Breakthrough Antiplatelets and Anticoagulants: Focus on brand new drugs

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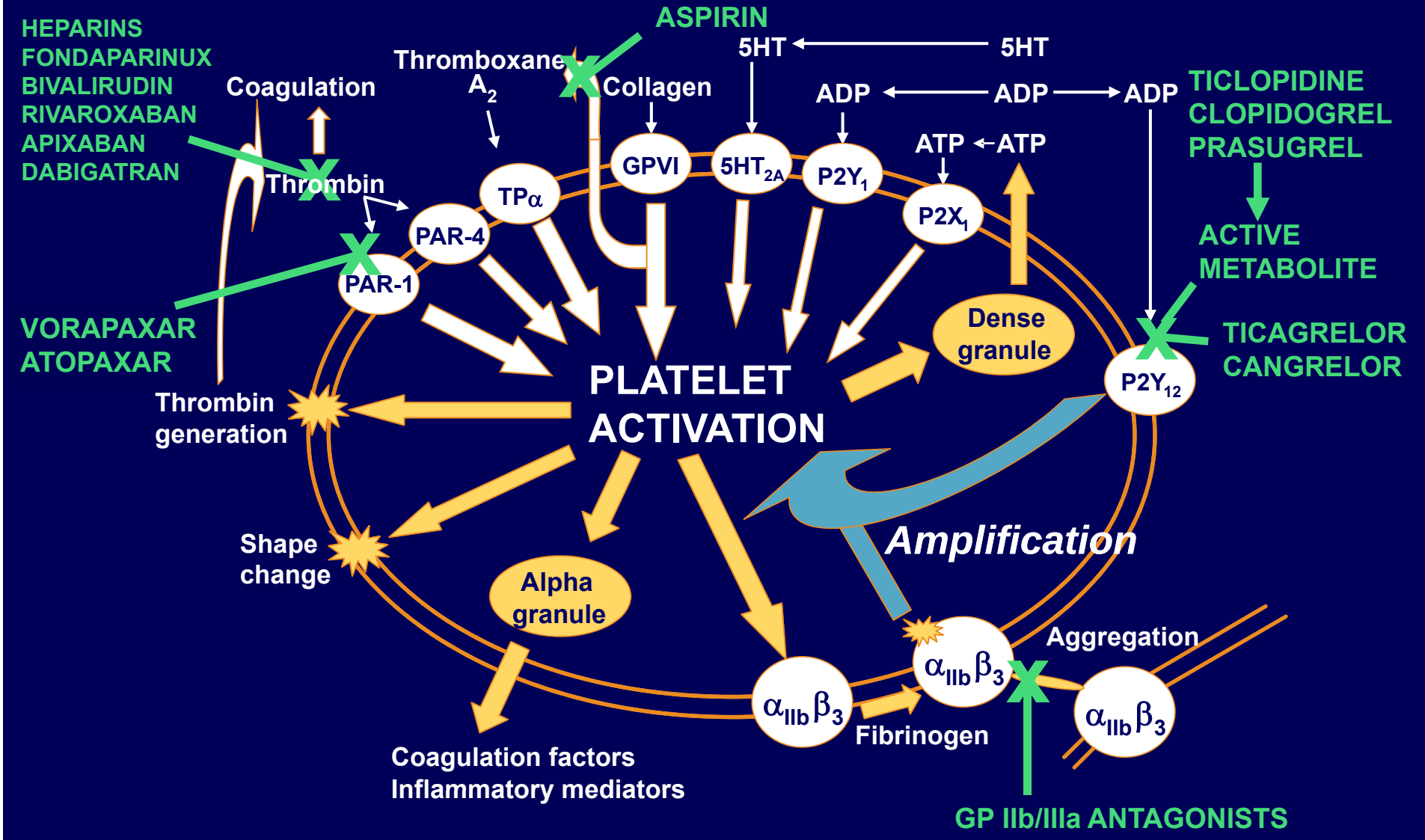
My Conflicts of Interest Are:

Company Name	Relationship
AstraZeneca	Research grant, honoraria, consultant
Eli Lilly / Daiichi Sankyo	Research/educational grants, honoraria, consultant
The Medicines Company	Consultant
Merck	Research grant, consultant
Novartis	Consultant
Sanofi aventis / BMS	Consultant
Eisai	Consultant
Medscape	Honoraria
Accumetrics	Educational grant, research consumables, consultant
Iroko	Honorarium

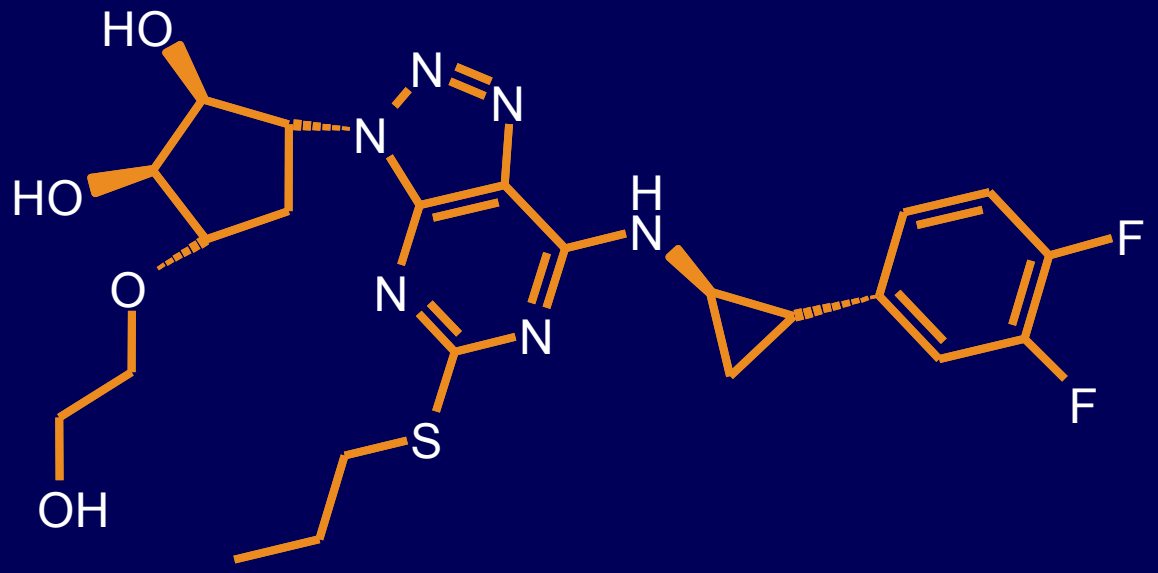
Antithrombotic mechanisms



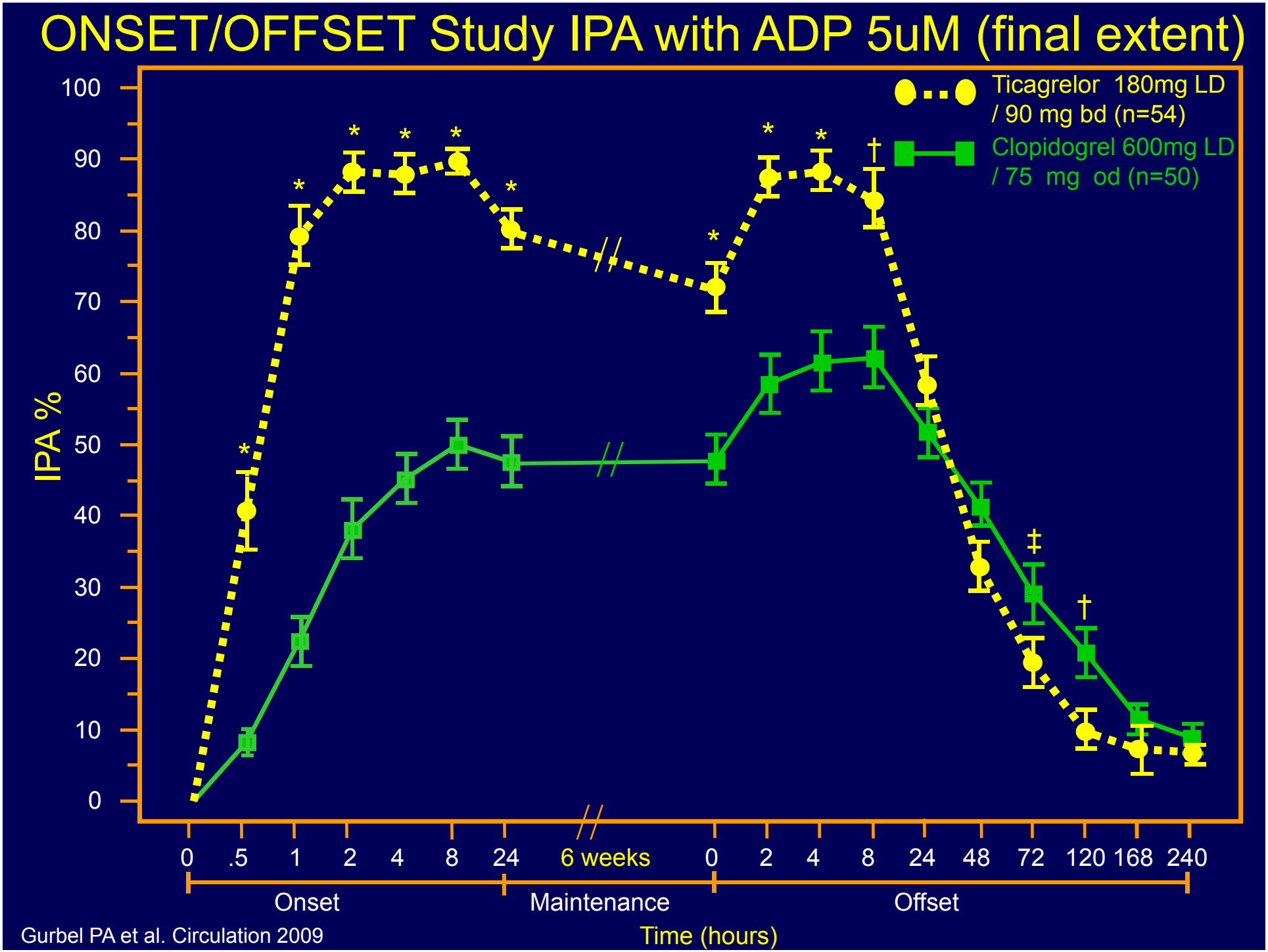
Oral reversibly-binding $P2Y_{12}$ inhibition: PLATO study

Ticagrelor vs clopidogrel

Ticagrelor: CPTP (Cyclo-Pentyl-Triazolo-Pyrimidine)

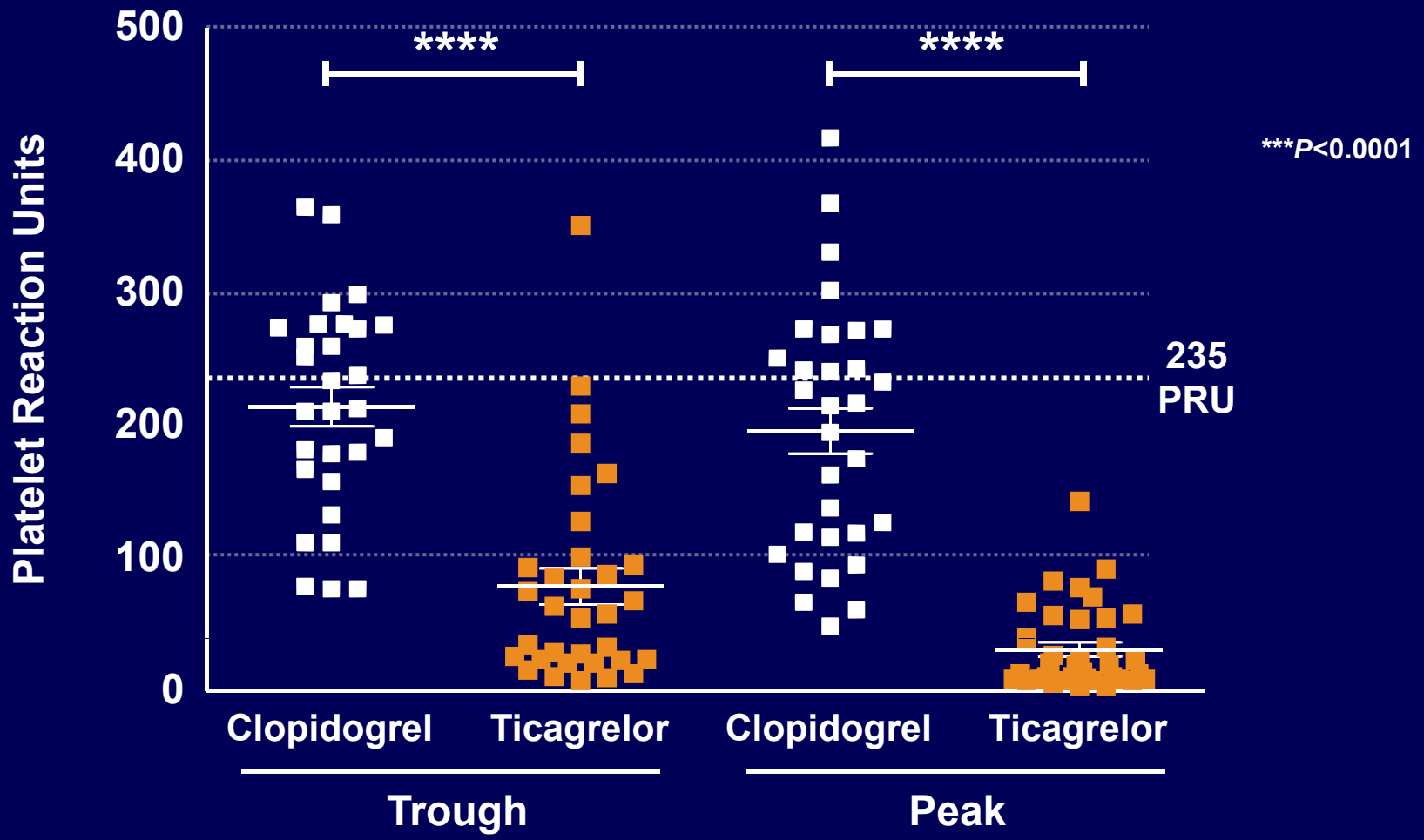


van Giezen JJJ, Humphries RG. *Semin Thromb Hemost.* 2005;31:195-204.


ONSET/OFFSET Study IPA with ADP 5uM (final extent)
Ticagrelor 180mg LD / 90 mg bd (n=54)
Clopidogrel 600mg LD / 75 mg od (n=50)
IPA %
100
90
80
70
60
50
40
30
20
10
0
0 .5 1 2 4 8 24 6 weeks 0 2 4 8 24 48 72 120 168 240
Onset
Maintenance
Offset
Time (hours)
Gurbel PA et al. Circulation 2009

PLATO PLATELET: VerifyNow $P2Y_{12}$ Assay

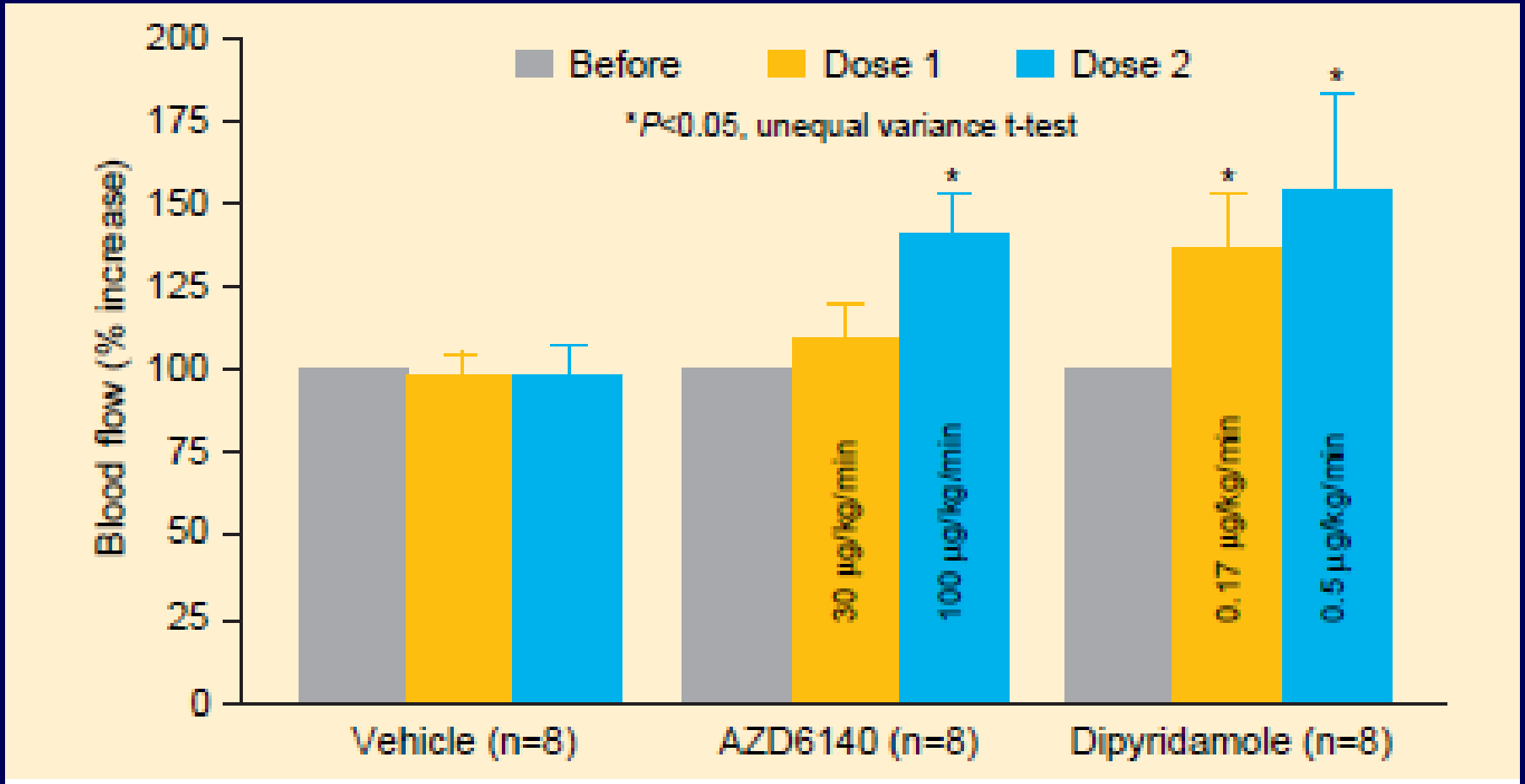
Comparing Maintenance Therapy with Clopidogrel vs Ticagrelor



Storey RF et al. J Am Coll Cardiol 2010

Ticagrelor and adenosine uptake

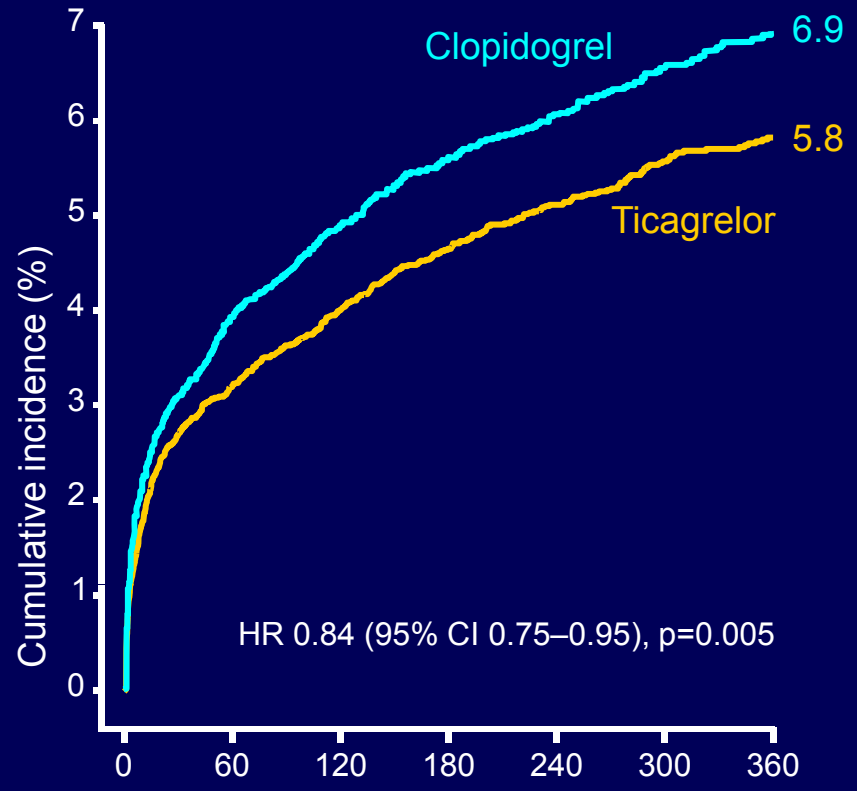
Coronary artery flow response to adenosine
30 µg/min intra-arterial infusion (mean ± SEM)



Jan-Arne Björkman, Ian Kirk, JJJ van Giezen. AHA 2007

Secondary efficacy endpoints over time

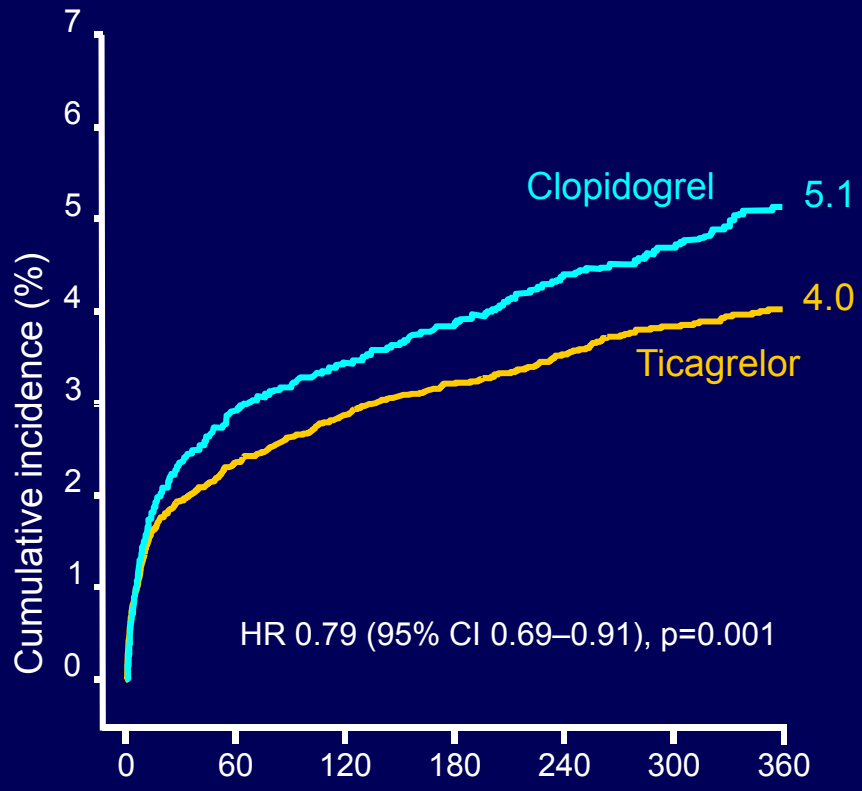
Myocardial infarction



No. at risk

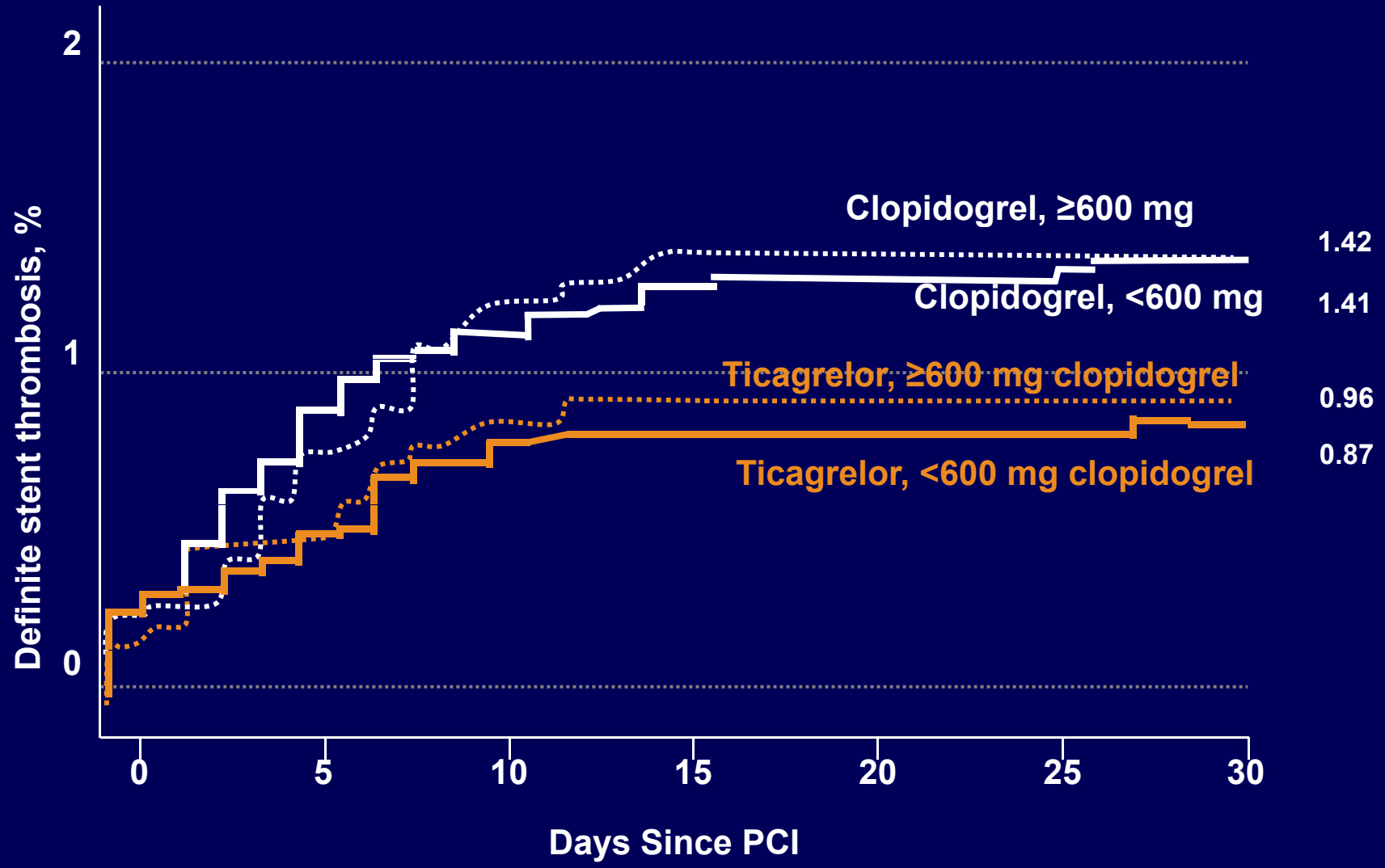
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

Cardiovascular death



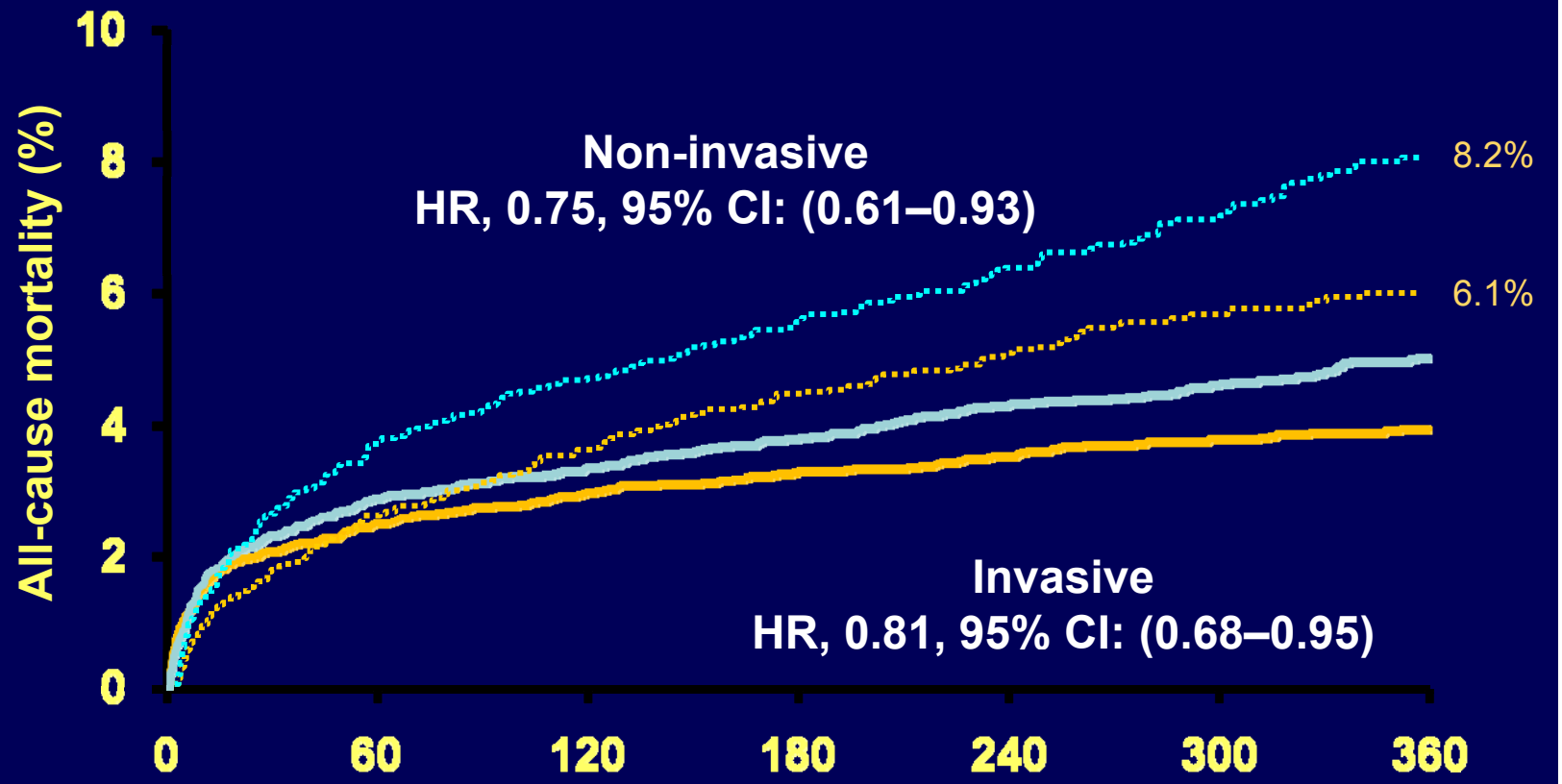
	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

PLATO Invasive
Definite Stent Thrombosis



Cannon CP, et al. *Lancet.* 2010;375:283-293.

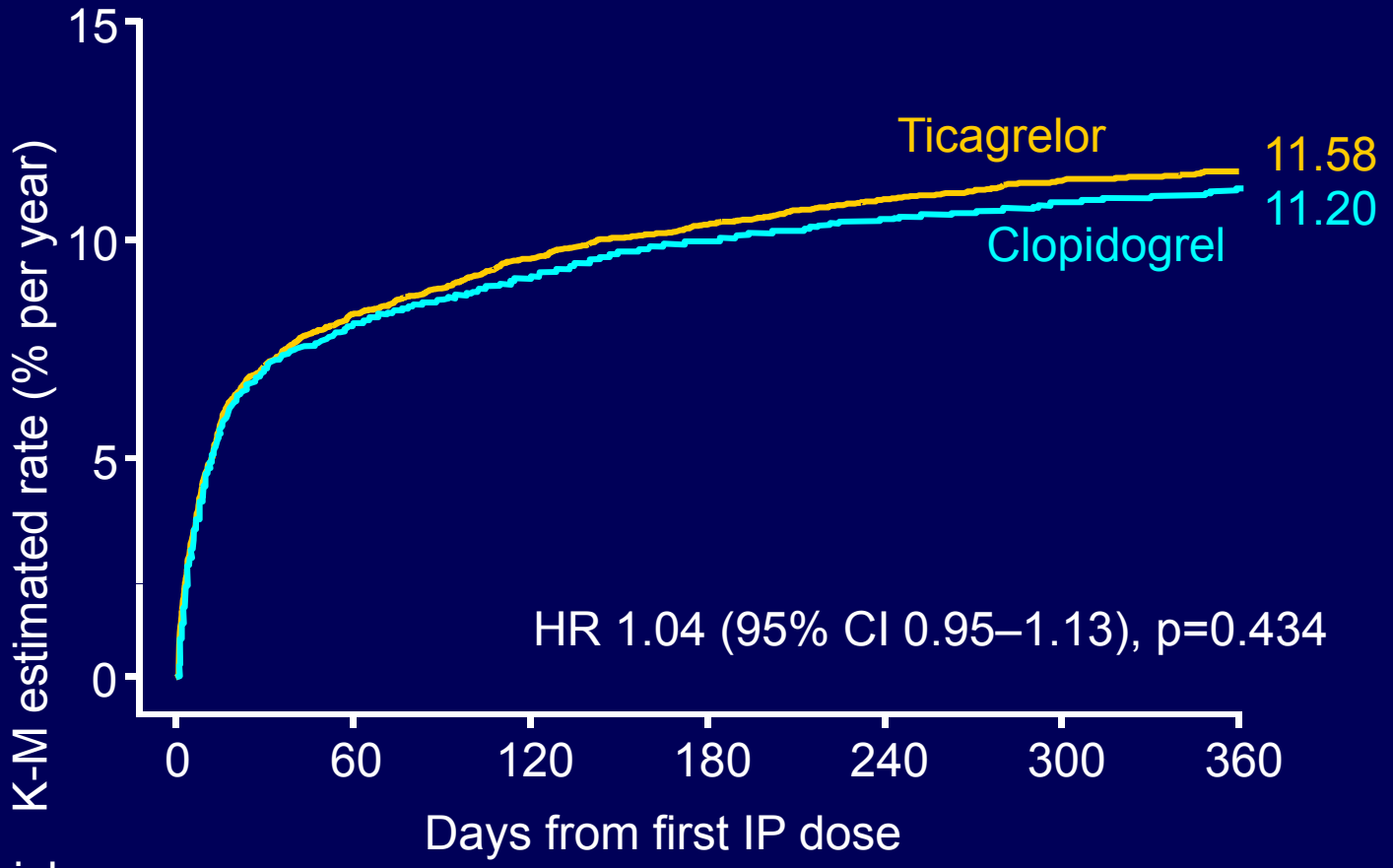
PLATO All-cause mortality – planned invasive vs non-invasive strategy



Number at risk							
Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

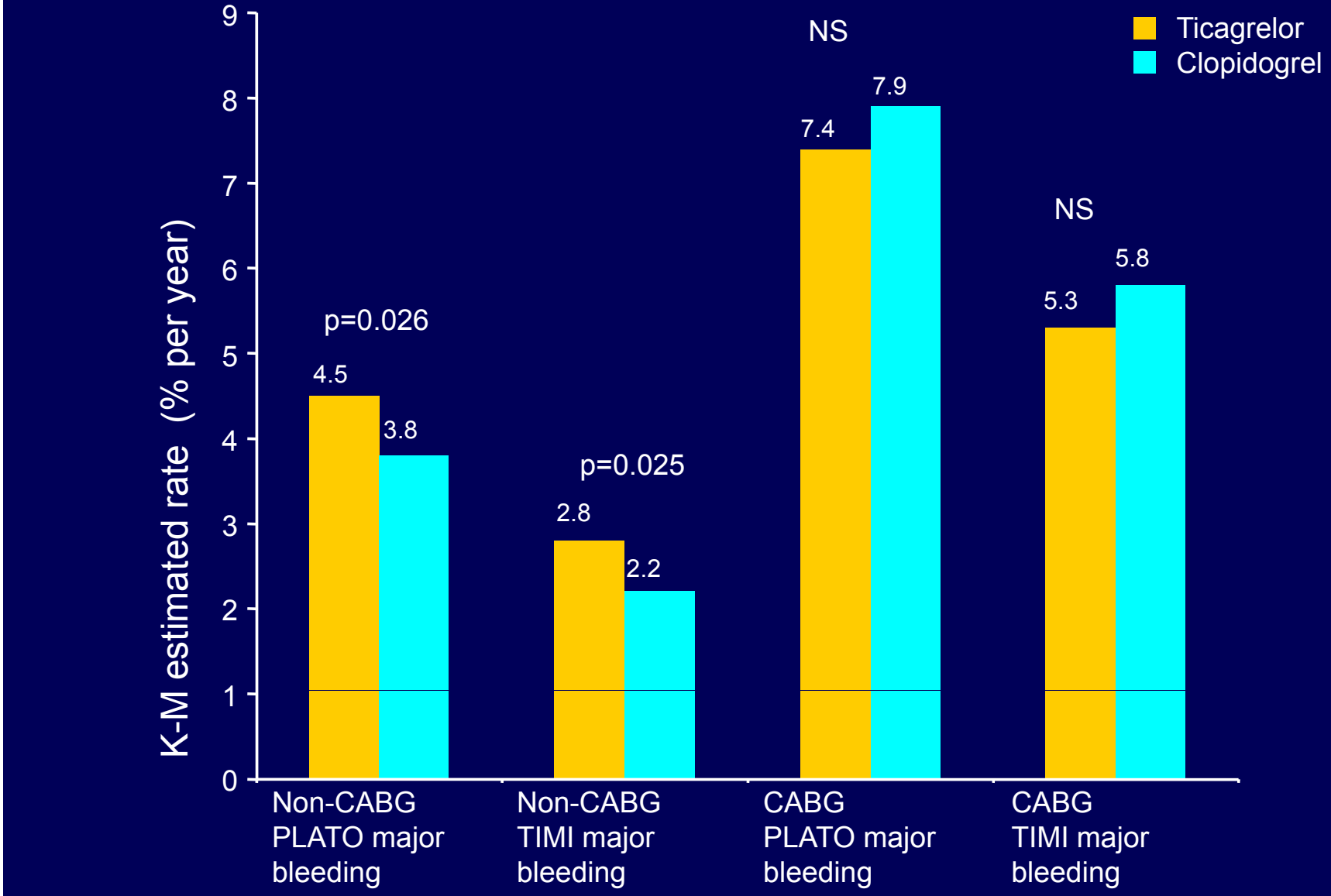
James S et al. Brit Med J 2011

Time to major bleeding – primary safety event



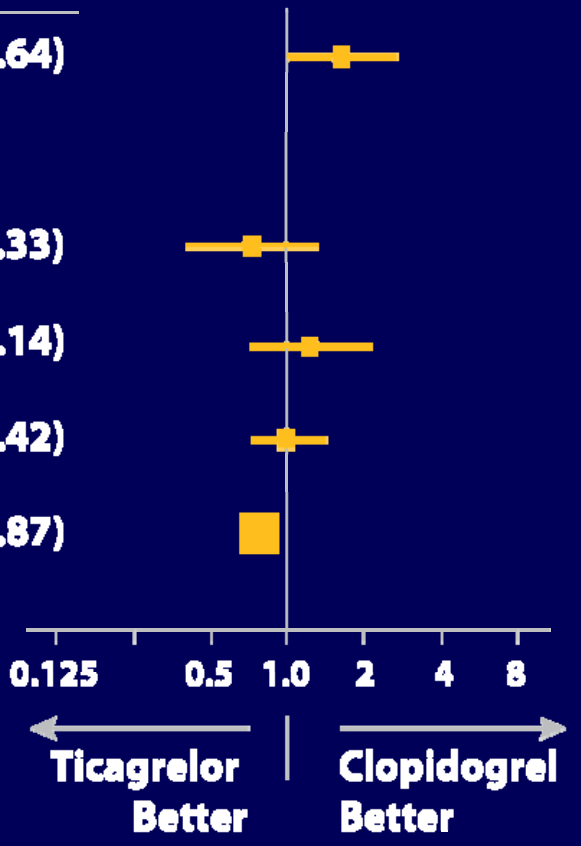
No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

PLATO
Non-CABG and CABG-related major bleeding



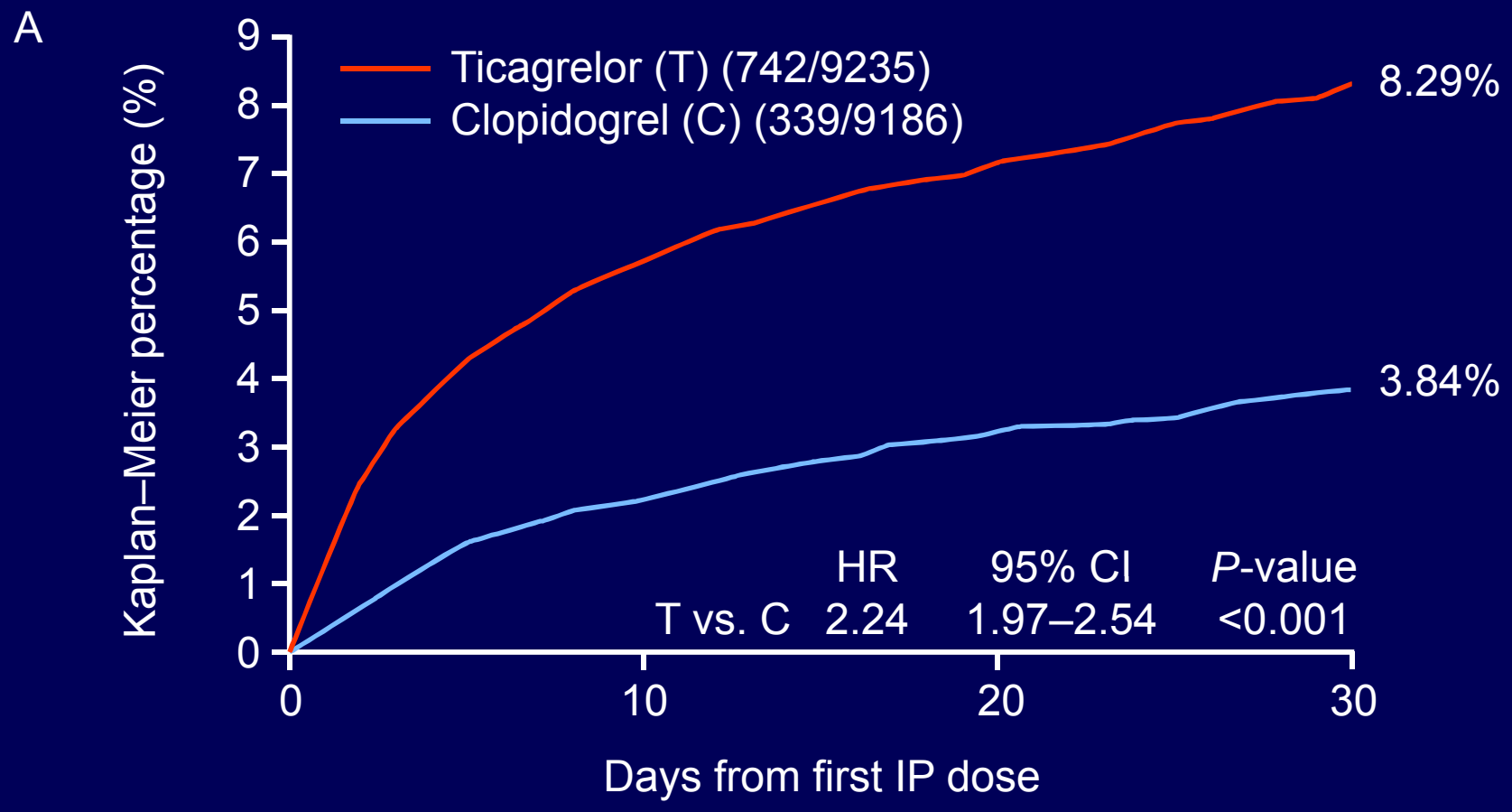
Primary Efficacy Outcome
US and Non-US and by ASA Dose

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



**Hazard ratio not calculated due to small number of events.*

PLATO: Any dyspnoea AE (≤30 days)



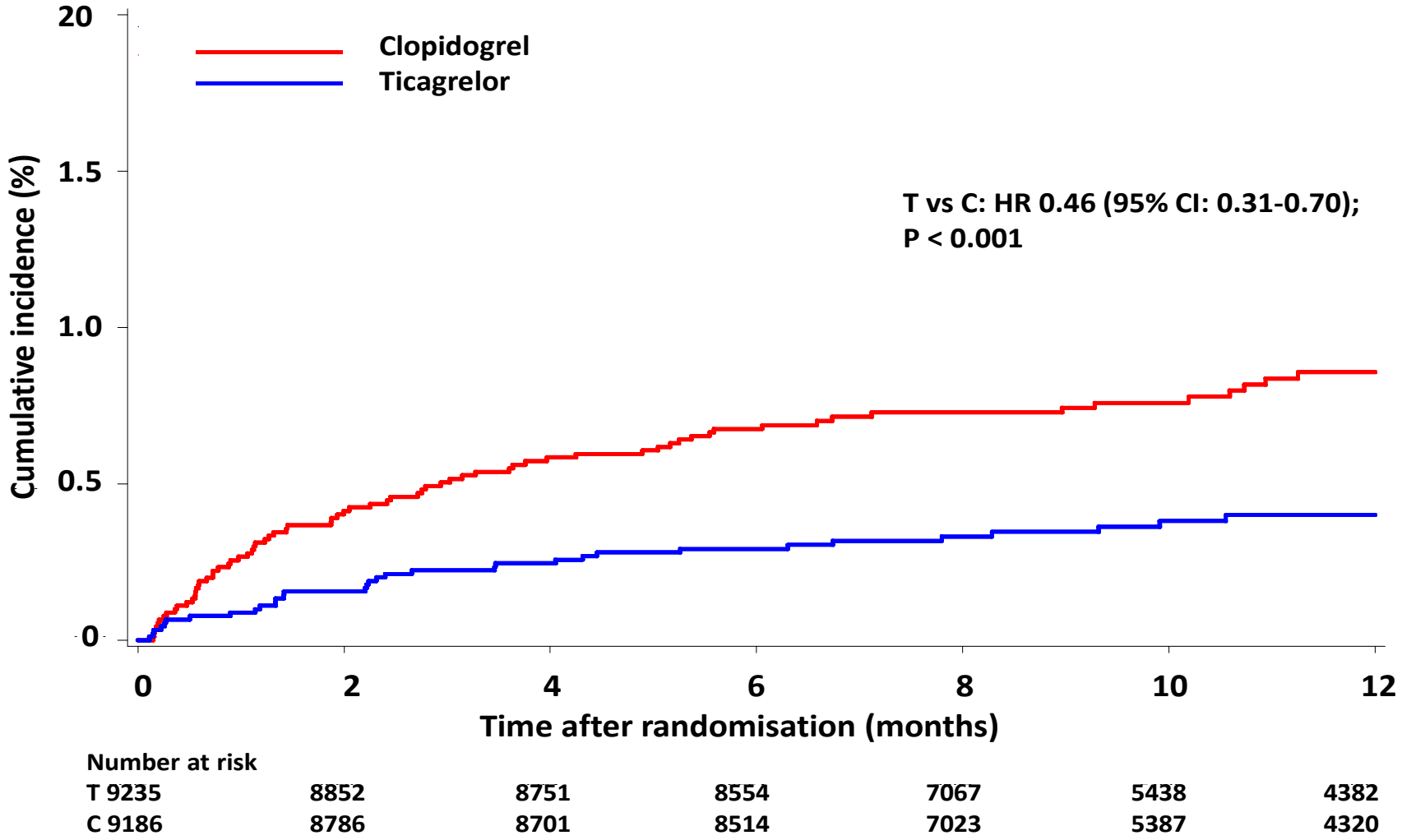
n at risk

T	9235	8380	7740	7470
C	9186	8644	8053	7844

Storey RF et al. Eur Heart J 2011.

AE = adverse event; CI = confidence interval; HR = hazard ratio; IP = investigational product.

Death following on-treatment pulmonary AE

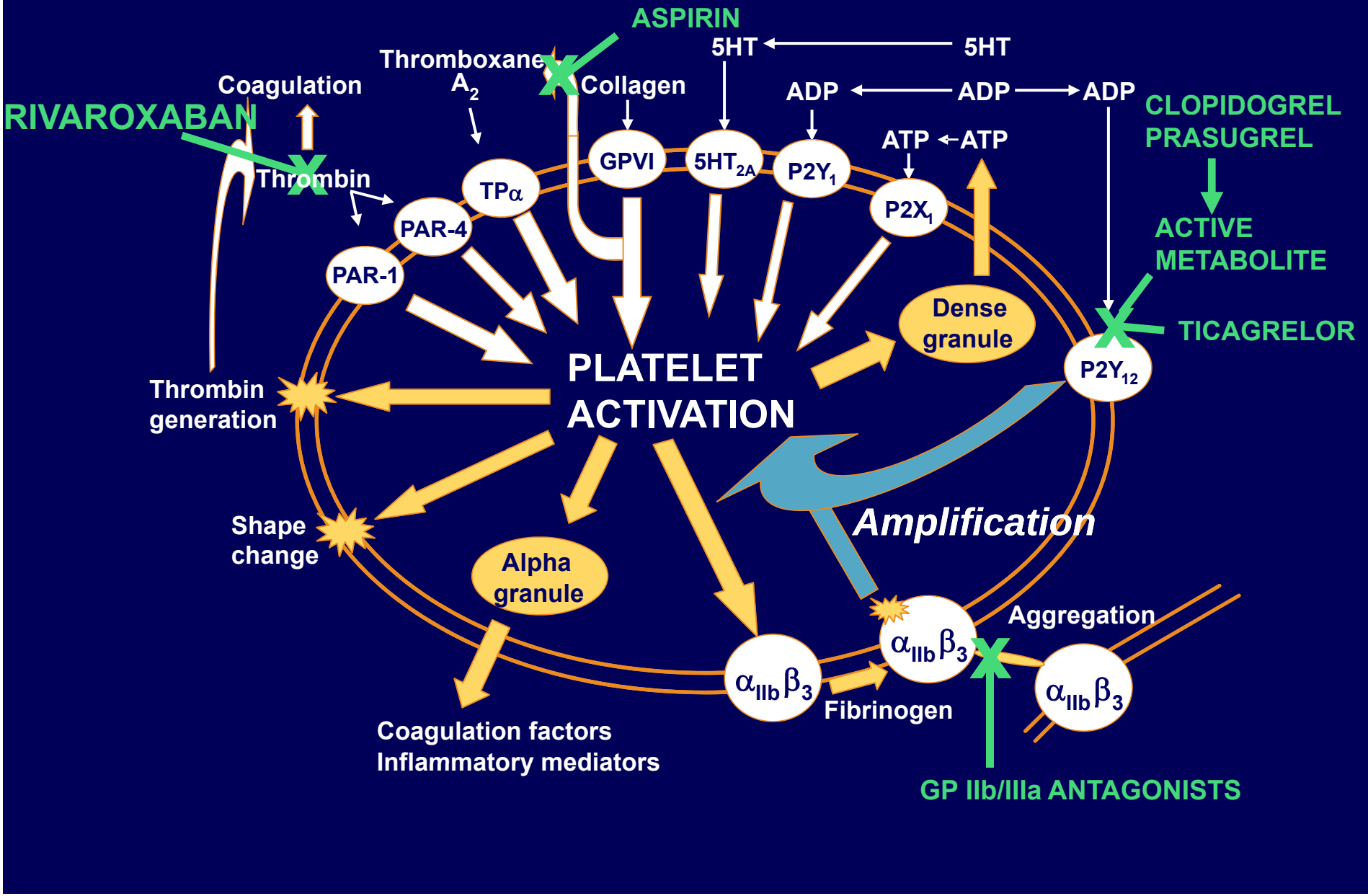


Storey RF et al. Presented at ACC 2012

Factor Xa antagonism in ACS: ATLAS studies

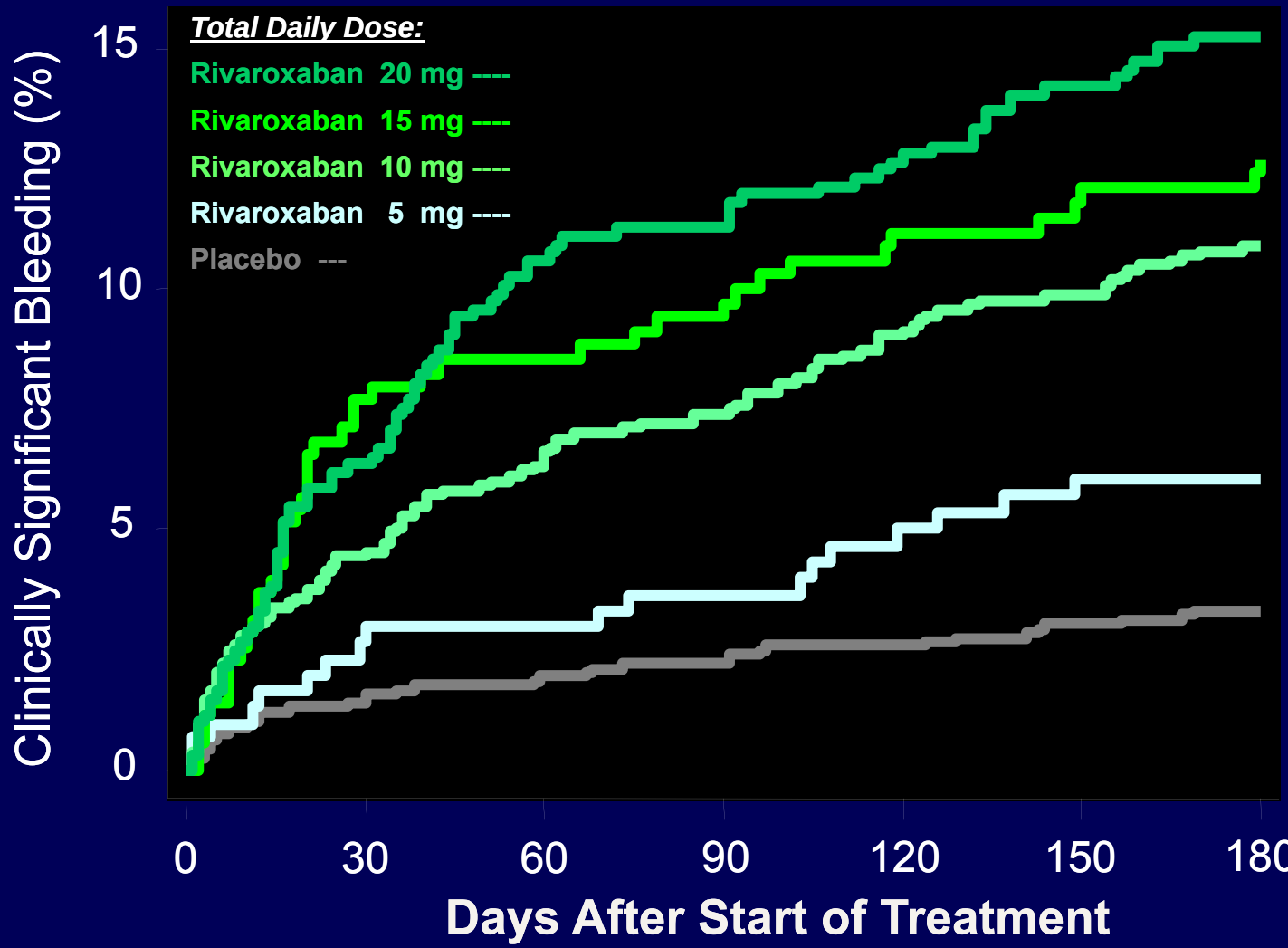
Rivaroxaban vs placebo

Antithrombotic action of rivaroxaban



PRIMARY SAFETY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

(= TIMI Major, TIMI Minor, Bleed Req. Med. Attn.)



	HR
15.3%	5.1 (3.4-7.4)
12.7%	3.6 (2.3-5.6)
10.9%	3.4 (2.3-4.9)
6.1%	2.2 (1.25-3.91)
3.3%	

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

Kaplan-Meier estimates for cumulative events, HR(CI), for bleeding rates during the 180 day period ; HR=Hazard Ratio; CI=Confidence Interval

Gibson CM, AHA 2008

Recent ACS: STEMI, NSTEMI, UA
No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine
Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

Placebo	RIVAROXABAN 2.5 mg BID	RIVAROXABAN 5.0 mg BID
N=5,176	n=5,174	N=5,176
ASA + Thieno, n=4,821	ASA + Thieno, n=4,825	ASA + Thieno, n=4,827
ASA, n=355	ASA, n=349	ASA, n=349

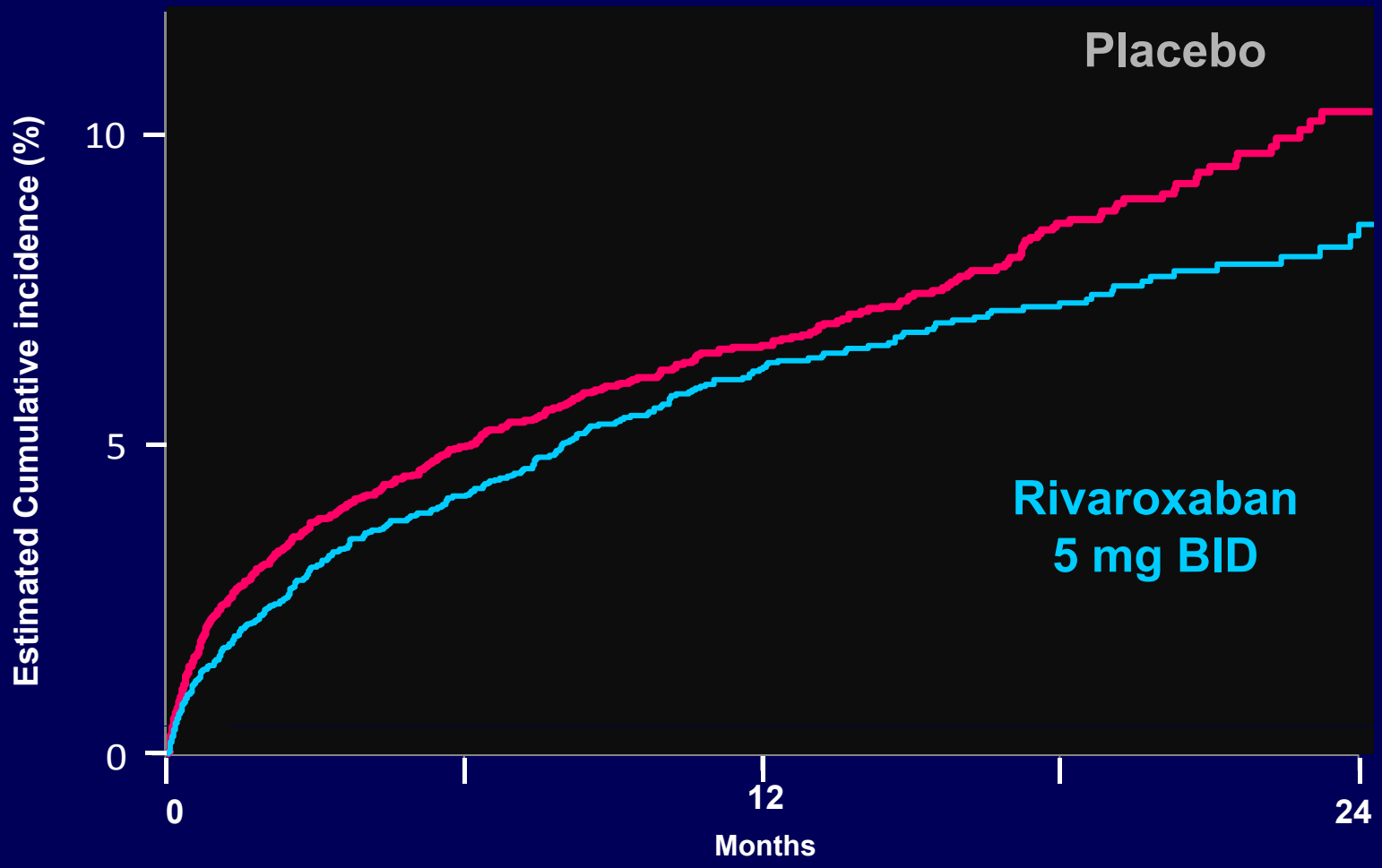
PRIMARY ENDPOINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke
** 184 subjects were excluded from the efficacy analyses prior to unblinding

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT: RIVAROXABAN 5.0 mg BID

CV Death / MI / Stroke*

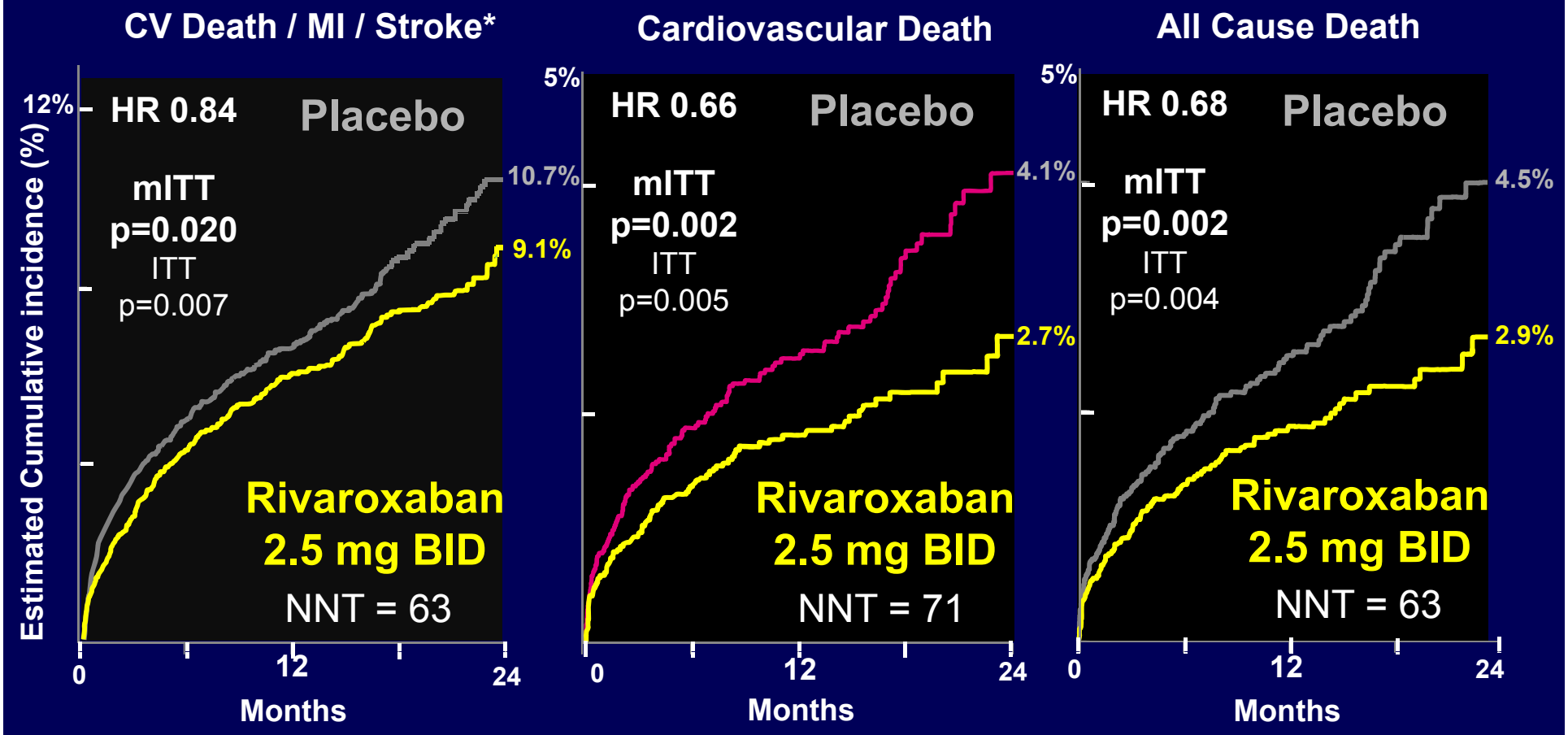


Rivaroxaban at 5 mg PO BID was associated with a numerical but not statistically significant reduction in mortality.

* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

ATLAS ACS 2 TIMI 51

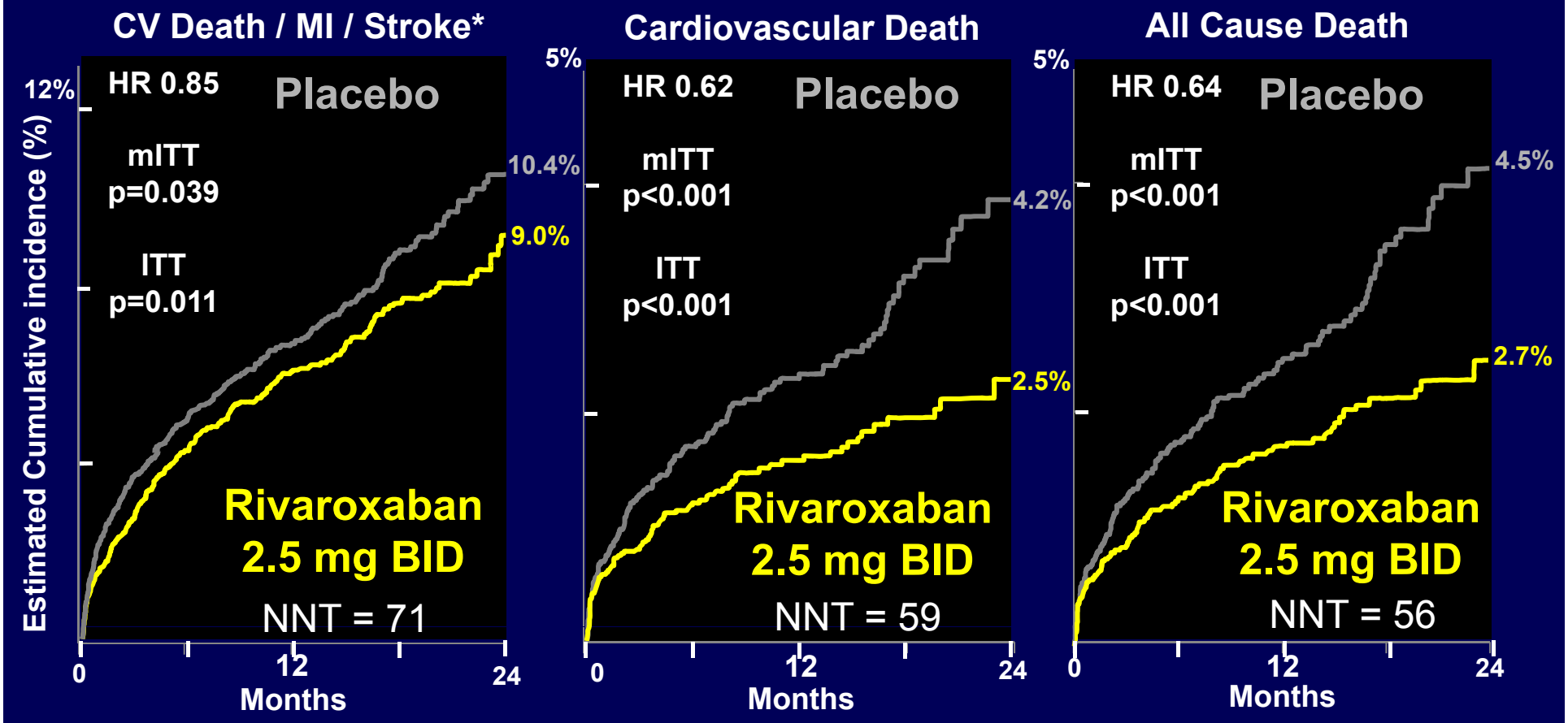
EFFICACY ENDPOINTS: RIVAROXABAN 2.5 mg PO BID



* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS: RIVAROXABAN 2.5 mg PO BID In Patients Treated with ASA + Thienopyridine



*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

TIMI Major non-CABG bleeding

Treatment-Emergent Non CABG TIMI Major Bleeding*

Analysis	Placebo	2.5 mg Rivaroxaban	5.0 mg Rivaroxaban
2 Yr KM Estimate	0.6%	1.8% HR 3.46	2.4% HR 4.47

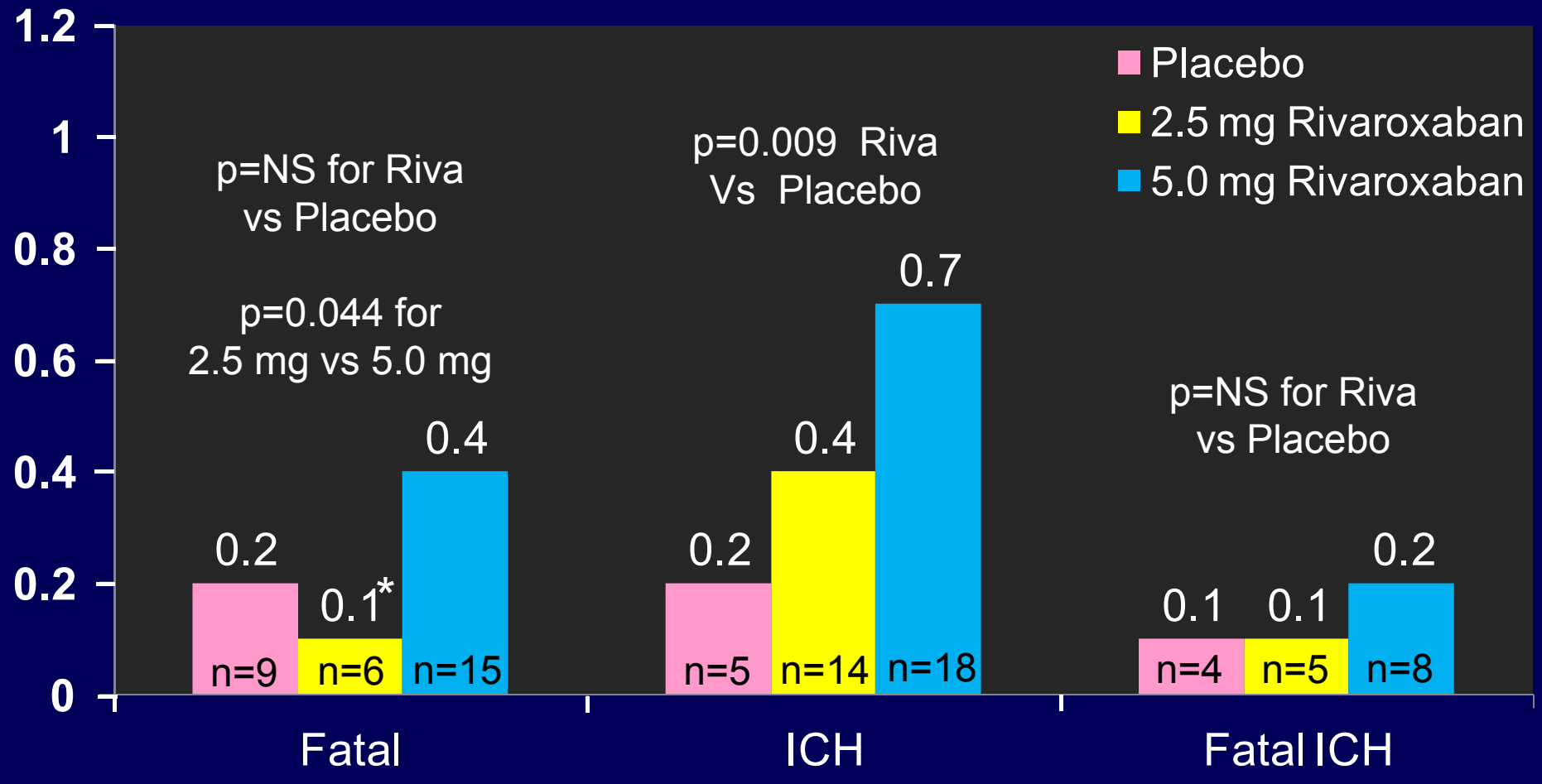
p<0.001

p<0.001

*: First occurrence of Non-CABG TIMI major bleeding events occurred between first dose to 2 days post last dose as adjudicated by the CEC across thienopyridine use strata; Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine are provided; Stratified log-rank p-values are provided; #: Raw percentage for CV death/MI/stroke (ischemic, hemorrhagic, uncertain) ; ##: Raw percentage of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement.

ATLAS ACS 2 TIMI 51

TREATMENT-EMERGENT FATAL BLEEDS AND ICH

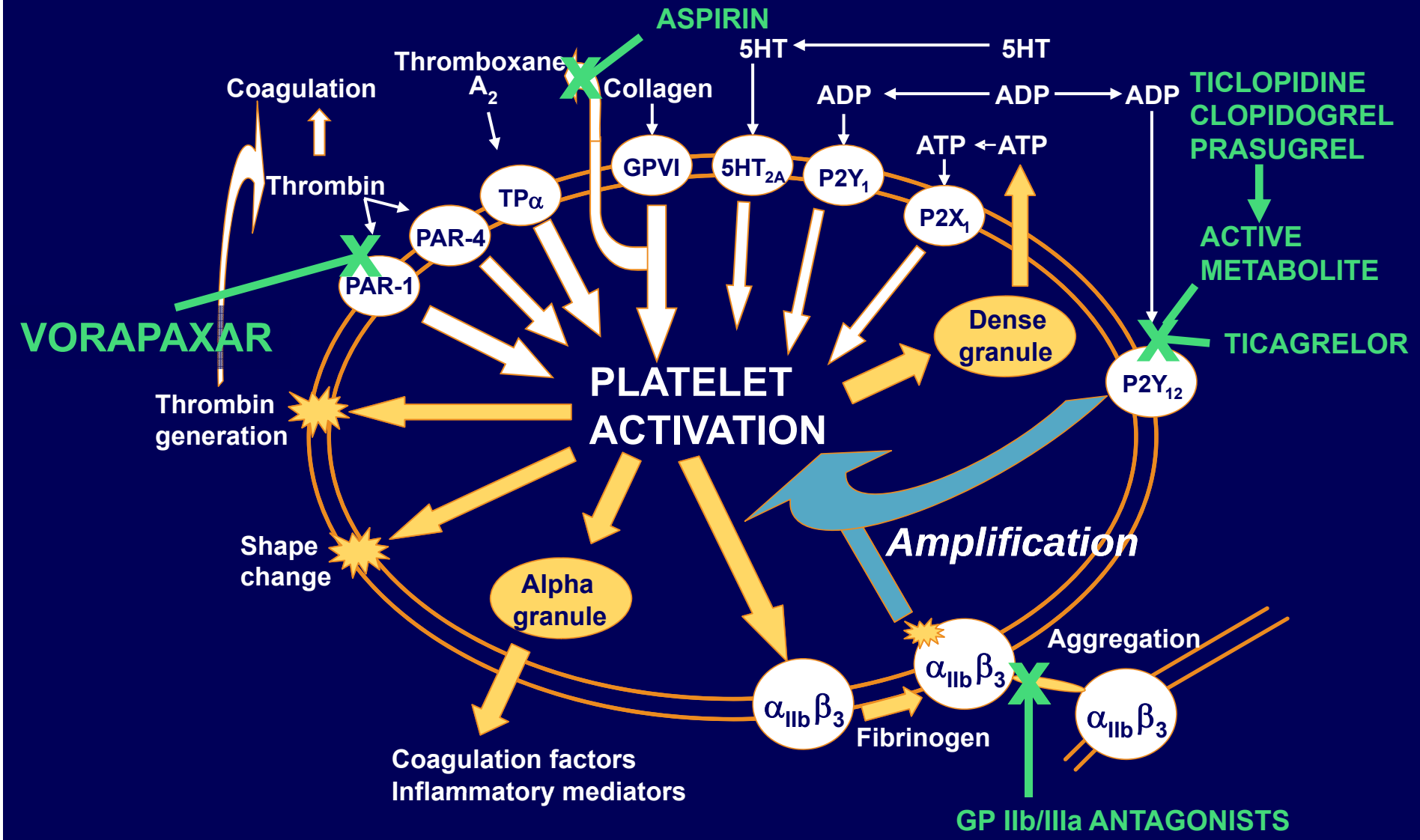


*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)

Thrombin receptor antagonism in ACS: TRACER study

Vorapaxar vs placebo

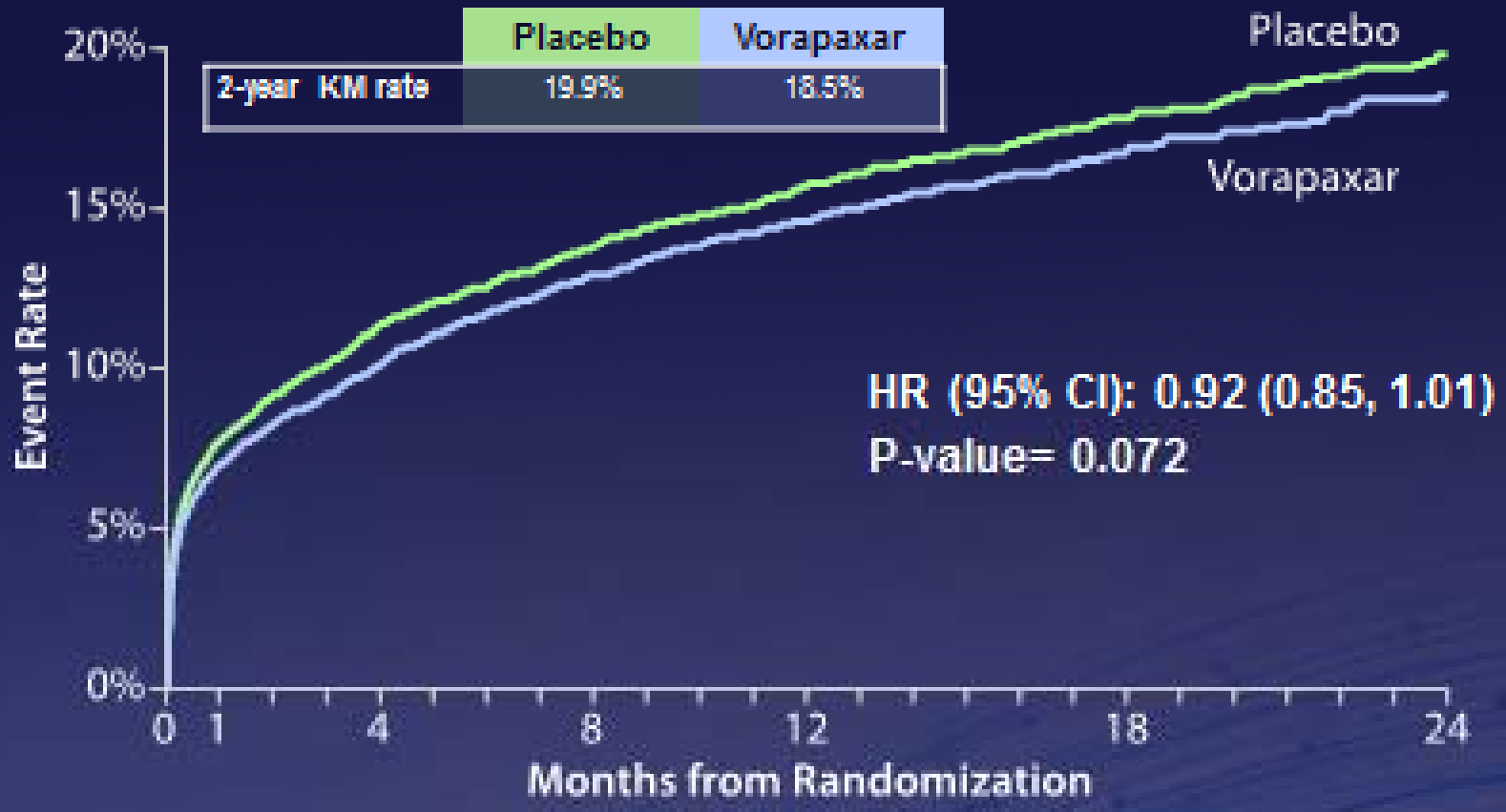
Antithrombotic action of vorapaxar



Primary Endpoint

CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

TRA·CER



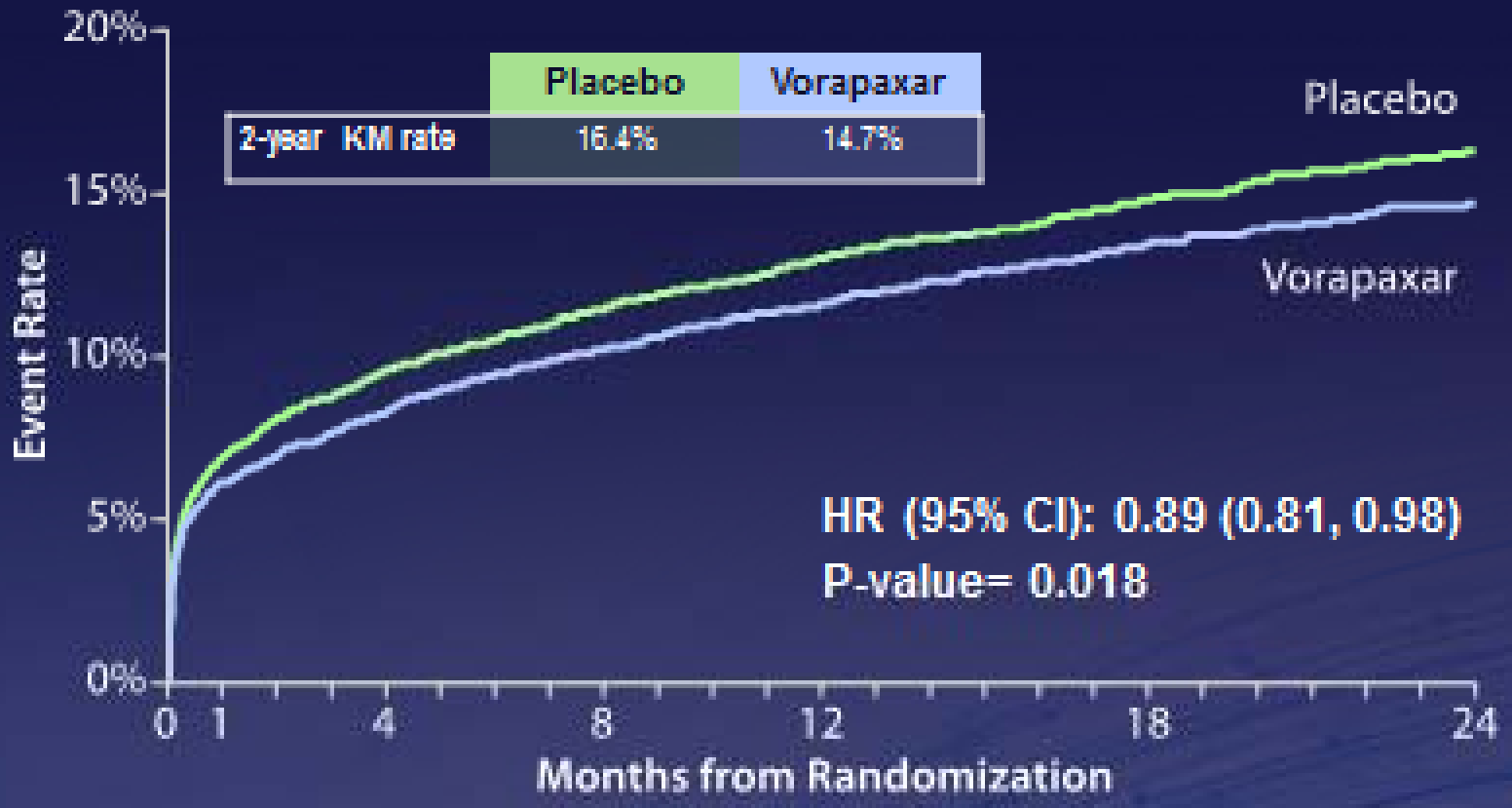
No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

Duke Clinical Research Institute

Key Secondary Endpoint

CV Death, MI, Stroke

TRA·CER



No. at risk

Placebo	6471	5895	5575	5263	3922	2383	830
Vorapaxar	6473	5949	5684	5356	4023	2427	868

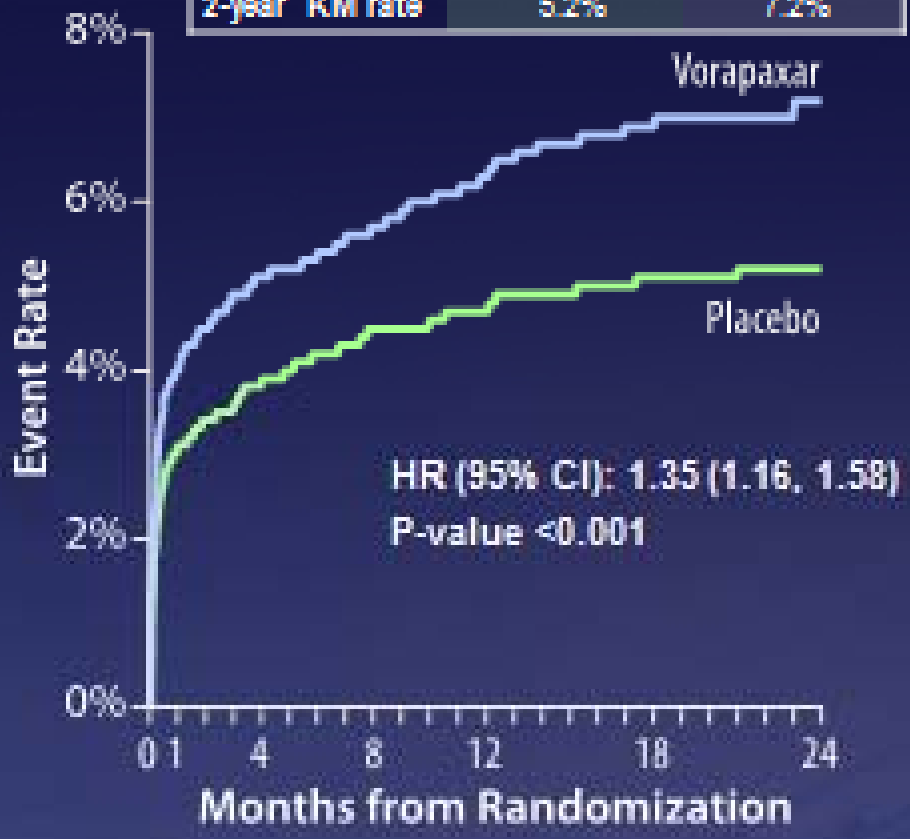
Duke Clinical Research Institute

Bleeding Outcomes

TRA·CER

GUSTO Moderate/Severe

	Placebo	Vorapaxar
2-year KM rate	5.2%	7.2%

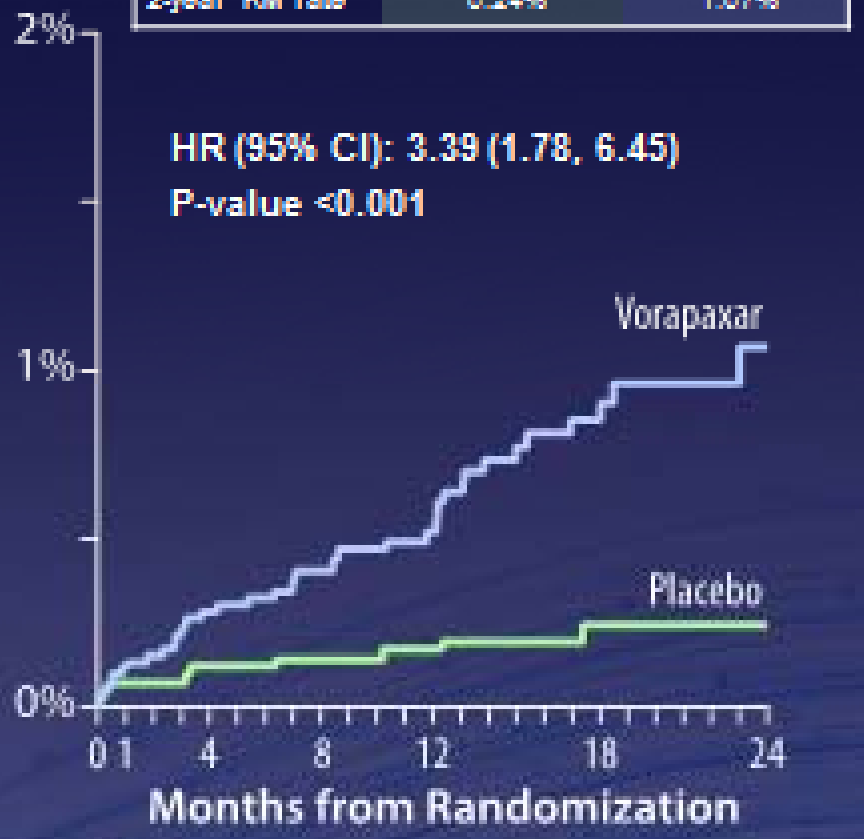


No. at risk

6441	5536	5137	4674	3393	1972	659
6445	5529	5108	4598	3278	1883	625

ICH

	Placebo	Vorapaxar
2-year KM rate	0.24%	1.07%



No. at risk

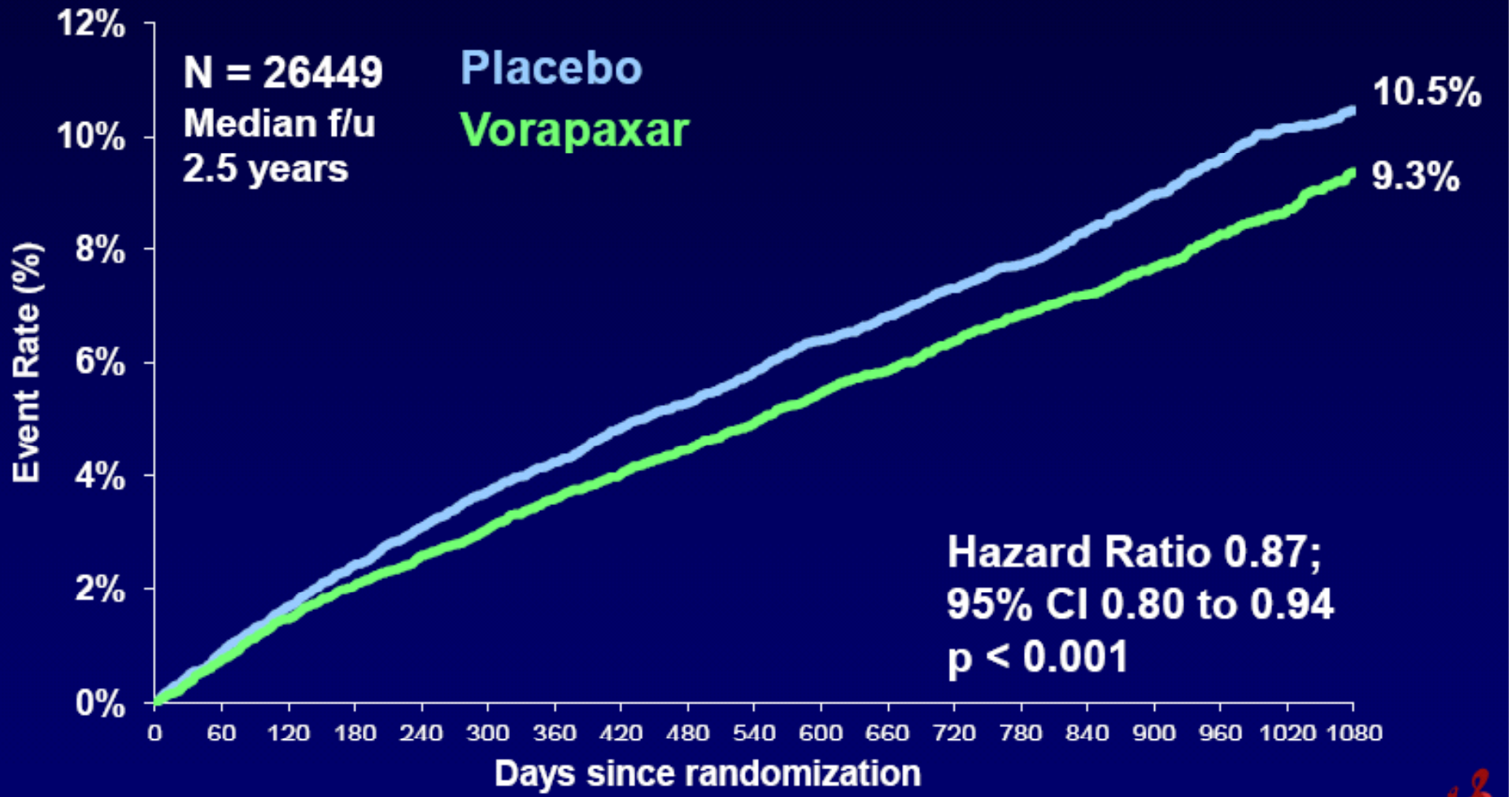
6441	5673	5281	4623	3511	2038	678
6445	5694	5272	4760	3411	1965	657

Duke Clinical Research Institute

TRA 2°P TIMI 50

Primary Efficacy Evaluation

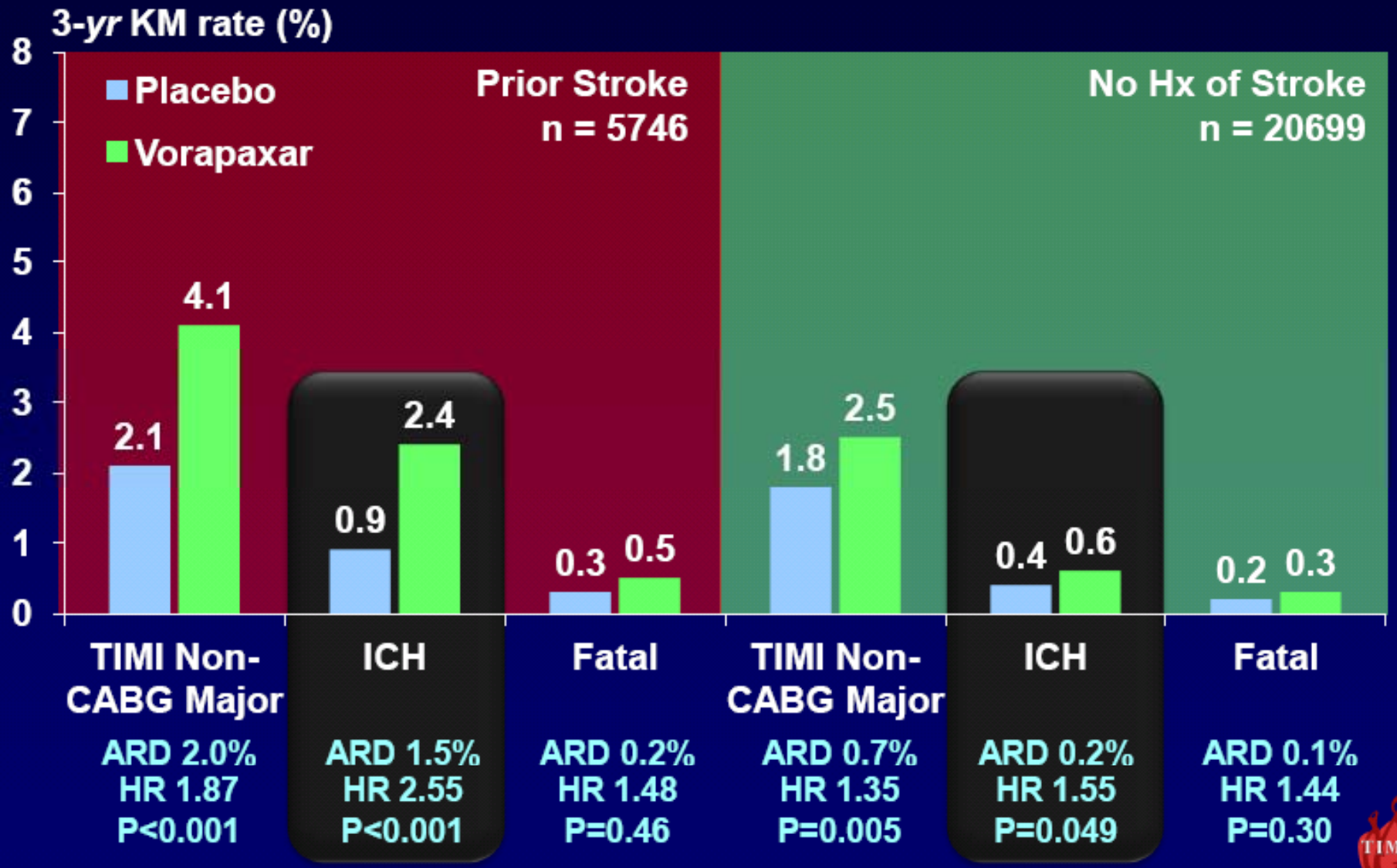
CV Death, MI, or Stroke



Morrow et al. ACC 2012, Chicago, March 24, 2012

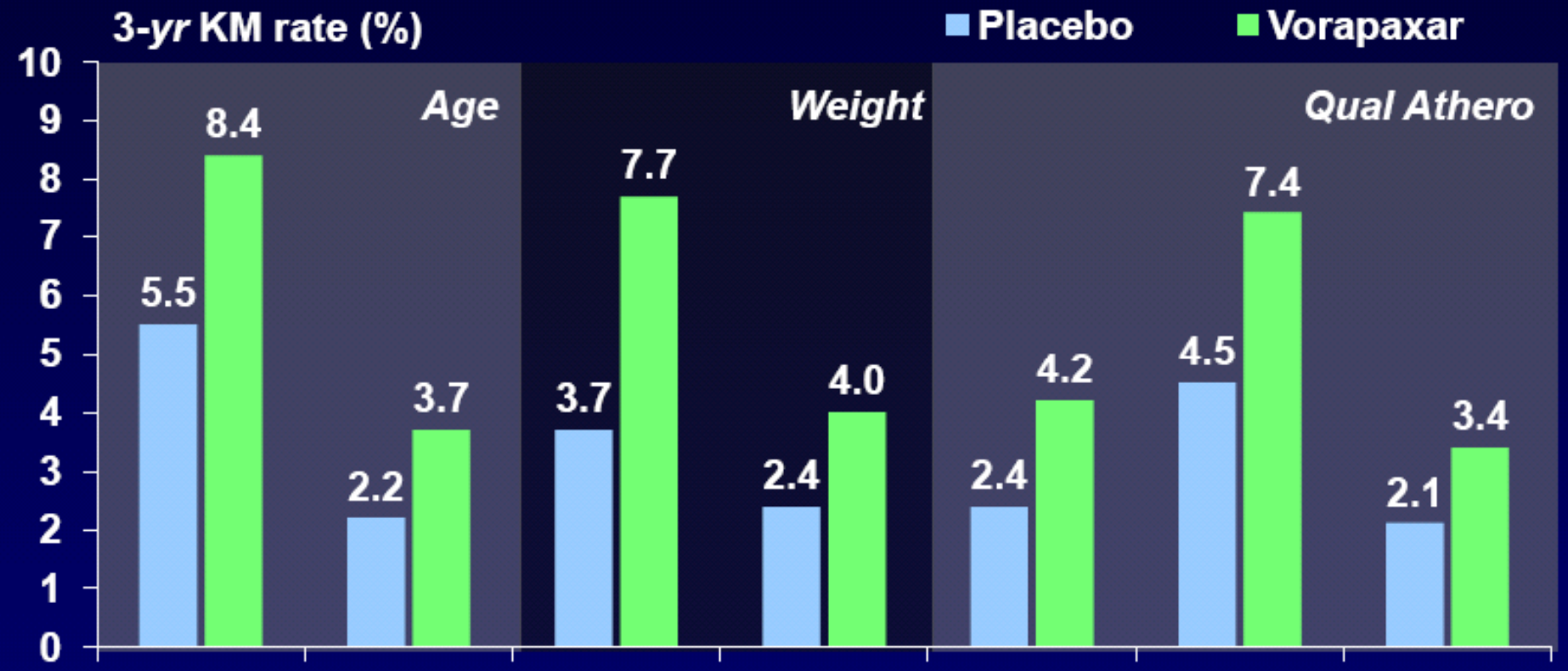
TRA 2°P TIMI 50

Major Bleeding Endpoints



Morrow et al. ACC 2012, Chicago, March 24, 2012

GUSTO Moderate or Severe Bleeding in Major Subgroups



ARD	2.9%	1.5%	4.0%	1.6%	1.8%	2.9%	1.3%
HR	1.69	1.65	1.95	1.64	1.93	1.62	1.61

P-interact *0.87* *0.50* *0.69*

SUMMARY

- **Ticagrelor:** novel mechanism of $P2Y_{12}$ inhibition, also an adenosine reuptake inhibitor, progressive mortality reduction over 12 months in ACS patients at expense of more dyspnoea and spontaneous bleeding
- **Rivaroxaban:** oral factor Xa inhibitor, net clinical benefit with mortality reduction at very low dose at expense of increased major bleeding ? patient selection, safety in combination with ticagrelor unknown
- **Vorapaxar:** thrombin receptor (PAR-1) antagonist, missed primary endpoint in ACS study, evidence of reduced MI at expense of increased major bleeding / ICH ? secondary prevention role in low bleeding risk subgroups

FUTURE STUDIES NEED TO ADDRESS IDEAL COMBINATIONS AND LONGTERM PROPHYLAXIS POST ACS

Thank you for listening!