

Erasmus MC
University Medical Center Rotterdam



***DOUBLE or TRIPLE
ANTI-TROMBOTIC THERAPY
in ACS***

Maarten L Simoons
Thoraxcenter - Erasmus MC
Rotterdam - The Netherlands

RECENT DEVELOPMENTS

Better anti-platelet agents:

Prasugrel and *Ticagrelor* to replace Clopidogrel in patients treated with aspirin

New anticoagulants:

Voraxapar: thrombin receptor antagonist

Apixaban, Rivaroxaban: factor Xa inhibitors administered on top of Aspirin and Clopidogrel

RECENT DEVELOPMENTS

Better anti-platelet agents:

Prasugrel and *Ticagrelor* to replace Clopidogrel in patients treated with aspirin.

New anticoagulants:

Voraxapar: thrombin receptor antagonist
Apixaban, Rivaroxaban: factor Xa inhibitors administered on top of Aspirin and Clopidogrel

Dose selection - Double- or triple therapy?

DOSE SELECTION - PHASE 2

To evaluate **the effect on bleeding (safety)** vs. placebo of different doses of Voraxapar / Apixaban / Rivaroxaban in patients with recent ACS on Aspirin (+Clopidogrel)

Double / Triple therapy

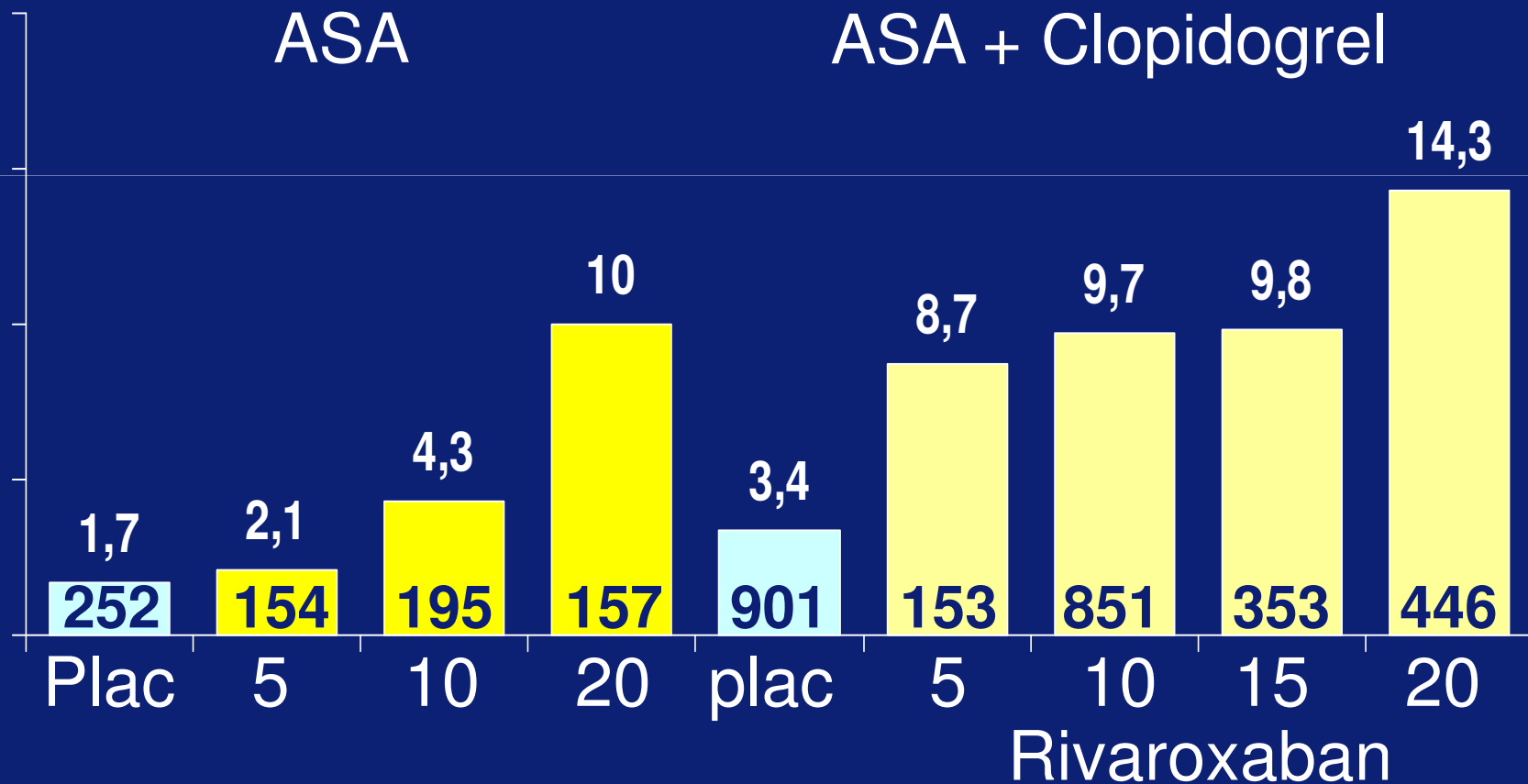
To assess (preliminary) **efficacy**

To determine the **optimal dose** for phase 3

Treatment up to 6 months after ACS event

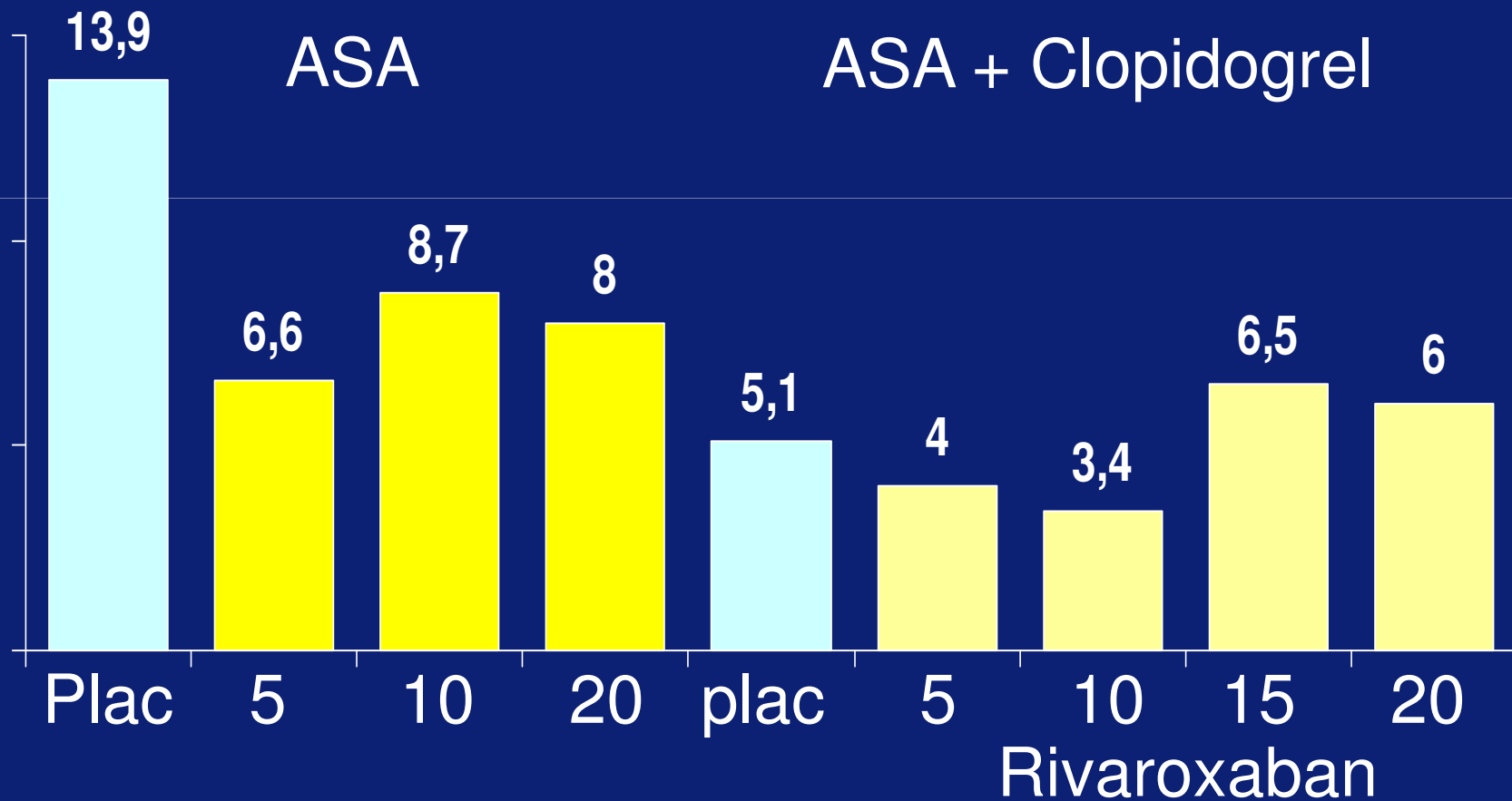
ATLAS-ACS BLEEDING RATES

Clinical significant bleeding %
Requiring medical attention, Lancet 2009



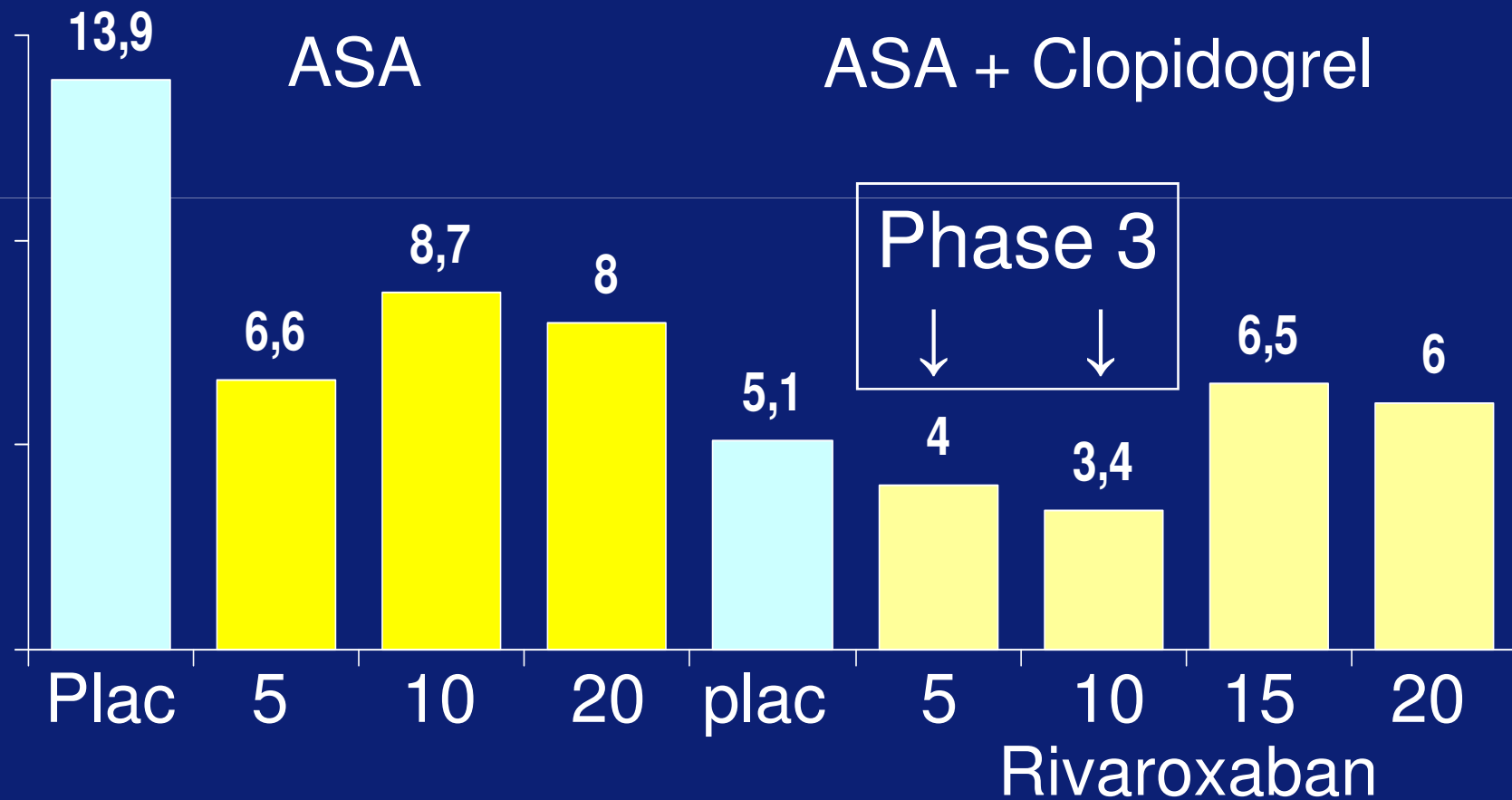
ATLAS-ACS ISCHEMIC OUTCOME

Death, MI, stroke, SRI %
Lancet 2009



ATLAS-ACS ISCHEMIC OUTCOME

Death, MI, stroke, SRI %
Lancet 2009



TRACER - ATLAS-ACS - APPRAISE-2

TRACER: Voraxapar vs placebo

Protease-activated-receptor antagonist
inhibits thrombin induced platelet aggregation
12,944 patients, 1 day after ACS

ATLAS-ACS: Rivaroxaban 2 doses vs placebo

Factor Xa inhibitor
15,526 patients, 5 days (3 – 6) after ACS

APPRAISE-2: Apixaban vs placebo

Factor Xa inhibitor
7392 *high risk* patients, 6 days (4 – 7) after ACS

TRACER ATLAS-ACS APPRAISE-2

	Voraxapar	Rivarox.	Apixaban
Patients	12,944	15,526	7392
Age (yr)	64	62	67
Female (%)	28	25	32
Previous MI (%)	29	27	25
Diabetes (%)	31	32	48
STEMI (%)	-	50	40
ASA (%)	99	99	97
Thienopyr. (%)	92	93	81
CABG/PCI (%)	68	60	45

TRACER ATLAS-ACS APPRAISE-2

	Voraxapar	Rivarox.	Apixaban
Patients	12,944	15,526	7392
Death	3.6	4.1	6.6
CV death	3.2	3.8	5.0
MI	7.9	6.0	9.2
Stroke	1.0	0.9	1.6
IC bleeding	0.1	0.2	0.2

Events / 100 pts / yr, placebo group

TRACER - ATLAS-ACS - APPRAISE-2

Different final results

APPRAISE-2 / TRACER stopped upon recommendation DSMB because of bleeding excess, with sufficient endpoints (TRACER) and without indication of benefit (APPRAISE-2)

ATLAS-ACS continued,
Significant reduction of CV death, MI, stroke at 13 m (mean), with increasing separation of event curves after the first year

TRACER

VORAXAPAR after ACS

12,944 NonSTEMI, 1 day after admission
Median follow-up 502 d 2 yr event rates

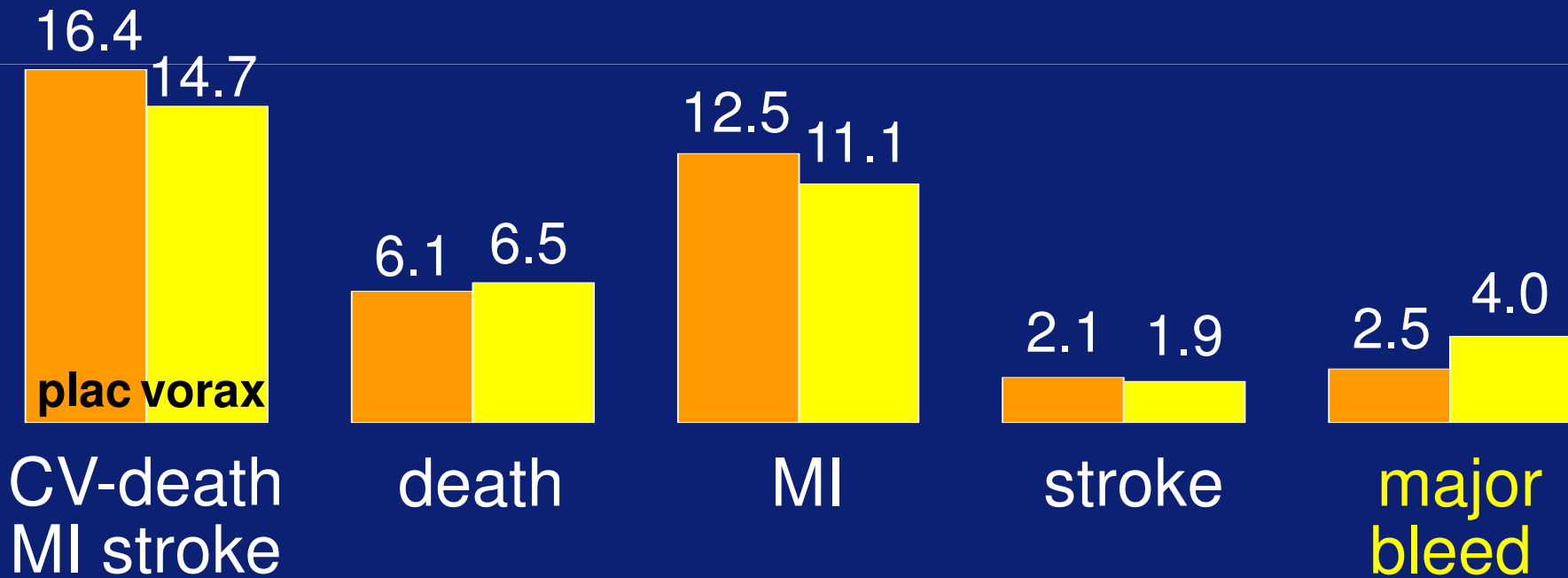
p=0.07 (ns)

ns

0.02

ns

<0.001

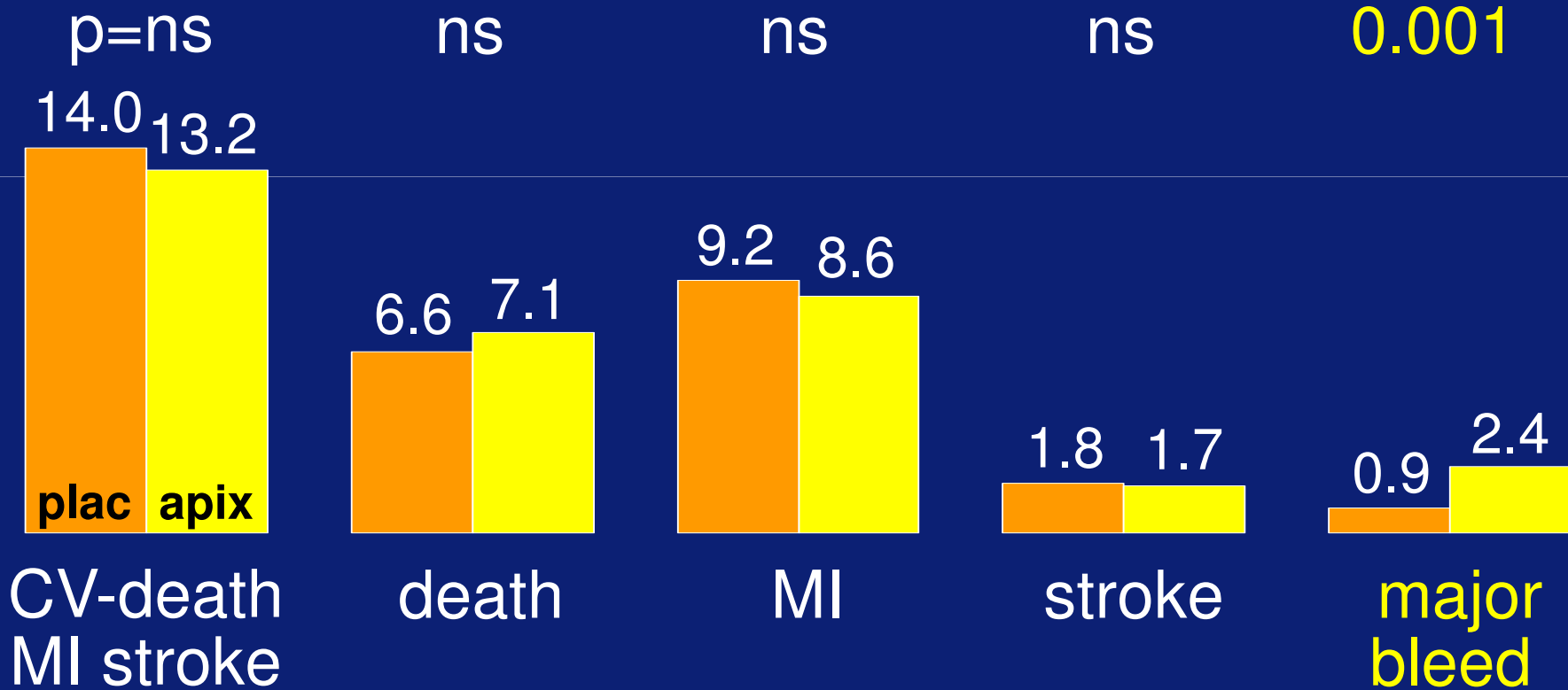


TRACER Tricoci et al. NEJMed 2011

APPRAISE-2

APIXABAN after ACS

7392 STEMI / NonSTEMI, 6 d after admission
median follow-up 8m events / 100 pts / yr



APPRAISE-2 Alexander et al. NEJMed 2011

ATLAS-ACS RIVAROXABAN after ACS

15,526 STEMI / NonSTEMI, 5 d after admission
median follow-up 13 m 2 yr event rates

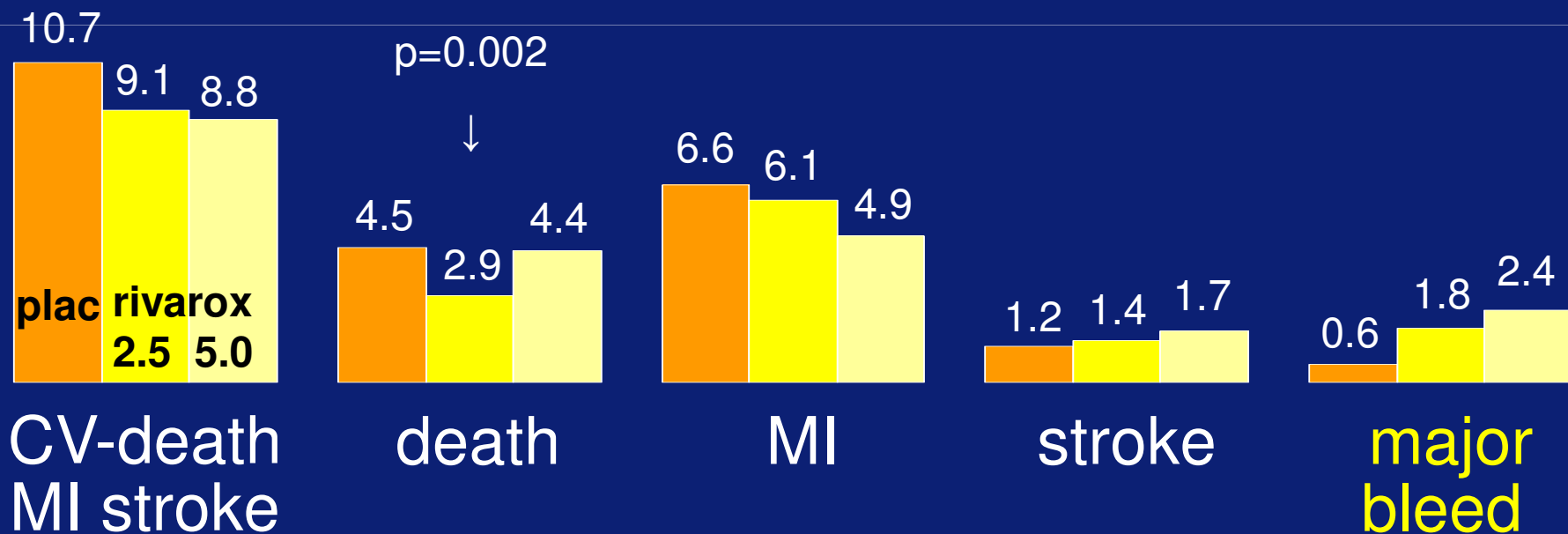
p=0.002

ns

0.01

ns

<0.001



ATLAS-ACS Mega et al. NEJMed 2011

TRACER - ATLAS-ACS - APPRAISE-2

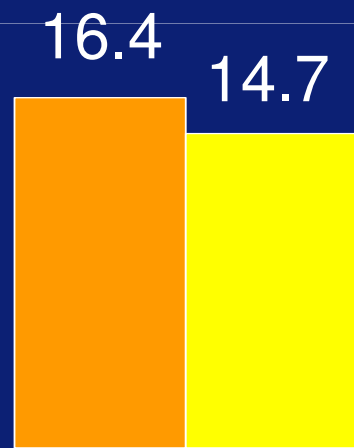
CV-death, MI, stroke (2 year follow-up)

P = ns

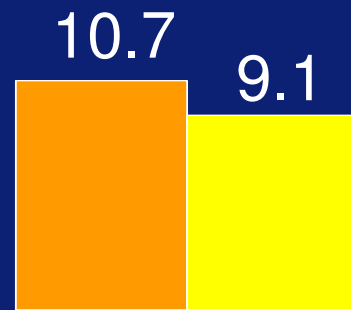
0.007

0.01

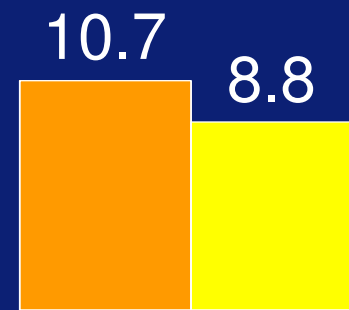
ns



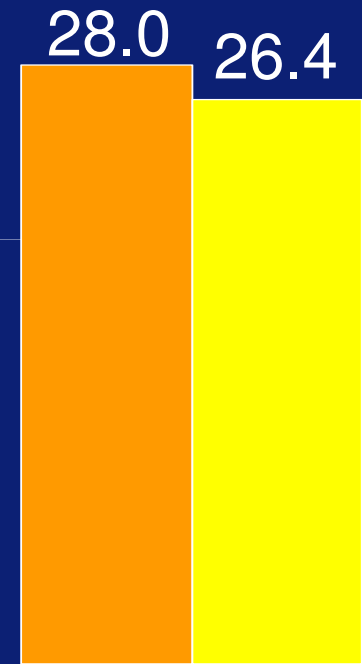
Voraxapar
2.5



Rivarox
2 x 2.5



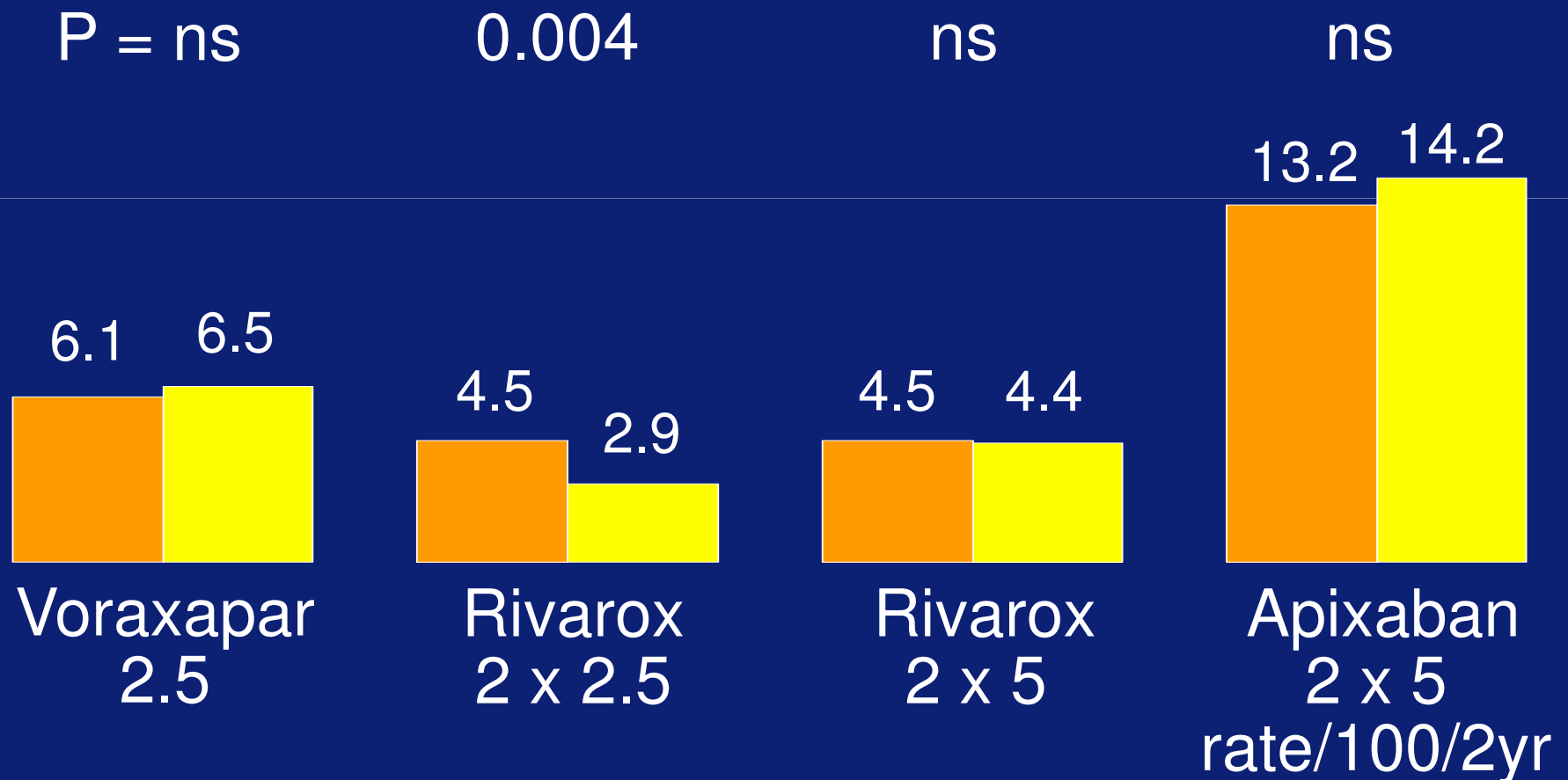
Rivarox
2 x 5



Apixaban
2 x 5
rate/100/2yr

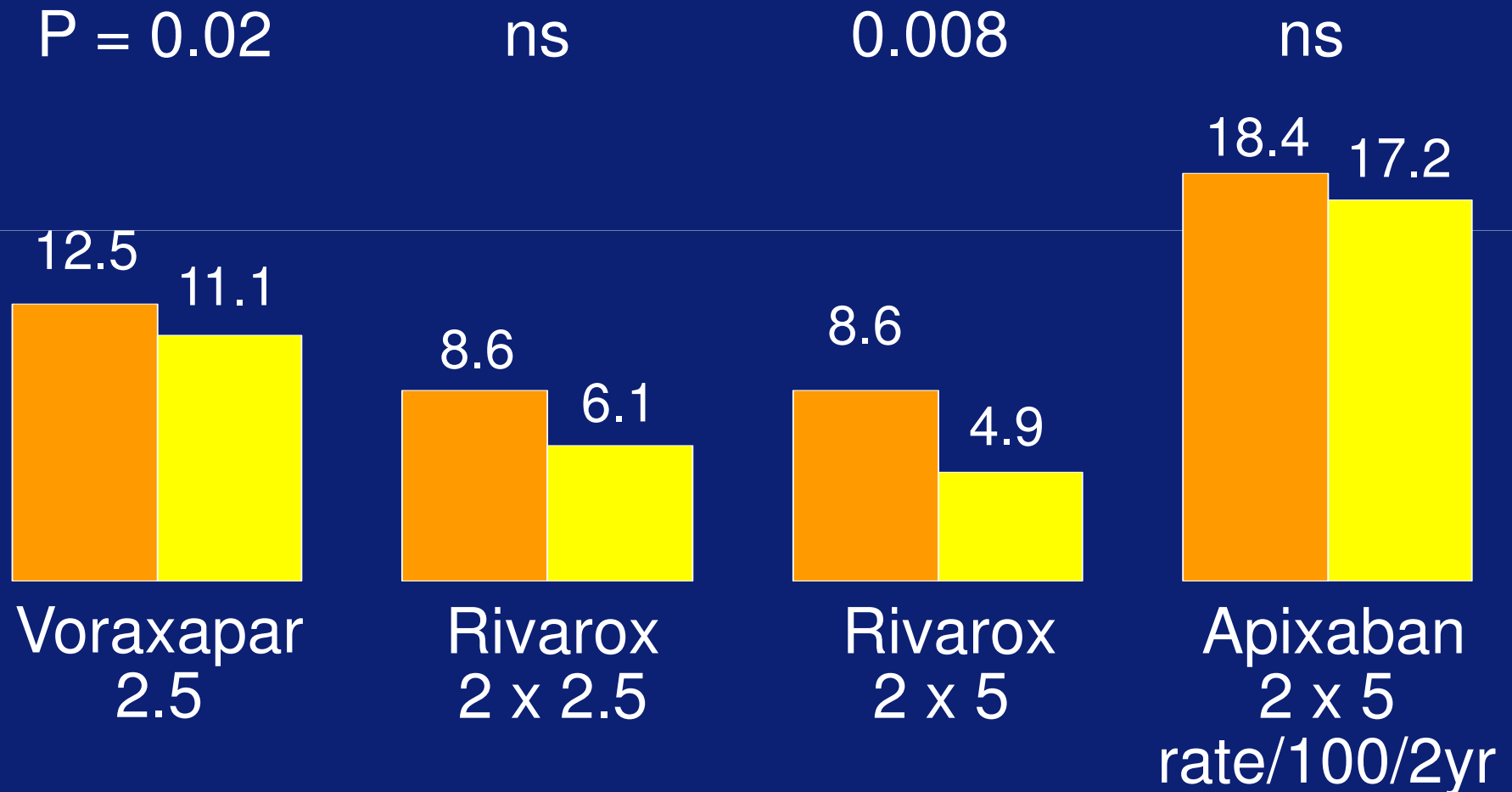
TRACER - ATLAS-ACS - APPRAISE-2

Death (2 year follow-up)



TRACER - ATLAS-ACS - APPRAISE-2

MI (2 year follow-up)



TRACER - ATLAS-ACS - APPRAISE-2

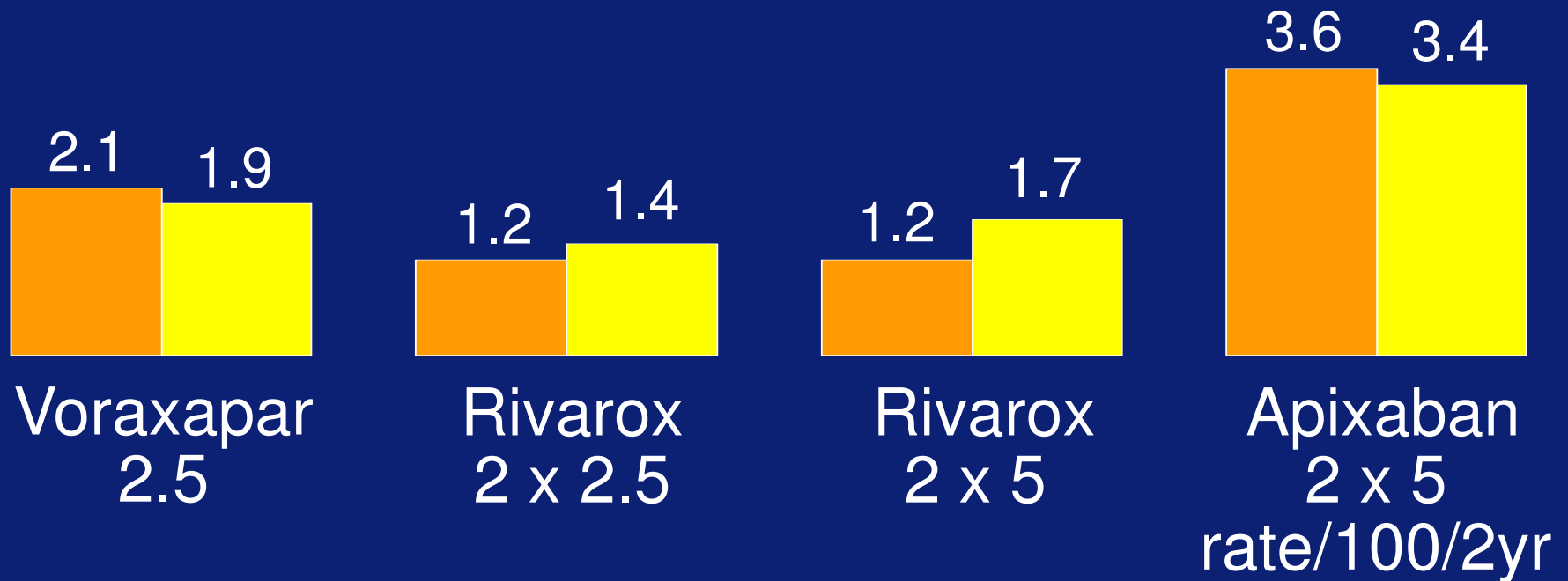
Stroke (2 year follow-up)

P = ns

ns

ns

ns



TRACER - ATLAS-ACS - APPRAISE-2

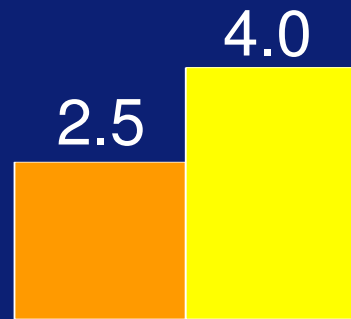
TIMI major bleed, non CABG (2 year follow-up)

P < 0.001

< 0.001

< 0.001

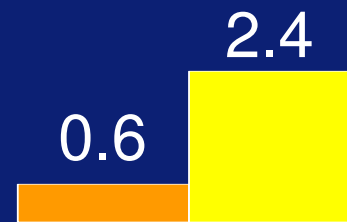
0.001



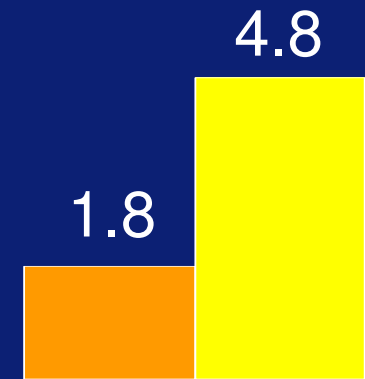
Voraxapar
2.5



Rivarox
2 x 2.5



Rivarox
2 x 5



Apixaban
2 x 5
rate/100/2yr

BLEEDING DEFINITIONS

	GUSTO severe	TIMI major	TIMI minor	ISHT major
Fatal	+	+		+
Intra cranial	+	+		+
Critical organ				+
Non-overt (Hb↓)			> 4	
Overt (Hb↓ mg%)		> 5	> 3	> 2
With intervention	+*			
Transfusion				> 2

+* hemodynamic compromise

TRACER - ATLAS-ACS - APPRAISE-2

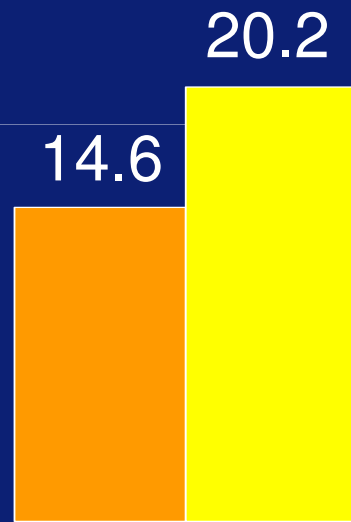
Clinically significant bleed (2 year follow-up)

P < 0.001

< 0.001

< 0.001

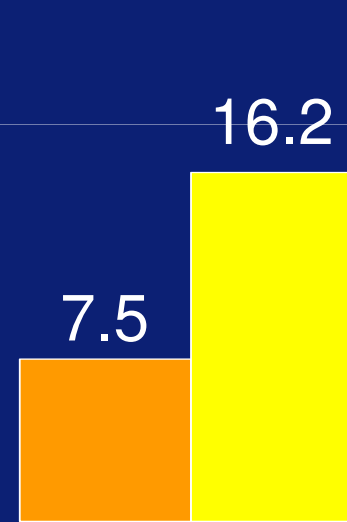
0.001



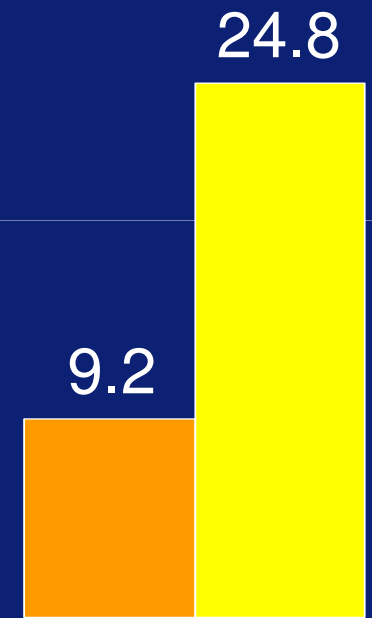
Voraxapar
2.5



Rivarox
2 x 2.5



Rivarox
2 x 5



Apixaban
2 x 5
rate/100/2yr

TRACER - ATLAS-ACS - APPRAISE-2

Overall conclusion

Triple therapy

(ASA + clopidogrel + TR-Antag / Xa inhibition)

in patients with / after ACS (1 d / 1 wk – 2 yr)

- reduces myocardial infarction
- at the cost of bleeding
- no consistent effect on stroke or mortality

TRACER - ATLAS-ACS - APPRAISE-2

Similar (un) safety

Increased bleeding rates:

Intra Cranial Bleeds:

VORAXAPAR	HR = 3.4	
APIXABAN	HR = 4.1 (5mg)	
RIVAROXABAN	HR = 3.7 (5mg)	2.8 (2.5mg)

TIMI-major bleeds, non-CABG:

VORAXAPAR	HR = 1.9	
APIXABAN	HR = 2.6 (5mg)	
RIVAROXABAN	HR = 4.5 (5mg)	3.5 (2.5mg)

TRACER - ATLAS-ACS - APPRAISE-2

Different final results

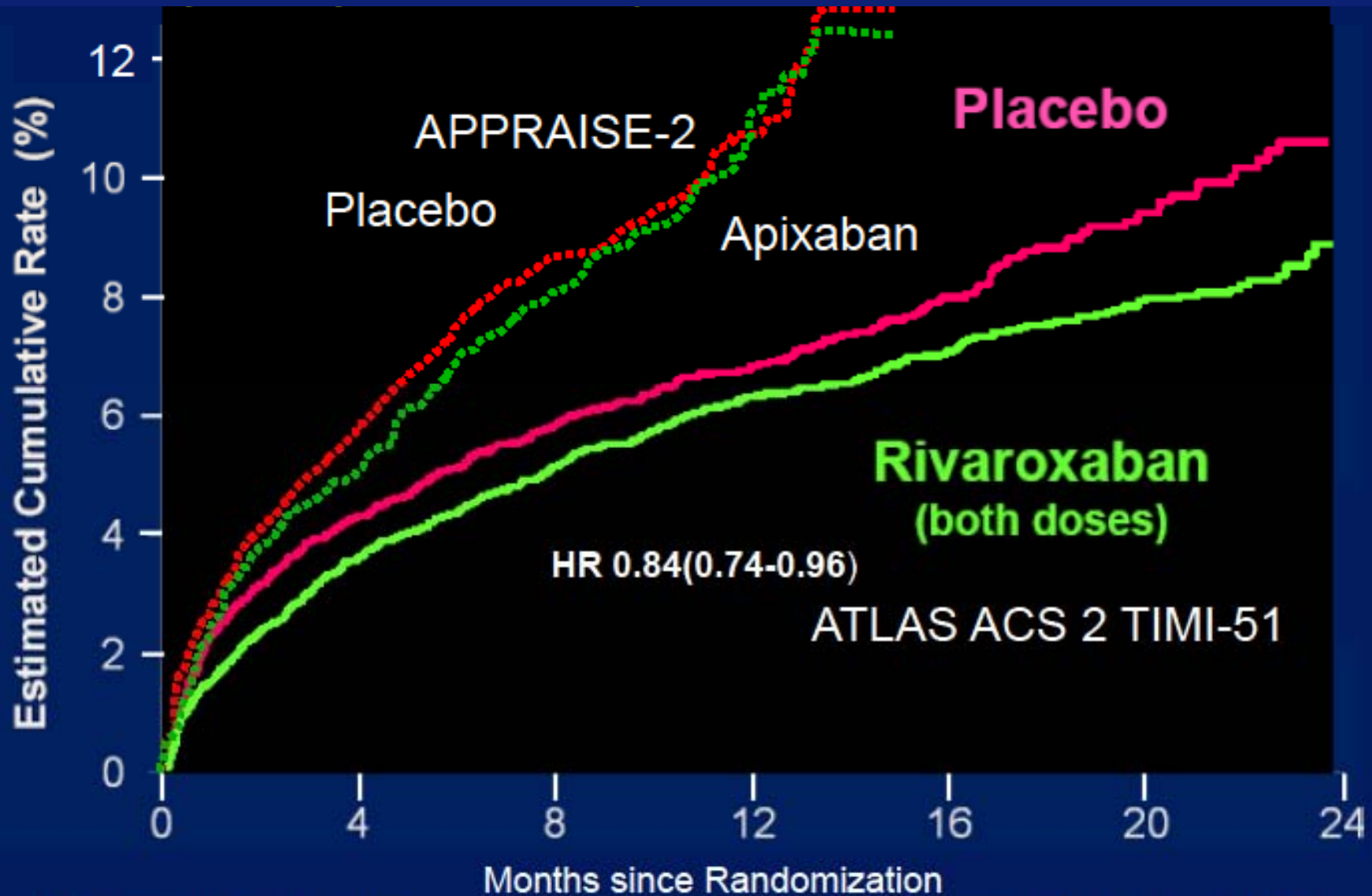
APPRAISE-2 / TRACER stopped upon recommendation DSMB because of bleeding excess, with sufficient endpoints (TRACER) and without indication of benefit (APPRAISE-2)

ATLAS-ACS continued,
Significant reduction of CV death, MI, stroke at 13 m (mean), with increasing separation of event curves after the first year:

HR 0.85, $p=0.03$ (5mg) HR 0.84, $p=0.02$ (2.5mg)

Reduction of death with 2.5mg, *explanation ??*

APIXABAN - RIVAROXABAN death, MI, ischemic stroke



^a Gibson 2011 AHA LBCT

Alexander 2011 *N Engl J Med*

ATLAS-ACS - APPRAISE-2

Overall conclusion:

Triple therapy (ASA + clopidogrel + Xa inhibition) reduces thrombotic events, in *patients at low risk* after ACS (1 wk – 2 yr), as in ATLAS-ACS, **but not in higher risk patients as in APPRAISE-2.**

Age ≥ 65 years, \uparrow markers + ST deviation, diabetes mellitus, Prior MI, ischemic stroke, TIA, asymptomatic carotid stenosis, PAD, prior symptomatic CHF or LVEF $<40\%$, non-revascularised multi-vessel CAD, mild / moderate renal insuff. (CrCl <90 ml/min)

ATLAS-ACS RIVAROXABAN after ACS

10,227 STEMI / NonSTEMI, 5 d after admission
median follow-up 13 m 2.5mg 2 yr event rates

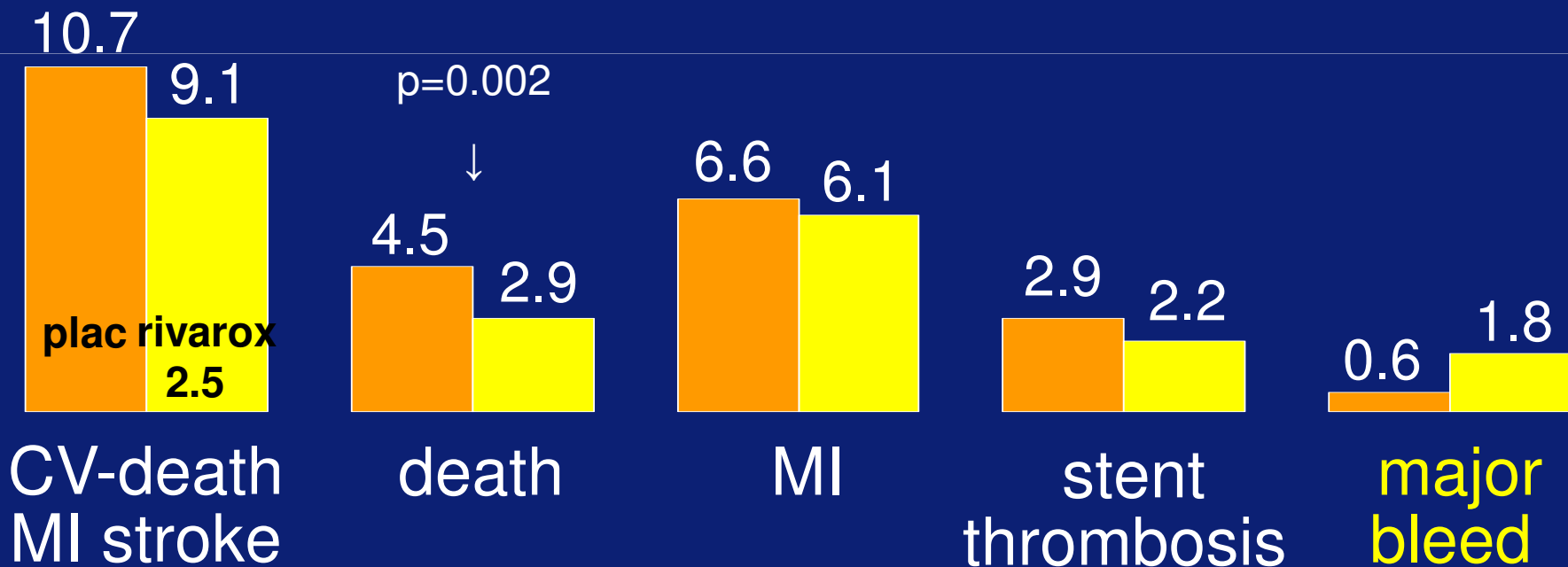
p=0.007

0.004

ns

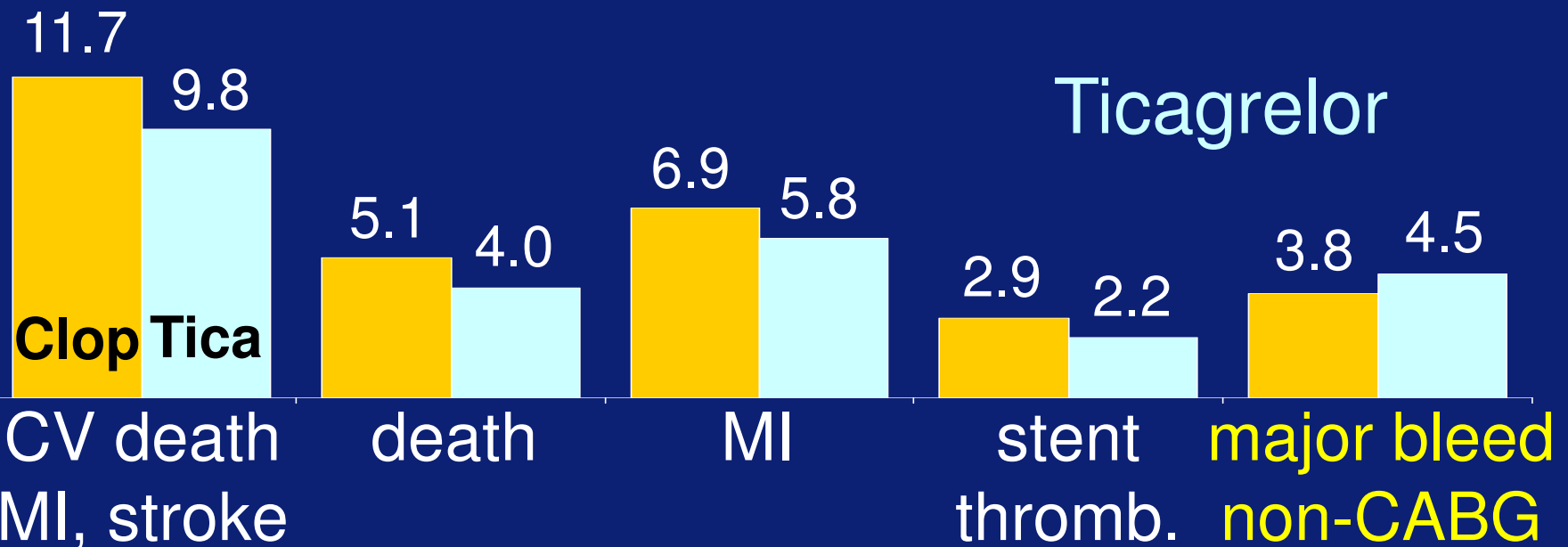
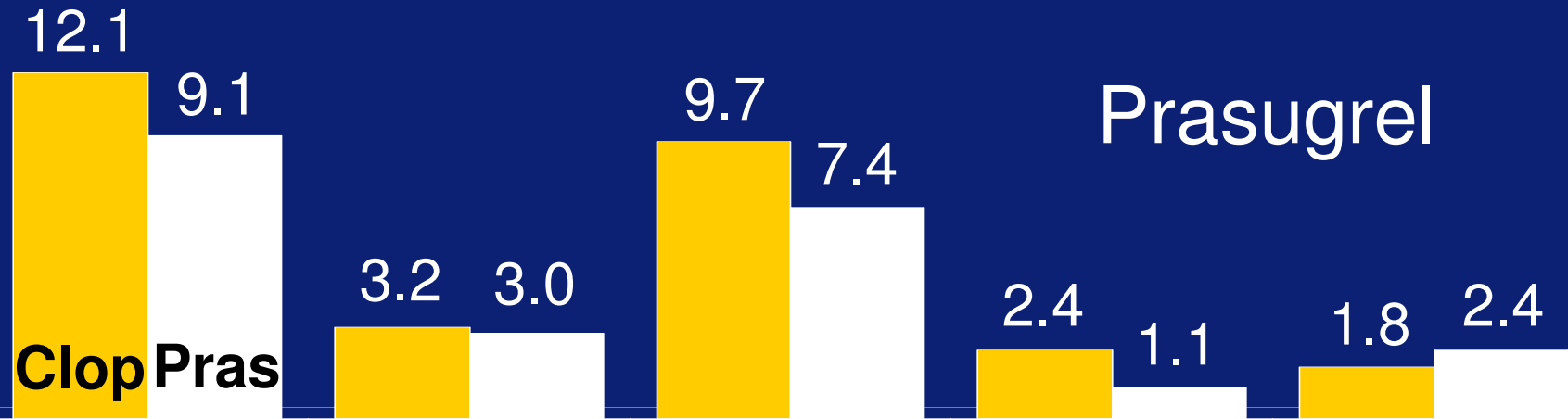
ns

<0.001



Mega et al. NEJMed 2011

PRASUGREL - TICAGRELOR



ATLAS-ACS - TRITON - PLATO

CV-death, MI, stroke

TIMI major bleed



ATLAS-ACS - TRITON - PLATO

Final conclusion:

Triple therapy (ASA + clopidogrel + Xa inhibition) reduces thrombotic events, at the cost of bleeding in patients after ACS.

Reduction of CV-death, MI, Stroke and increase of bleeding with triple therapy similar to ASA + prasugrel (TRITON) or + ticagrelor (PLATO).

ASA + prasugrel / ticagrelor, the best choice.

