

Guidelines in de dagelijkse praktijk

JM ten Berg
St Antonius Ziekenhuis

Oktober 2014

Casus

- 72 jaar, man 87 kg, L 167
- Hypercholesterolemie, type 2 DM, minor stroke 2009, nierinsufficiëntie, COPD gold II
- DM II medicatie, statine, ASA
- 'S nachts pijn op de borst gedurende 1 uur
- Bij presentatie pijnvrij, RR 135/76, HF 78/min

Clinical presentation

ECG: SR, ST depressie 1 mm I, AvL V4-V6

Laboratory Results:

- Creatinin 160 $\mu\text{mol/L}$
- Troponin T = 0.4 (N< 0.015) top, up and down
- TTE: Normal LVEF \longrightarrow NSTEMI

Beleid?

ESC/EACT Guidelines

■ Considering the large number of patients and the heterogeneity of NSTEMI-ACS, early risk stratification is important to identify patients at high immediate and long-term risk of death and cardiovascular events, in whom an early invasive strategy with its adjunctive medical therapy may reduce that risk

■ So, strategy and medical therapy is linked..

Recommendations for diagnosis and risk stratification 1

Recommendations	Class ^a	Level ^b
In patients with a suspected NSTEMI-ACS, diagnosis and short-term ischaemic/bleeding risk stratification should be based on a combination of clinical history, symptoms, physical findings, ECG (repeated or continuous ST monitoring), and biomarkers.	I	A
ACS patients should be admitted preferably to dedicated chest pain units or coronary care units.	I	C
It is recommended to use established risk scores for prognosis and bleeding (e.g. GRACE, CRUSADE).	I	B
A 12-lead ECG should be obtained within 10 min after first medical contact and immediately read by an experienced physician. This should be repeated in the case of recurrence of symptoms, and after 6–9 and 24 h, and before hospital discharge.	I	B
Additional ECG leads (V ₃ R, V ₄ R, V ₇ –V ₉) are recommended when routine leads are inconclusive.	I	C

At Admission (in-hospital/to 6 months)

At Discharge (to 6 months)

Age

70-79

HR

70-89

SBP

120-139

Creat.

1.6-1.99

CHF

I (no CHF)

SI Units

☐ Cardiac arrest at admission

☒ ST-segment deviation

☒ Elevated cardiac enzymes/markers

Probability of

Death

Death or MI

In-hospital

8%

22%

To 6 months

17%

40%

Reset

Display Score



Bleeding Score Calculator

INTRODUCTION

CALCULATOR

ABOUT

REFERENCES

LINKS

DISCLAIMER

DOWNLOADS

Last Updated:
March 2008

Enter values in drop-down boxes below:

Baseline Hematocrit ?

37 - 39.9

Prior Vascular Disease ?

Yes

GFR: Cockcroft-Gault ?

31 - 60

Calculate GFR

Diabetes Mellitus

Yes

Heart rate on admission

71 - 80

Signs of CHF on admission ?

No

Systolic blood pressure
on admission

12

Sex

Male

CRUSADE Bleeding Score

The CRUSADE Bleeding Score (range 1-100 points) equals the sum of the weighted scores for each of the eight predictors.

Patients are categorized into quintiles of risk groups based on the following Bleeding Scores: <21 Very Low Risk, 21-30 Low Risk, 31-40 Moderate Risk, 41-50 High Risk, and >50 Very High Risk.

CRUSADE
Bleeding Score ?

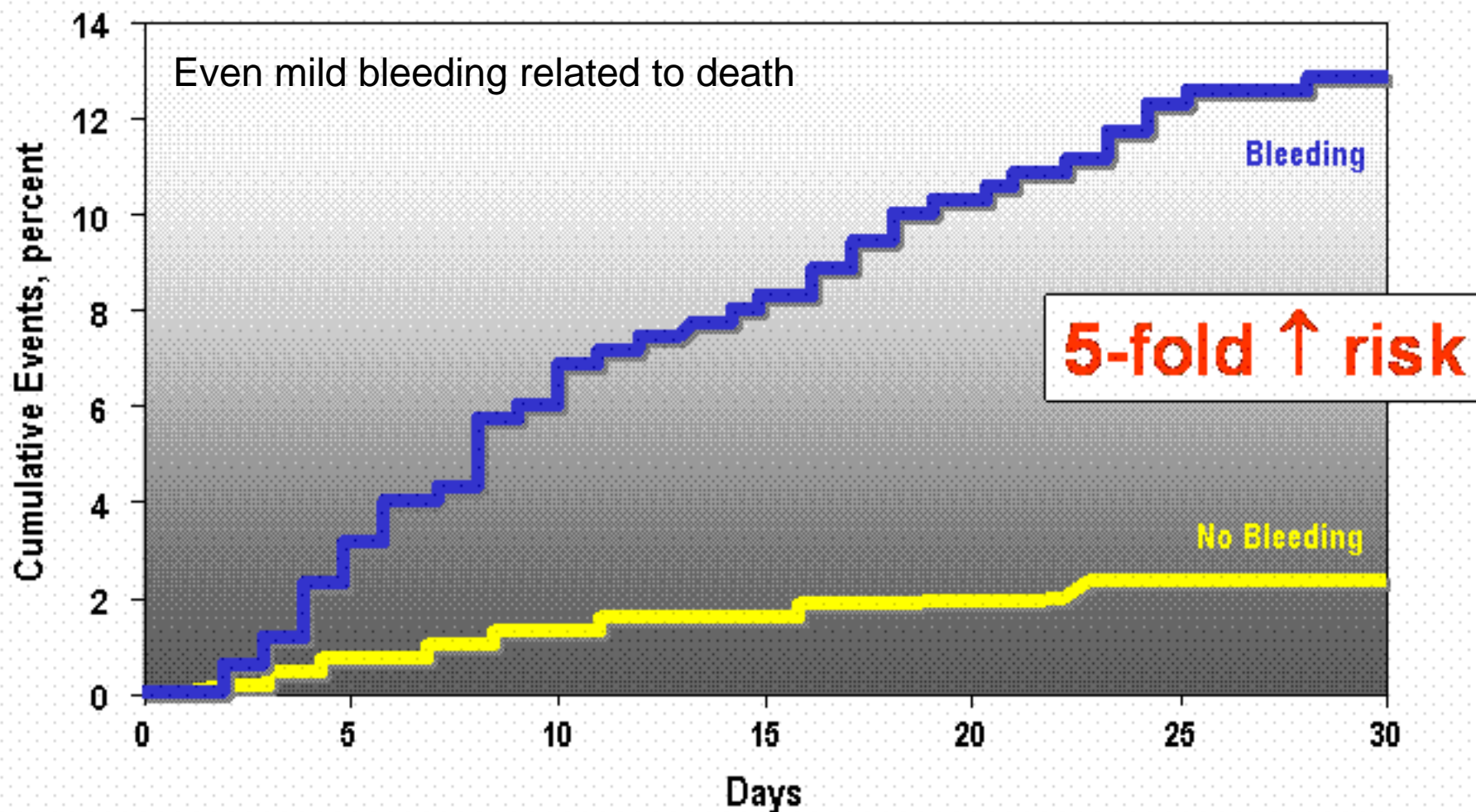
44

High Risk

Rate of In-Hospital
Major Bleeding ?

10.4%

30 Day Death According to Bleeding OASIS Registry, OASIS-2, CURE

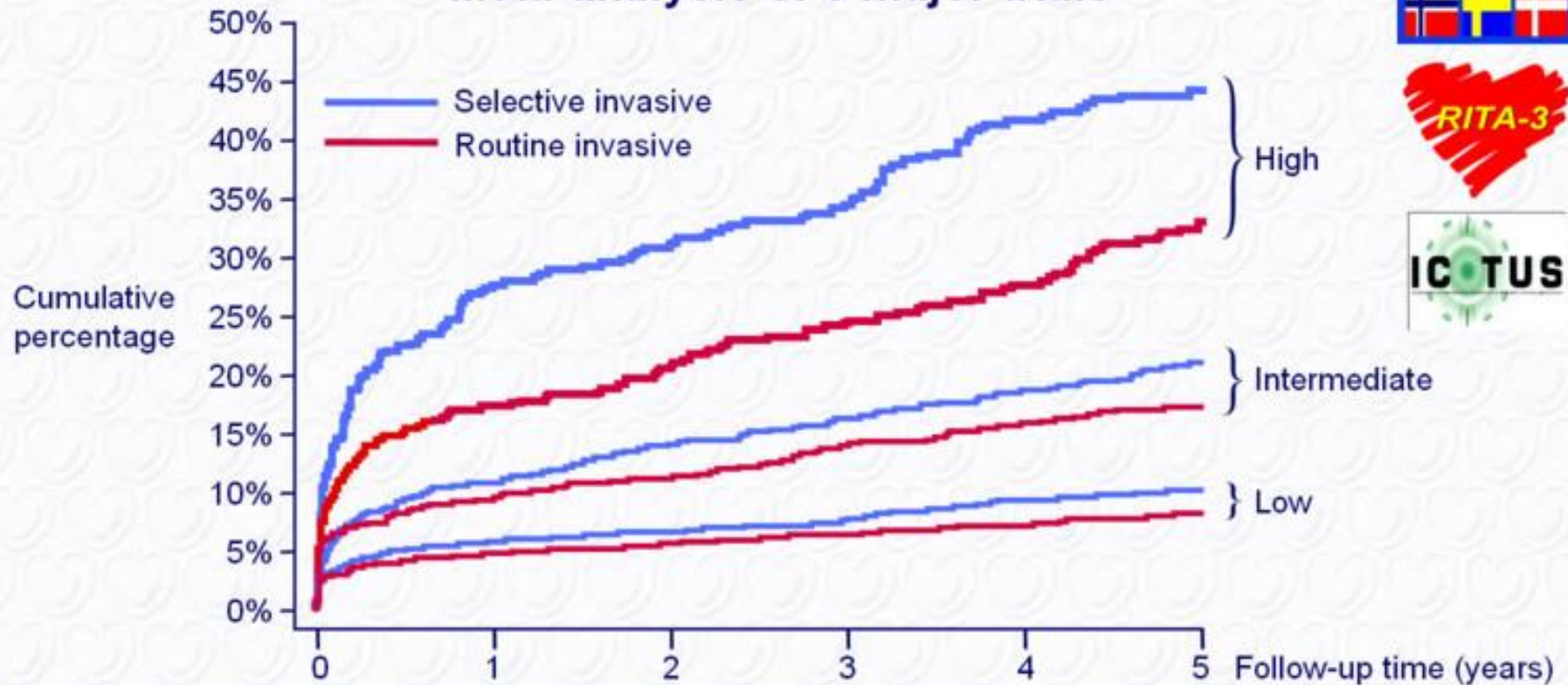


Eikelboom *Circulation* 2006; 114: 774 - 782



Intended Early Invasive vs. Conservative Strategy

Long term outcome by initial Risk Score Meta-analysis of 3 major trials



Selective invasive	2746	2452	2351	2178	2077	2005
Routine invasive	2721	2485	2410	2235	2166	2079

Fox KA et al. JACC 2010;55(22):2435-45

Question I: timing?

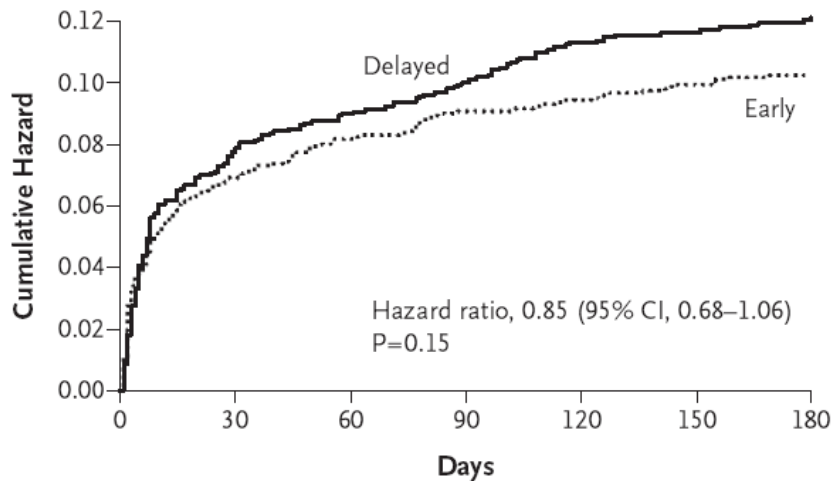
1. CAG early
2. Immediate CAG ('STEMI like')

Early versus Delayed Invasive Intervention in Acute Coronary Syndromes

Early (≤ 24 h, median=14h) or delayed intervention (≥ 36 h, median=50h)
N=3000

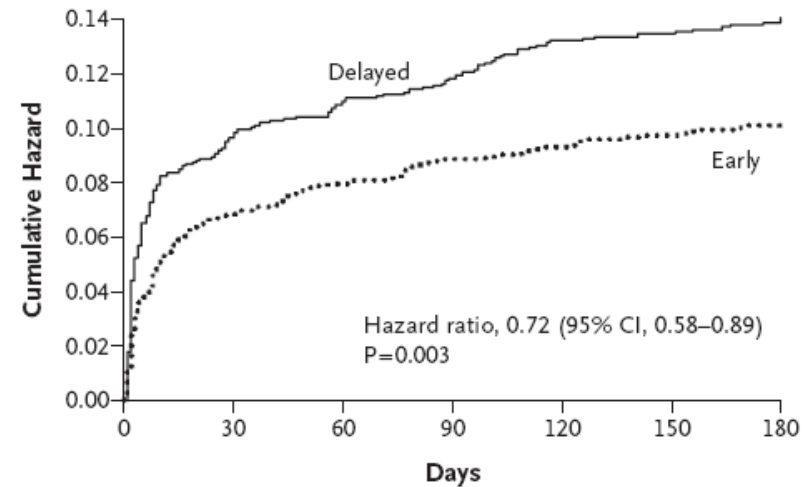
Death, MI, Stroke

Primary Outcome



Death, MI, Refractory Angina

Secondary Outcome



CONCLUSIONS

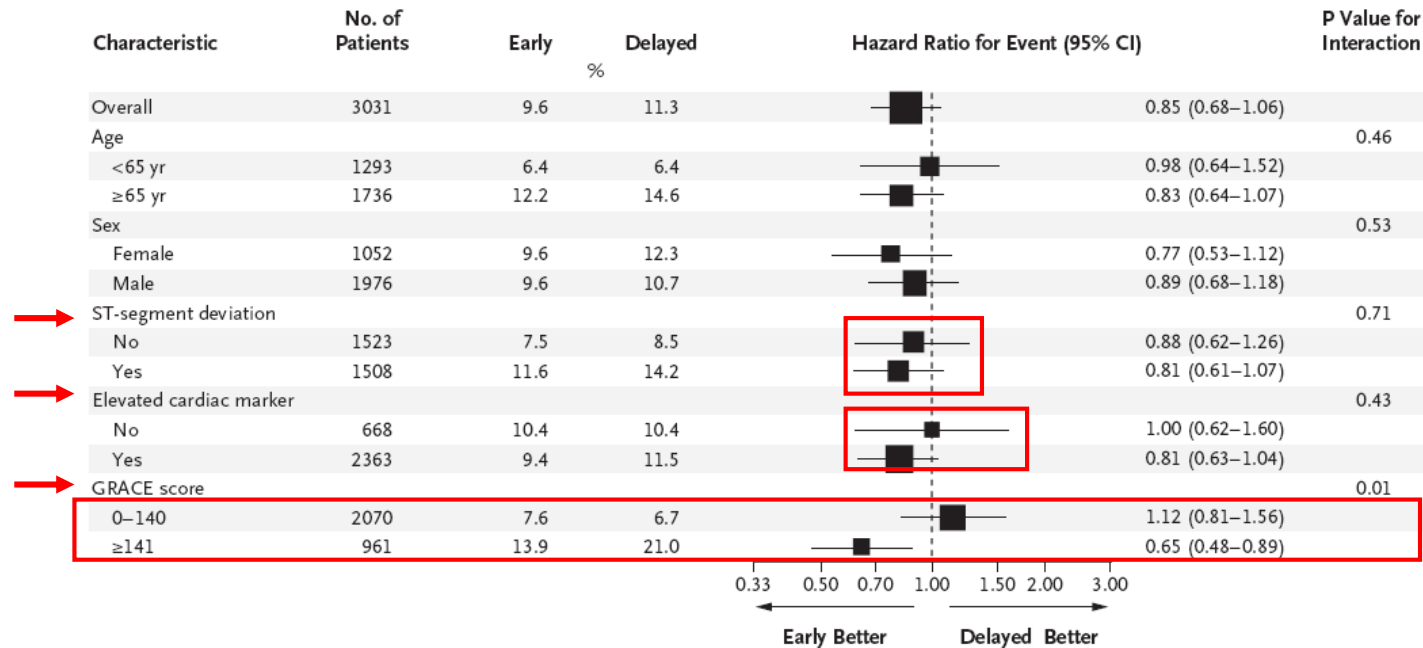
Early intervention did not differ greatly from delayed intervention in preventing the primary outcome, but it did reduce the rate of the composite secondary outcome of death, myocardial infarction, or refractory ischemia

N=3031

Early versus Delayed Invasive Intervention in Acute Coronary Syndromes

Early (≤ 24 h, median=14h) or delayed intervention (≥ 36 h, median=50h)

A Primary Outcome



CONCLUSIONS

Early intervention

was superior to delayed

intervention in high-risk patients.

N=3031



ABOARD study design

NSTE-ACS N=350

2 of 3 Criteria: Ischemic symptom, ST-T change, troponin rise

with TIMI score ≥ 3

IVRS RANDOMIZATION

Immediate cath
1.1 h

Next day cath

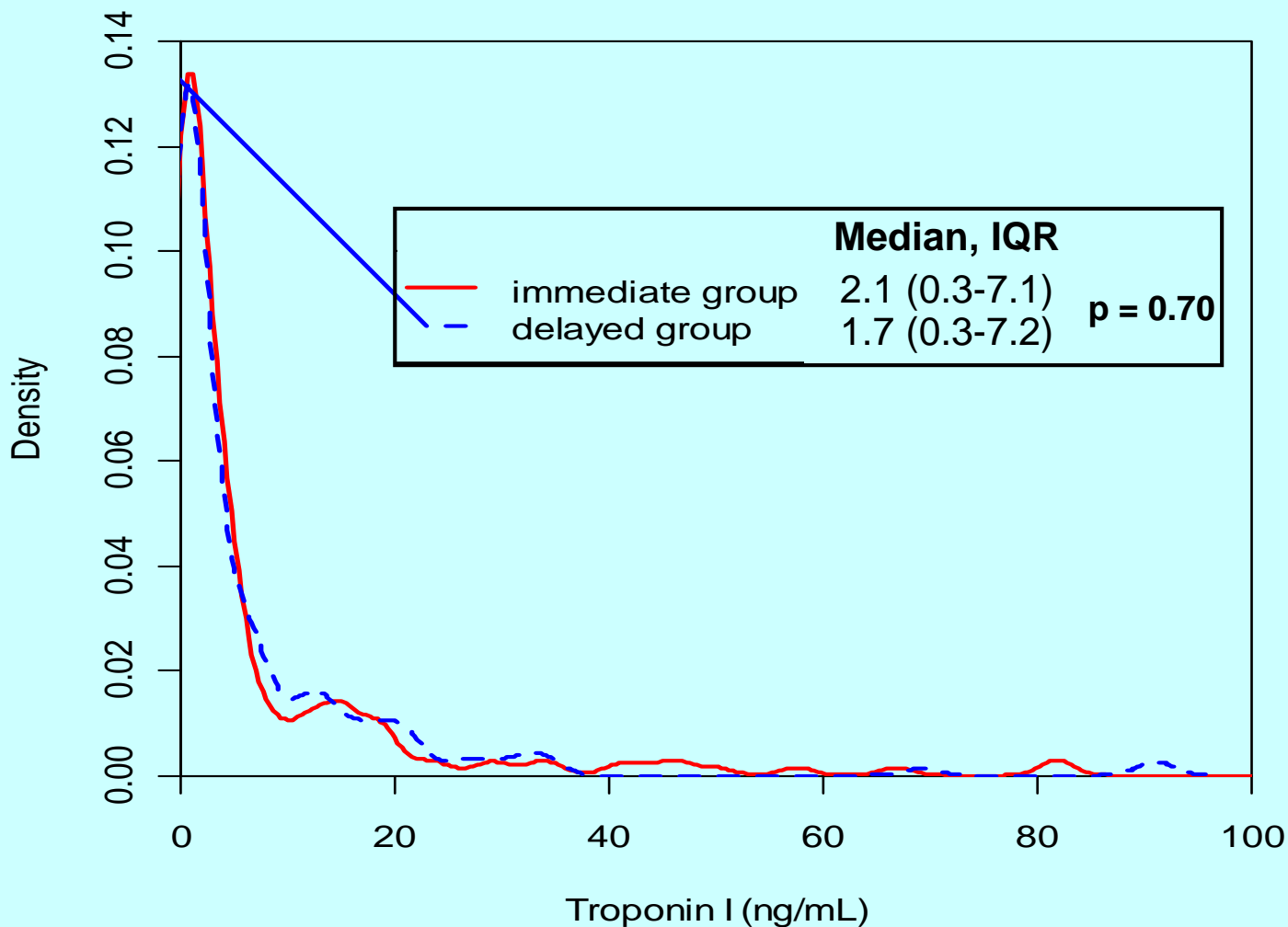
All PCIs on abciximab (60%)

1-month Follow-up



Primary EP (peak of troponin I)

Peak values of troponin I in the 2 groups





Safety outcomes at 1 month

	Immediate	Delayed	<i>P</i>
Major bleeding at 1 month, (%)	4.0	6.8	0.25
Non-CABG related major bleeding,	2.3	5.1	0.26
CABG-related major bleeding	1.7	1.7	1.00
Transfusion \geq 2 units	3.4	5.6	0.32
Transfusion \geq 5 units	1.1	1.1	1.00
Thrombocytopenia at 1 month, (%)	2.9	4.5	0.41
Non-CABG thrombocytopenia, (%)	2.3	4.0	0.54
Post-CABG thrombocytopenia, (%)	0.6	0.6	1.00

Q Antiplatelet therapy in CCU ?

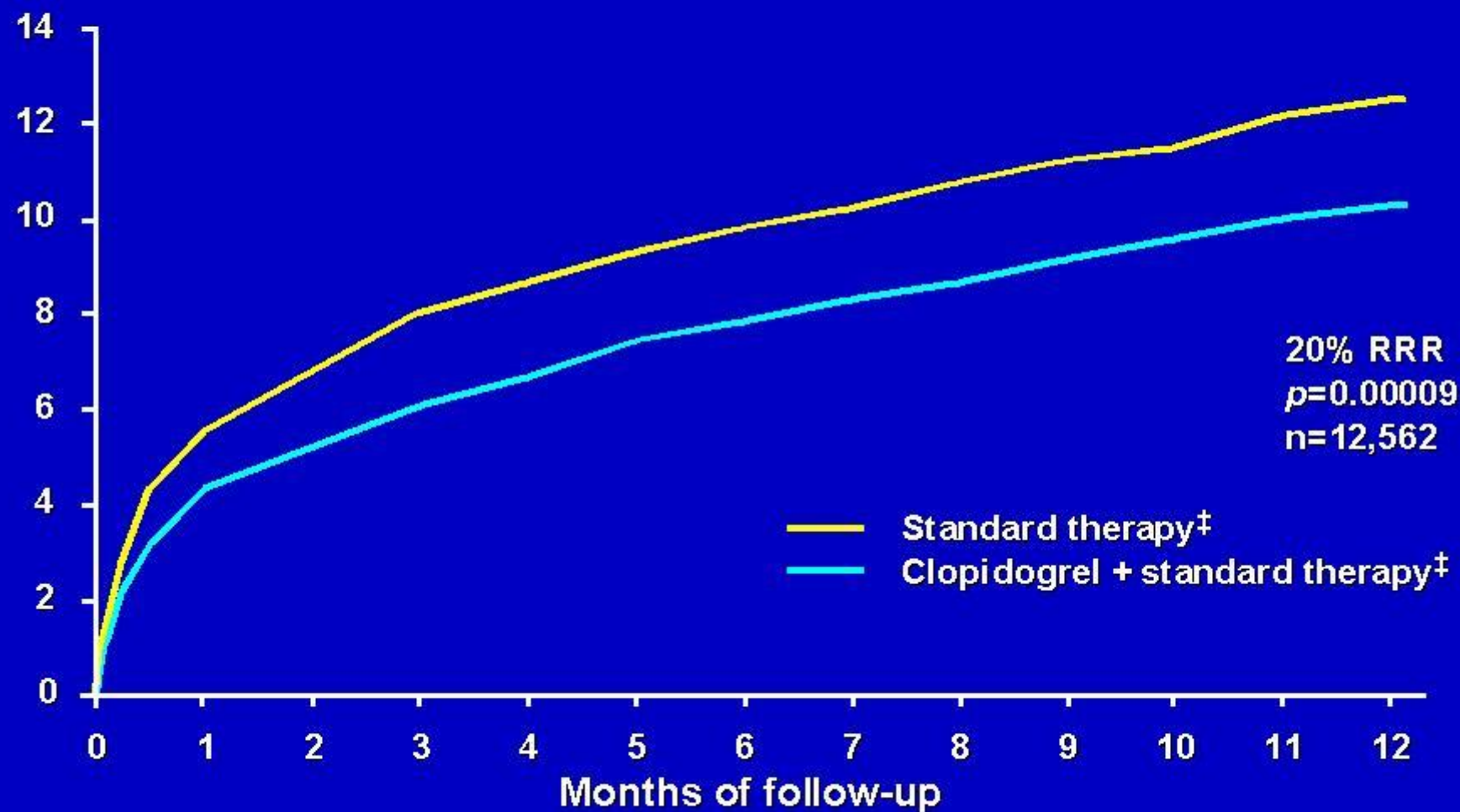
1. Aspirin + Clopidogrel LD 600 mg
1. Aspirin + Prasugrel LD 60 mg
2. Aspirin + Ticagrelor LD 180 mg
3. Aspirin only, no P2Y₁₂ inhibitor before angio, only after PCI (ACCOAST trial)

CURE – Main Efficacy Results



Primary endpoint (1)

% of patients with recurrent ischemic event*



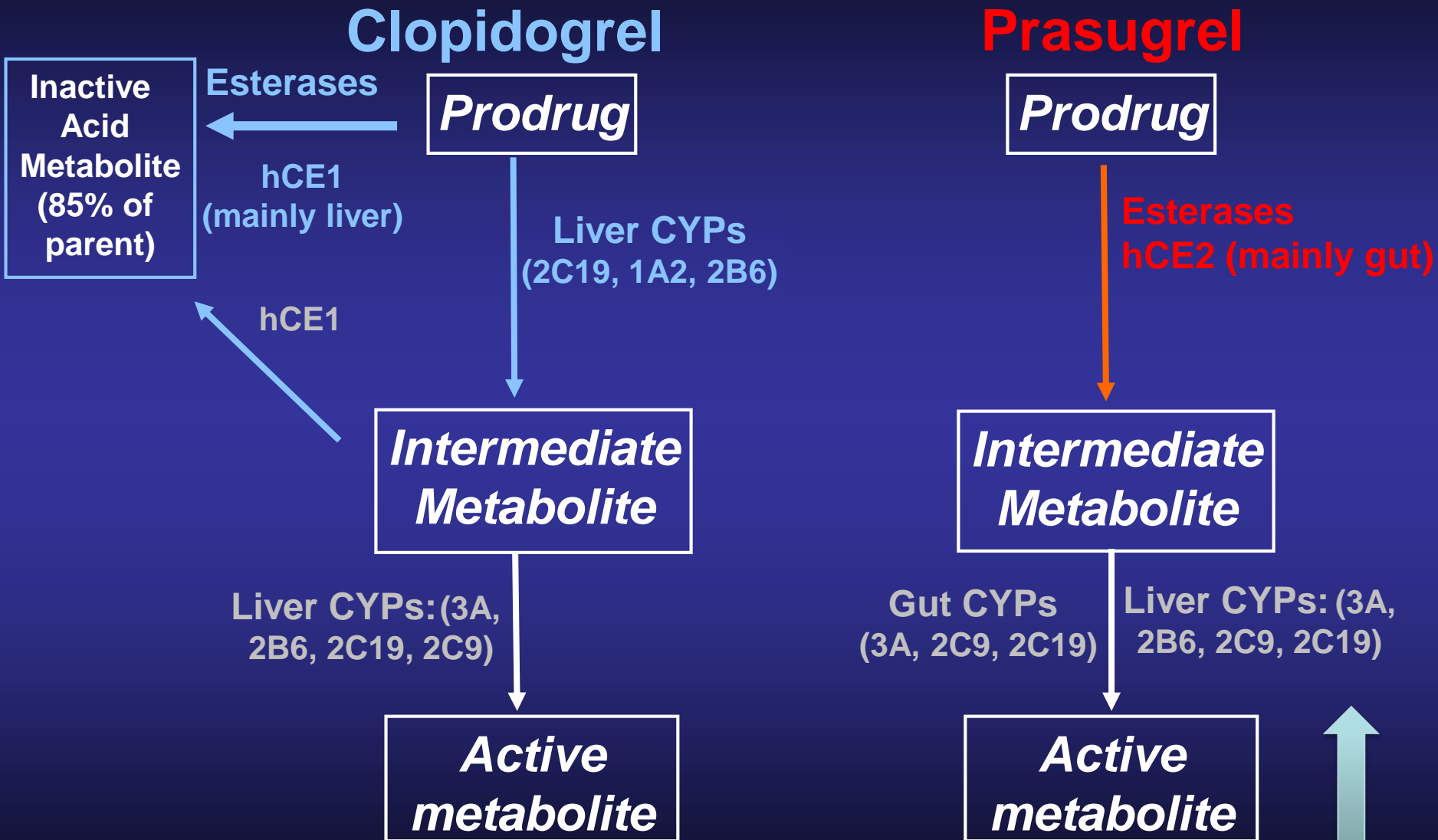
†including ASA

The CURE Investigators. *N Eng J Med* 2001;345:494-502

*cardiovascular death, MI, or stroke

Data on file

Active Metabolite Formation

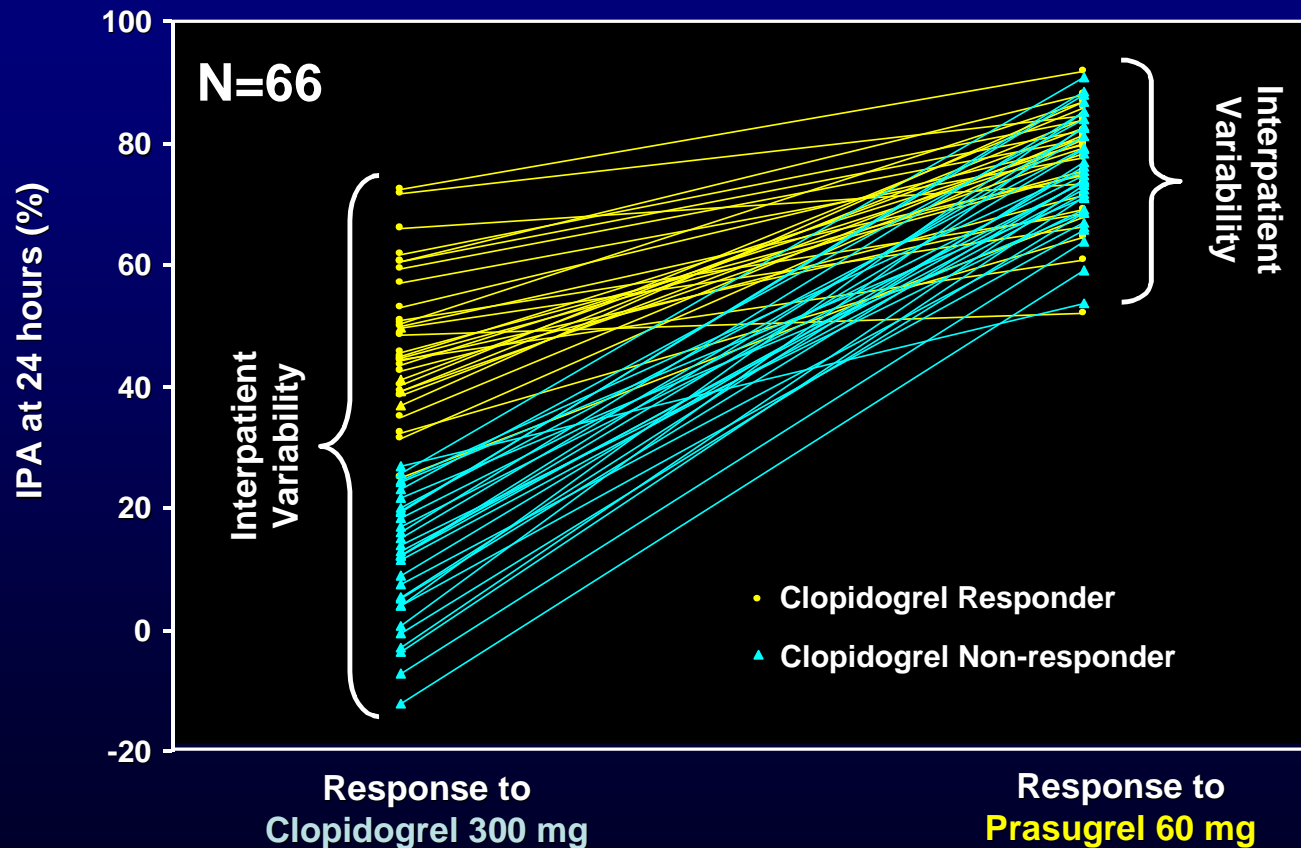


Alternatives Molecules



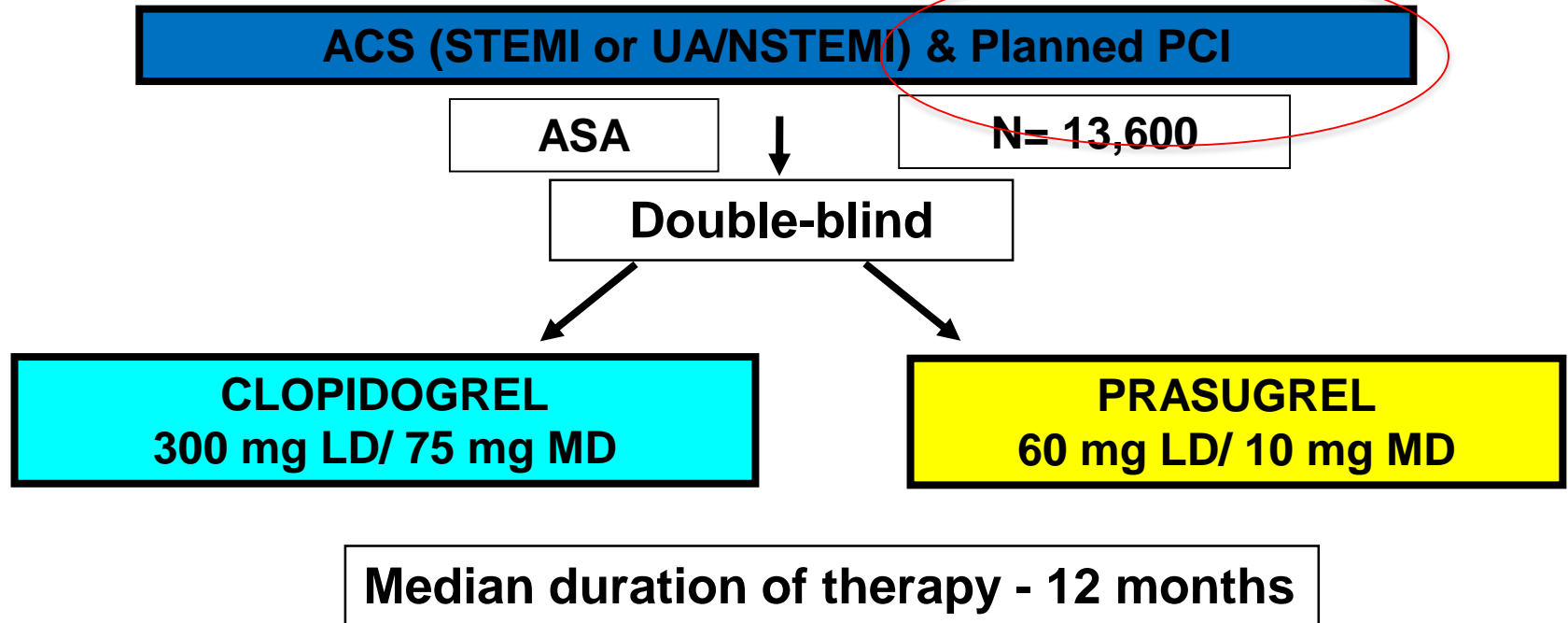
TRITON TIMI-38

Healthy Volunteer Crossover Study



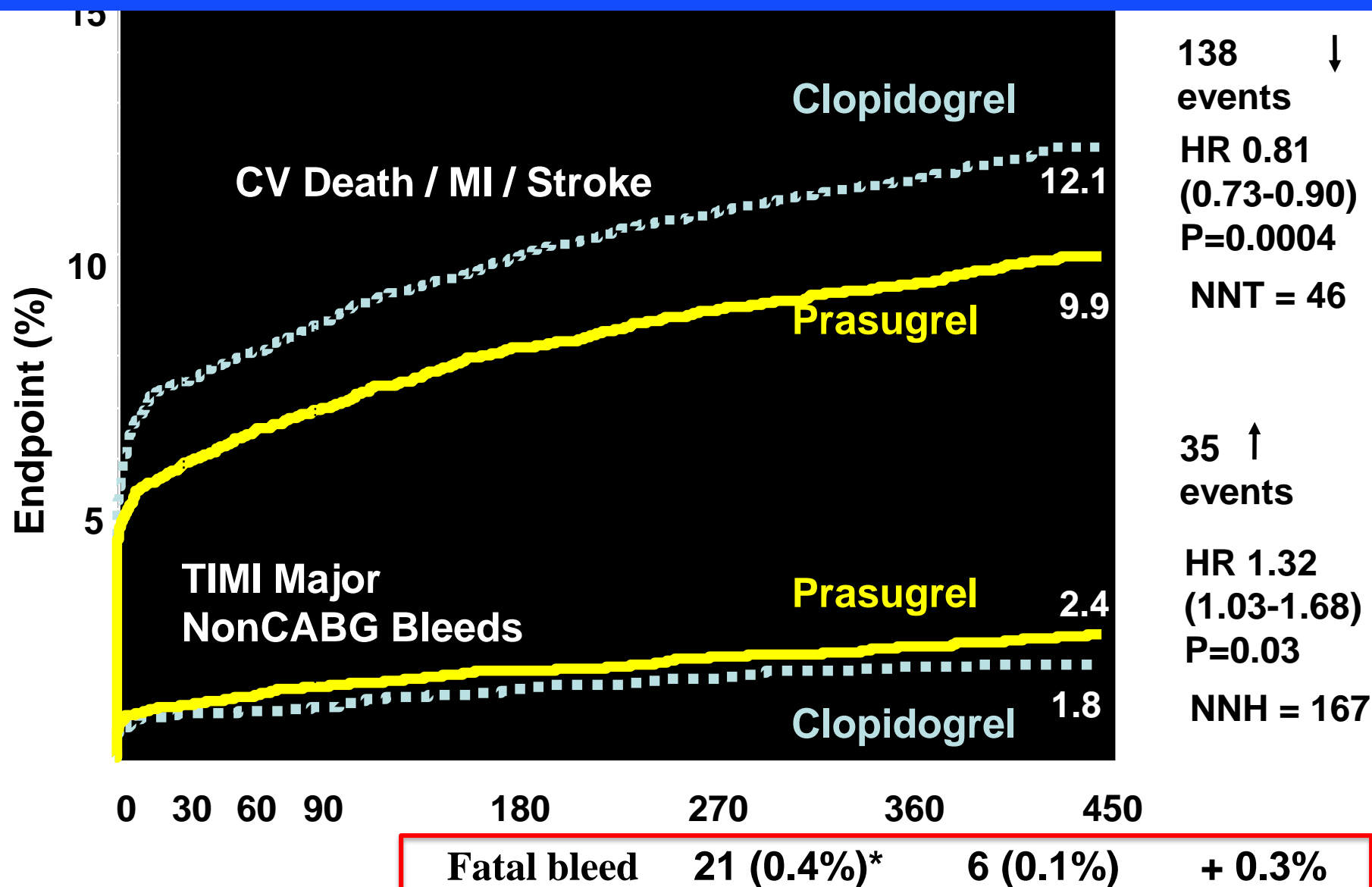
From Brandt JT AHJ 153: 66e9,2007

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes



1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch
V death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)
Safety endpoints: TIMI major bleeds, Life-threatening bleeds
Key Substudies: Pharmacokinetic, Genomic

Balance of Efficacy and Safety

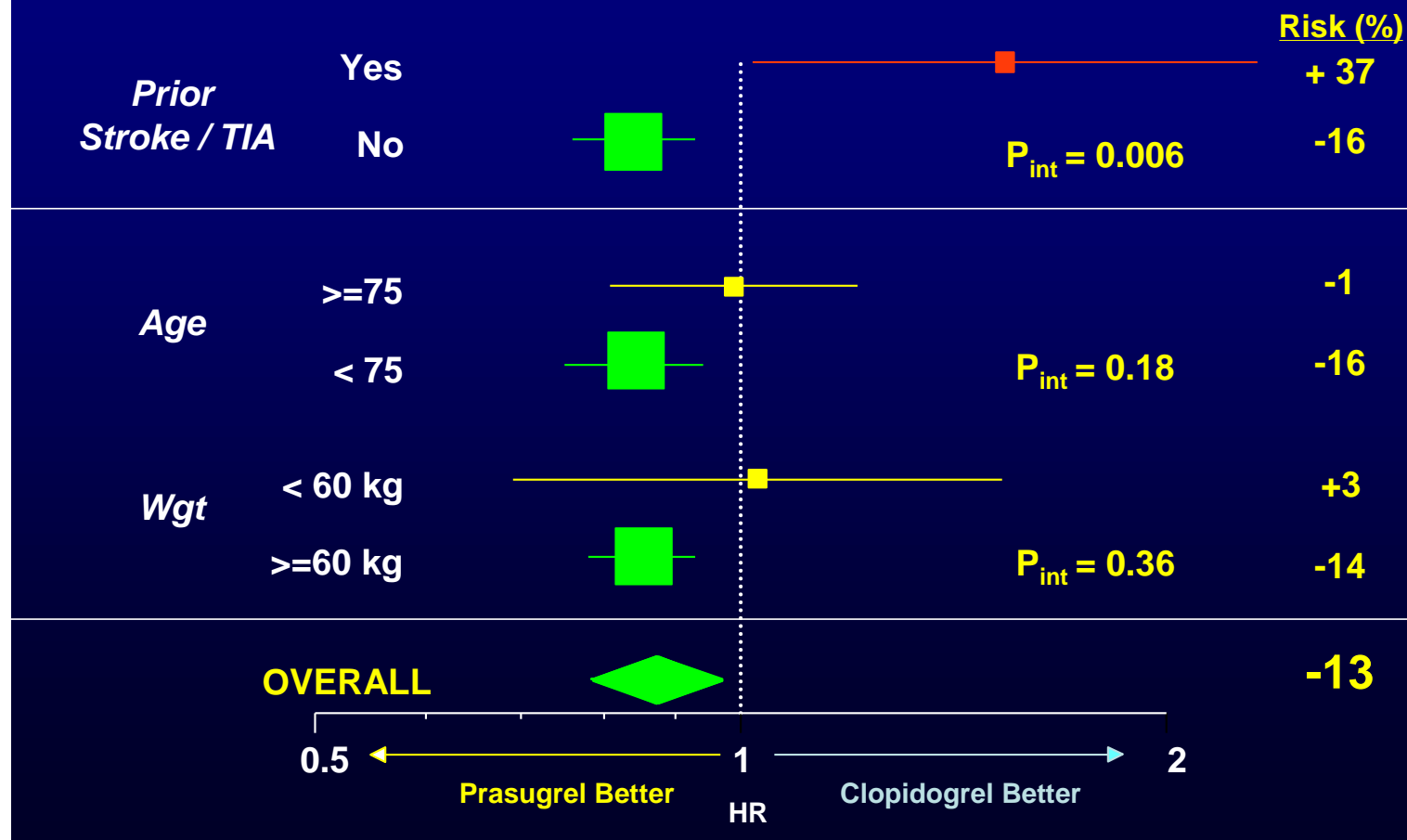


Tailored for Bleeding Risk ?

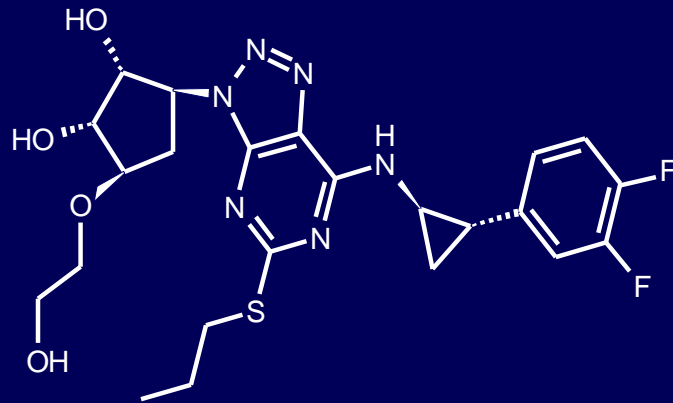


TRITON TIMI-38

Net Clinical Benefit Bleeding Risk Subgroups Post-hoc analysis



Ticagrelor (AZD 6140): an oral reversible P2Y₁₂ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- Direct acting
 - Not a prodrug; does not require metabolic activation
 - Rapid onset of inhibitory effect on the P2Y₁₂ receptor
 - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
 - Degree of inhibition reflects plasma concentration
 - Faster offset of effect than clopidogrel
 - Functional recovery of all circulating platelets

PLATO study design

**NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)**

Clopidogrel

**If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)**

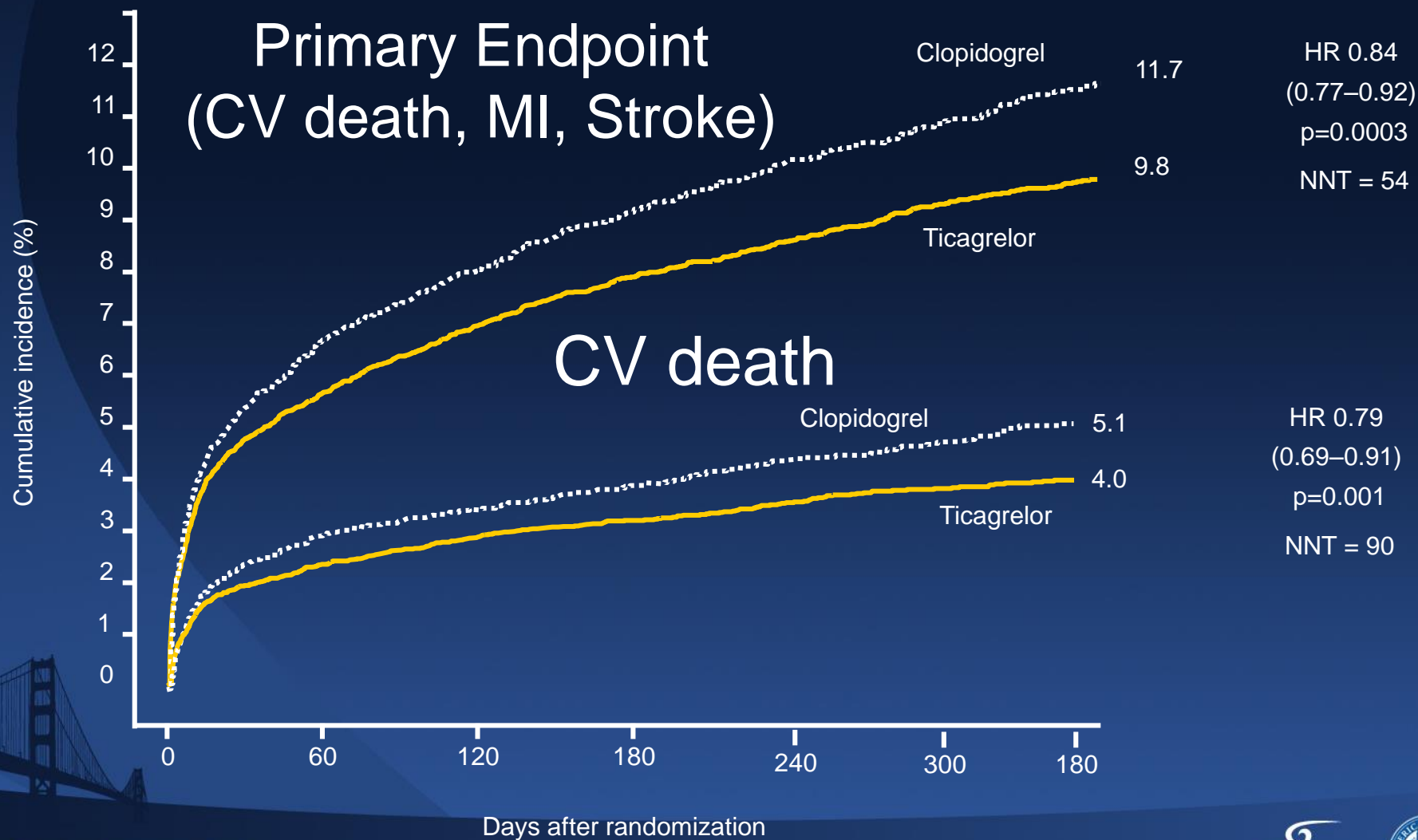
Ticagrelor

**180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)**

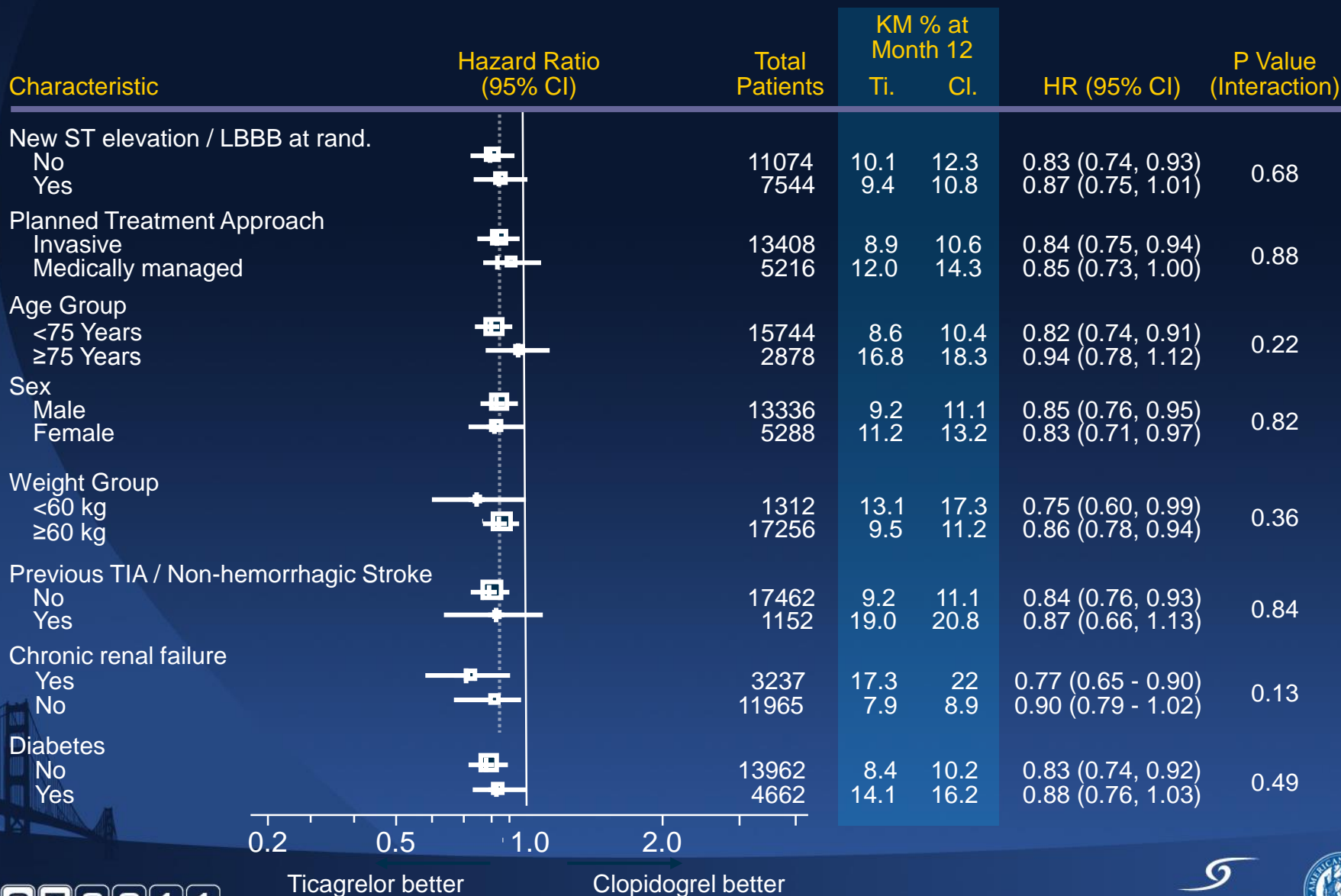
6–12-month exposure

**Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding**

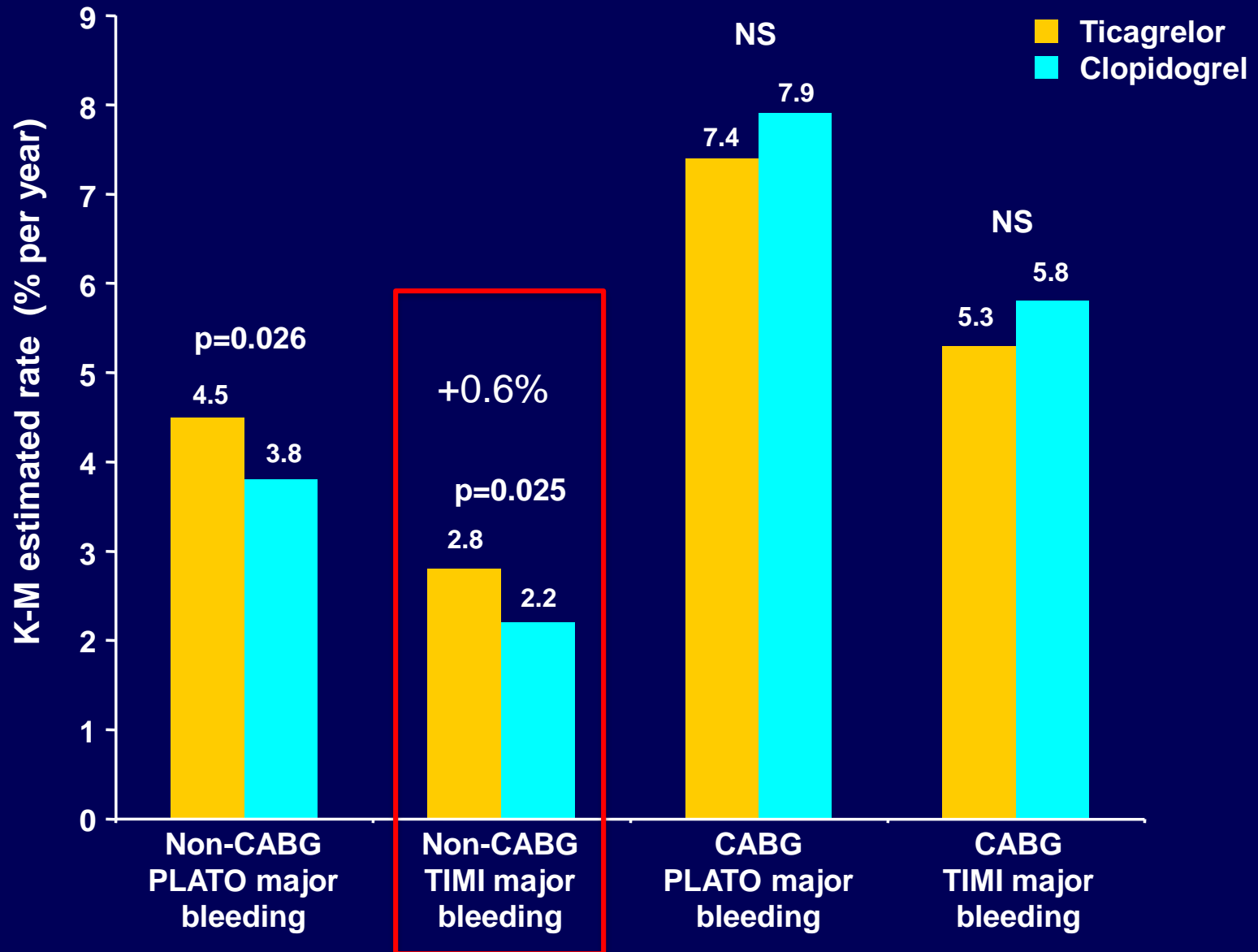
PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack



Consistency across subgroups

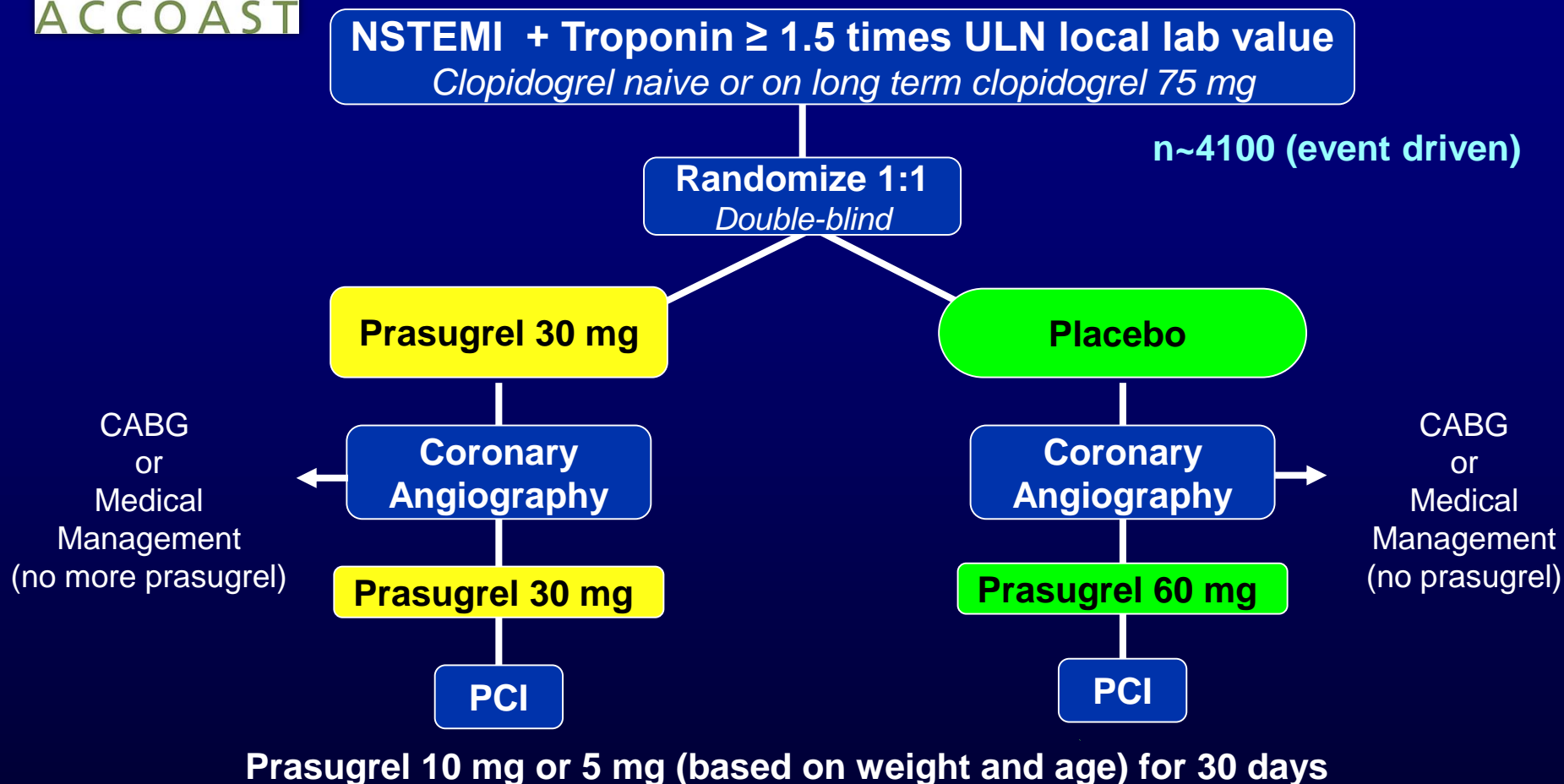


Non-CABG and CABG-related major bleeding





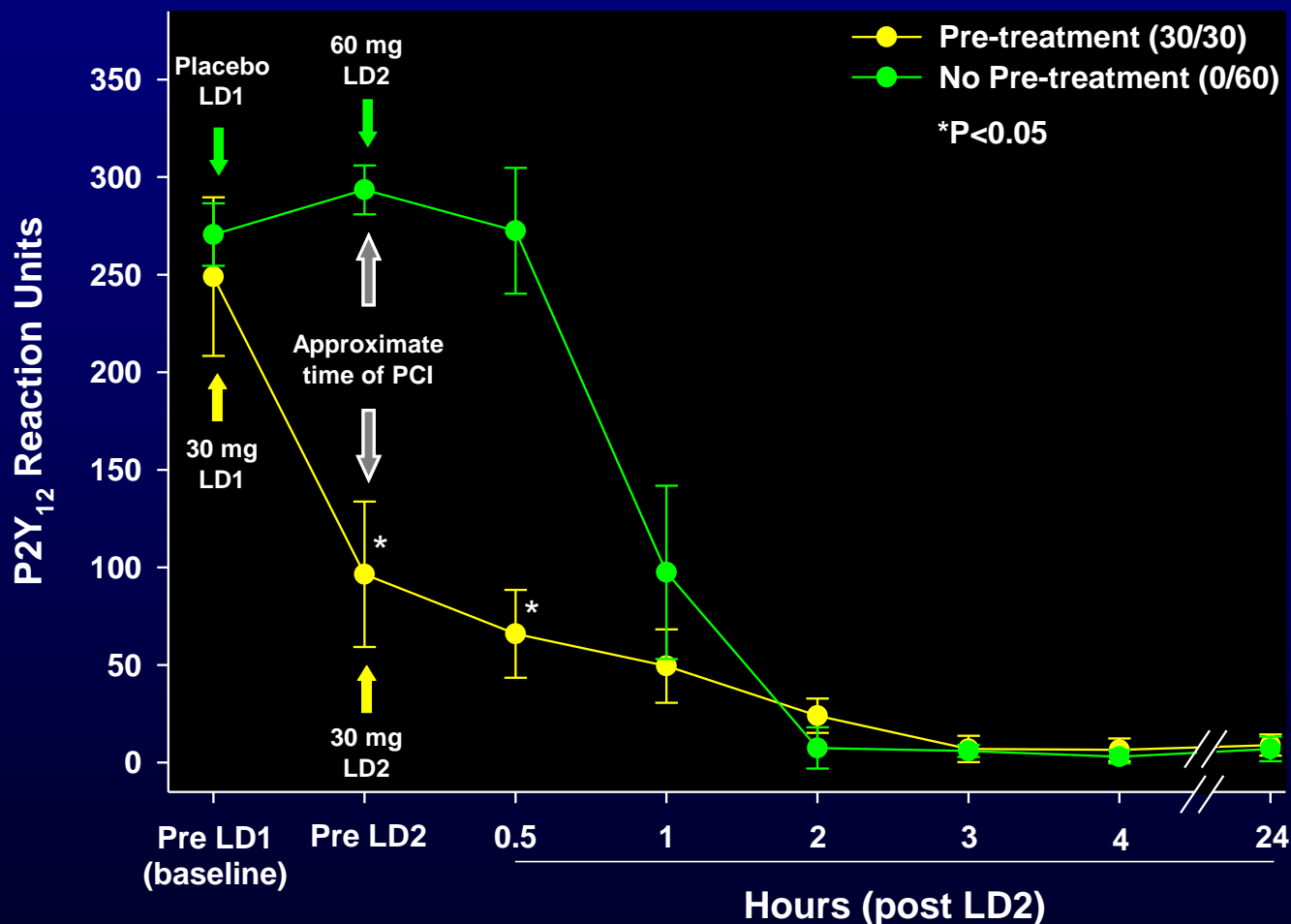
ACCOAST design



1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days



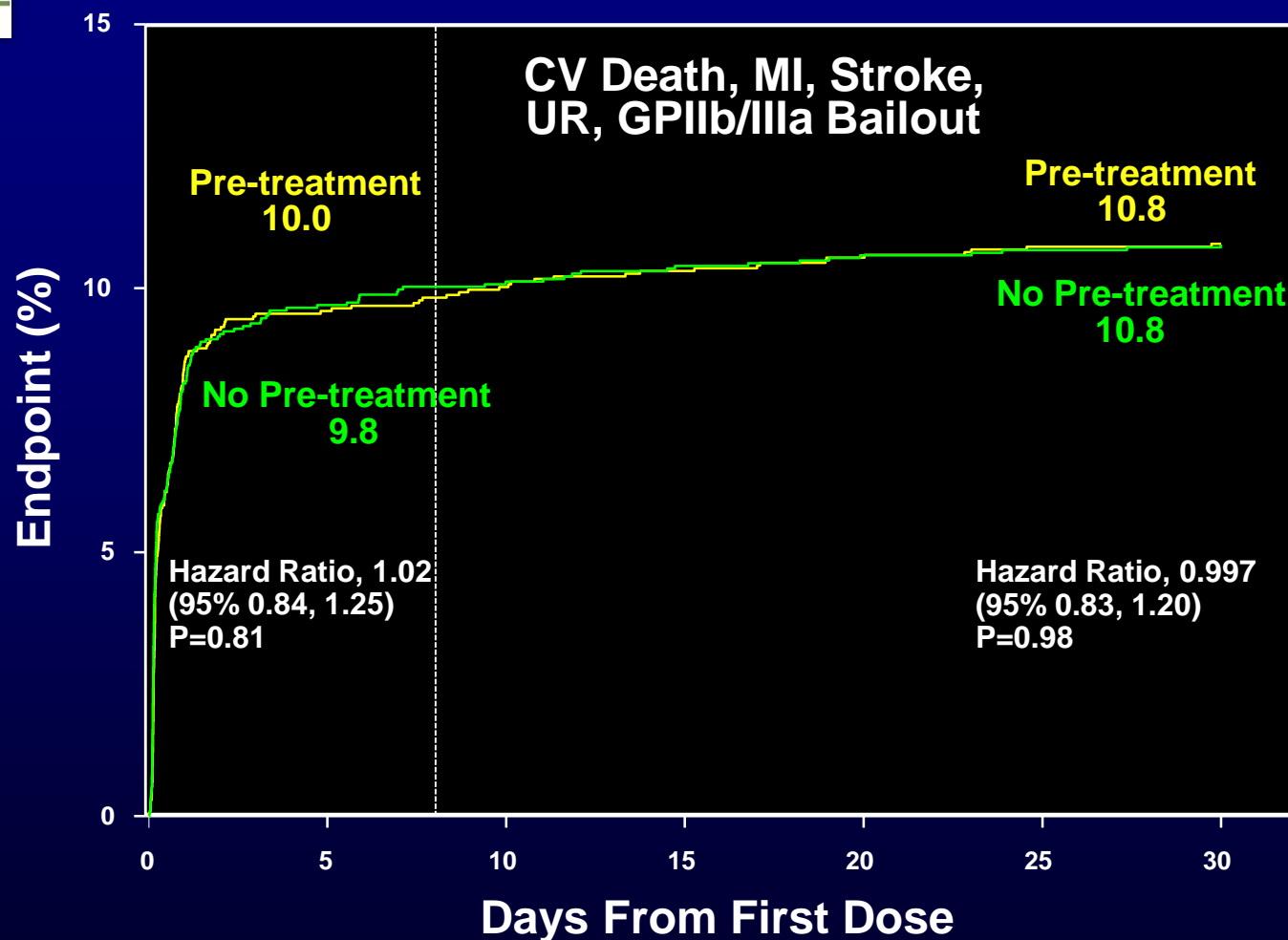
Pharmacodynamic Sub-Study



Data presented as median ± SEM. * p<0.05 relative to the No pre-treatment group. LD = loading dose. Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg



1° Efficacy End Point @ 7 + 30 days (All Patients)

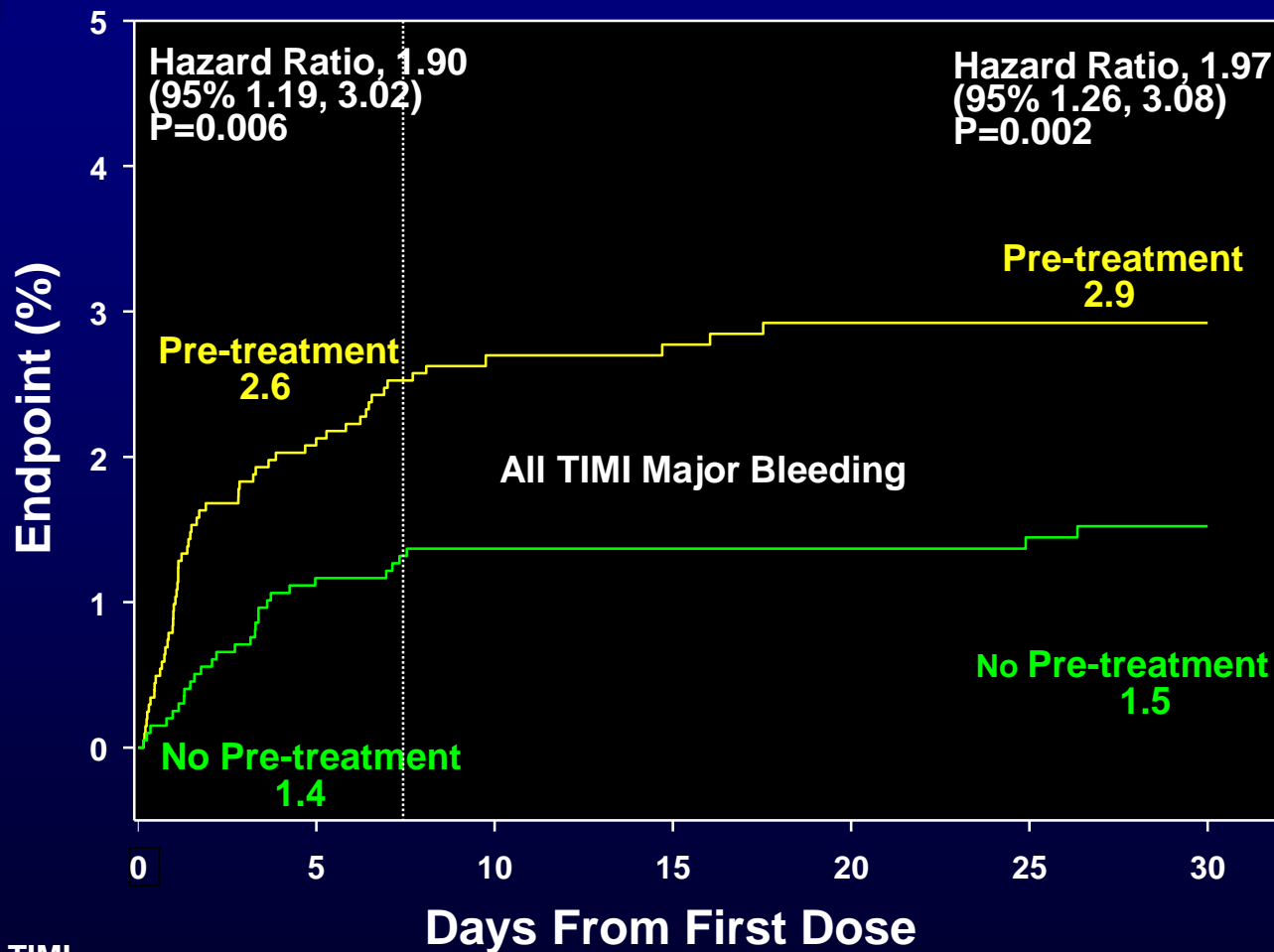


No. at Risk, Primary
Efficacy End Point:

No pre-treatment	1996	1788	1775	1769	1762	1752	1621
Pre-treatment	2037	1821	1809	1802	1797	1791	1616



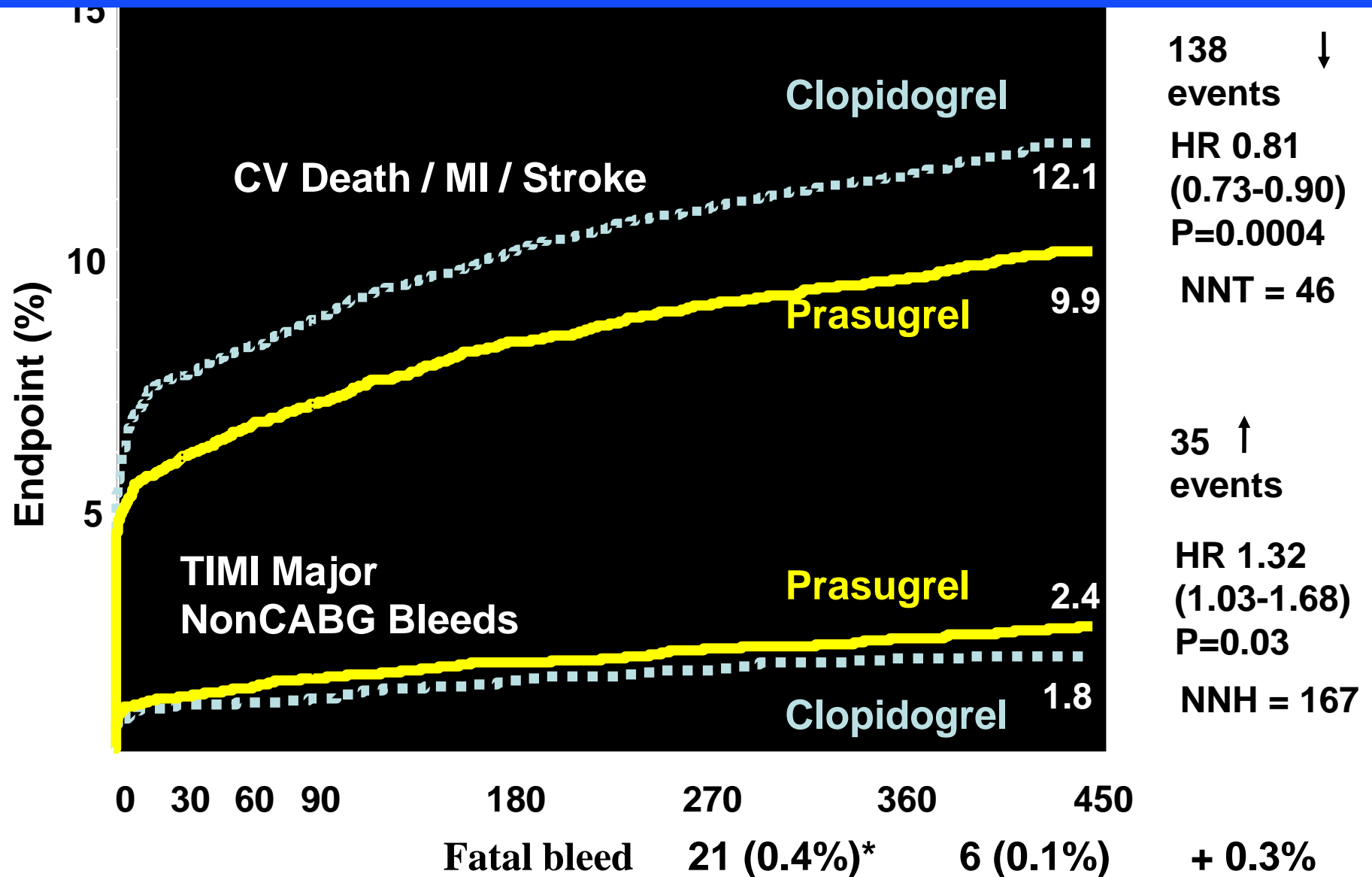
All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)



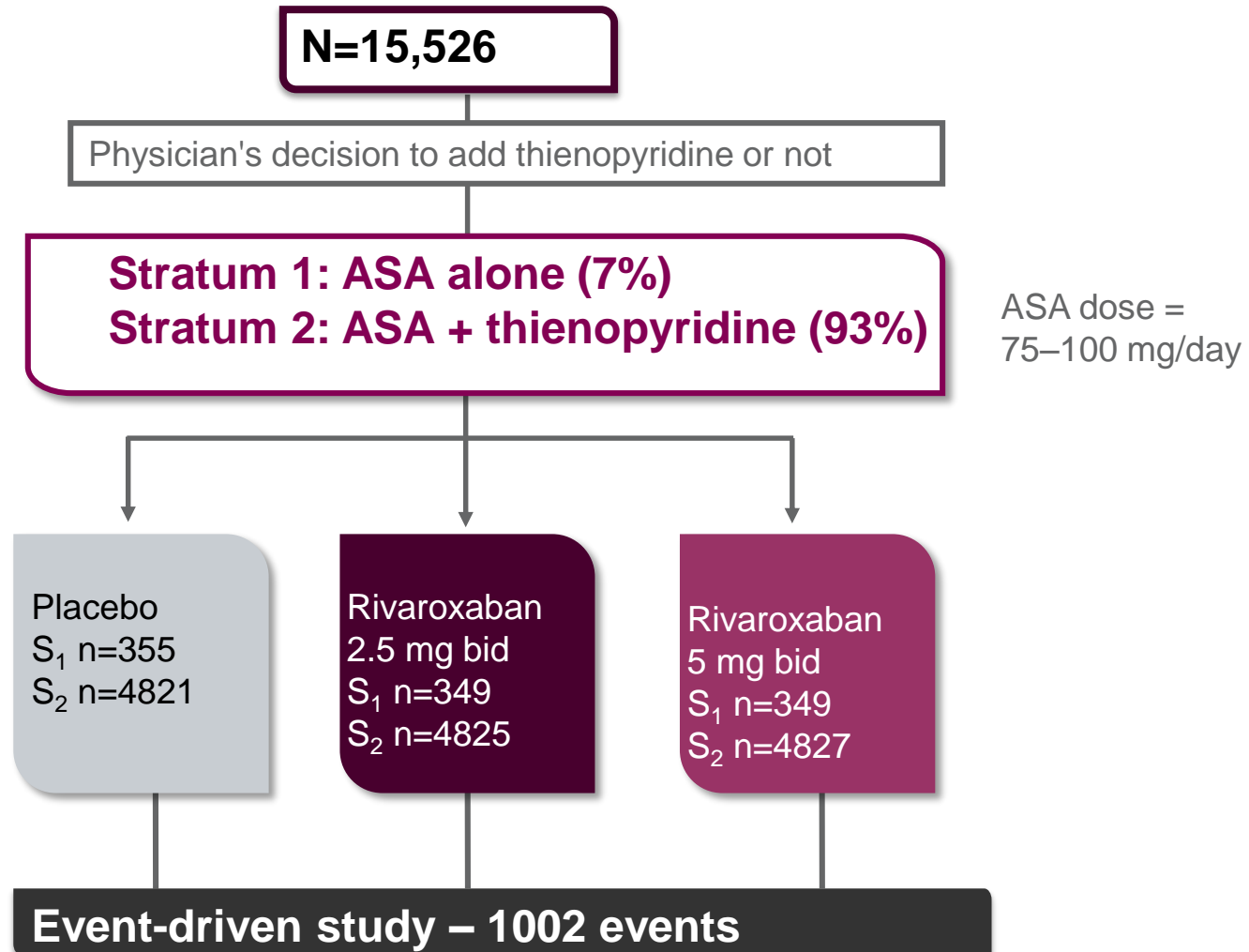
No. at Risk, All TIMI
Major Bleeding:
No pre-treatment
Pre-treatment

1996	1947	1328	1297	1288	1284	1263
2037	1972	1339	1310	1299	1297	1280

Balance of Efficacy and Safety



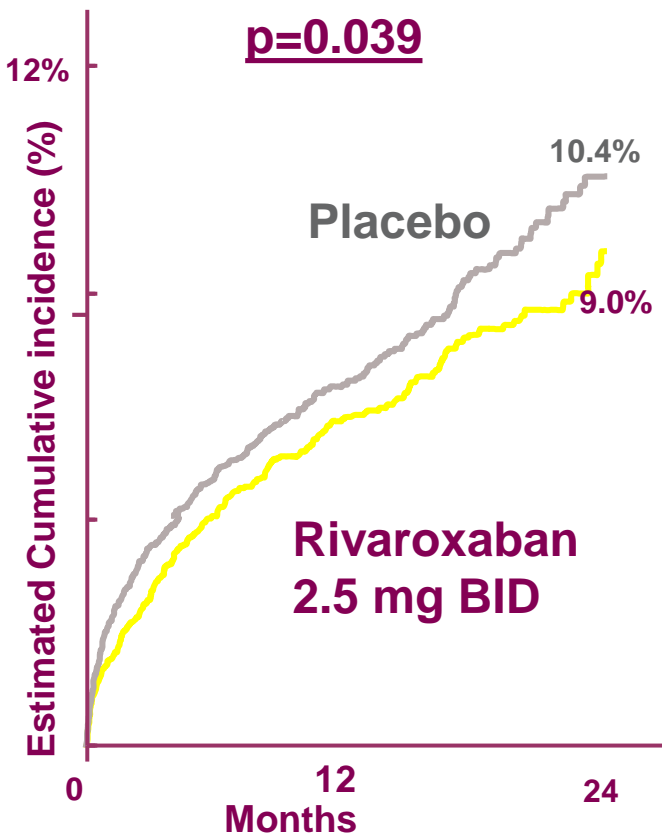
ATLAS ACS 2 TIMI 51



“Very Low Dose” Rivaroxaban (2.5 mg BID)

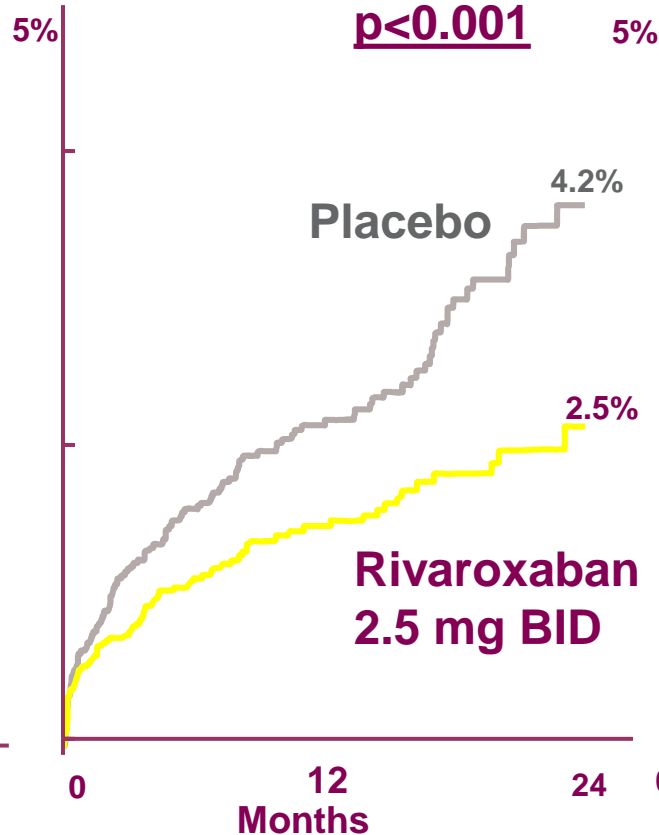
CV Death / MI / Stroke

HR 0.85
p=0.039



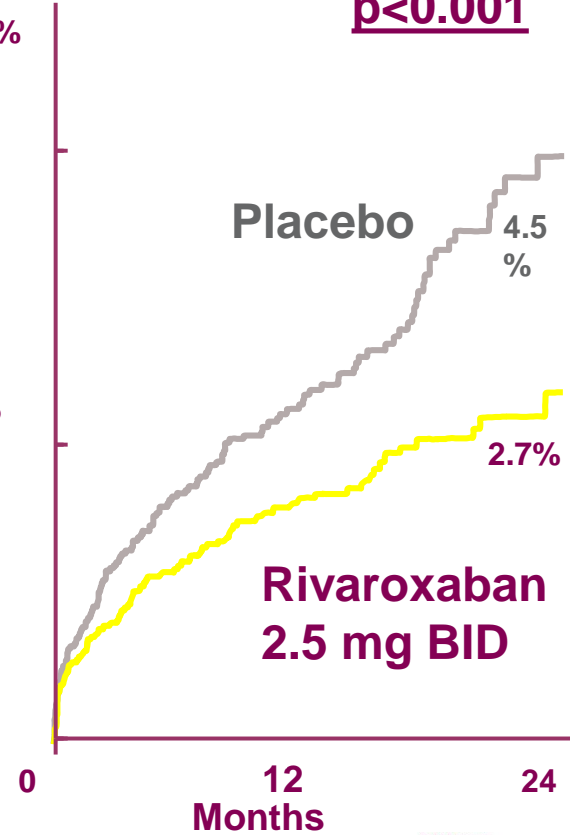
Cardiovascular Death

HR 0.62
p<0.001



All Cause Death

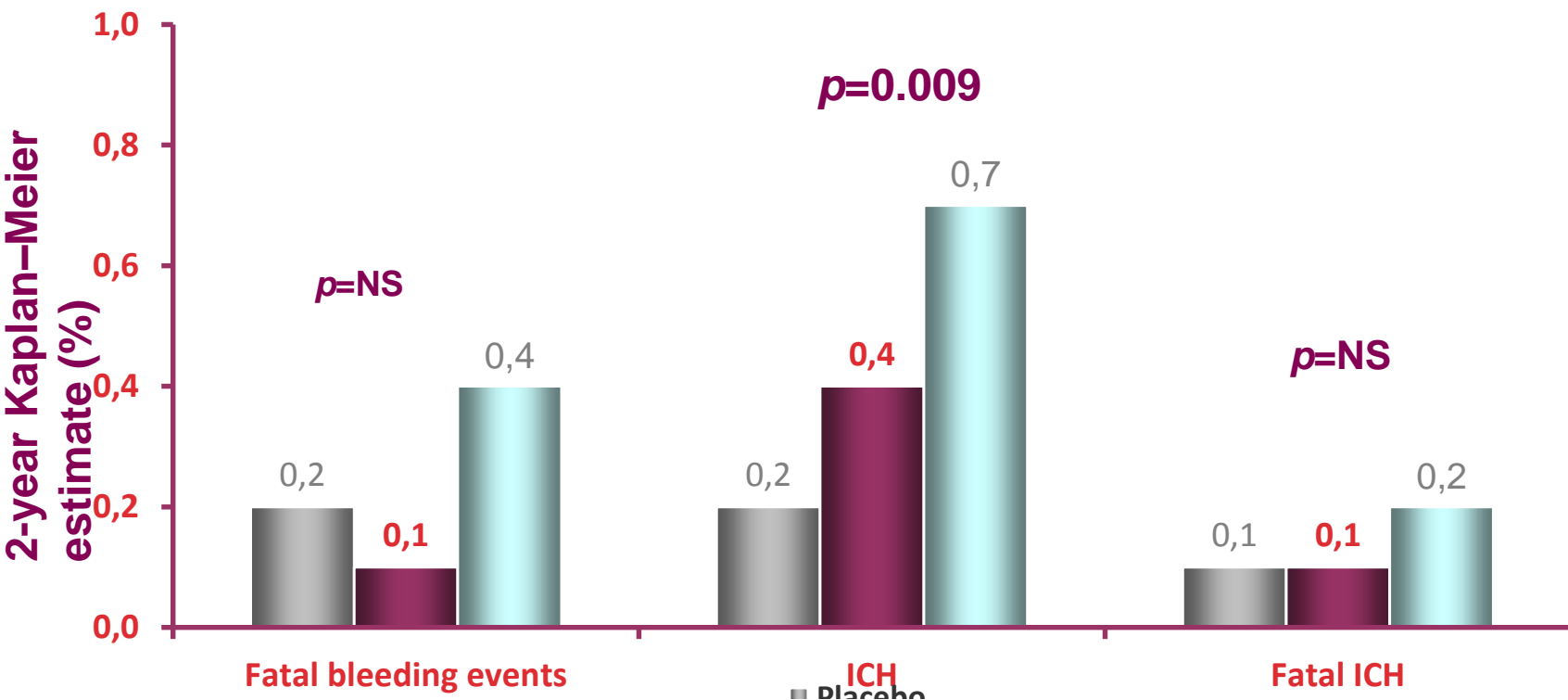
HR 0.64
p<0.001



ATLAS ACS2 TIMI 51: Safety endpoint

On top of ASA plus clopidogrel

Fatal bleeding events and ICH



With more potent P2Y₁₂ inhibitors:

How to Reduce Bleeding Risk in ACS ?

Aspirin + Clopidogrel, CURE Study

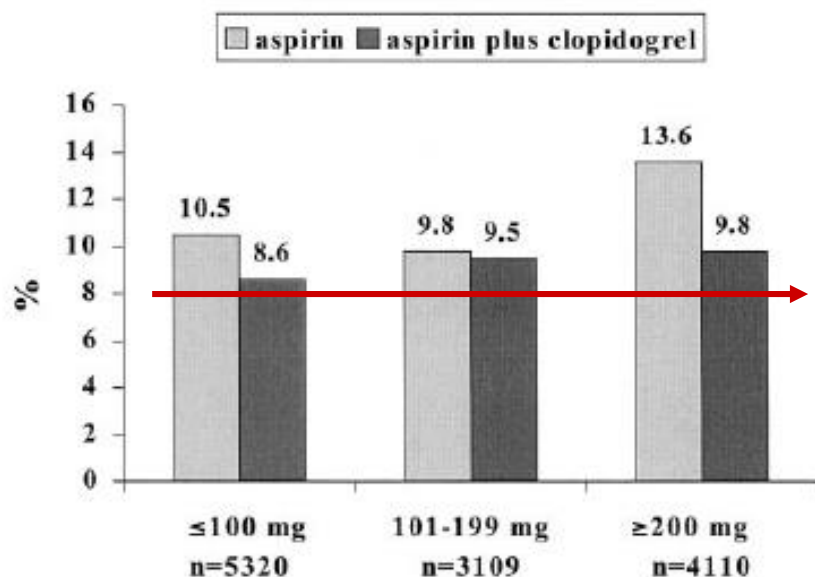


Figure 1. Aspirin dose and incidence of first coprimary outcome (CV death, nonfatal MI, and stroke).

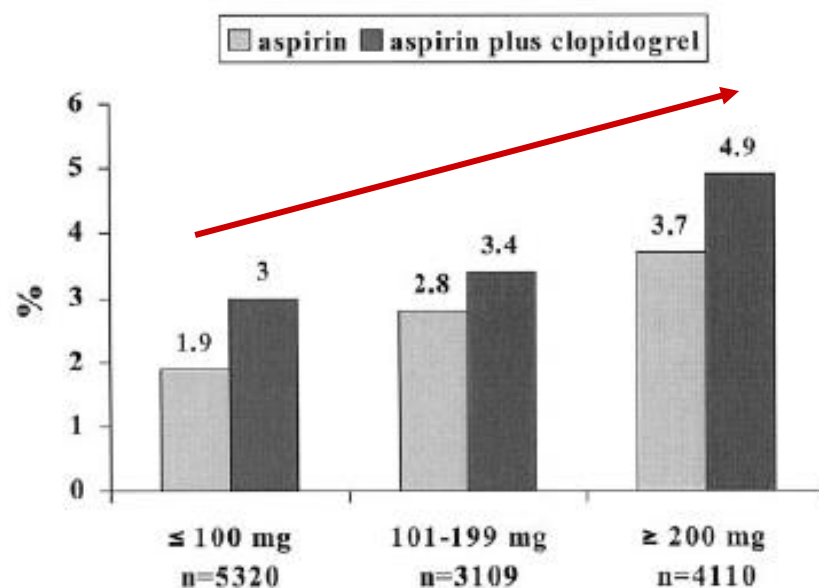
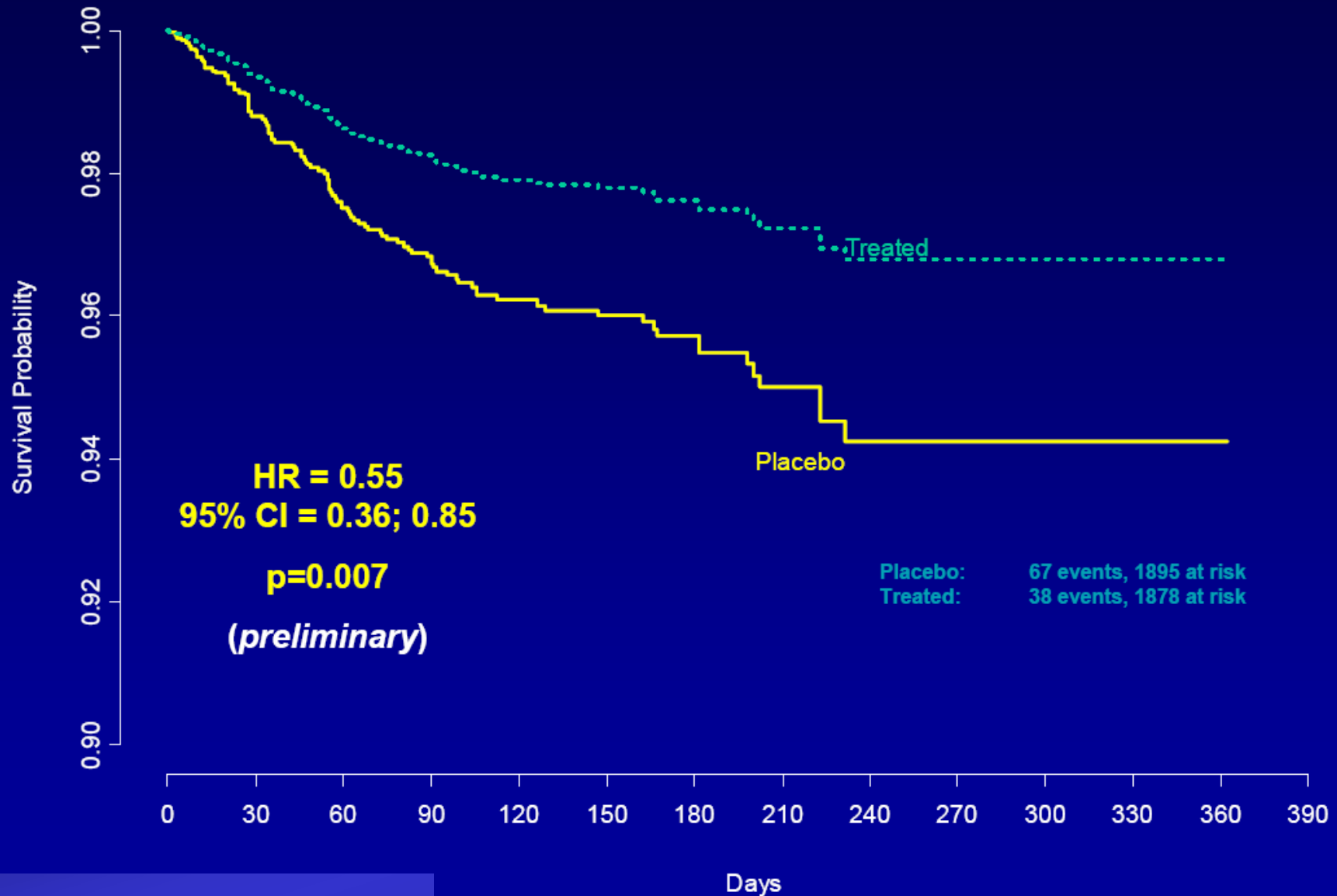


Figure 3. Aspirin dose and the incidence of major bleeding.

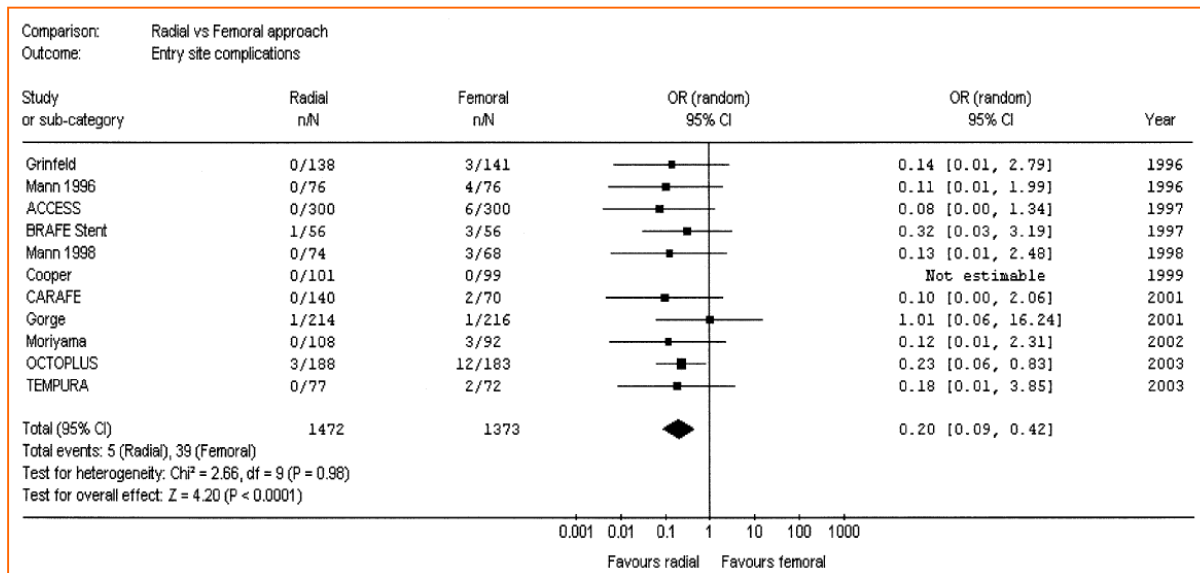
No ischemic benefit and increased bleeding risk

Use of PPI

Survival Curves for PPI Treated vs Placebo Composite GI Events

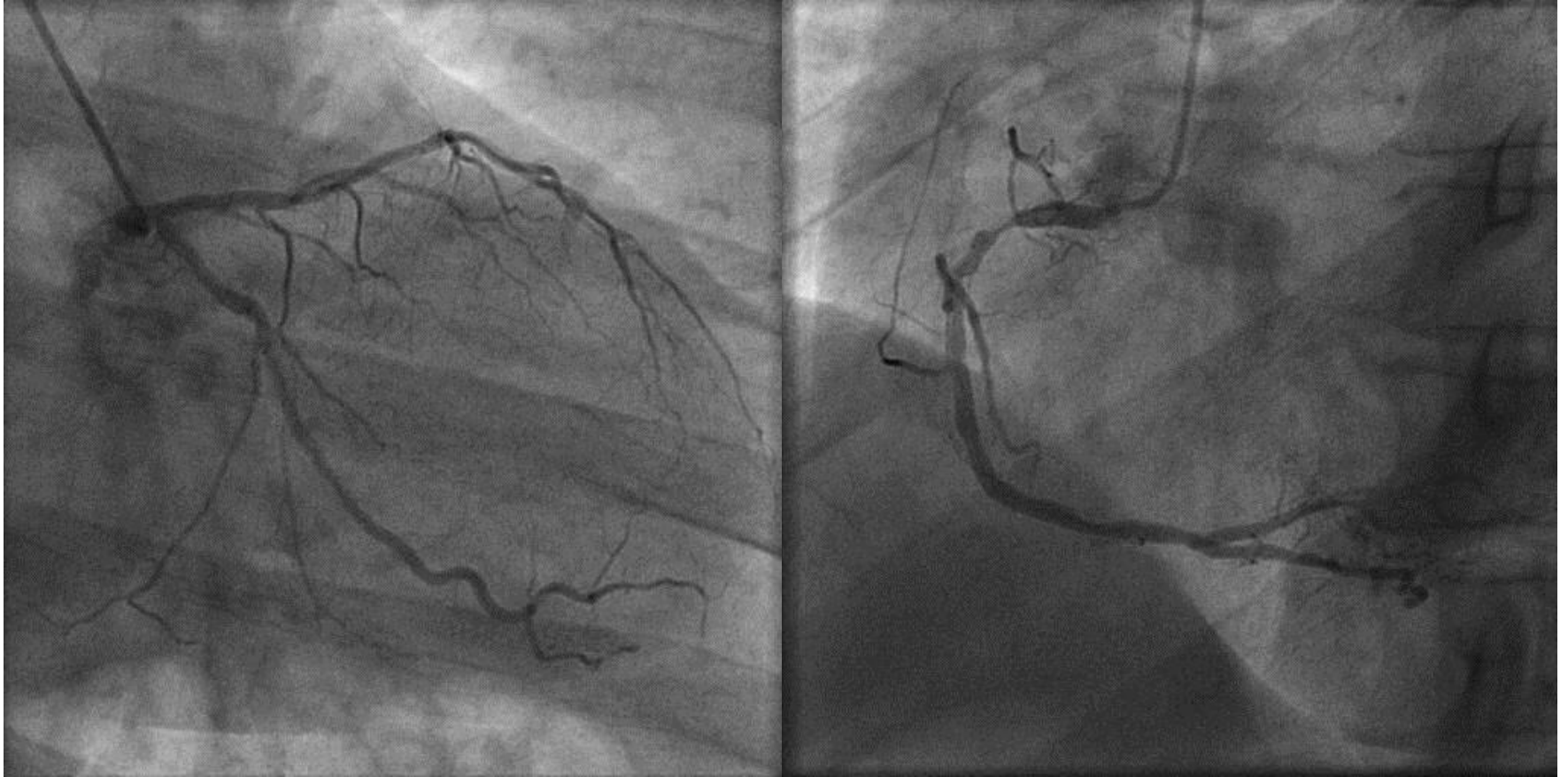


Radial Access



80 % Access site bleeding complication

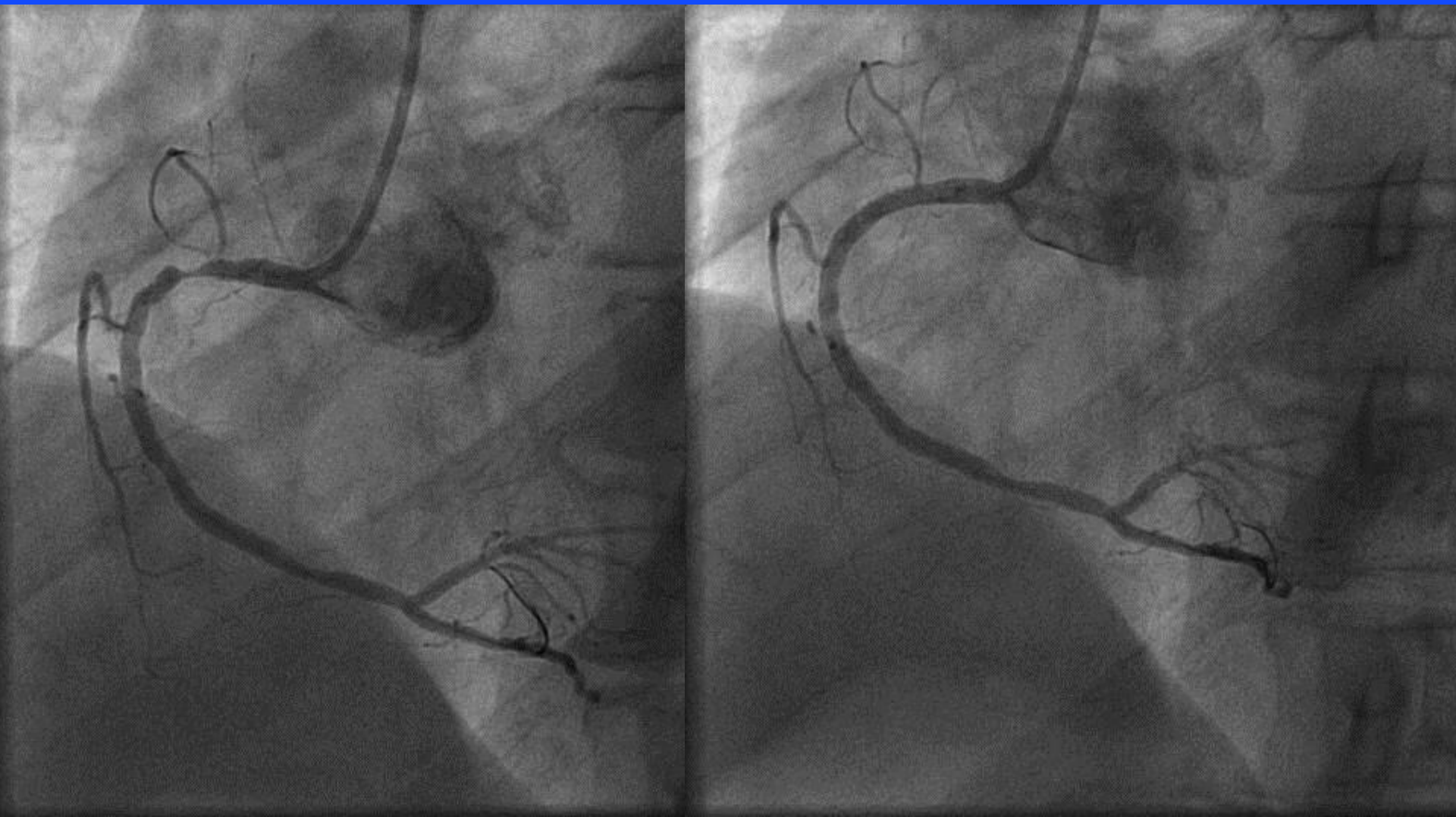
Treatment our patient: CAG next day



Right Radial Access, 6 French

Ticagrelor 180, 90/day, Fonda and UFH 70 IU/kg before cath

PCI



PCI with Direct Stenting. Low dose ASA/tica/PPI post PCI