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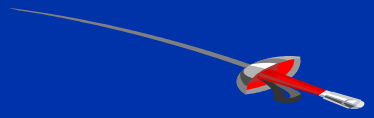
The Safety and Tolerability of Atopaxar (E5555) in the Treatment of Patients with Acute Coronary Syndromes: *The LANCELOT-ACS Trial*



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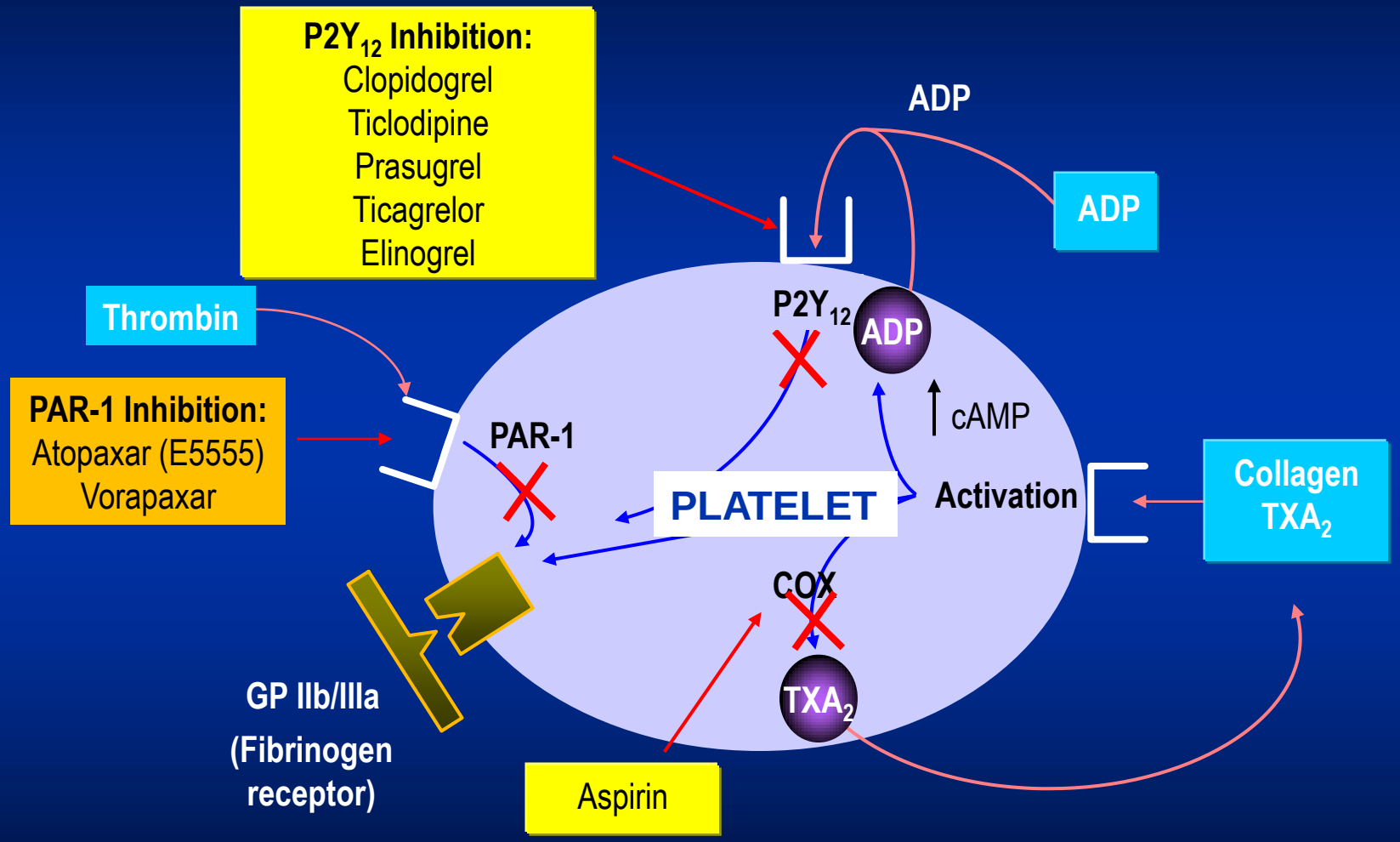
Oral Anti-Platelet Therapies



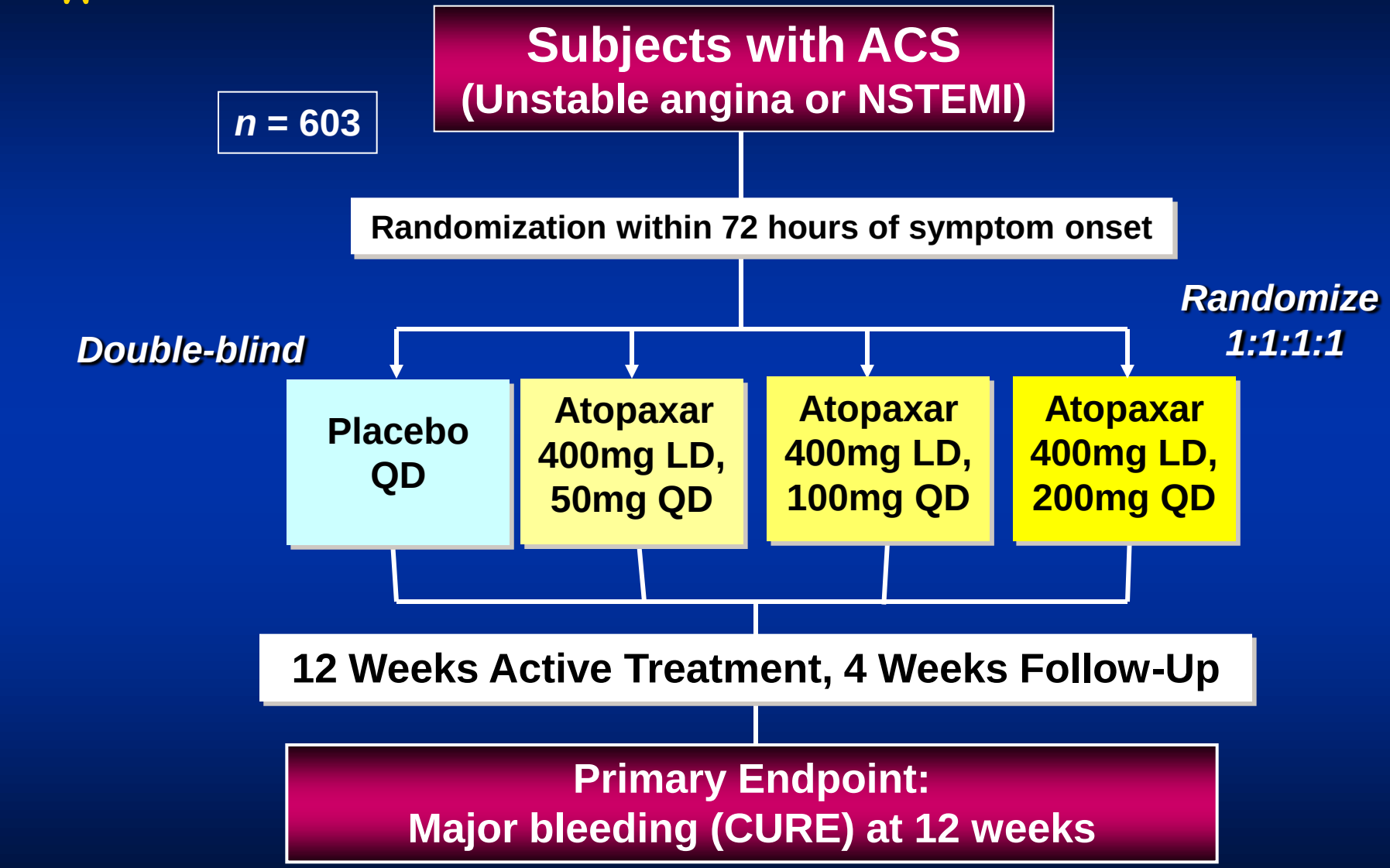
Adapted from Schafer. *Am J Med*. 1996;101:199-209.

Primary Objective

To investigate the safety and tolerability of atopaxar (E5555) in subjects admitted to the hospital with symptoms of an acute coronary syndrome (ACS)

Key Secondary Objectives

- To determine the effects of atopaxar on the incidence of major adverse cardiac events (MACE), including CV death, myocardial infarction (MI), stroke, or recurrent ischemia
- To determine the effect of atopaxar on the incidence of transient ischemia by continuous ECG (Holter)
- To determine the effect of atopaxar on platelet aggregation (at selected sites)



Inclusion Criteria

- Male or female; aged 18-80 years
- Presenting with features of unstable angina or non-ST-elevation MI
- At least one of the following:
  1. Troponin T or I or CK-MB ≥ upper limit of normal
  2. ECG changes compatible with ischemia (i.e. ST depression at least 1 mm in 2 contiguous leads or T wave inversion > 3 mm or any dynamic ST shift or transient ST elevation)
- Randomization and treatment ≤ 72 hours of the onset of symptoms

Major Exclusion Criteria

- Increased risk of bleeding, anemia (Hb <10 g/dL), thrombocytopenia (<100x10^3/µL), history of pathological intracranial findings
- Planned elective major surgery
- Planned use of oral anticoagulants (e.g., warfarin), fibrinolytics, or regular NSAIDs
- Known hepatic disease or creatinine clearance <30 ml/min

Trial Organization

Principal Investigators	Marcus D. Flather, MBBS Deepak L. Bhatt, MD, MPH
TIMI Study Group Brigham and Women's Hospital Harvard Medical School	Eugene Braunwald, MD Michelle O'Donoghue, MD, MPH Stephen D. Wiviott, MD
Clinical Events Committee:	Cleveland Clinic
ECG Core Lab:	Shaun Goodman, MD, MSc
Platelet Function Study: Java Clinical Research	Desmond J. Fitzgerald, MD
Sponsor: Eisai, Inc.	Lee Golden, MD Rafal Ziecina, MD
Data Safety Monitoring Board:	Richard C. Becker, MD (Chair) Frederick Spencer, MD Kerry Lee, PhD Freek Verheugt, MD Jeffrey I. Weitz, MD Christopher P. Cannon, MD (1st meeting only)

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Top Enrolling Countries

(184 sites, 22 countries)

	Poland	22.7%		Bulgaria	4.1%
	India	15.6%		Italy	1.8%
	Russia	13.3%		UK	1.8%
	Israel	9.3%		France	1.7%
	Germany	7.1%		Argentina	1.5%
	Belgium	6.6%		USA	1.5%
	South Africa	4.8%		Australia	1.3%

Baseline Characteristics

	Placebo (N=142)	Atopaxar 50mg (N=156)	Atopaxar 100mg (N=157)	Atopaxar 200mg (N=148)	Atopaxar Active Total (N=461)
Age (Year), median	62.0	59.0	61.0	61.5	60.0
Male	67%	71%	72%	64%	69%
Current tobacco use	25%	31%	32%	33%	32%
Diabetes mellitus	21%	25%	21%	23%	23%
Dyslipidemia	50%	48%	48%	49%	48%
Peripheral artery disease	3.6%	2.6%	10%	6.8%	6.5%
Hypertension	71%	70%	68%	73%	70%
Prior MI	30%	19%	22%	30%	24%
Prior PCI	17%	16%	12%	19%	16%
Prior CABG	7.9%	7.1%	9.6%	6.8%	7.8%
Prior TIA or Stroke	1.4%	3.9%	5.1%	6.1%	5.0%
Congestive Heart Failure	16%	12%	10%	14%	12%

Concomitant Therapies

	Placebo (N=142)	Atopaxar			
		50 mg (N=156)	100 mg (N=157)	200 mg (N=148)	Active Total (N=461)
Aspirin	98%	96%	94%	95%	95%
Thienopyridine	84%	82%	78%	79%	80%
Statin	90%	90%	88%	81%	86%
Beta blocker	85%	88%	82%	85%	85%
Glycoprotein IIb/IIIa inhibitor	19%	14%	18%	16%	16%

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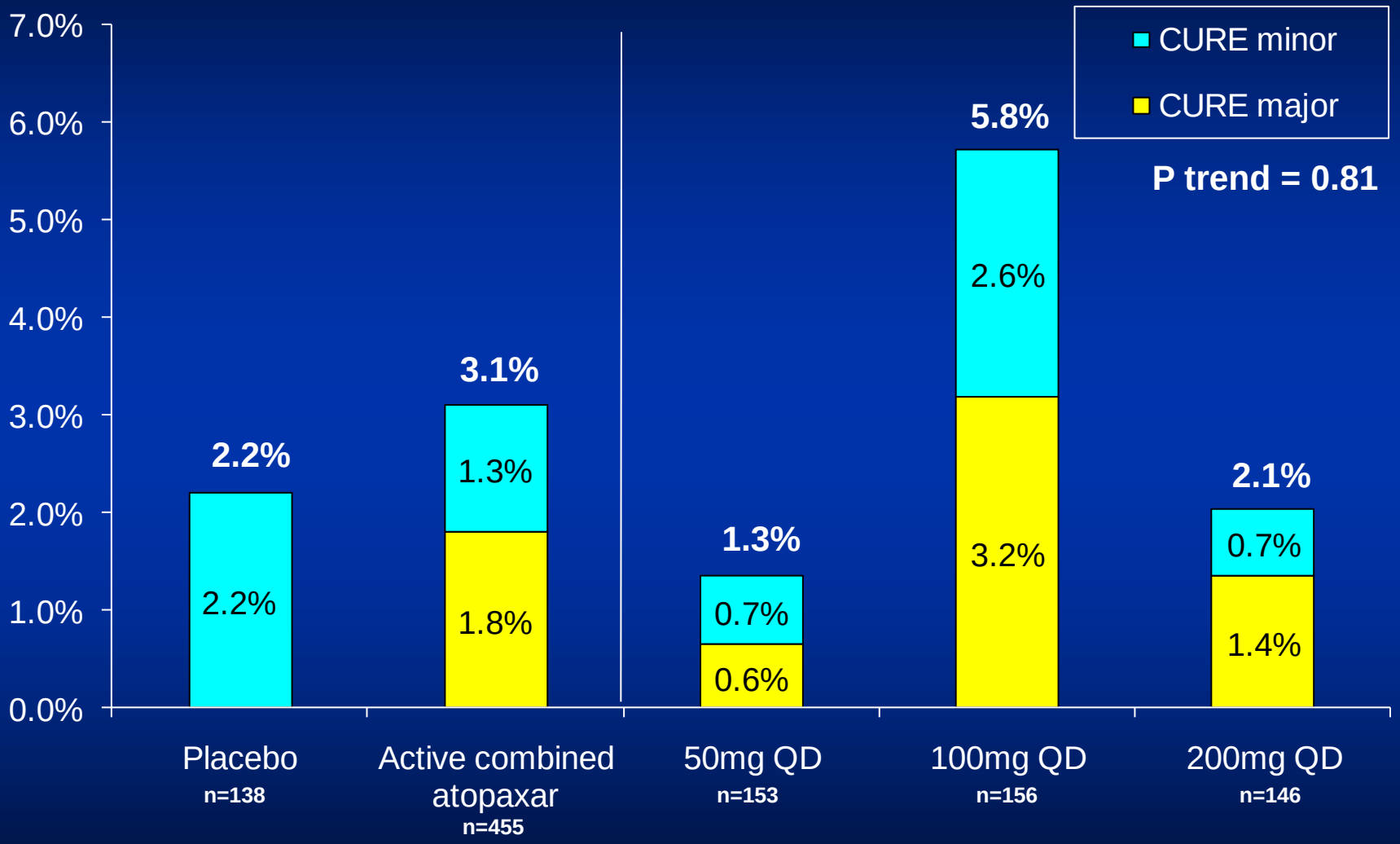
Incidence of any CURE Bleeding



Relative Risk (95% CI) vs. placebo

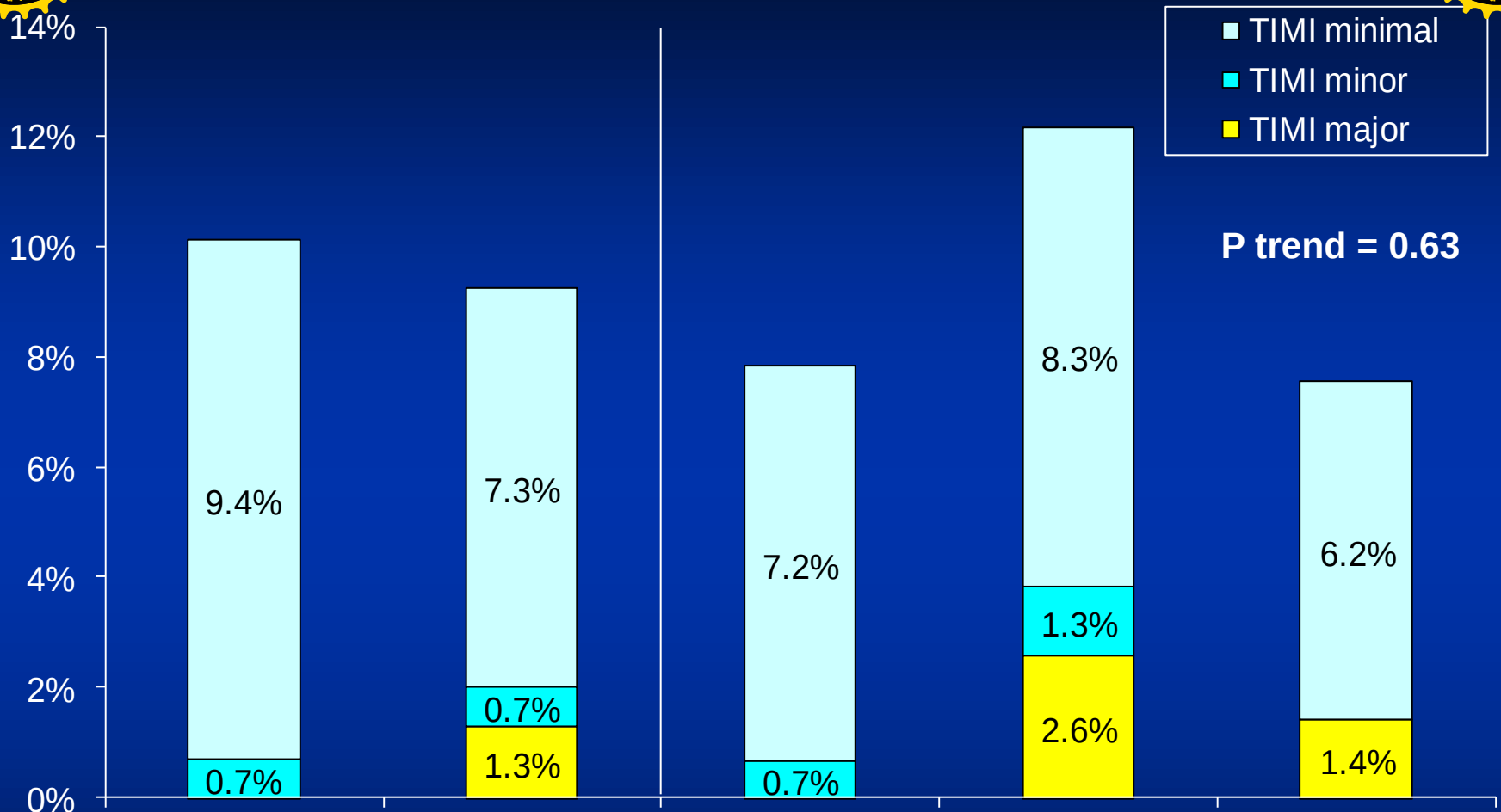
RR 1.42 (0.44-4.8)
P = 0.63

RR 0.60 (0.11-3.00)
P = 0.62

RR 2.65 (0.78-10.3)
P = 0.13

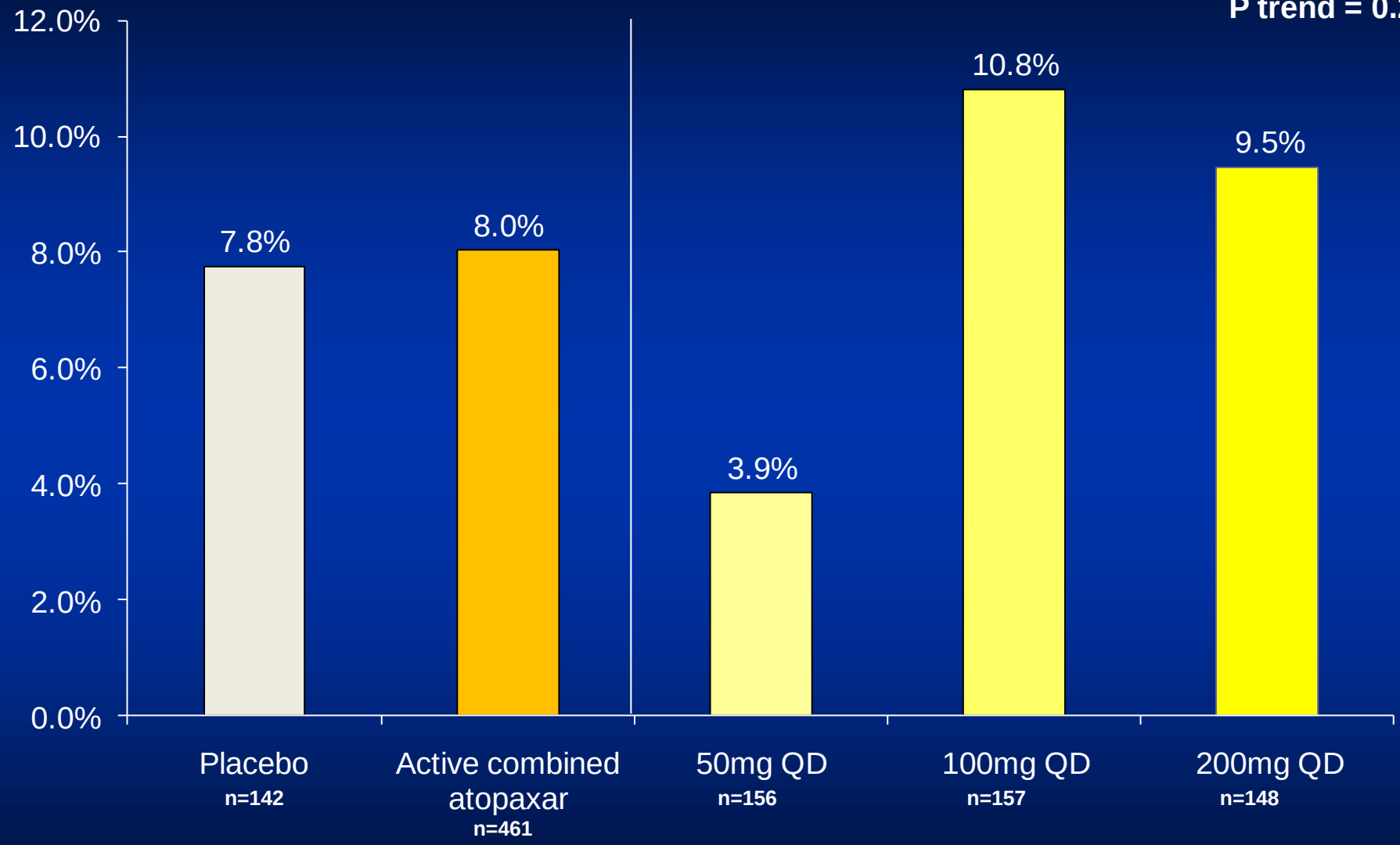
RR 0.95 (0.18-5.04)
P = 0.99

Incidence of any TIMI Bleeding



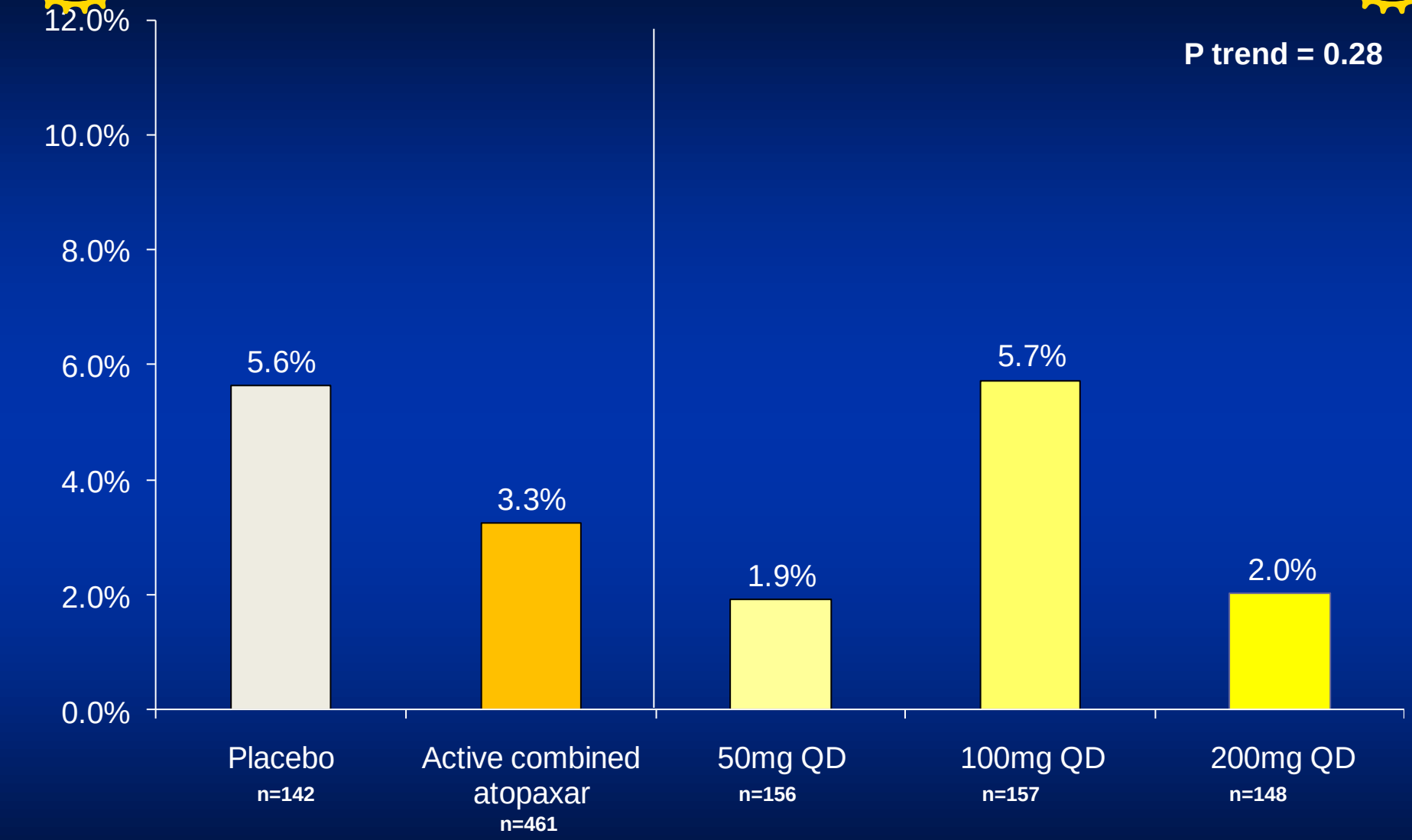
	Placebo	Active combined atopaxar	50mg QD	100mg QD	200mg QD
	n=138	n=455	n=153	n=156	n=146
RR (95% CI) vs. placebo		RR 0.91 (0.52-1.63)	RR 0.77 (0.38-1.60)	RR 1.20 (0.63-2.29)	RR 0.74 (0.35-1.56)
		P = 0.77	P = 0.53	P = 0.60	P = 0.46

Incidence of CV death, MI, Stroke, or Recurrent ischemia



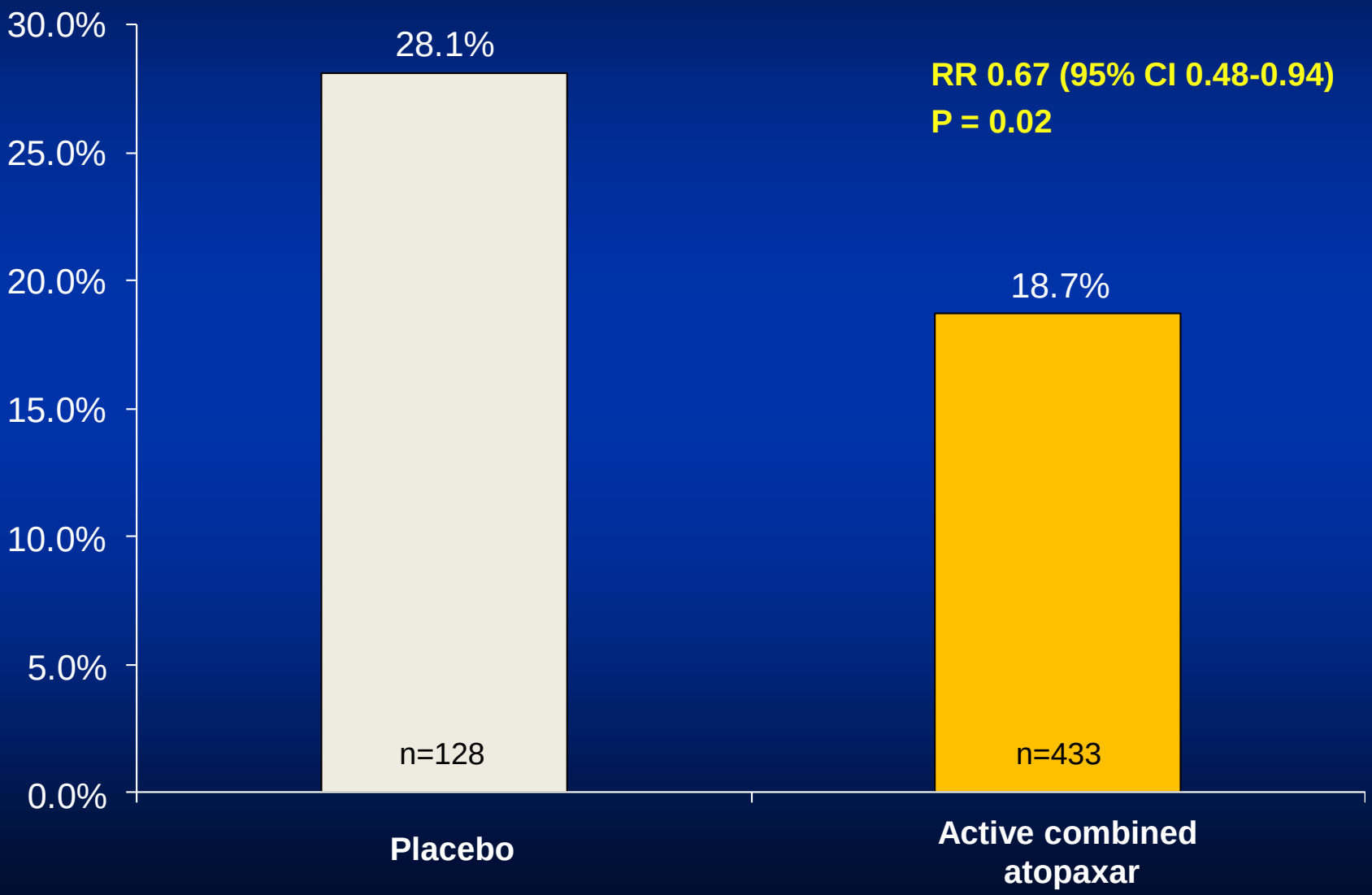
RR (95% CI) vs. placebo	RR 1.04 (0.55-1.97) P = 0.93	RR 0.50 (0.16-1.27) P = 0.18	RR 1.40 (0.68-2.86) P = 0.37	RR 1.22 (0.58-2.57 P = 0.63

Incidence of CV death, MI, or stroke



RR (95% CI) vs. placebo	RR 0.58 (0.25-1.41)	RR 0.34 (0.10-1.18)	RR 1.02 (0.41-2.50)	RR 0.36 (0.11-1.24)
	P = 0.20	P = 0.10	P = 0.99	P = 0.12

Incidence of Holter-Detected Ischemia at 48 Hours following 400mg Loading Dose

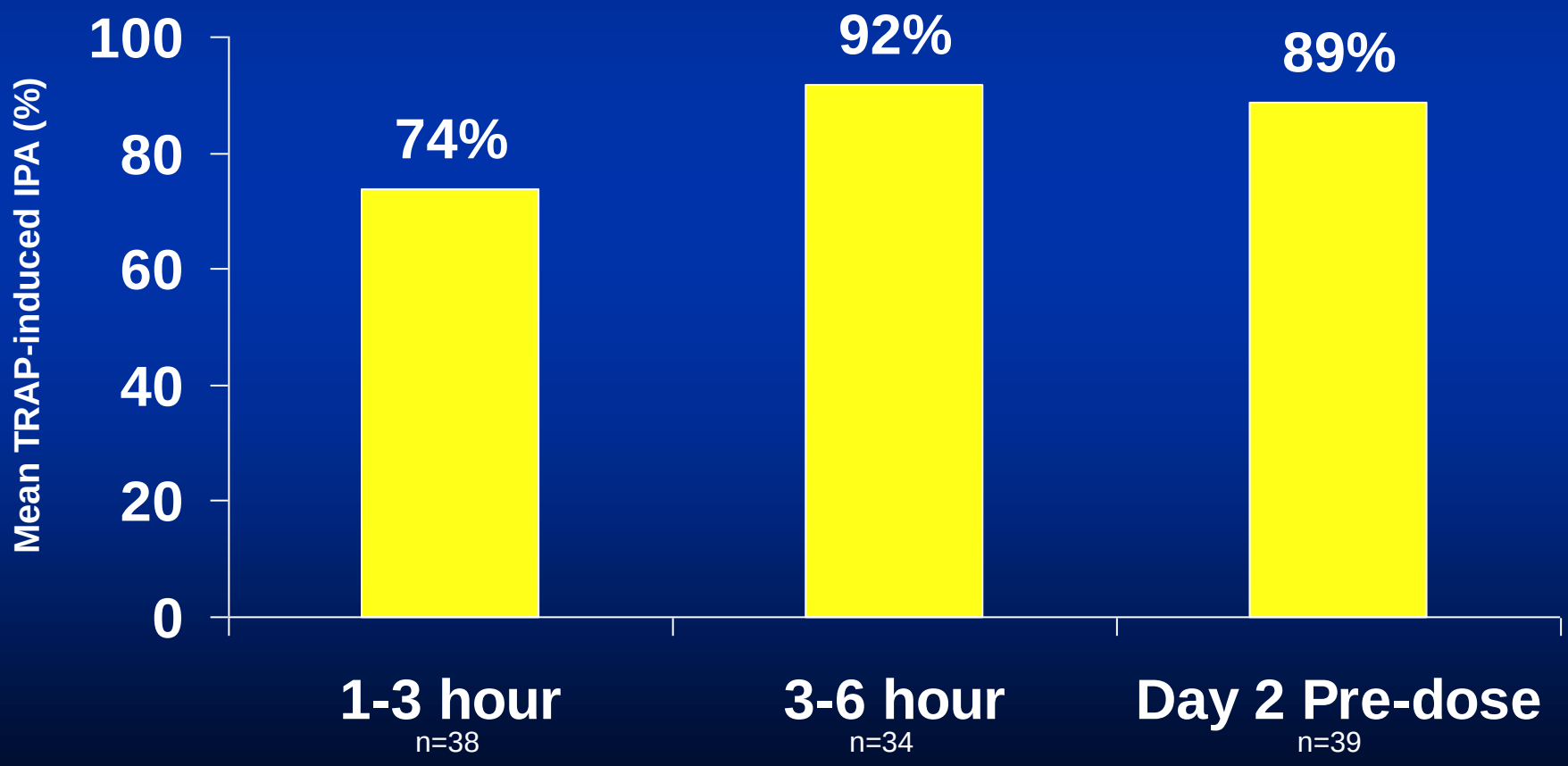


RR 0.67 (95% CI 0.48-0.94)

P = 0.02

Platelet Function Data - Loading Dose Phase* -

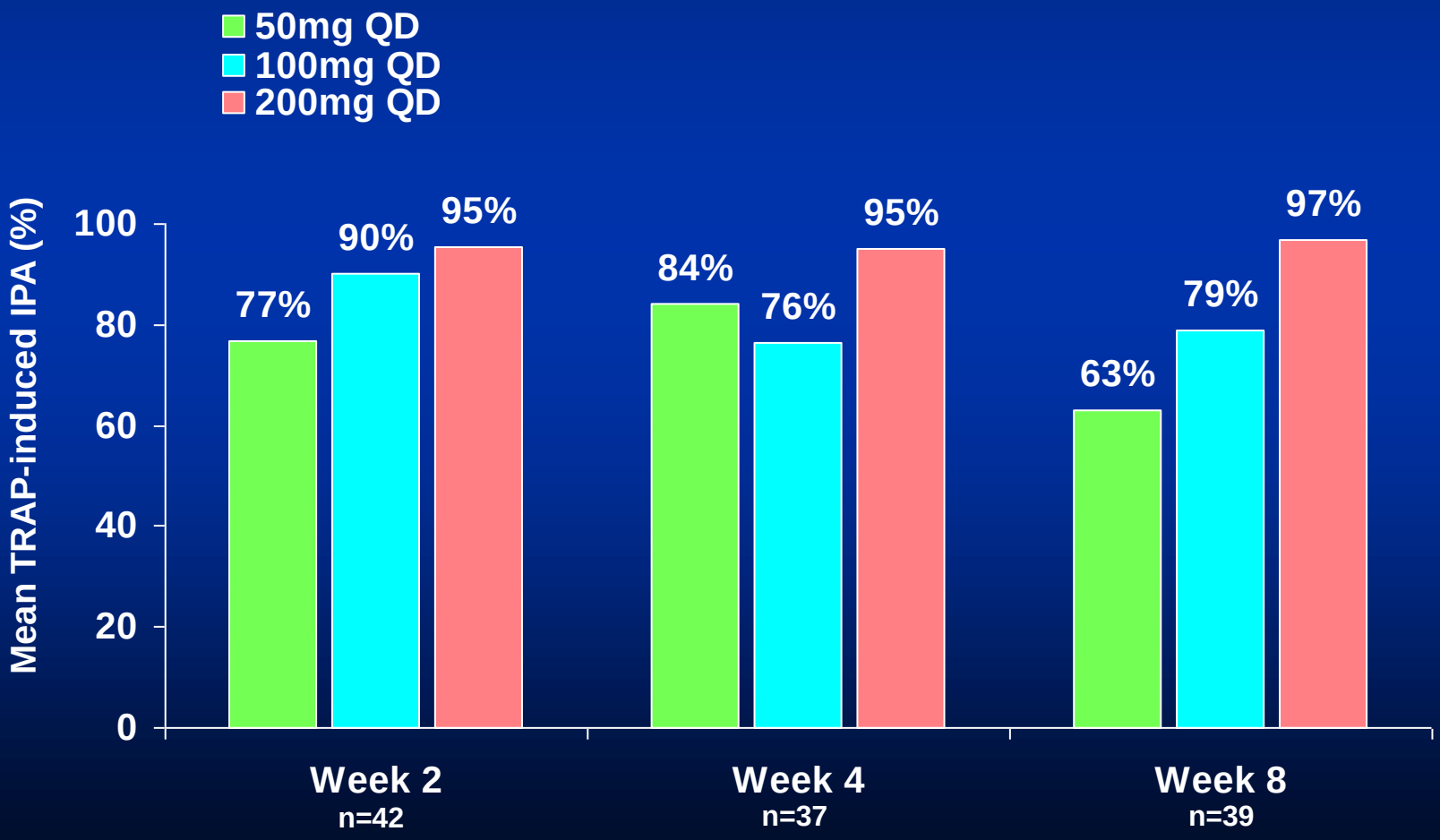
Thrombin receptor-activated peptide (TRAP, 15 µM)-induced inhibition of platelet aggregation



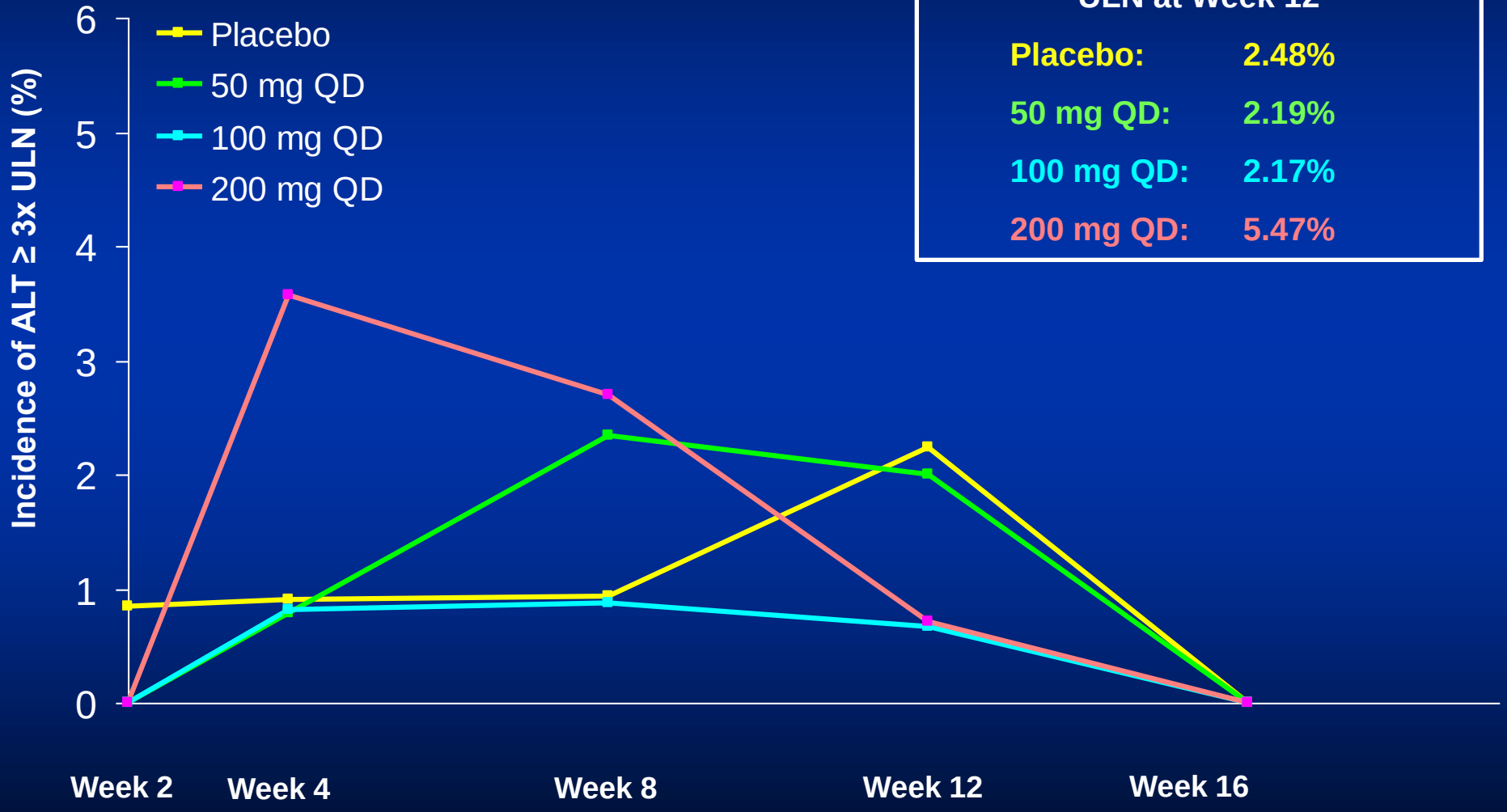
*400 mg loading dose

Platelet Function Data - Maintenance Dose Phase -

Thrombin receptor-activated peptide (TRAP, 15 µM)-induced inhibition of platelet aggregation



Incidence of ALT ≥ 3x ULN



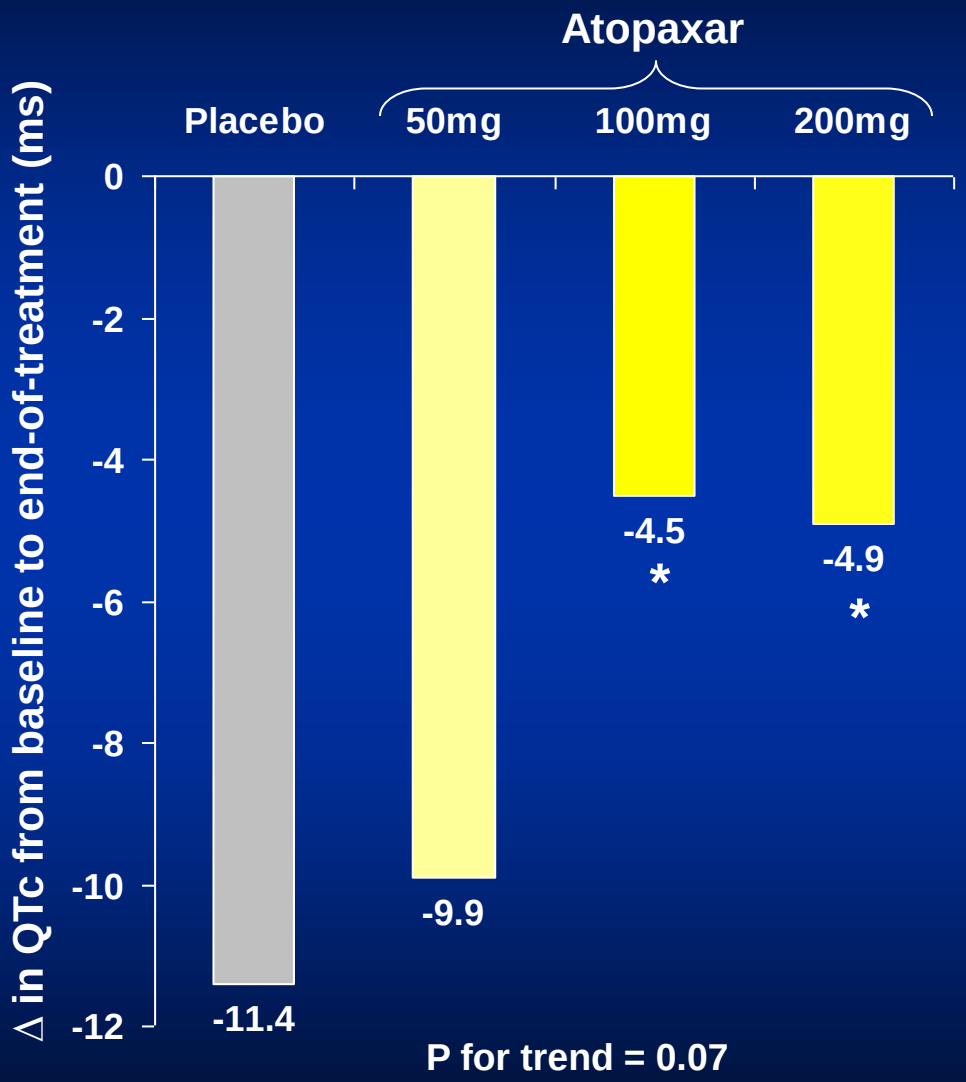
Cumulative incidence ALT ≥ 3x ULN at Week 12

Placebo:	**2.48%**
50 mg QD:	**2.19%**
100 mg QD:	**2.17%**
200 mg QD:	**5.47%**

No cases of Hy's Law were observed

3 subjects with LFT changes discontinued drug

QTc Interval



P for trend = 0.07

* P<0.05, for comparison with placebo

- Overall shortening of QTc was seen in all study arms from randomization to end of treatment
- The mean decrease in QTc was greater in the placebo group than the combined atopaxar group (P=0.04)
- This effect was dose-dependent
- There were no associated cases of syncope or known malignant arrhythmias

Conclusions

- Atopaxar achieves potent and rapid platelet inhibition via the PAR-1 receptor without a significant increase in bleeding in patients with ACS
- Favorable trends for efficacy were supported by a significant reduction in Holter-detected ischemia
- Overall the drug was well tolerated, but dose-dependent transaminitis and relative QTc prolongation were observed with the higher doses of atopaxar
- Future studies will be required to fully establish safety and efficacy of atopaxar, but PAR-1 blockade appears promising