2013 TCTAP

Wrap-Up Interview

Antithrombotic Therapies

Moderator

David J. Cohen

Interviewees

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Issues in Brief

Antiplatelet Controversy

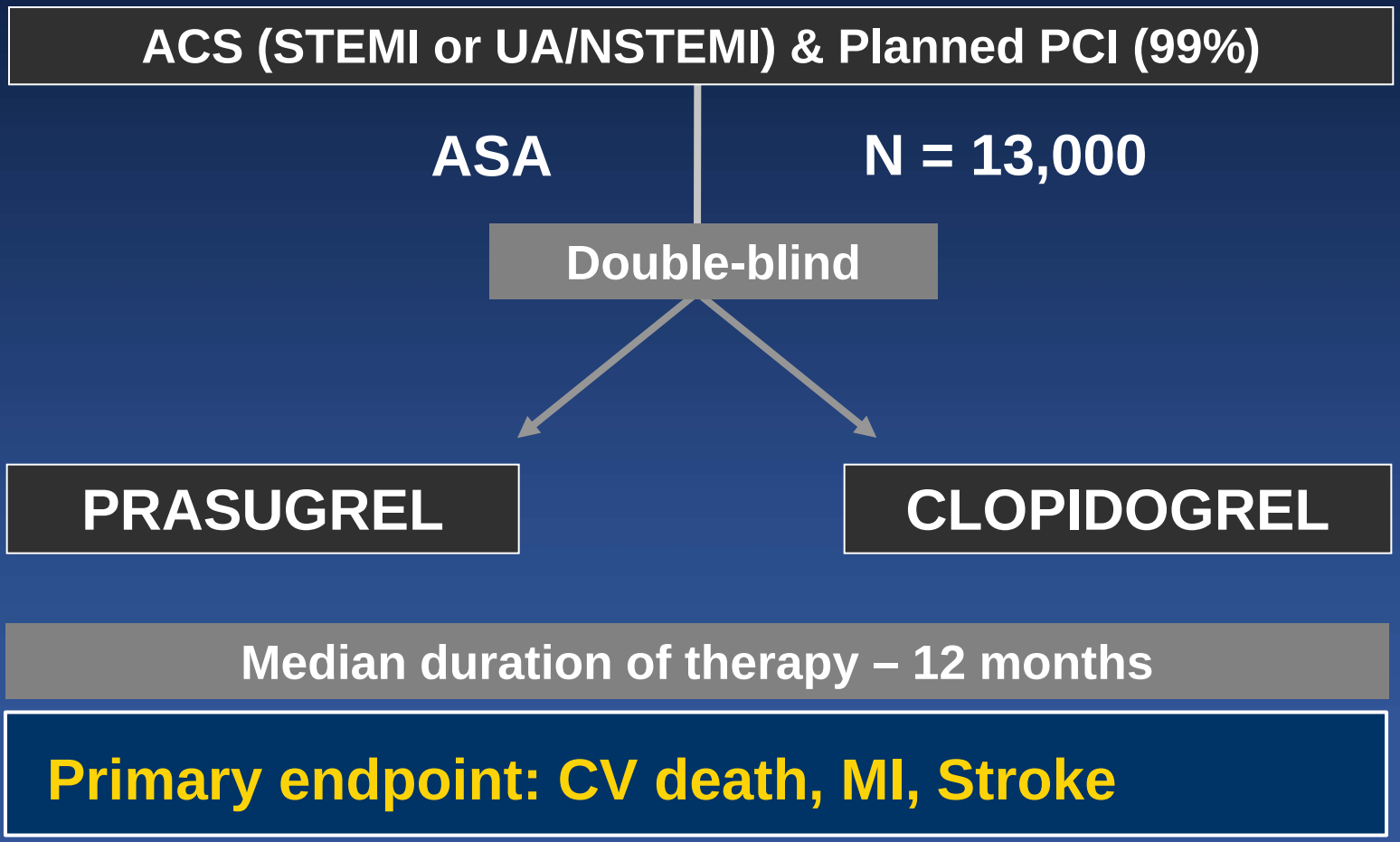
New P2Y12 inhibitors for ACS patients
- Clinical studies: TRITON-TIMI38, TRILOGY, PLATO
- Discussion: Why adoption low?, How to switch?

Monitoring of antiplatelet therapy
- Clinical studies: GRAVITAS, ARCTIC, TRILOGY substudy
- Discussion: Interpretation, Future perspective

Oral Factor Xa Inhibitors

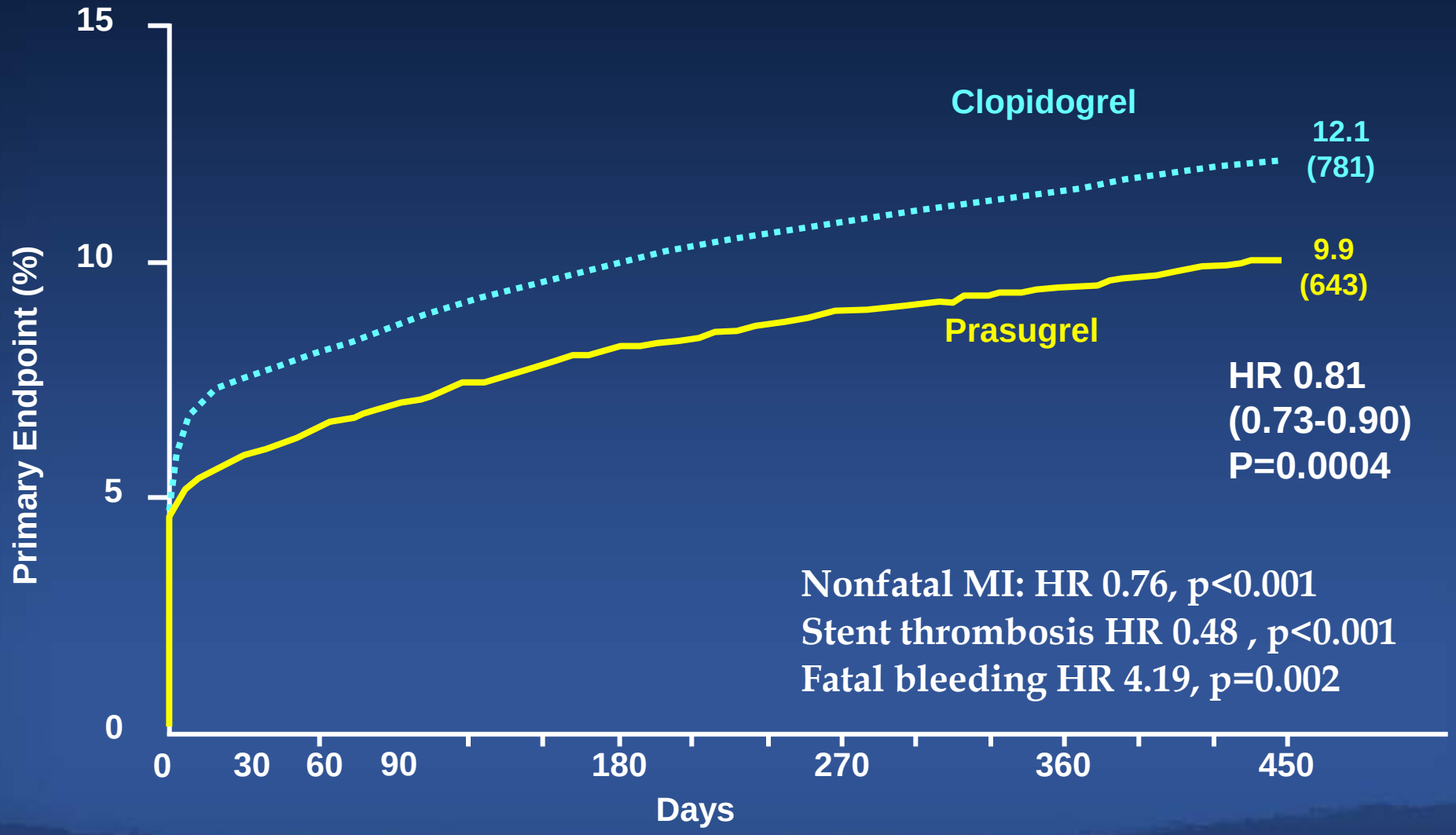
- Clinical studies: APPRAISE-2, ATLAS ACS2
- Discussion: U-shape, ATLAS ACS2 vs. PLATO, Clinical implication

TRITON–TIMI 38

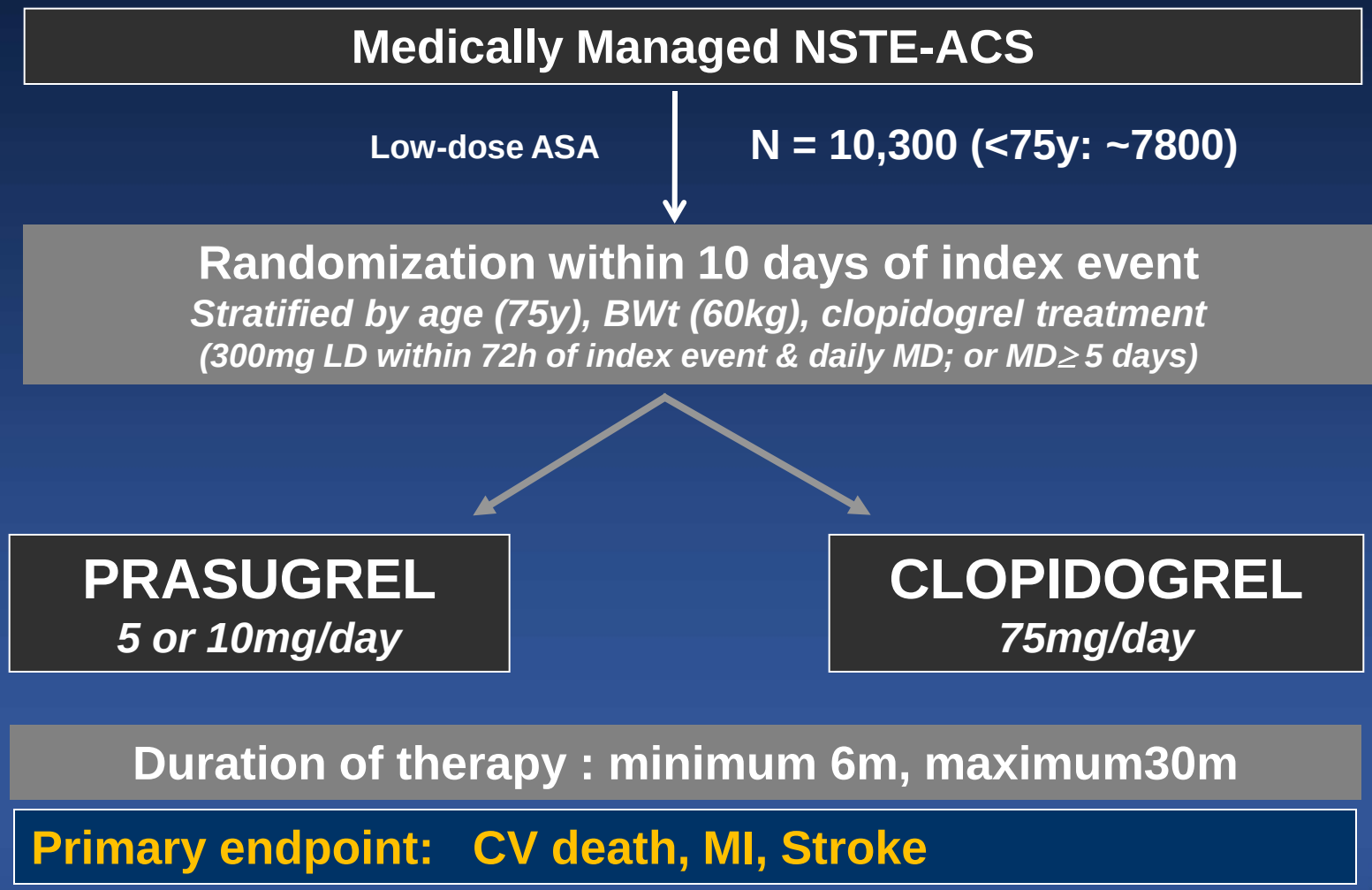


NEJM 2007;357:2001-15

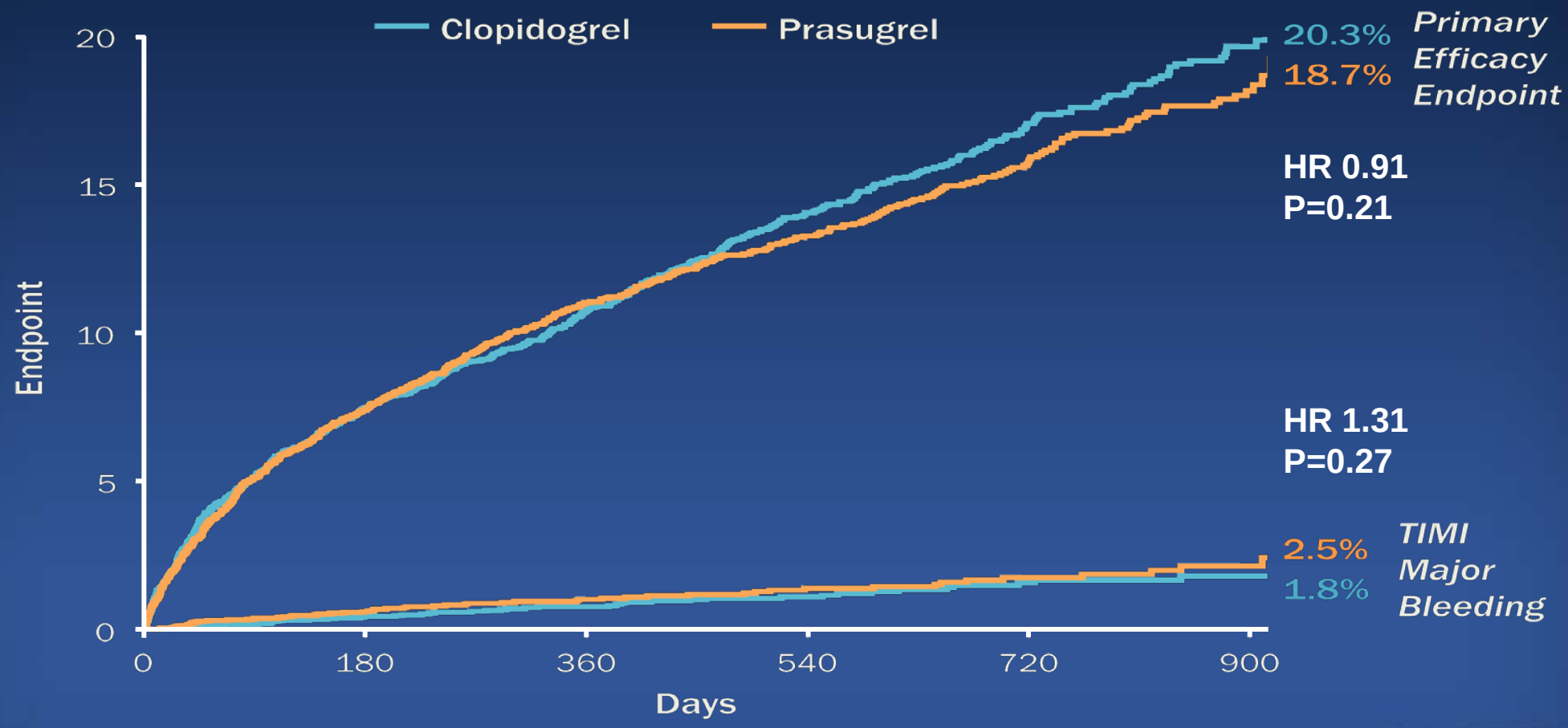
Primary Endpoint: CV Death, MI, Stroke



TRILOGY–ACS


Medically Managed NSTE-ACS
Low-dose ASA
N = 10,300 (<75y: ~7800)
Randomization within 10 days of index event
Stratified by age (75y), BWt (60kg), clopidogrel treatment
(300mg LD within 72h of index event & daily MD; or MD≥5 days)
PRASUGREL
5 or 10mg/day
CLOPIDOGREL
75mg/day
Duration of therapy : minimum 6m, maximum30m
Primary endpoint: CV death, MI, Stroke

Primary Endpoint: CV Death, MI, Stroke



PLATO

ACS (STEMI/NSTEMI) (<24 h after chest pain)

ASA ↓ **N = 18,624**

Double-blind

IIbIIIa 27%

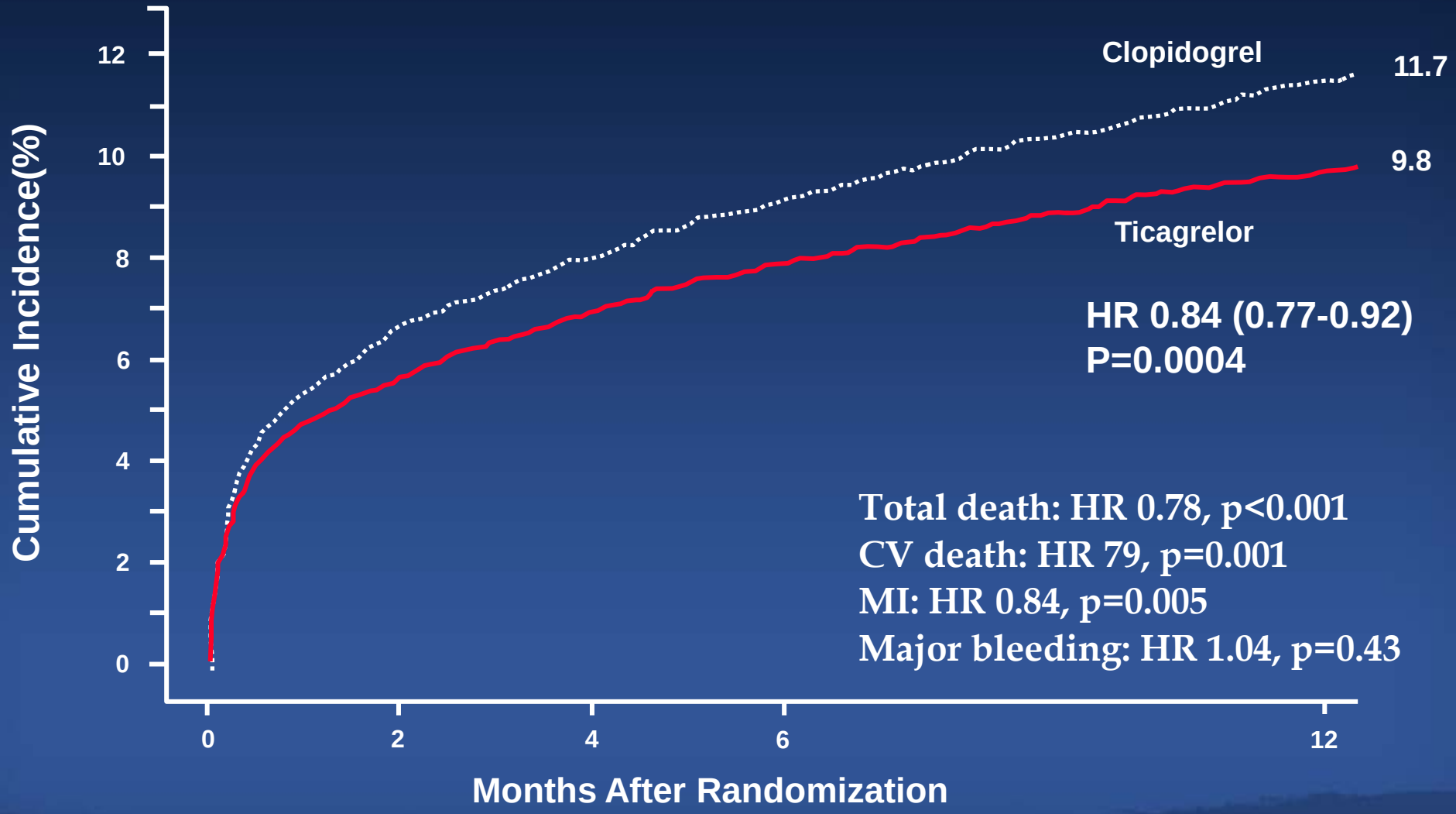
Ticagrelor | **Clopidogrel**

Median duration of therapy: 6-12 months

Primary endpoint: CV death, MI, Stroke (15%RRR)

NEJM 2009;361:1045-57

Primary Endpoint: CV Death, MI, Stroke

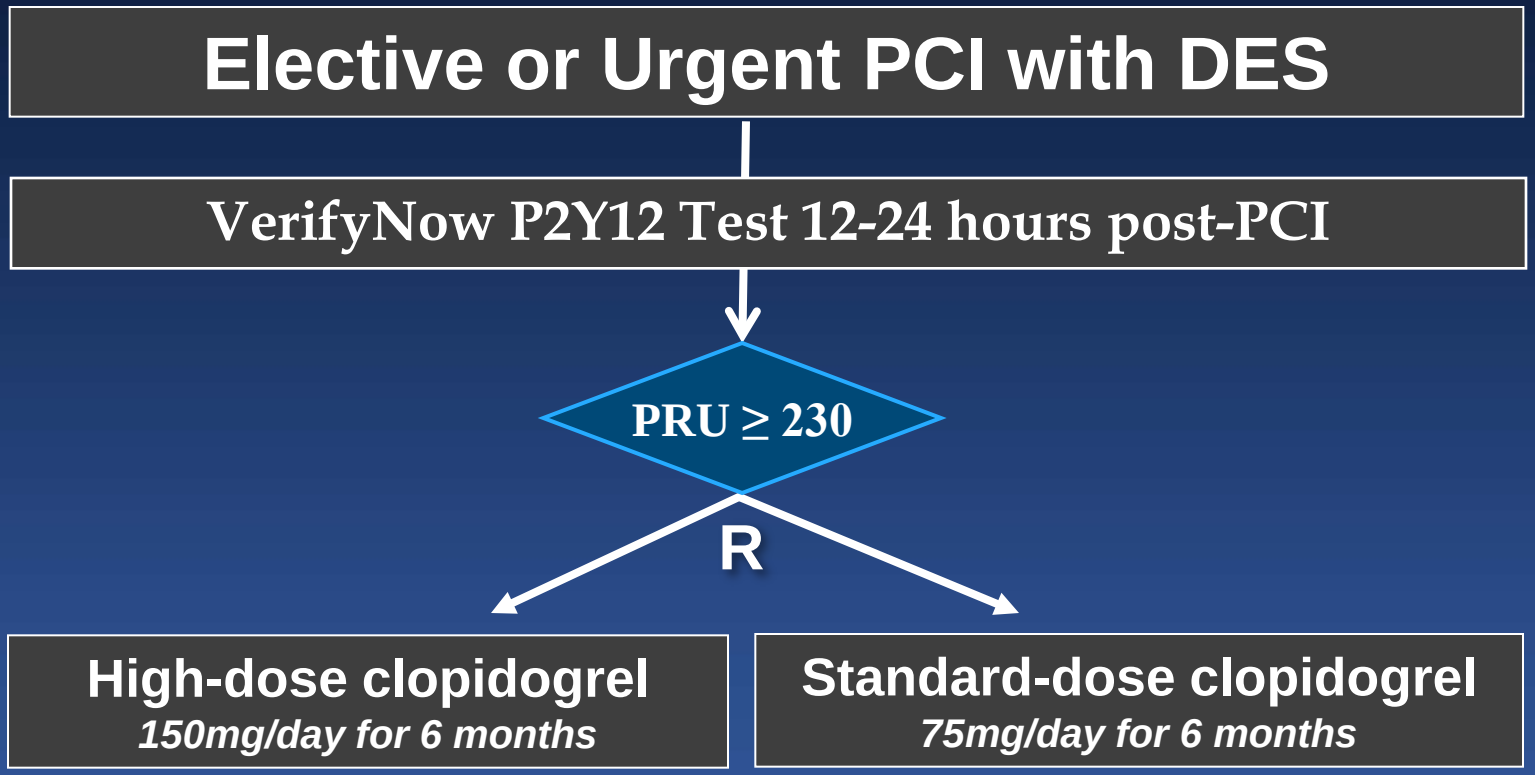


Discussion

- **ACCF/AHA Guidelines: $P2Y_{12}$ Inhibitors**
  - NSTE ACS
  - STEMI

- **New Agents in Clinical Practice**
  - Why is adoption so low?
  - How to switch?

GRAVITAS

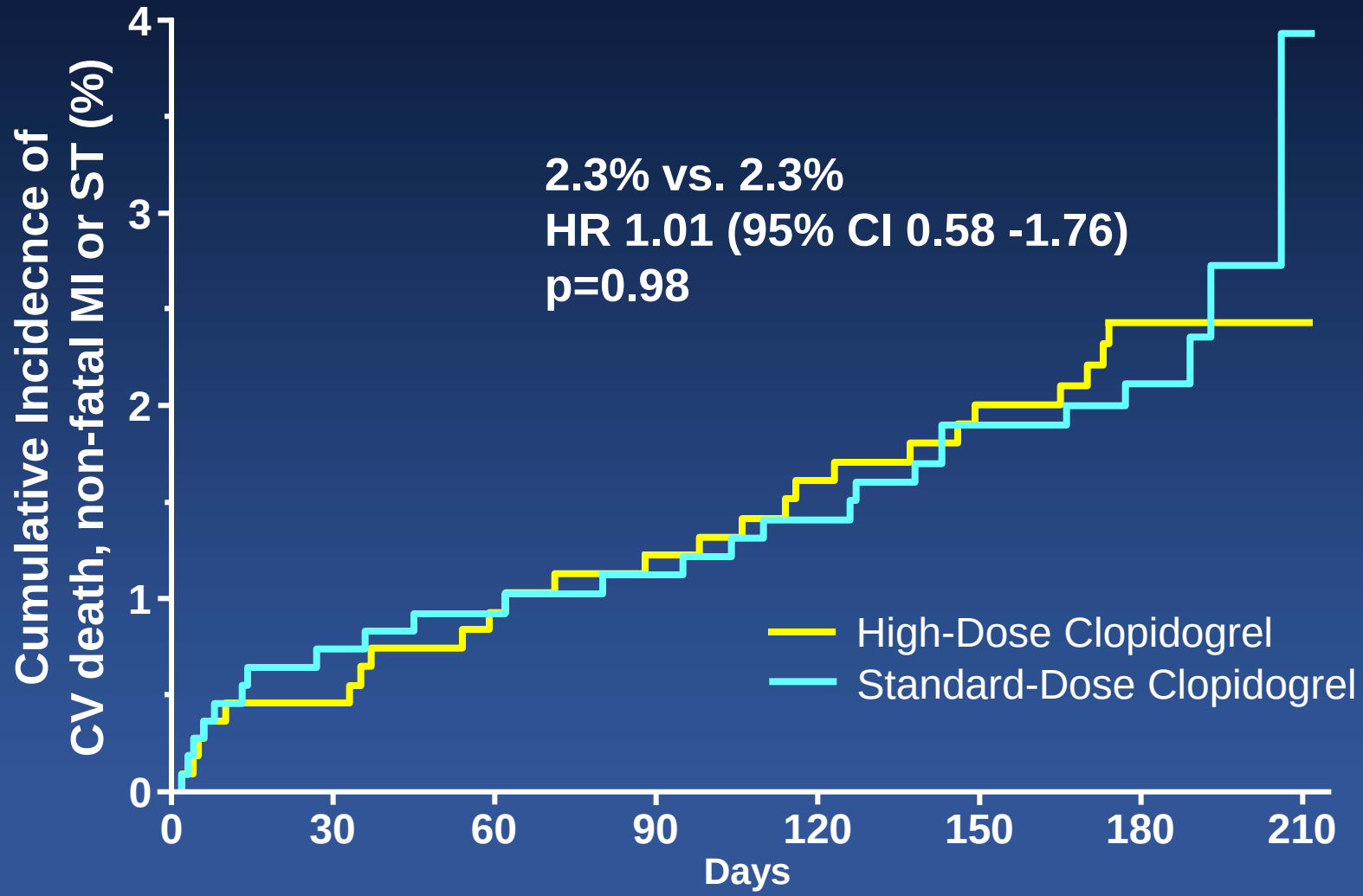


Primary endpoint: CV death, MI, Stent thrombosis at 6 months
Safety endpoint: GUSTO moderate or severe bleeding

All patients received aspirin (81-162mg daily).

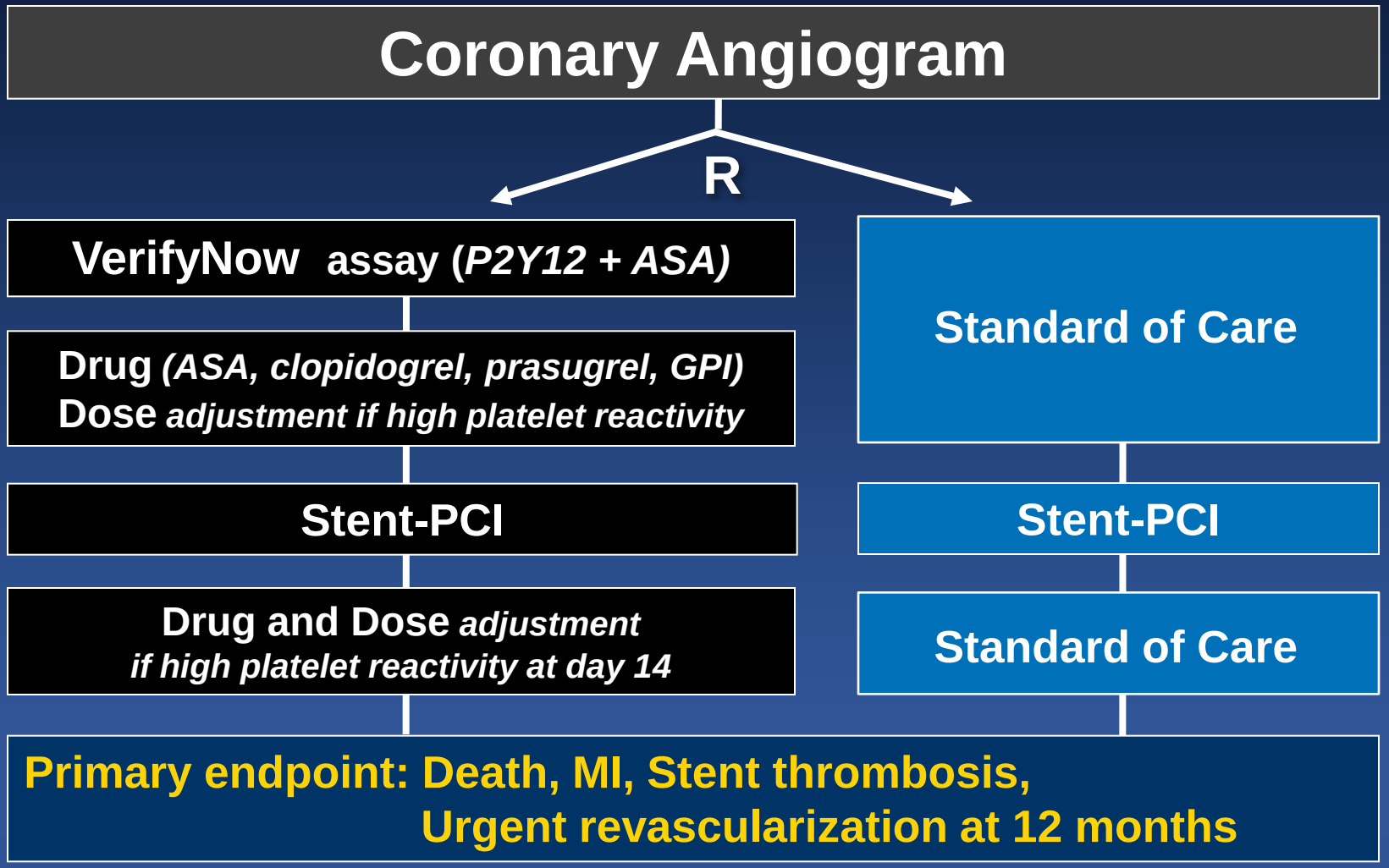
JAMA 2011;305:1097-105

Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk								
High Dose Clopidogrel	1109	1056	1025	1017	1007	998	747	54
Standard-Dose Clopidogrel	1105	1057	1028	1020	1015	1005	773	53

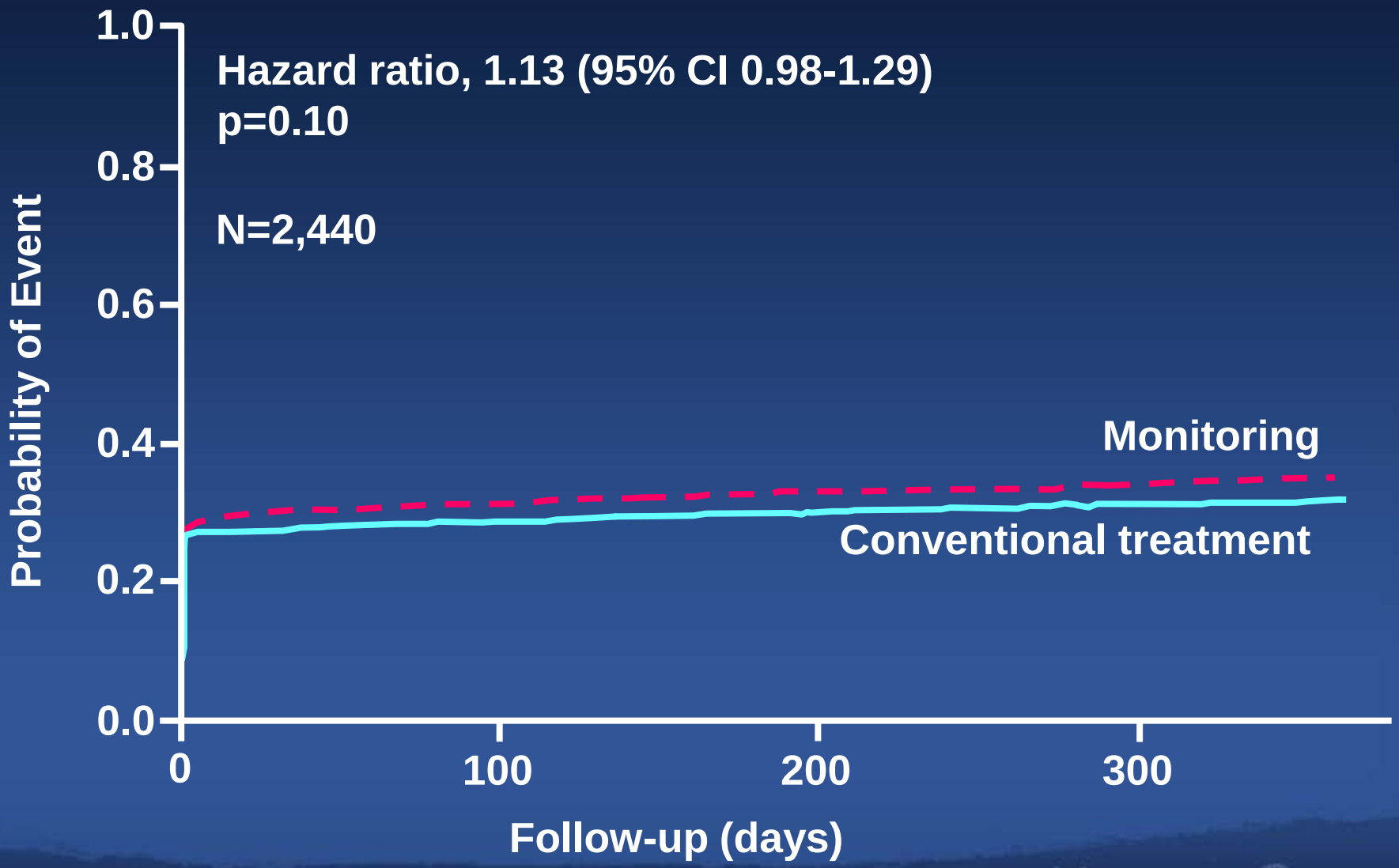
ARCTIC



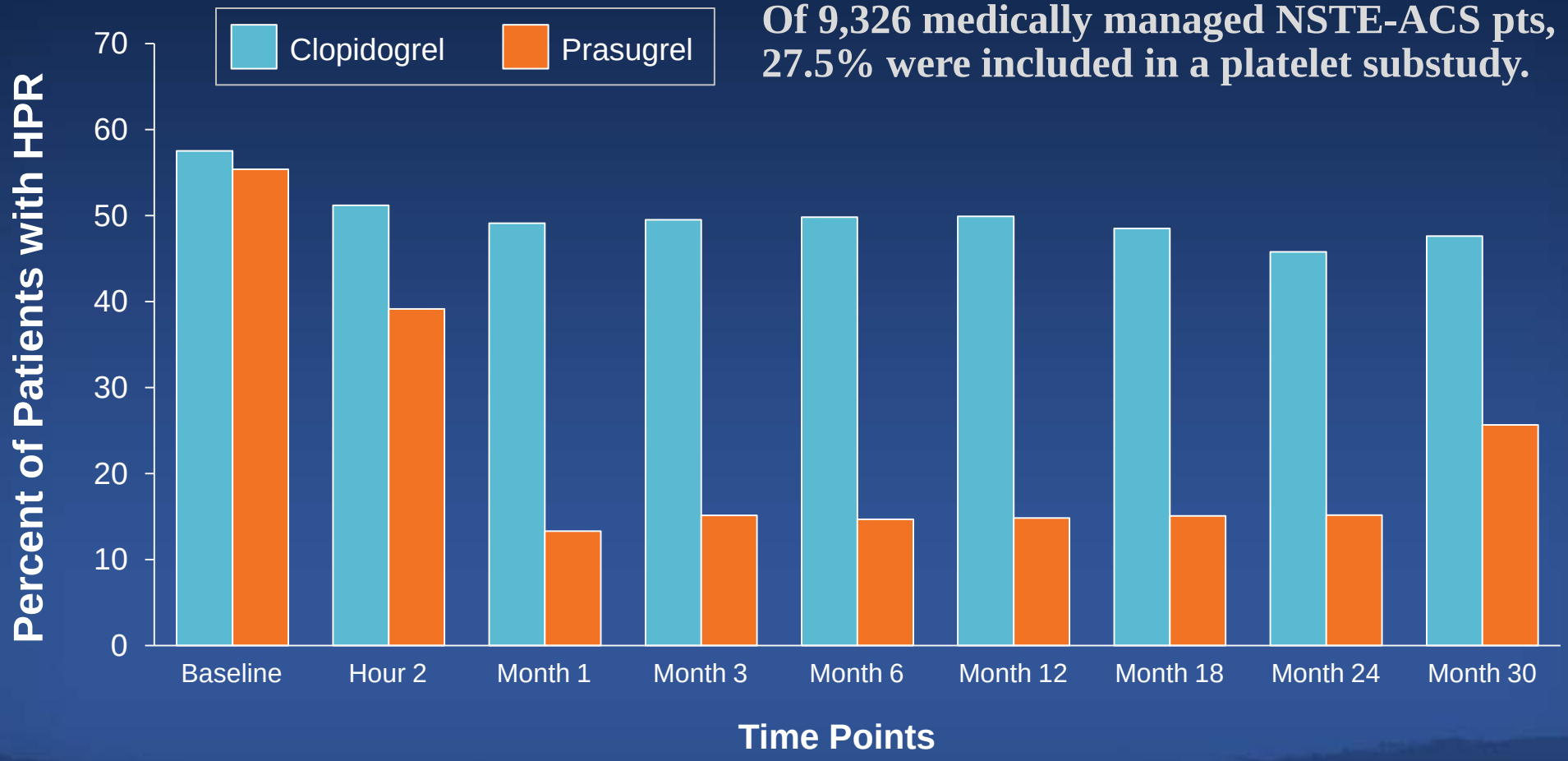
NEJM 2012;367:2100-9

Primary Endpoint:

Death, MI, Stent Thrombosis, Urgent Revascularization



TRILOGY Platelet Function Substudy: Frequency of High Platelet Reactivity (HPR) > 208 PRU (N=2564)



Of 9,326 medically managed NSTE-ACS pts, 27.5% were included in a platelet substudy.

JAMA2012;308:1785-94

TRILOGY Platelet Function Substudy: Relationship of PRU Values with Ischemic Event Through 30 Months

	Unadjusted Results		Adjusted Results	
	HR (95% CI)	p-value	HR (95% CI)	p-value
PRU as time-dependent covariate (per 60-unit increase)				
CVD/MI/stroke	**1.09 (1.02-1.16)**	**0.008**	1.03 (0.96-1.11)	0.44
All-cause death	**1.09 (1.01-1.18)**	**0.03**	0.99 (0.90-1.08)	0.79
All MI	1.02 (0.94-1.11)	0.60	0.97 (0.88-1.07)	0.53
30-day HPR PRU cut-point > 208				
CVD/MI/stroke	**1.43 (1.10-1.86)**	**0.01**	1.16 (0.89-1.52)	0.28
All-cause death	1.38 (0.99-1.91)	0.06	1.03 (0.74-1.44)	0.84
All MI	1.37 (0.96-1.95)	0.08	1.13 (0.79-1.62)	0.50
30-day HPR PRU cut-point > 178				
CVD/MI/stroke	**1.35 (1.05-1.73)**	**0.02**	1.13 (0.87-1.45)	0.35
All-cause death	1.27 (0.92-1.75)	0.15	0.99 (0.71-1.38)	0.95
All MI	1.34 (0.96-1.86)	0.09	1.13 (0.80-1.58)	0.49

Univariate, but not independent, association between platelet reactivity and ischemic events in medically managed ACS patients.

Discussion

- **Platelet Function Test in Patients Undergoing Stent Implantation**
  - **New data: Disappointing results**
  - **Interpretation: Wrong hypothesis? Wrong test? Wrong patients?**

- **Tailored Therapy Using Platelet Function Test**
  - **Ongoing trials: ANTARCTIC (ACS/PCI≥75 years)**
  - **Future perspective**

APPRAISE-2

Recent (≤ 7 d) Acute Coronary syndrome (STEMI or NSTE-ACS) At Least 2 Additional Risk Factors

N= 10,800

Aspirin & other antiplatelet therapy

R

Apixaban, 5 mg 2x/d

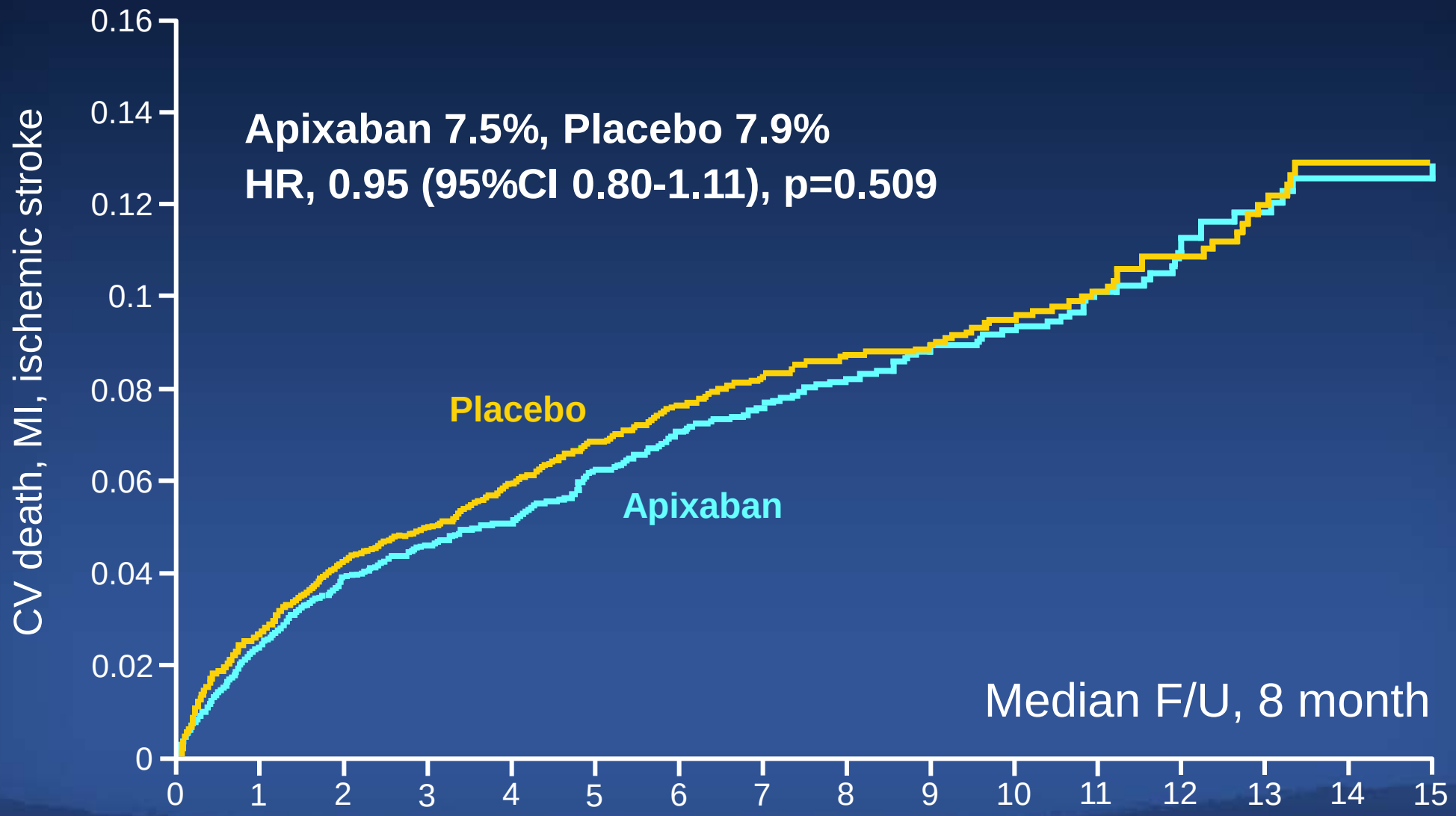
CrCl < 40 mL/min, 2.5 mg 2x/d

Placebo

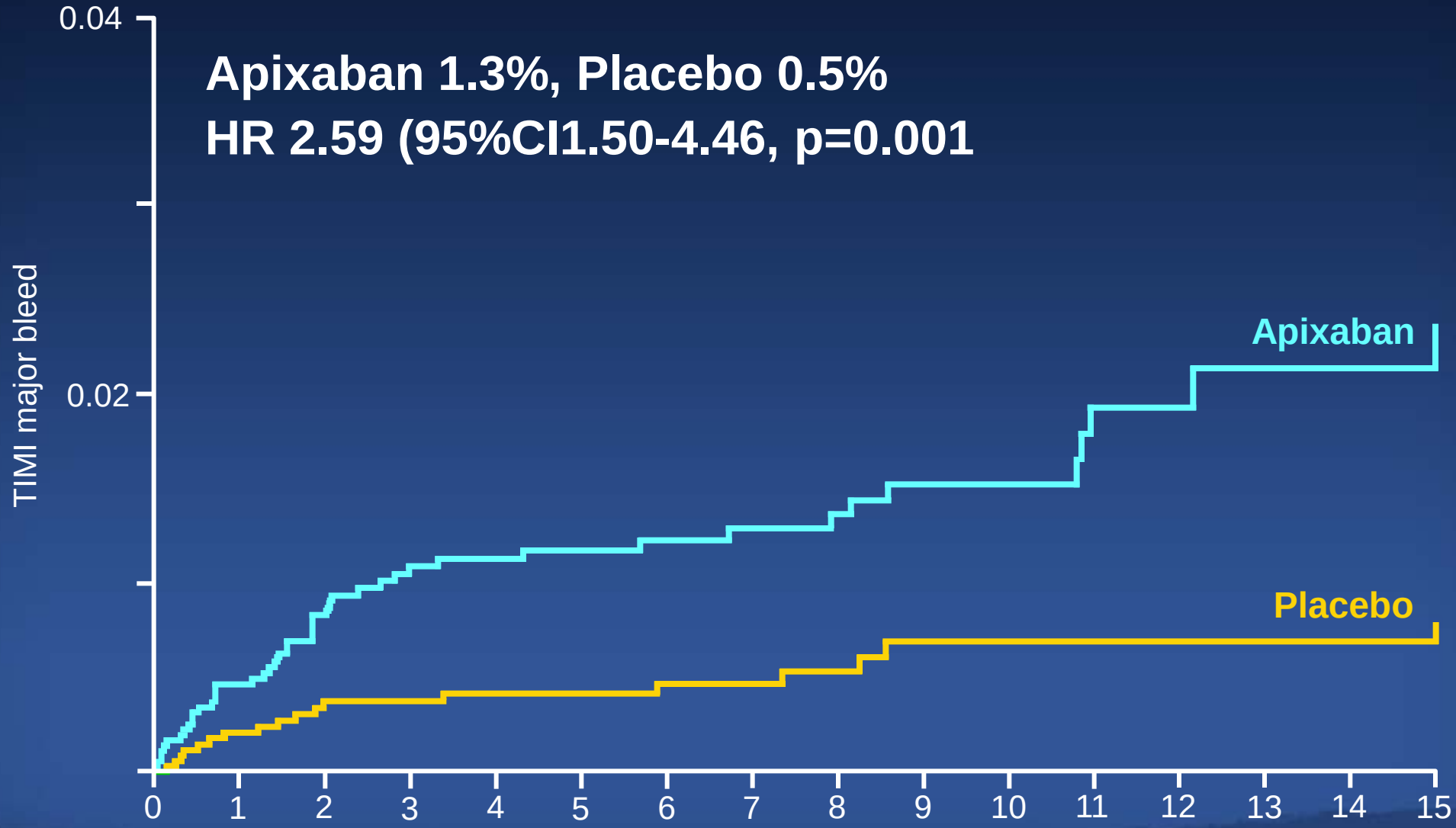
Primary endpoint: CV death, MI, Ischemic Stroke
Safety endpoint: TIMI major bleeding

NEJM 2011;365:699-708

Primary Endpoint: CV Death, MI, Stroke



TIMI Major Bleeding



ATLAS ACS 2

Recent ACS: STEMI, NSTEMI, UA
Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

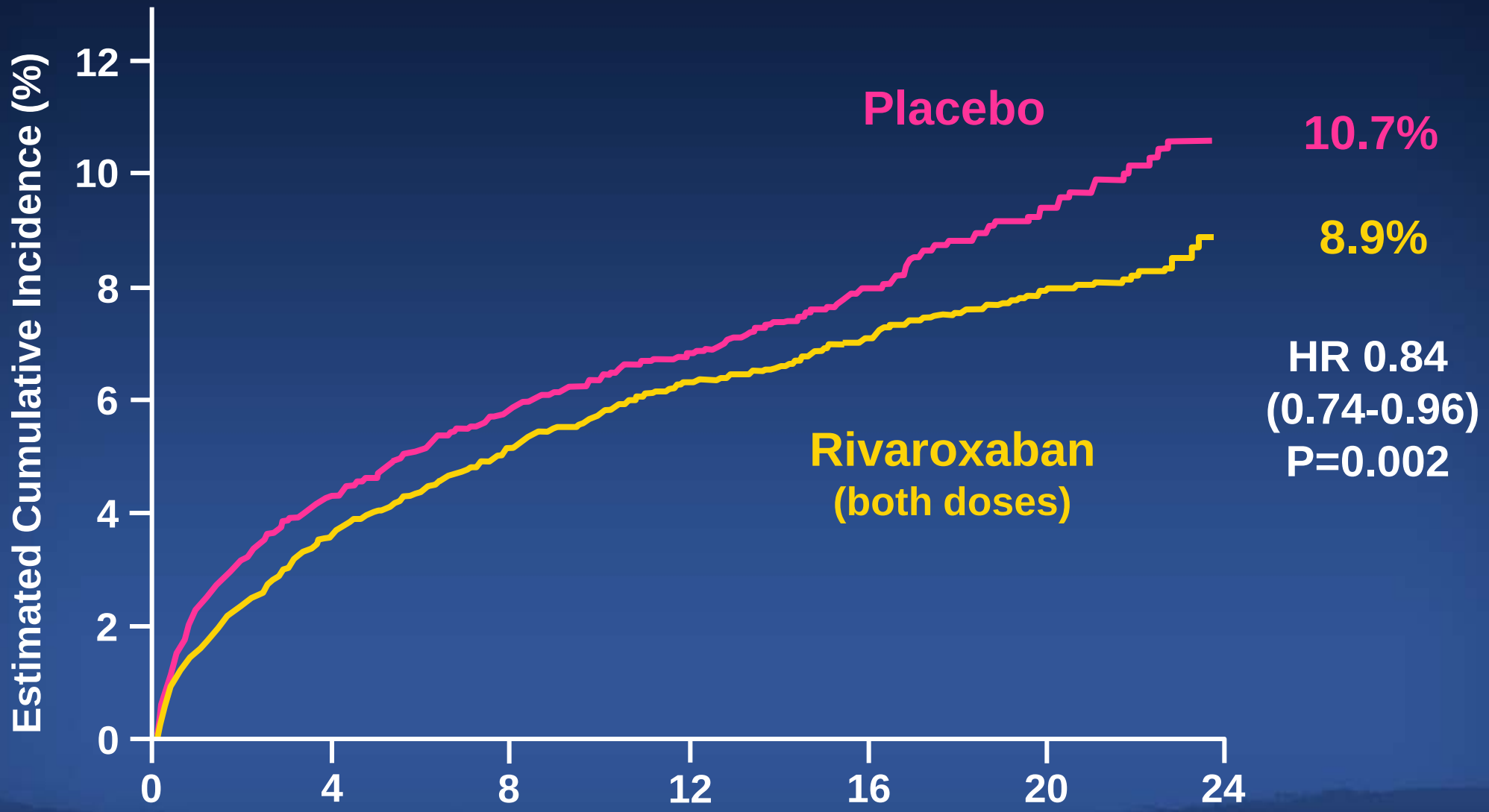
Stratified by Thienopyridine Use at MD Discretion

Placebo	Rivaroxaban	rivaroxaban
n=5,176	2.5 mg BID n=5,174	5.0 mg BID n=5,176

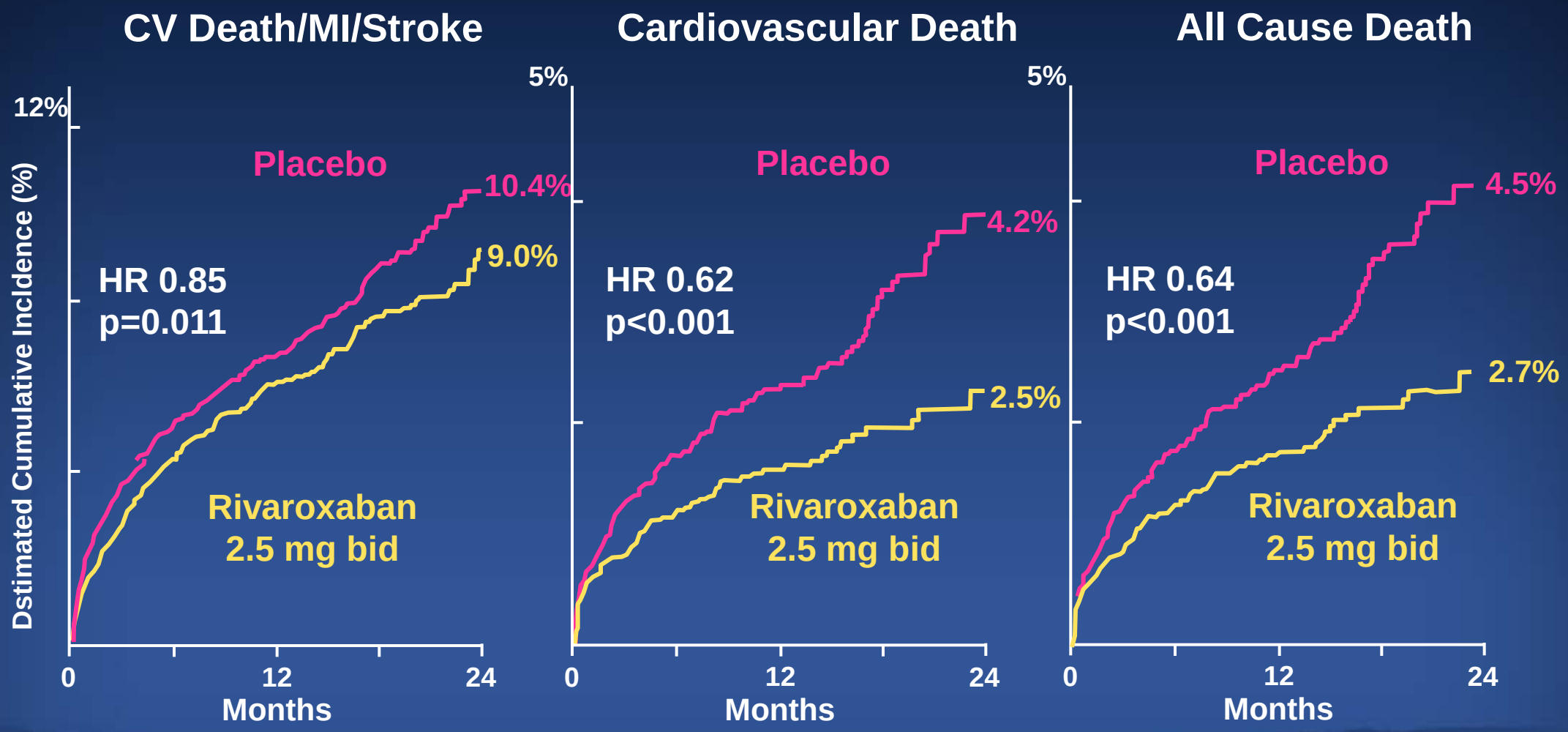
Primary endpoints:
Efficacy: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
Safety: TIME major bleeding not associated with CABG

NEJM 2012;366:9-19

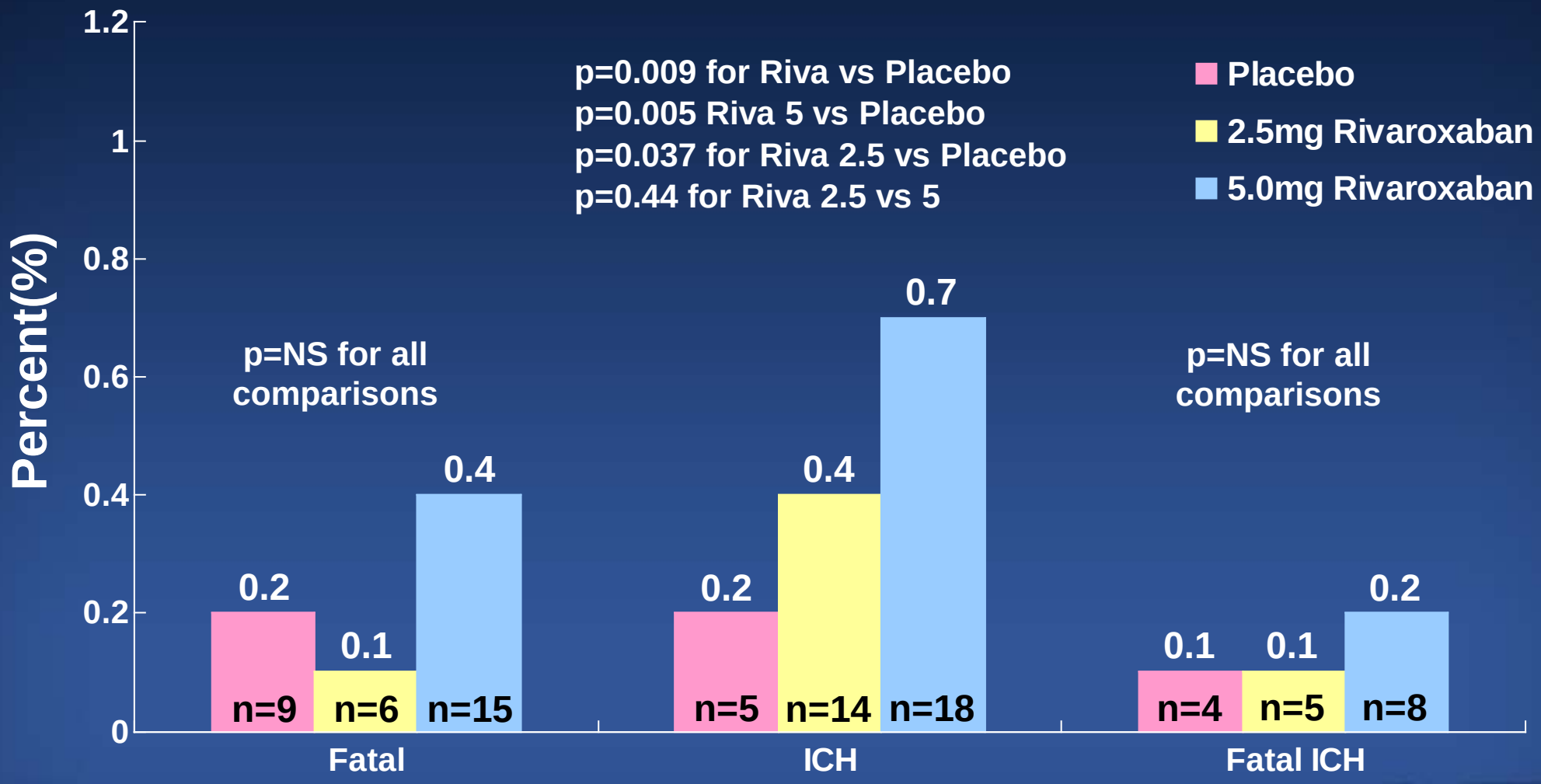
Primary Endpoint: CV Death, MI, Stroke



Primary Endpoint: Very Low Dose Rivaroxaban



Fatal Bleed and ICH

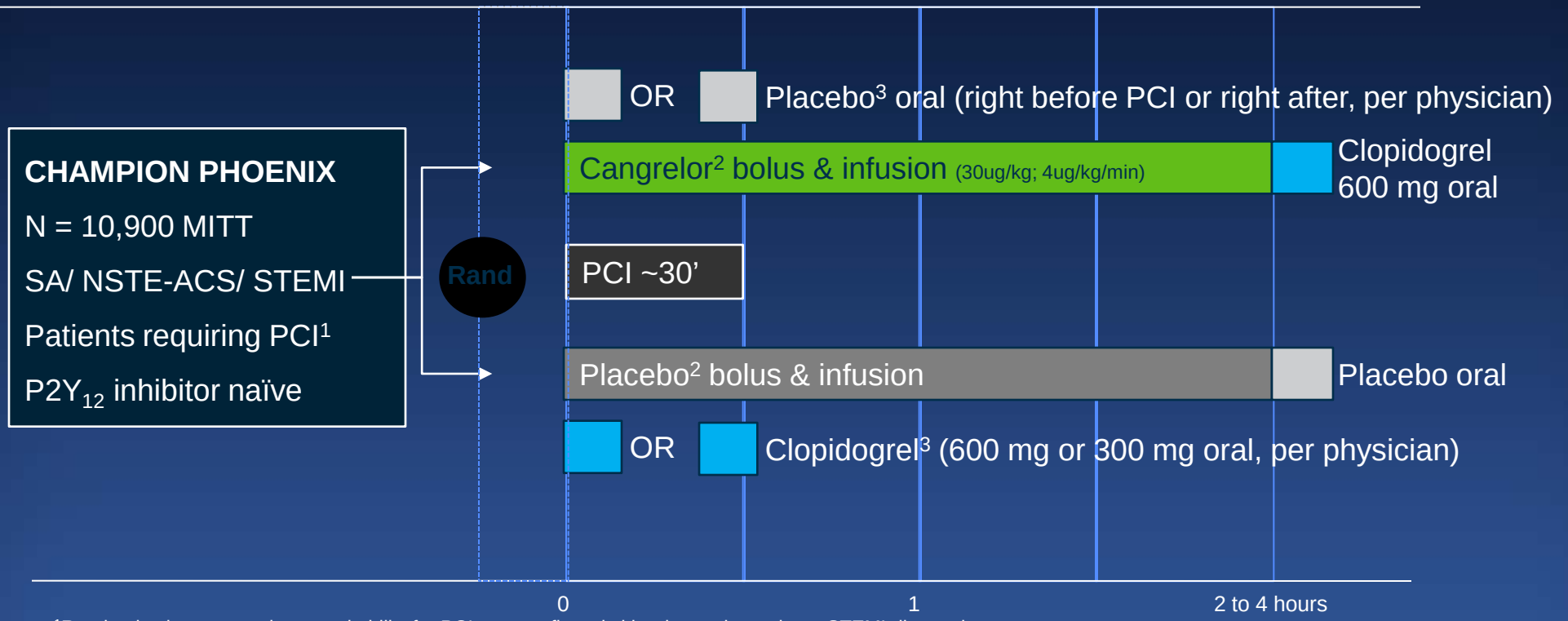


Discussion

- **U-shaped Dose Responses**
  - APPRAISE2 vs. ATLAS ACS2

- **Triple Therapy for ACS Patients**
  - High residual risk after ACS
  - ATLAS ACS2 vs. PLATO
  - Which drug for whom?

CHAMPION PHOENIX Study Design



[1]Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

[2]Study drug Infusion (cangrelor or matching placebo) was continued for 2-4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

[3]Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.

Primary Efficacy Outcomes at 48 Hours, MITT

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P-value
Primary Analysis Adjusted[1]				
Death/MI/IDR/ST	257/5470 (4.7%)	322/5469 (5.9%)	0.78 (0.66, 0.93)	0.005

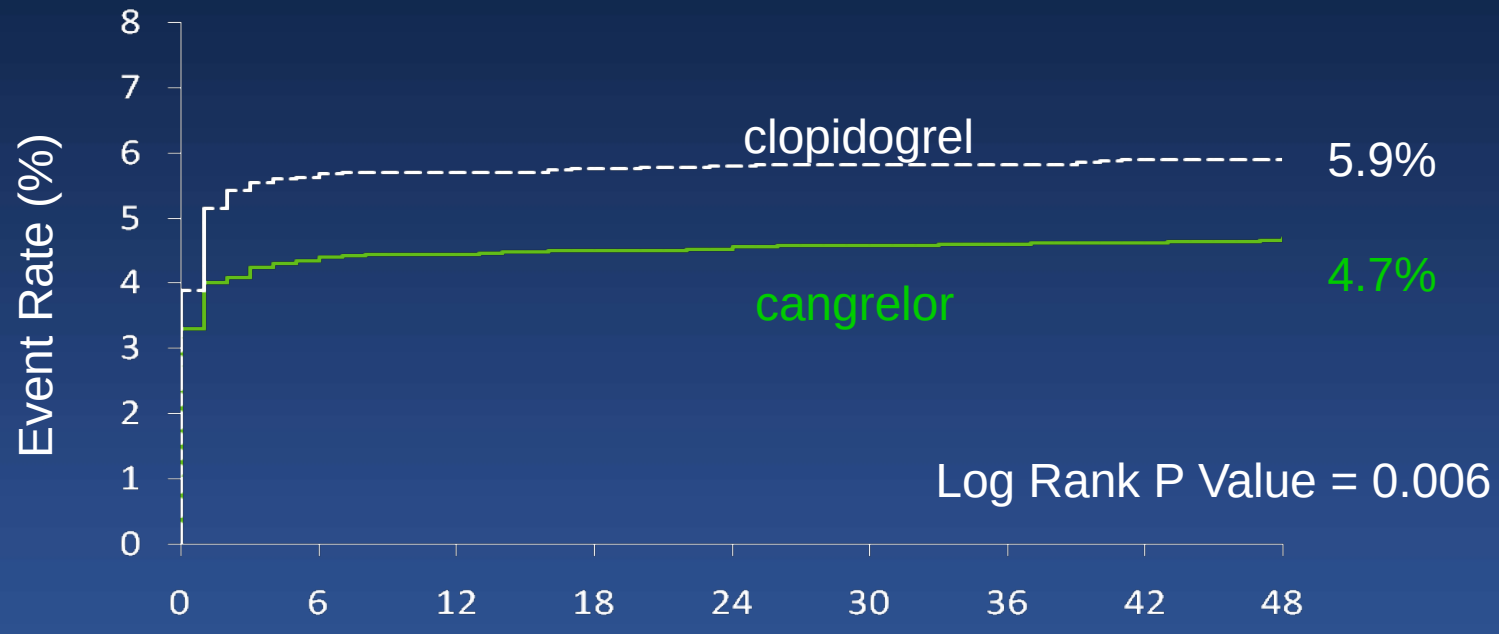
Secondary Efficacy Outcomes at 48 Hours, MITT

Stent thrombosis (key secondary endpoint)	46/5470 (0.8%)	74/5469 (1.4%)	0.62 (0.43,0.90)	0.01
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67,0.97)	0.02
Q-wave MI	11/5470 (0.2)	18/5469 (0.3)	0.61 (0.29,1.29)	0.19
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45,1.20)	0.22
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99
CV Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52,1.92)	>0.99

[1] The logistic model was adjusted for baseline status and clopidogrel dose. P value of 0.006 shown on the KM curve is log rank p value.

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

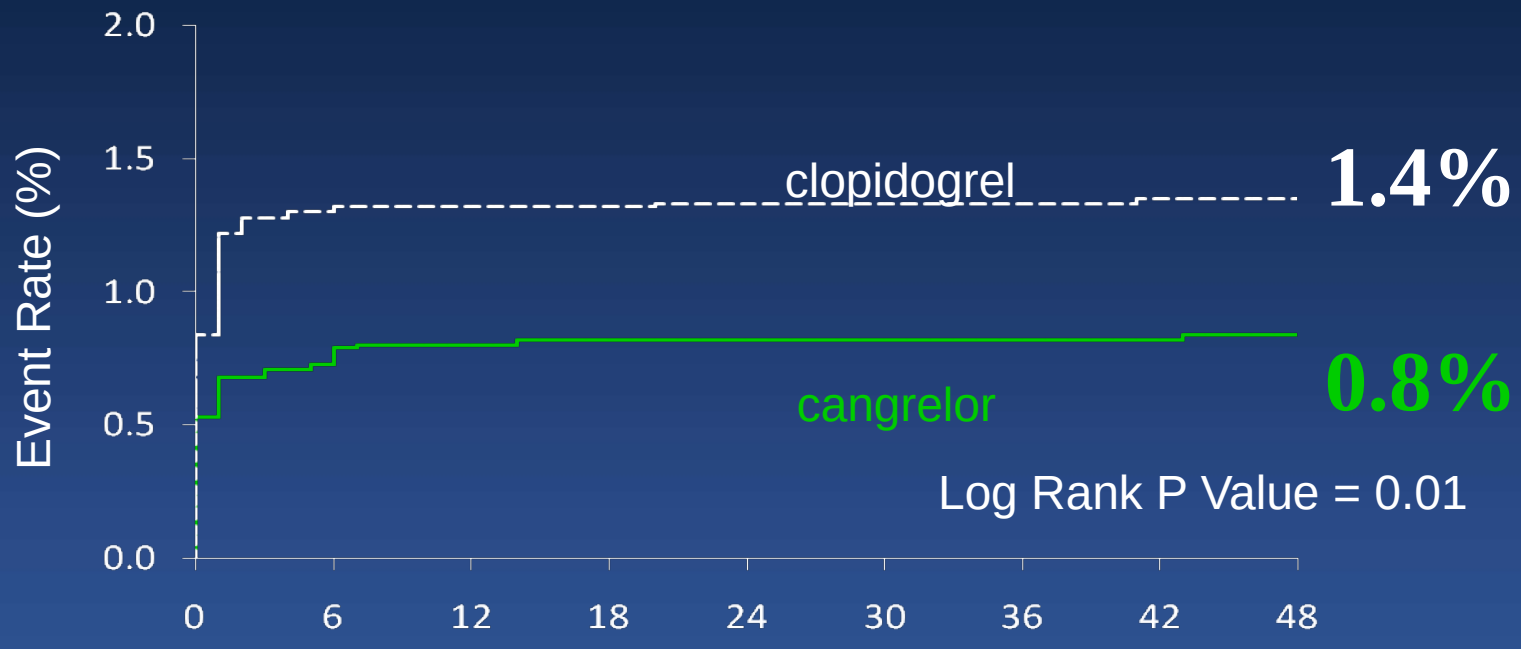
Death/ MI/ IDR/ Stent Thrombosis



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

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Stent Thrombosis within 48 Hours



Patient at Risk									
Cangrelor:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

Bhatt DL, Stone GW, Mahaffey KW, et al…. Harrington RA. NEJM 2013 at www.nejm.org

Discussion

- **Are the clinical results compelling?**
- **Is this the end of "upstream" therapy for ACS patients?**
- **How will you choose between cangrelor and more potent oral P2Y12 inhibitors?**