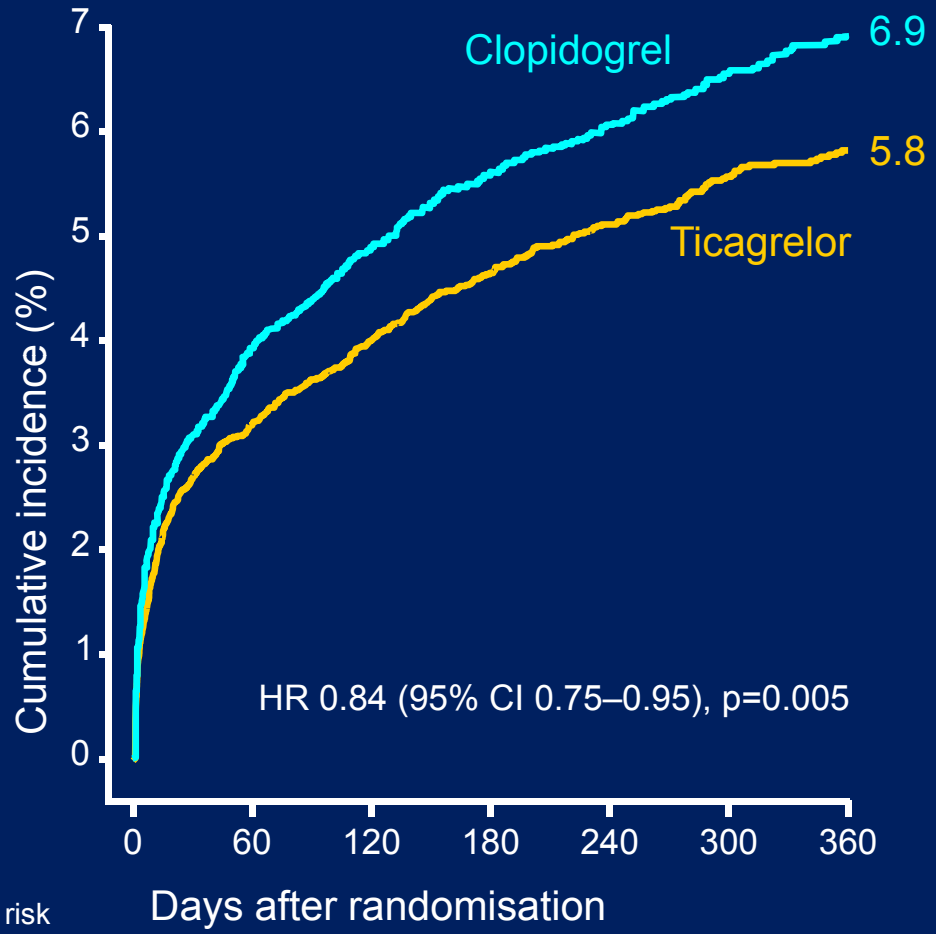


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Curves are Kaplan-Meier rates, HR = hazard ratio; CI = confidence interval

Secondary efficacy endpoints over time

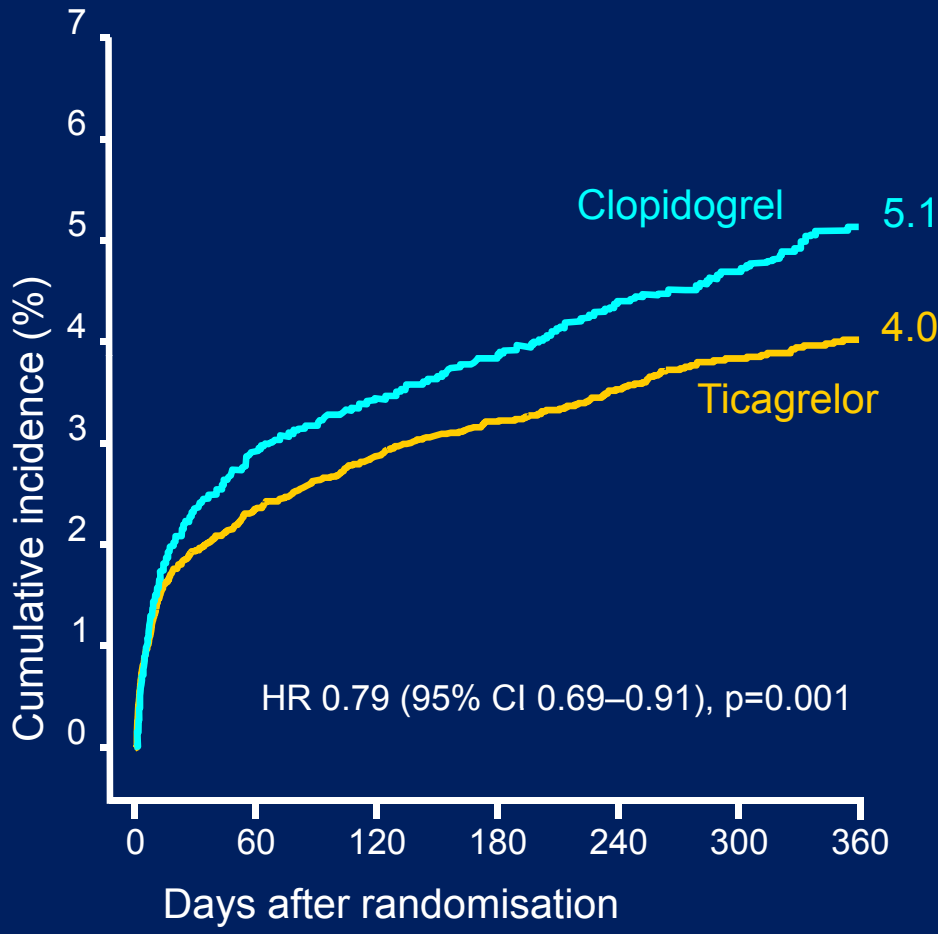
Myocardial infarction



No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

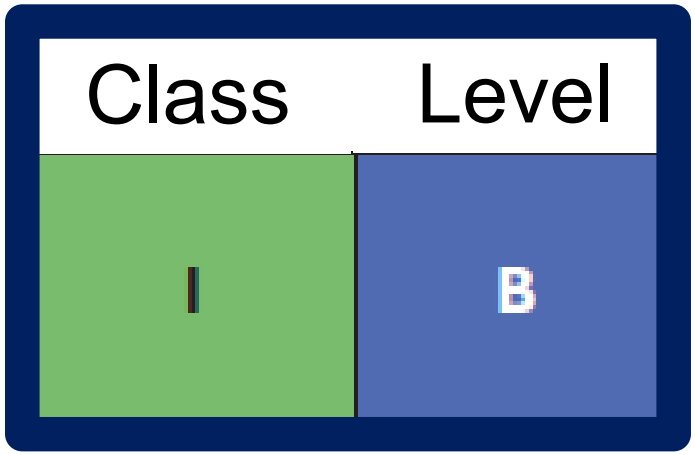
Cardiovascular death



	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

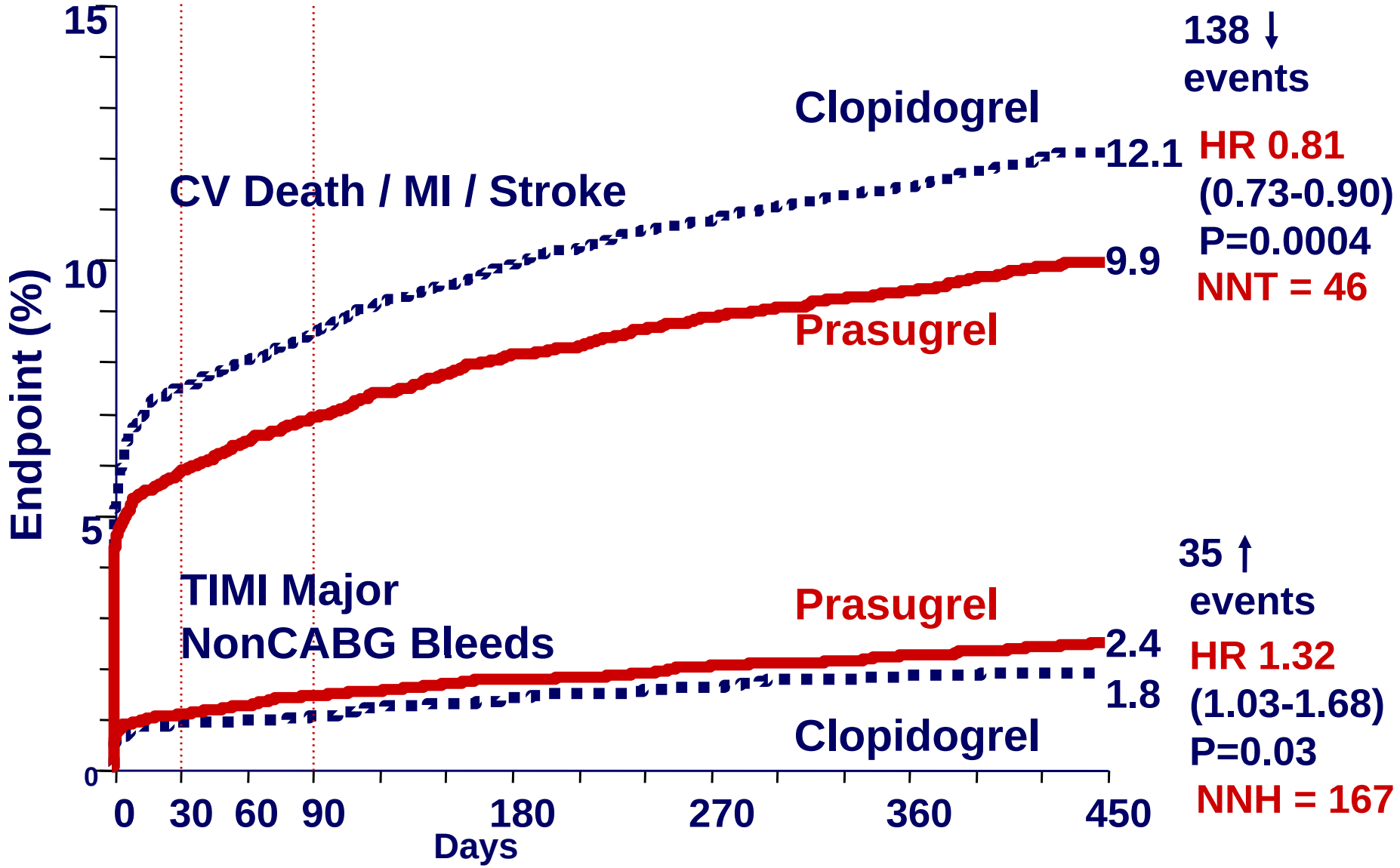
Ticagrelor

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced)



TRITON TIMI-38

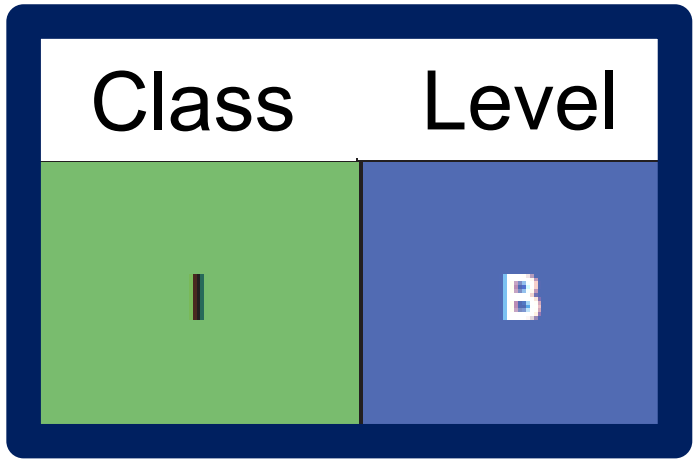
- Efficacy and Safety of Prasugrel -



Wiviott et al, N Engl J Med 2007; 357: 2001-15

Prasugrel

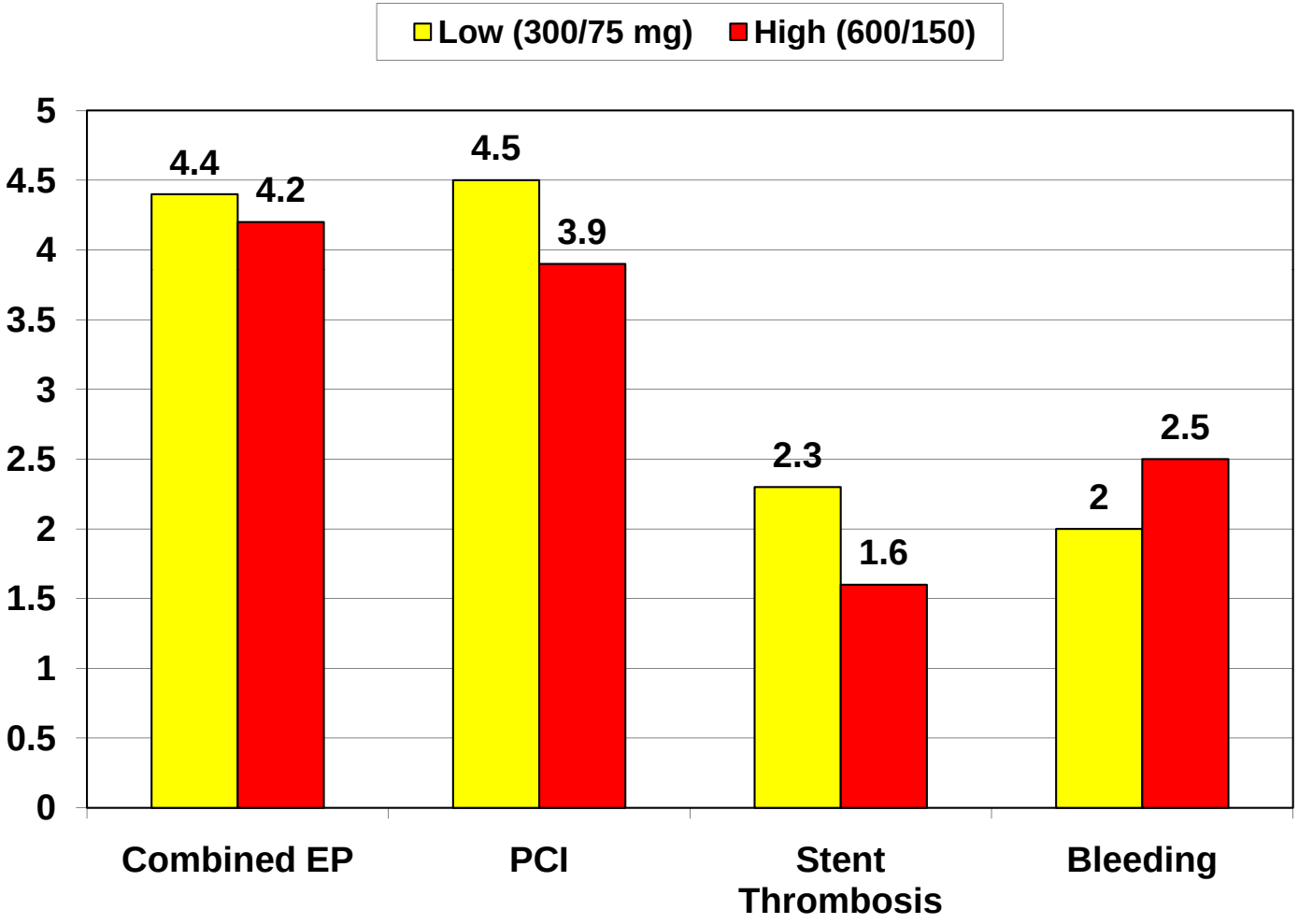
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications



CURRENT-OASIS 7

High dose versus low dose Clopidogrel

Results after 30 days



Clopidogrel dosing

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel

Class	Level
I	A

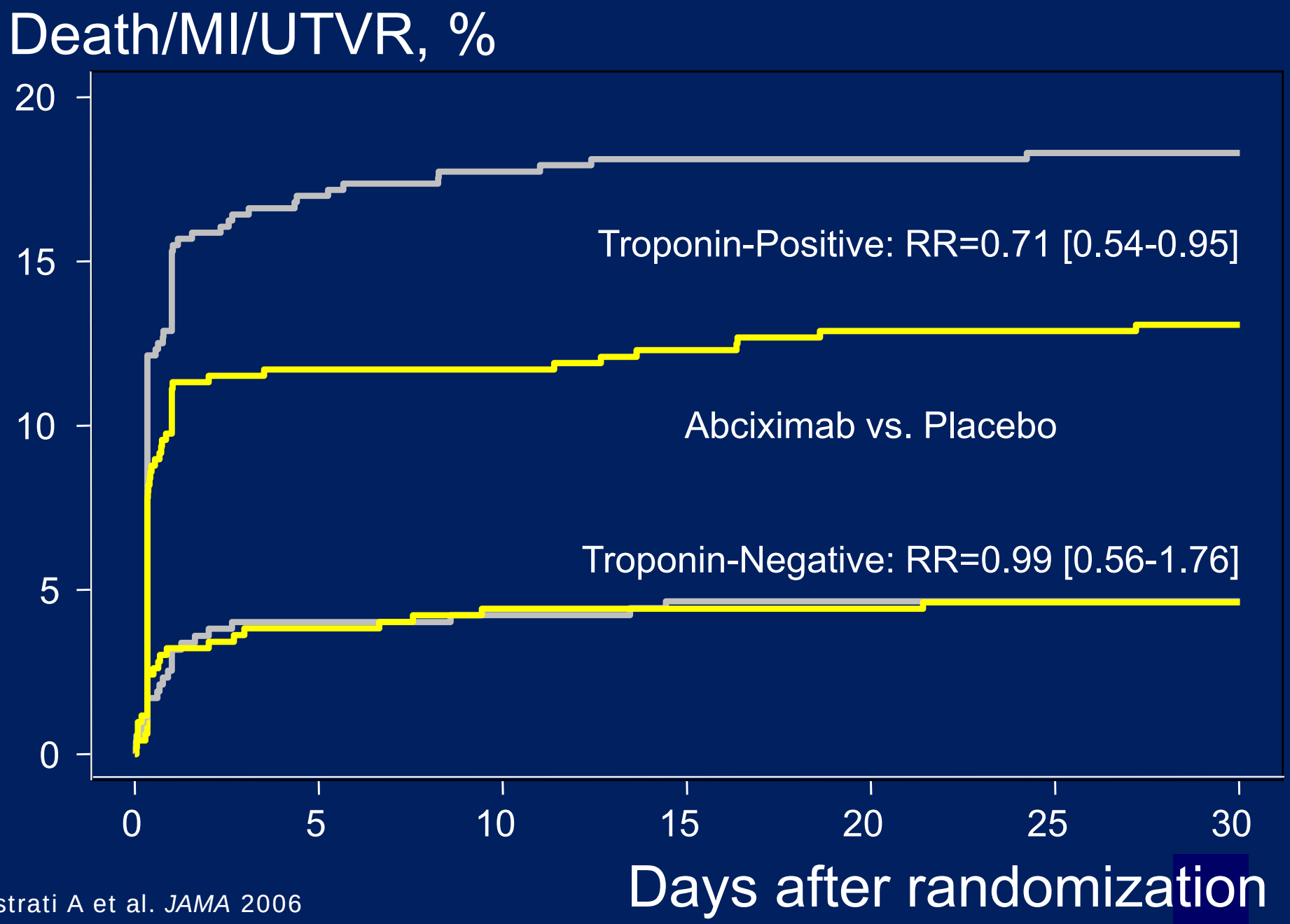
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option

Class	Level
I	B

A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding

Class	Level
IIa	B

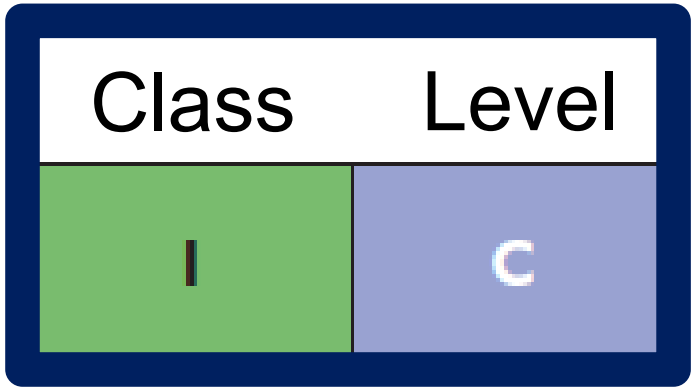
ISAR-REACT 2: Outcomes according to Tn level



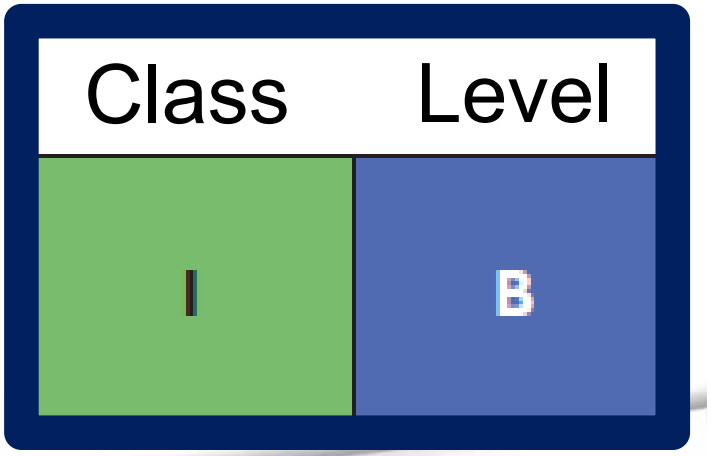
Kastrati A et al. *JAMA* 2006

GP IIb/IIIa receptor inhibitor

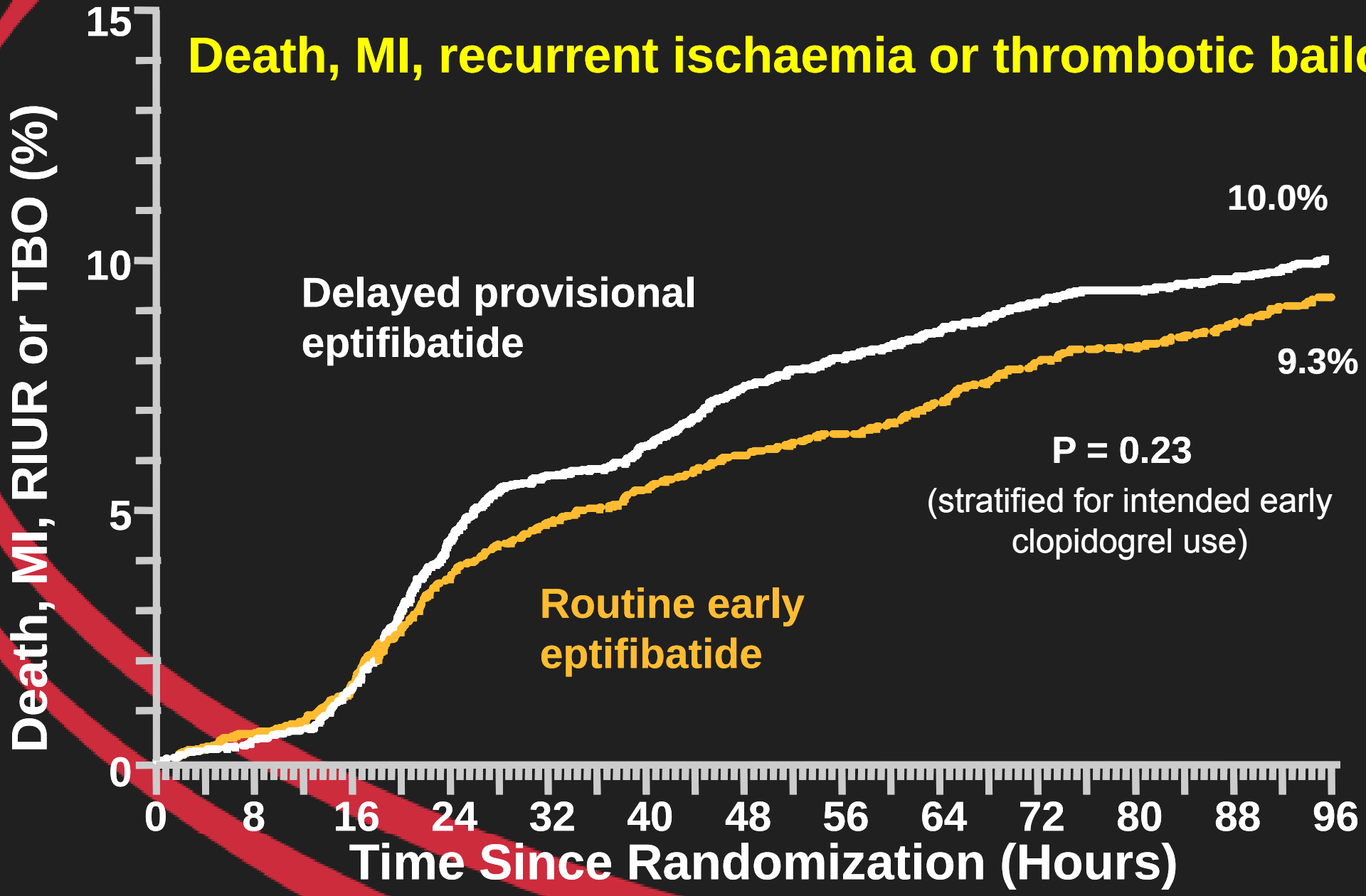
The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events



Among patients who are already treated with DAPT, the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low



Routine upstream GP IIb/IIIa in NSTE-ACS
Kaplan-Meier Curves for Primary Endpoint



EARLY ACS

Safety Results (through 120 hours)

	Routine Eptifibatide (n=4686)	Early Delayed Provisional Eptifibatide (n=4643)	OR (95% CI)	P
Bleeding (all patients, %)				
TIMI major	2.6	1.8	1.42 (1.07-1.89)	0.015
TIMI major or minor	5.8	3.4	1.75 (1.43-2.14)	<0.001
GUSTO severe	0.8	0.9	0.99 (0.64-1.55)	0.97
GUSTO moderate or severe	7.6	5.1	1.52 (1.28-1.80)	<0.001
PRBC transfusion	8.6	6.7	1.31 (1.12-1.53)	0.001

Upstream GP IIb/IIIa receptor inhibitor

In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low

Class	Level
IIb	C

GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy

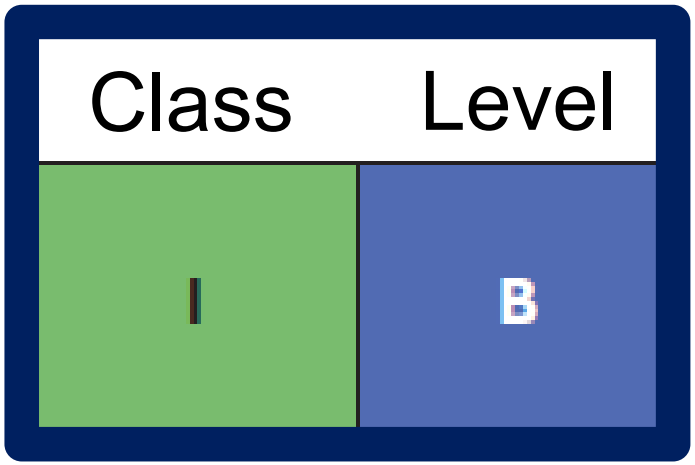
Class	Level
III	A

GP IIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively

Class	Level
III	A

Bivalirudin vs GPIIb/IIIa antagonists

Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GPIIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding



Anticoagulants

Anticoagulation is recommended for all patients in addition to antiplatelet therapy

Class	Level
I	A

The anticoagulation should be selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent

Class	Level
I	C

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

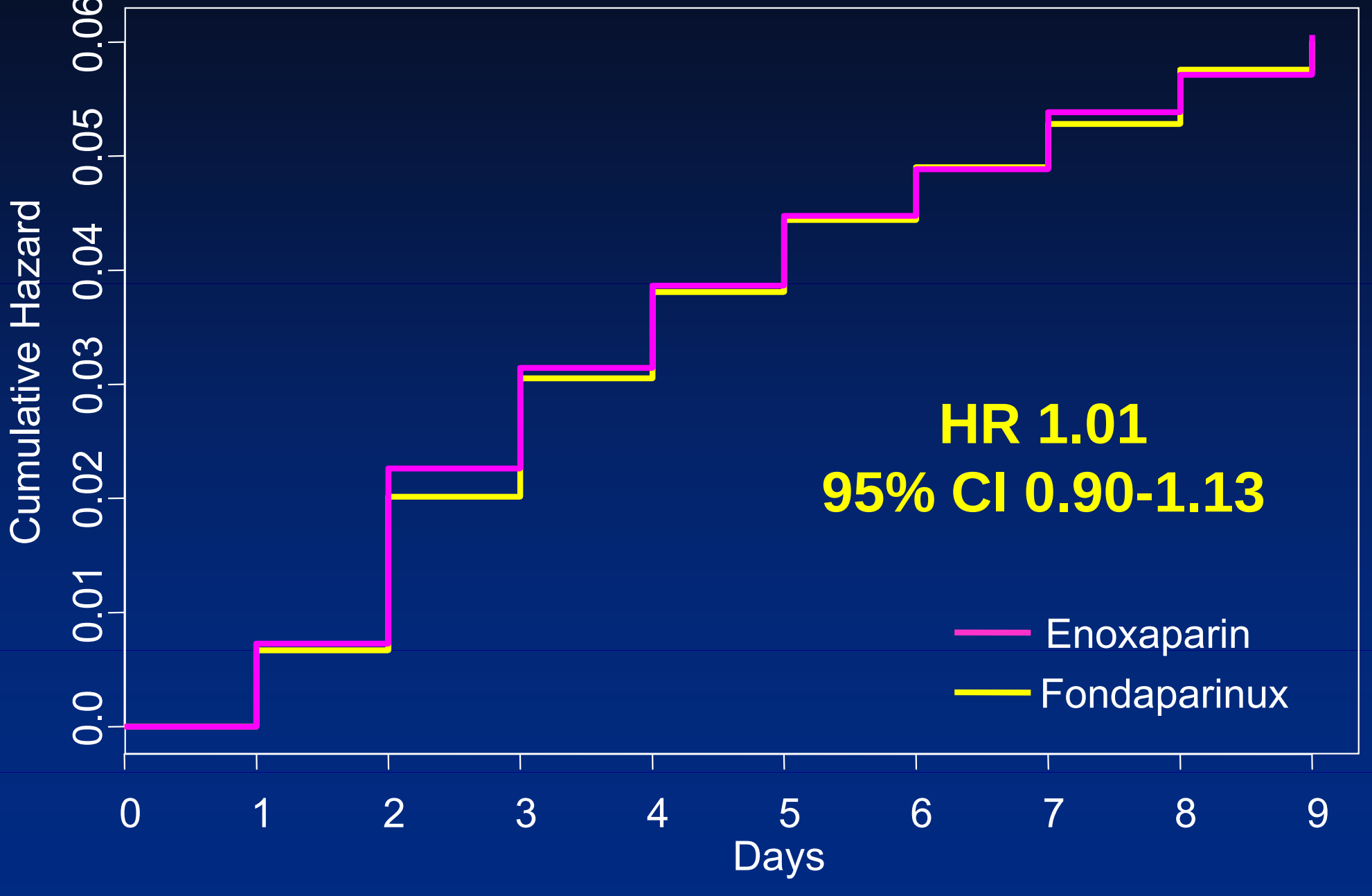
Outcomes

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

Death/MI/RI: Day 9



Major Bleeding: 9 Days

HR 0.52
95% CI 0.44-0.61
P<0.001

Enoxaparin

Fondaparinux

Cumulative Hazard

0.0
0.01
0.02
0.03
0.04

0 1 2 3 4 5 6 7 8 9

Days

Mortality: Day 30

Enoxaparin

Fondaparinux

HR 0.83
95% CI 0.71-0.97
P=0.022

Cumulative Hazard

0.0
0.01
0.02
0.03

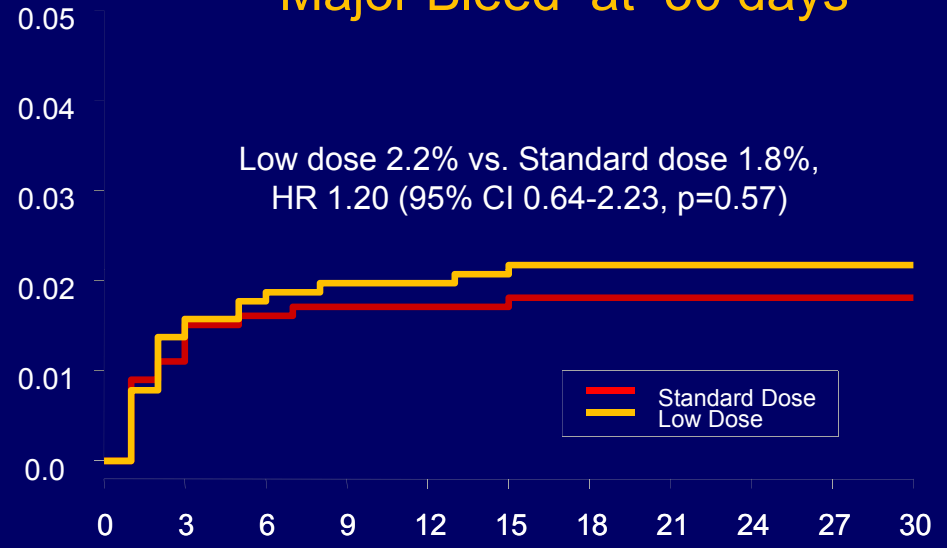
0 3 6 9 12 15 18 21 24 27 30

Days

FUTURA

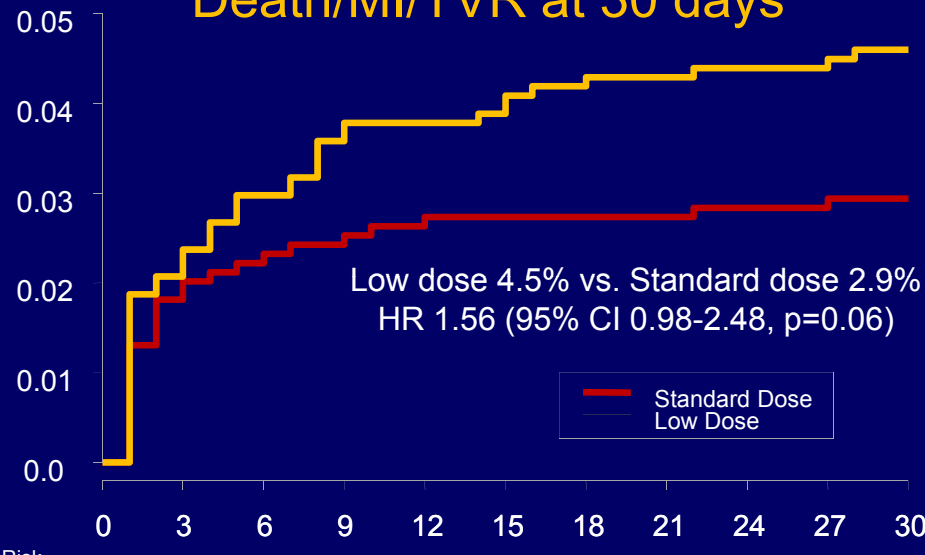
Outcomes to 30 days

Major Bleed at 30 days



No. at Risk						
Standard Dose	1002	986	981	980	980	978
Low Dose	1024	1002	1001	998	997	994

Death/MI/TVR at 30 days

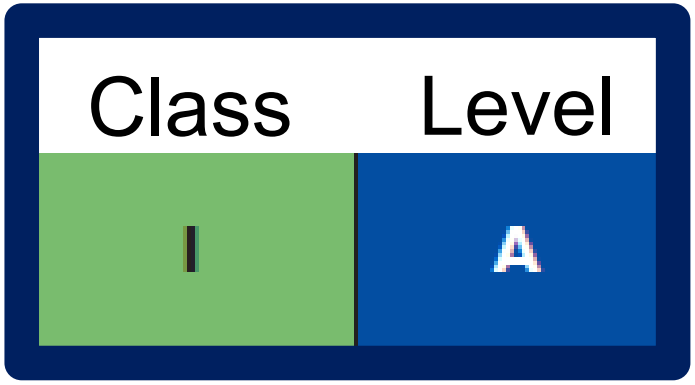


No. at Risk						
Standard Dose	1002	980	975	975	974	971
Low Dose	1024	997	988	982	981	978

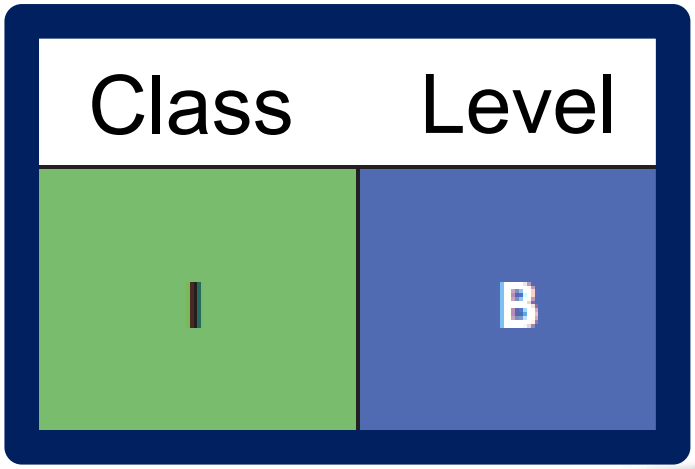
Subgroup analysis showed consistent results for primary outcome and for death/MI/TVR for pre-specified subgroups of: Age, Sex, GP IIb/IIIa, BMI, CrCl, Arterial access site

Fondaparinux

Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy–safety profile with respect to anticoagulation

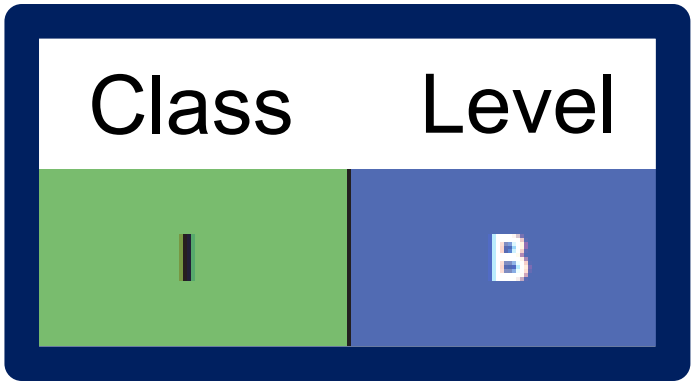


If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) should be added at the time of PCI

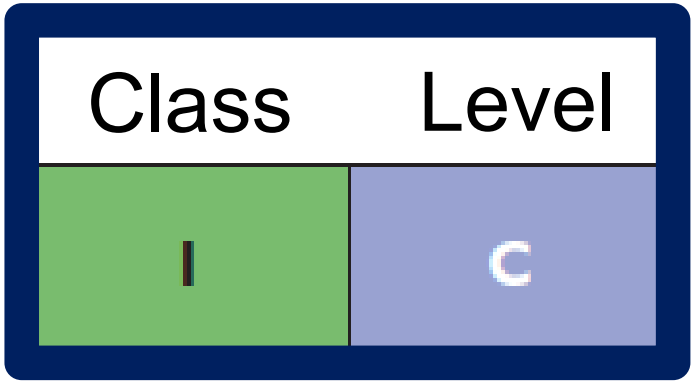


Heparins

Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available



If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50–70 s or other LMWHs at the specific recommended doses are Indicated



Ten Take home messages

6 - Antiplatelet treatment

- Aspirin lifelong for all, plus
- Ticagrelor (12 months) or
- Prasugrel (only with PCI)
- Clopidogrel , if ticagrelor and prasugrel not available
- Glycoprotein IIb/IIIa in high risk patients, but not routinely upstream

7 - Anticoagulation

- Fondaparinux best benefit/ risk profile (add UFH if PCI)
- Enoxaparin, other low molecular weight heparins or unfractionated heparin are less recommended options
- Bivalirudin in high risk bleeding as alternative to GP IIb/IIIa + UFH in patients undergoing PCI