Cardiovascular and Renal Drugs Advisory Committee Meeting

BRILINTA (ticagrelor)

AstraZeneca

July, 2010

Ticagrelor

- First orally active, reversibly binding, $P2Y_{12}$ antagonist
- Superior to clopidogrel in reducing CV death, MI or stroke in ACS
- No increase in overall risk of major bleeding vs clopidogrel
  - Similar profile for fatal, fatal+life-threatening, or CABG-related bleeding
  - More non-CABG, including non-procedural, bleeding
- CV mortality benefit a rare trial result
  - Especially for an active-controlled trial
  - Not seen in most contemporary ACS trials

Ticagrelor: Important Characteristics

- Not a prodrug; does not require metabolic activation
- Rapid onset of inhibitory effect
  - Important in urgent management of ACS
- Greater and more consistent inhibition than clopidogrel
  - Higher average inhibition of platelet aggregation
  - Less variability in individual response than clopidogrel
- Binding to the target $P2Y_{12}$ receptor is reversible
  - Recovery of platelet function does not depend on generation of new platelets
  - Faster offset of platelet inhibition than clopidogrel

BRILINTA (Ticagrelor) Proposed Indication

- Ticagrelor is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be
  - Managed medically
  - Managed invasively
    - With percutaneous coronary intervention (with or without stent) and/or CABG
- Ticagrelor as compared to clopidogrel has been shown to decrease the rate of
  - A combined endpoint of cardiovascular death, MI or stroke
  - The difference between treatments was driven predominantly by CV death and MI with no difference on strokes
- Ticagrelor as compared to clopidogrel has also been shown separately to reduce the rate of
  - CV death
  - MI

Ticagrelor: Sponsor Presentation Plan

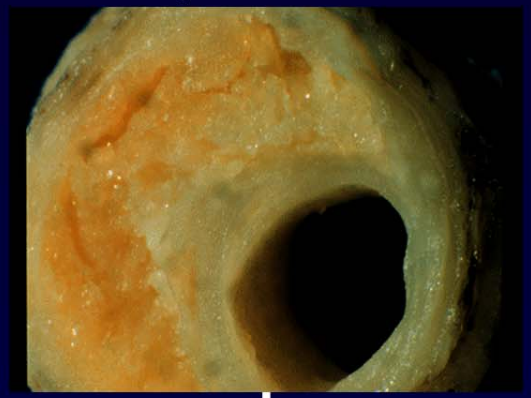
Introduction	**Jonathan Fox, MD, PhD** Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	**Lars Wallentin, MD, PhD** Professor of Cardiology Director Uppsala Clinical Research Center University Hospital, Uppsala, Sweden
PLATO: Design and Results	**Robert A Harrington, MD** Professor of Medicine Duke University School of Medicine Director, Duke Clinical Research Institute
Ticagrelor Safety Profile	**Kristen K Buck, MD** Director, Clinical Development AstraZeneca
PLATO: North America	**Kevin J Carroll, BSc, MSc, FRSS** VP Statistics and Chief Statistician AstraZeneca
Benefit and Risk of Ticagrelor	**Robert A Harrington, MD**

Ticagrelor: Sponsor Presentation Plan

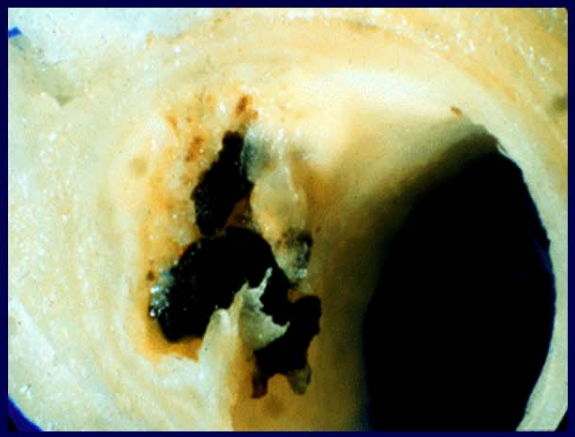
Introduction	Jonathan Fox, MD, PhD Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	**Lars Wallentin, MD, PhD** **Professor of Cardiology** **Director Uppsala Clinical Research Center** **University Hospital, Uppsala, Sweden**
PLATO: Design and Results	Robert A Harrington, MD Professor of Medicine Duke University School of Medicine Director, Duke Clinical Research Institute
Ticagrelor Safety Profile	Kristen K Buck, MD Director, Clinical Development AstraZeneca
PLATO: North America	Kevin J Carroll, BSc, MSc, FRSS VP Statistics and Chief Statistician AstraZeneca
Benefit and Risk of Ticagrelor	Robert A Harrington, MD

The Spectrum of Acute Coronary Syndrome

Coronary atherosclerosis



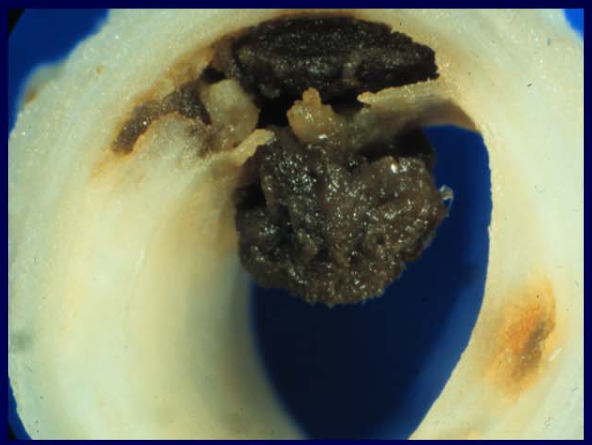
Plaque erosion + thrombus



Chest pain episodes

Unstable Angina

Plaque fissure + thrombus



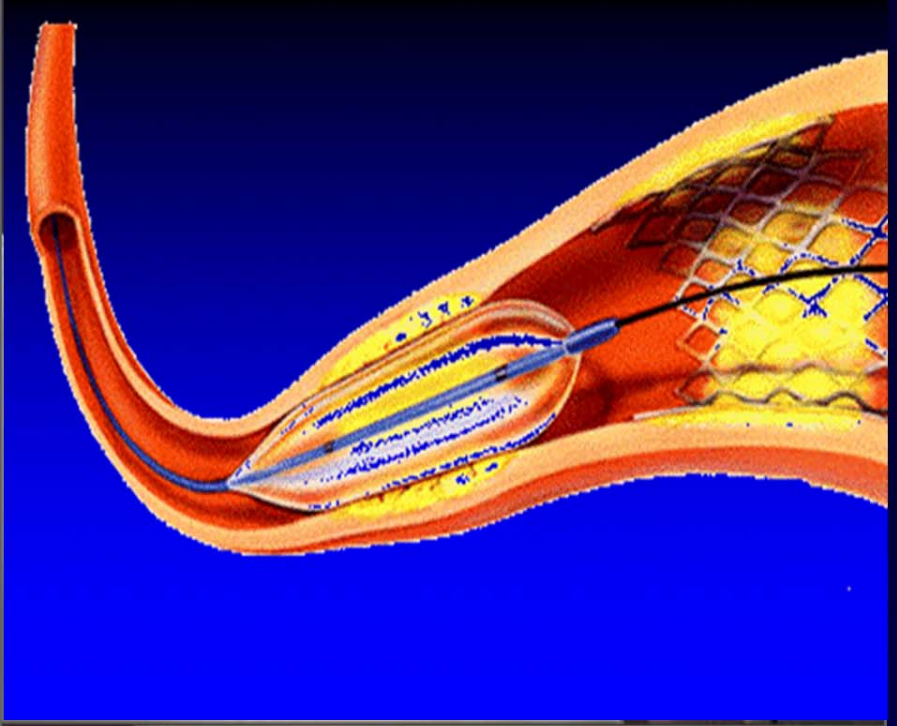
ST-dep. Troponin

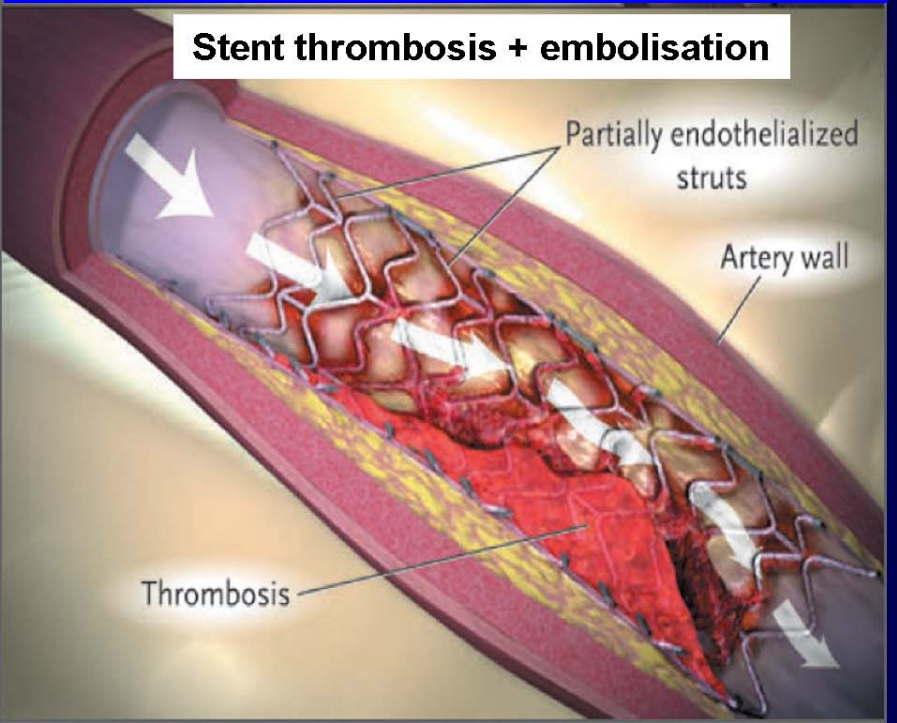
Non STEMI

Plaque rupture + occlusion

ST-elevation

STEMI



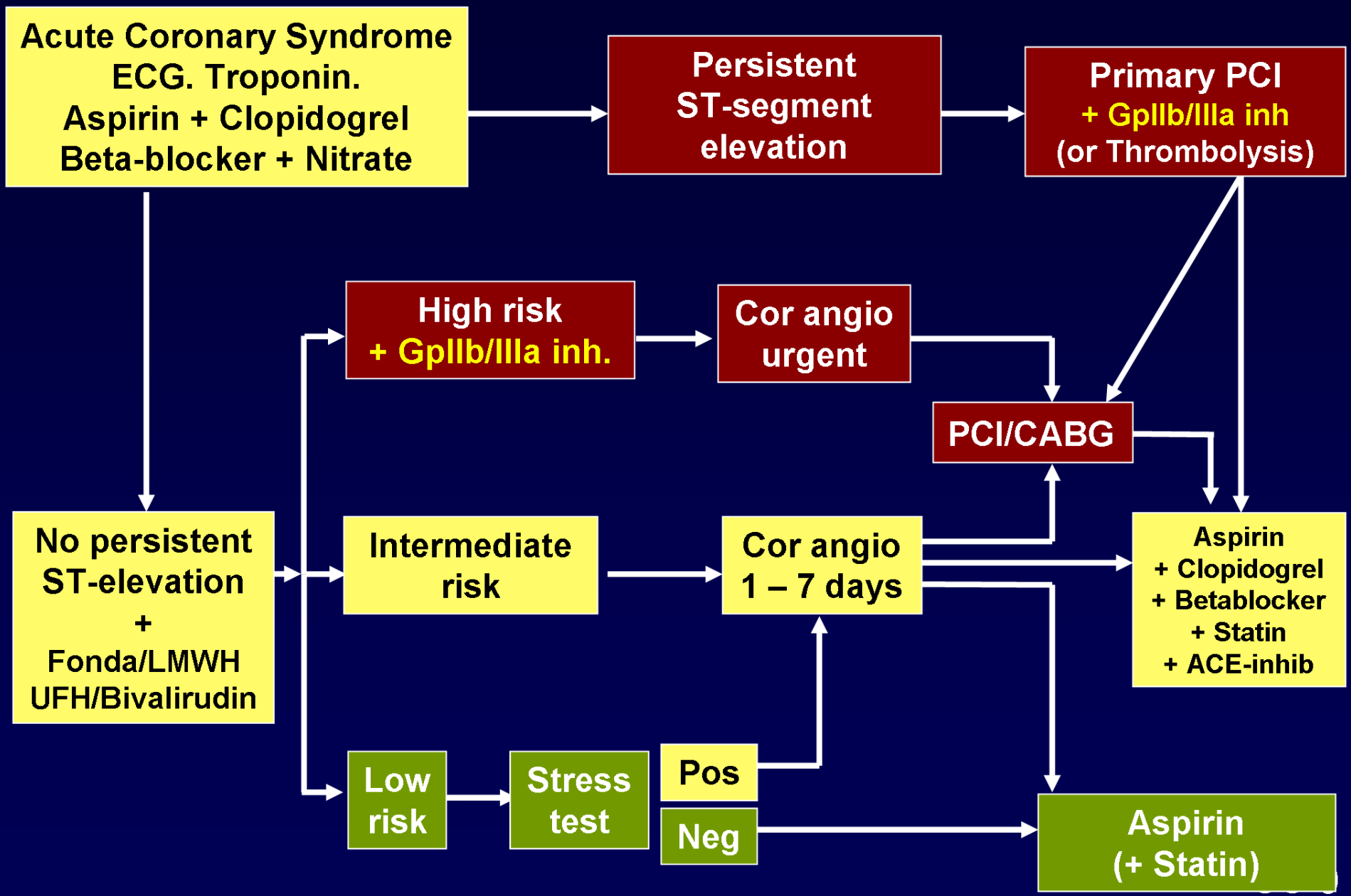


Invasive Treatment of ACS
New Pathophysiology of MI

by

- Stent thrombosis
- Myocardial embolisation
- Biomarker elevation
- Peri-procedural MI
- Spontaneous MI (NSTEMI, STEMI)
- Death

ACC/AHA/ESC ACS Treatment Guidelines



ACS: Standard of Care

- Advances in treatment including dual antiplatelet treatment have improved outcomes in ACS
- Benefits of clopidogrel in multinational controlled trials
  - CURE – Non-STE-ACS (n=12562) 12 months; 20% RRR in CV-death, MI, Stroke
  - CLARITY – STEMI (n=3491) 7 days after fibrinolysis; 36% RRR in infarct related artery occlusion or MI or death before angiography
  - COMMIT – STEMI (n=45851) 30 days medical treatment; 7% RRR in total mortaltiy and 9% RRR in the composite of death, MI or stroke
  - CLASSICS, CREDO, many observational and loading dose trials have established protection against stent thrombosis and all MACE after stenting
- Reflected in ACC-AHA-ESC Guidelines for ACS and PCI
  - Class IA recommendation for clopidogrel for 12 months in patients with ACS and PCI-stent procedures

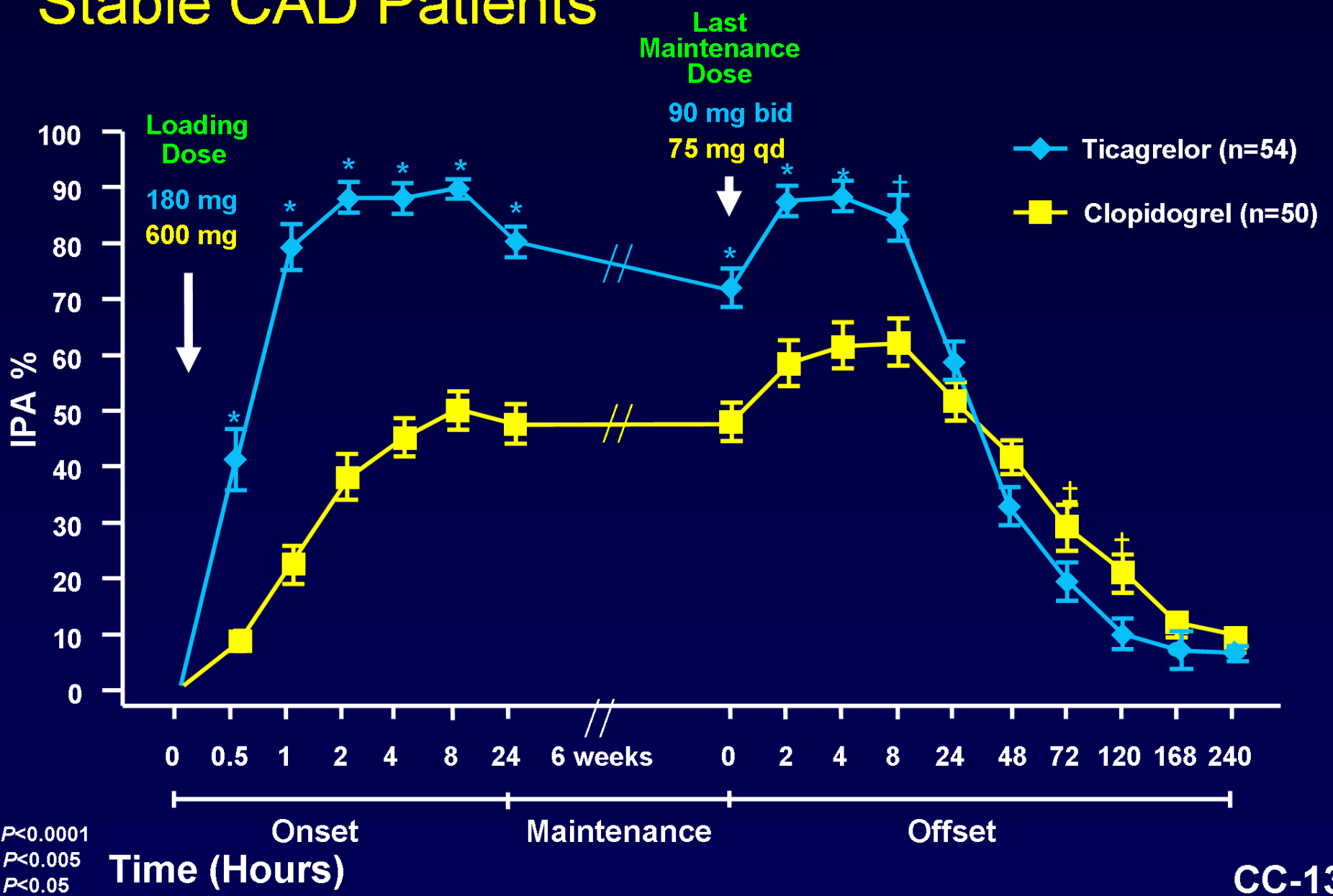
ACS: The Therapeutic Gap

- Despite the benefits of clopidogrel, there remains an important therapeutic gap
  - Morbidity and mortality in ACS remain high
    - ~11% of ACS patients sustain a subsequent CV event within a year
    - One third may die, have another ACS episode, or require rehospitalization within 6 months
- Some reasons for the gap: clopidogrel's limitations
  - Prodrug requiring metabolic activation
  - Gradual onset and delayed peak of antiplatelet activity
  - Individual patient response highly variable
  - Irreversible binding → irreversible platelet inhibition
  - Lacks a generalized mortality benefit

Ticagrelor: Early Clinical Development

- 41 Phase 1 studies (PK/PD, DDI, etc.)
- 4 Phase 2 studies
  - DISPERSE: Greater and more consistent IPA than clopidogrel
  - DISPERSE2: Similar bleeding risk
    - Supported dose selection of 90mg bid for Phase 3
    - Dyspnea, pauses, uric acid, renal effects identified
  - RESPOND
  - ONSET/OFFSET

ONSET/OFFSET: Pharmacodynamics in Stable CAD Patients



* $P<0.0001$
† $P<0.005$
‡ $P<0.05$

CC-13

PLATO: Goals of the Trial

- PLATO was designed to
  - Mimic closely current clinical practice: randomize any ACS pt based on initial presentation and ECG, within 24hr
    - NSTE or STE on initial ECG
    - Planned invasive or medical management
  - Demonstrate superiority vs. clopidogrel on the primary endpoint of CV death, MI or stroke
  - Quantify bleeding risk compared to clopidogrel
  - Characterize safety and tolerability of ticagrelor
  - Enhance knowledge of platelet biology and human disease
- To meet these goals: 18,624 patients, 43 countries, 862 sites, academic governance, extensive infrastructure

PLATO: Independent Scientific Governance

Executive Steering Committee

- Lars Wallentin, Co-Chair
  - Uppsala Clinical Research Center, Uppsala, SE
- Robert A Harrington, Co-Chair
  - Duke Clinical Research Institute & Duke University School of Medicine, Durham, NC
- Richard C Becker
  - Duke Clinical Research Institute & Duke University School of Medicine, Durham, NC
- Christopher P Cannon
  - TIMI Group, Brigham & Women's Hospital & Harvard Medical School, Boston, MA
- Steen Husted
  - Århus University Hospital, DK
- Hugo Katus
  - Universitätsklinikum Heidelberg, DE
- Allan Skene
  - Worldwide Clinical Trials, Nottingham, UK
- Ph. Gabriel Steg
  - INSERM Unité 698, Hôpitaux de Paris, and Université de Paris, FR
- Robert F Storey
  - University of Sheffield, UK
- Non-voting members
  - AZ physicians (2), ClinOps (1)

PLATO: Independent Scientific Governance

Steering Committee

(with representation from 43 countries)

ICAC
Independent Central Adjudication Committee
Led by
Kenneth W Mahaffey
DCRI

Biostatistics
Worldwide Clinical Trials, Inc

DSMB
Data Safety Monitoring Board

Jeffrey L. Anderson (Chair)

David DeMets

Frans Van de Werf

Maarten Simoons

Robert Wilcox

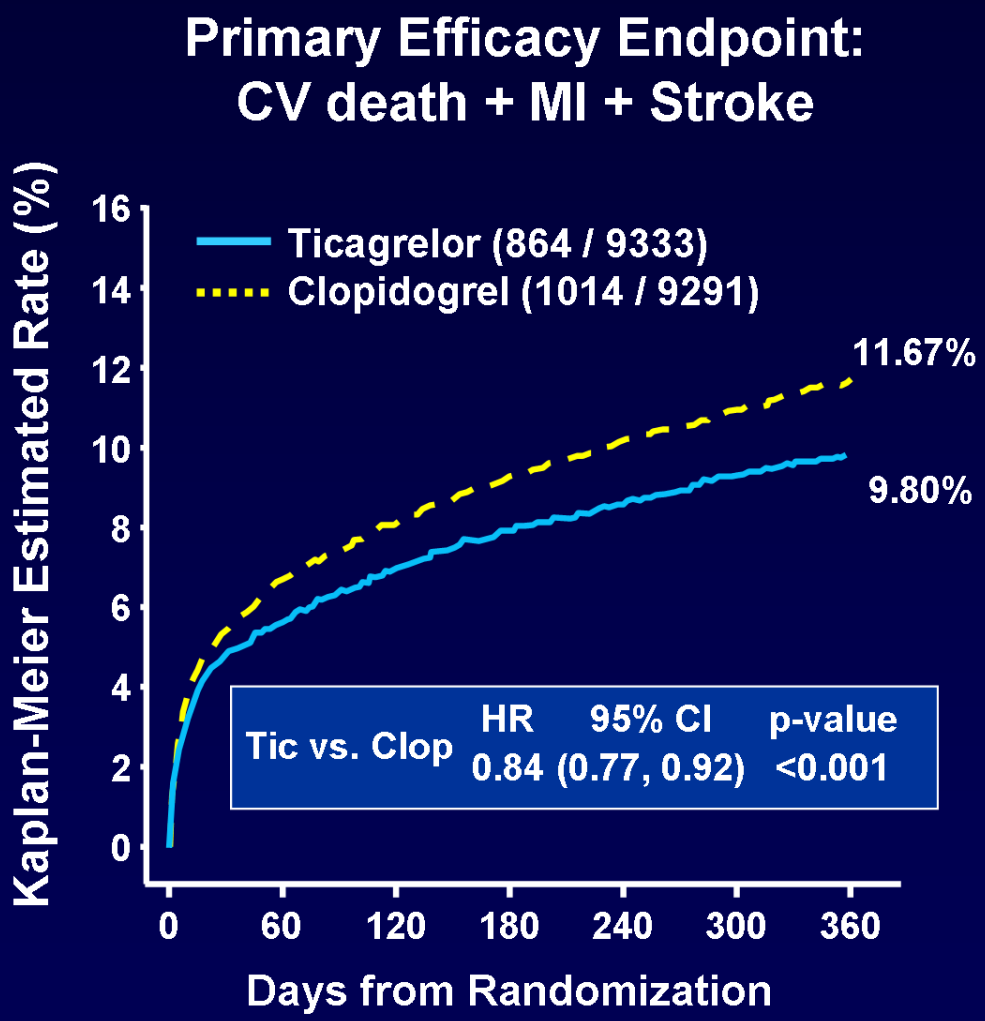
Ticagrelor: Sponsor Presentation Plan

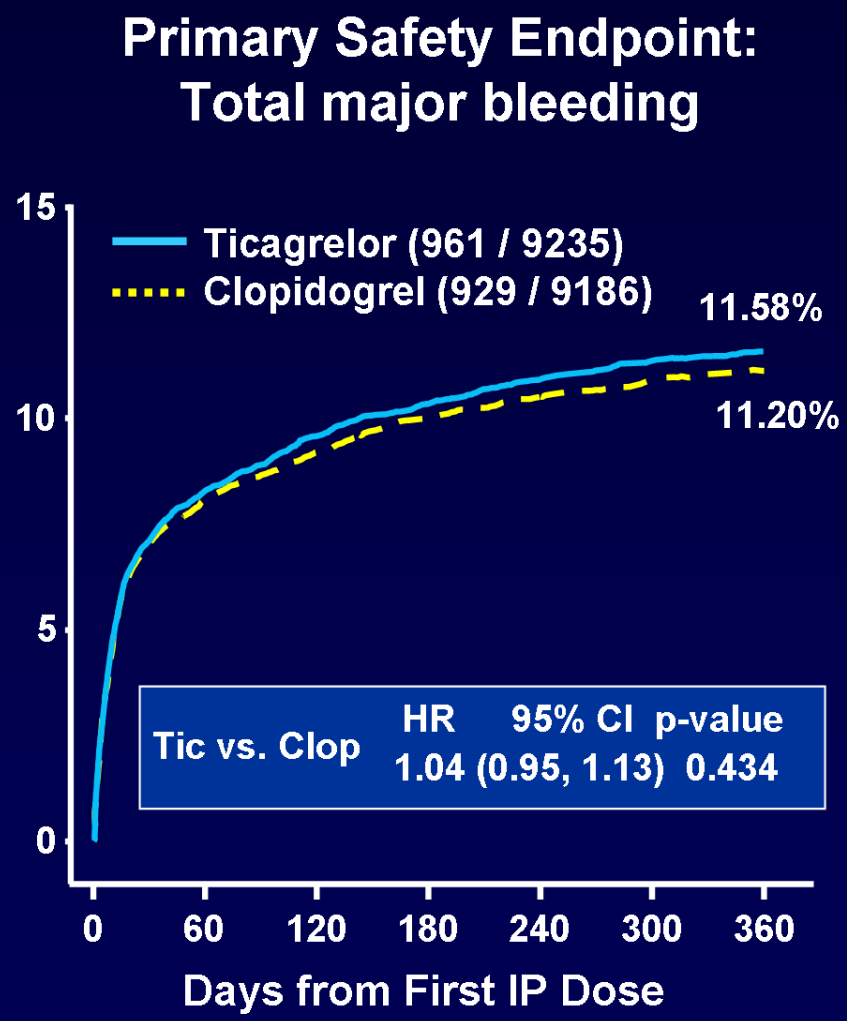
Introduction	Jonathan Fox, MD, PhD Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	Lars Wallentin, MD, PhD Professor of Cardiology Director Uppsala Clinical Research Center University Hospital, Uppsala, Sweden
PLATO: Design and Results	**Robert A Harrington, MD** **Professor of Medicine** **Duke University School of Medicine** **Director, Duke Clinical Research Institute**
Ticagrelor Safety Profile	Kristen K Buck, MD Director, Clinical Development AstraZeneca
PLATO: North America	Kevin J Carroll, BSc, MSc, FRSS VP Statistics and Chief Statistician AstraZeneca
Benefit and Risk of Ticagrelor	Robert A Harrington, MD

Main Ticagrelor Results from PLATO

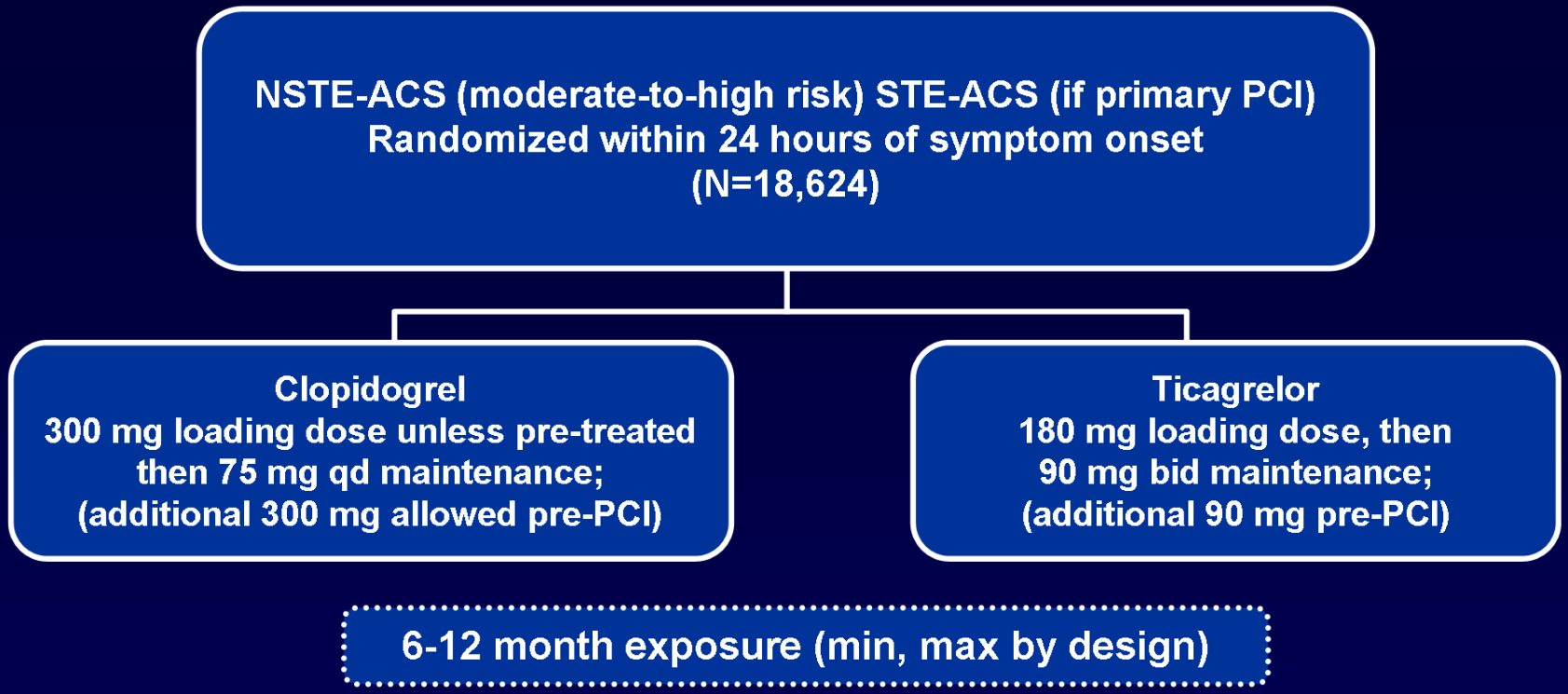
- Superior to clopidogrel
  - 16% RRR in primary composite endpoint of CV death, MI or stroke
  - Driven by CV death and MI
  - Benefit consistent across multiple efficacy endpoints and patient subgroups
- No difference in overall major bleeding
  - Similar fatal or fatal + life-threatening bleeding
  - Similar CABG bleeding
  - More non-CABG, including non-procedural, bleeding
  - Numerically more ICH, including more fatal ICH, but less fatal extracranial bleeding (e.g., GI)

Main Ticagrelor Results from PLATO





PLATO: Study Design



Primary efficacy endpoint: CV death + MI + Stroke
Primary safety endpoint: Total Major bleeding

PLATO Statistical Design Elements

- 11% / year primary composite event rate predicted from CURE
- 15% target relative risk reduction
- 20% treatment discontinuations → need to detect 13.5% RRR
- 90% power requires 1780 events from 18,000 patients

- Single interim analysis by DSMB
- Hierarchical testing of primary then multiple secondary efficacy outcomes
- Efficacy and safety endpoint adjudication by ICAC

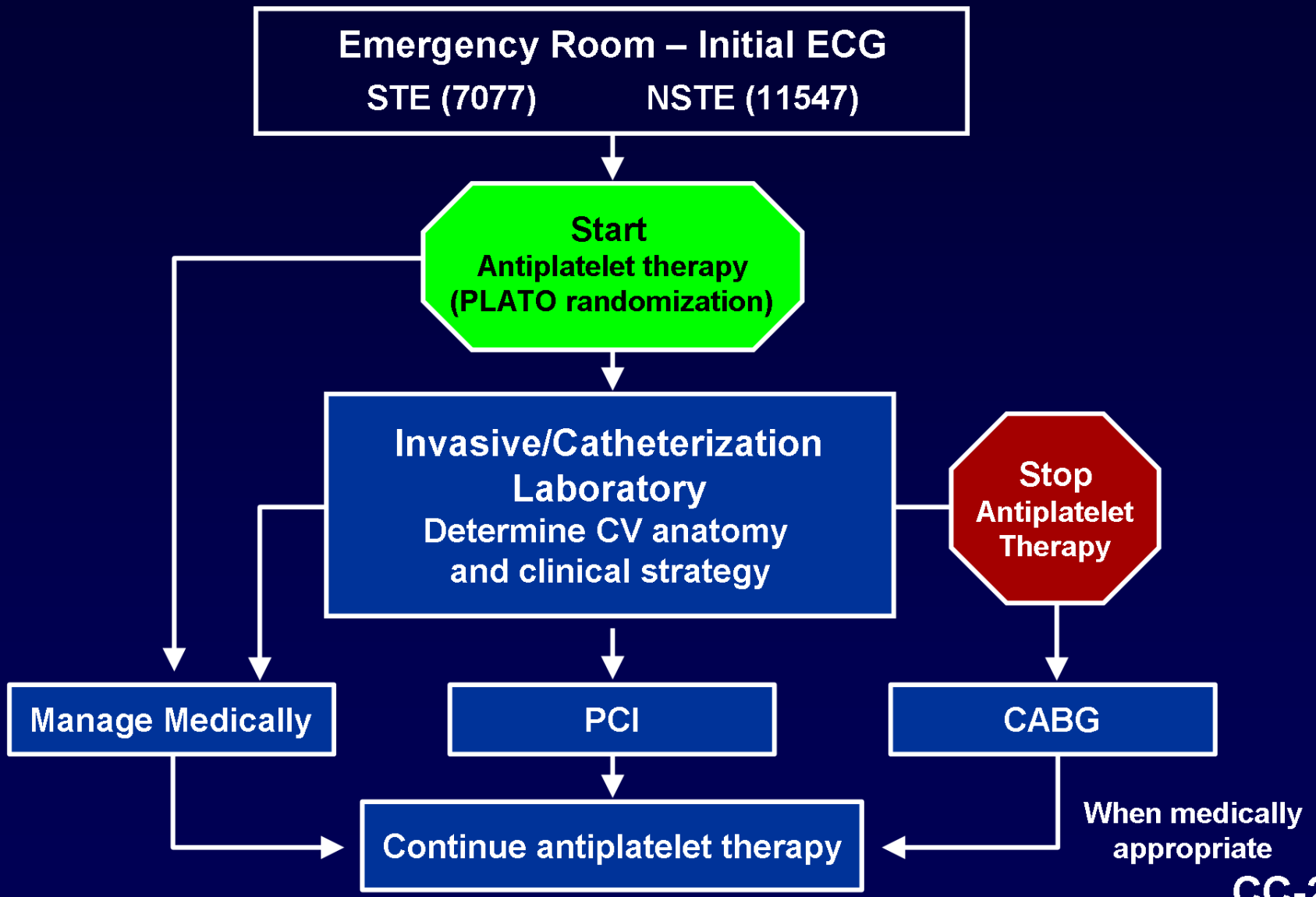
PLATO Enrolled a Representative ACS Cohort

Characteristic	Ticagrelor (n = 9333)	Clopidogrel (n = 9291)
Age (years; mean ± SD)	62±11	62±11
Age ≥75 years (%)	15.0	16.0
Women (%)	28.4	28.3
CV risk factors (%)		
Habitual smoker	36.0	35.7
Hypertension	65.8	65.1
Dyslipidemia	46.6	46.7
Diabetes mellitus	24.9	25.1
History (%)		
MI	20.4	20.7
PCI	13.6	13.1
CABG	5.7	6.2

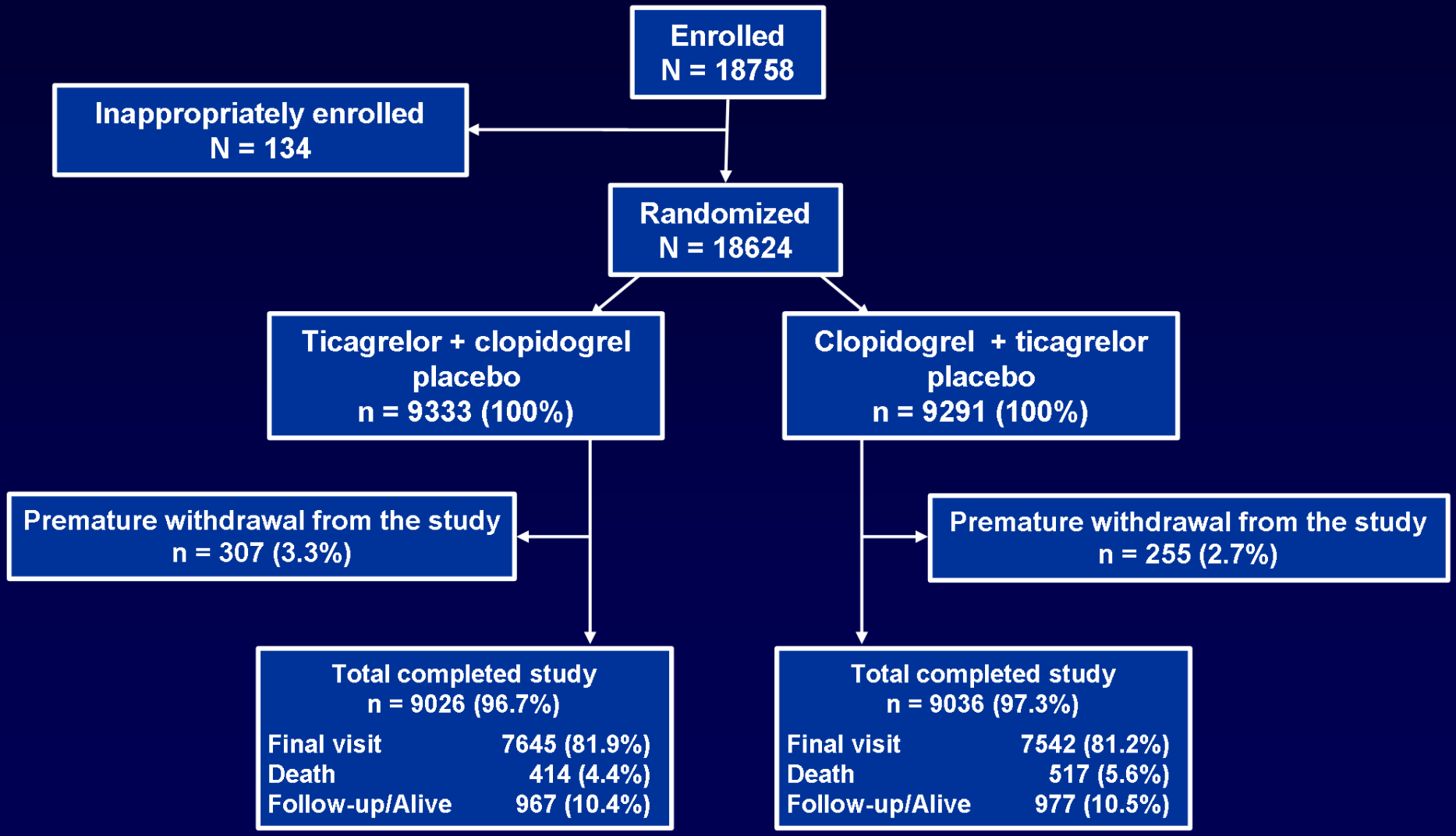
PLATO Enrolled a Representative ACS Cohort

- Comparison to ACTION registry
  - ACC/AHA collaborative ACS registry from 500 US hospitals
- Overall, demographics similar to PLATO
- 71% of US patients in the ACTION registry of STEMI and NSTEMI (UA not included) would have been eligible for PLATO

PLATO: Patient Disposition by Treatment Pathway (Index Event)

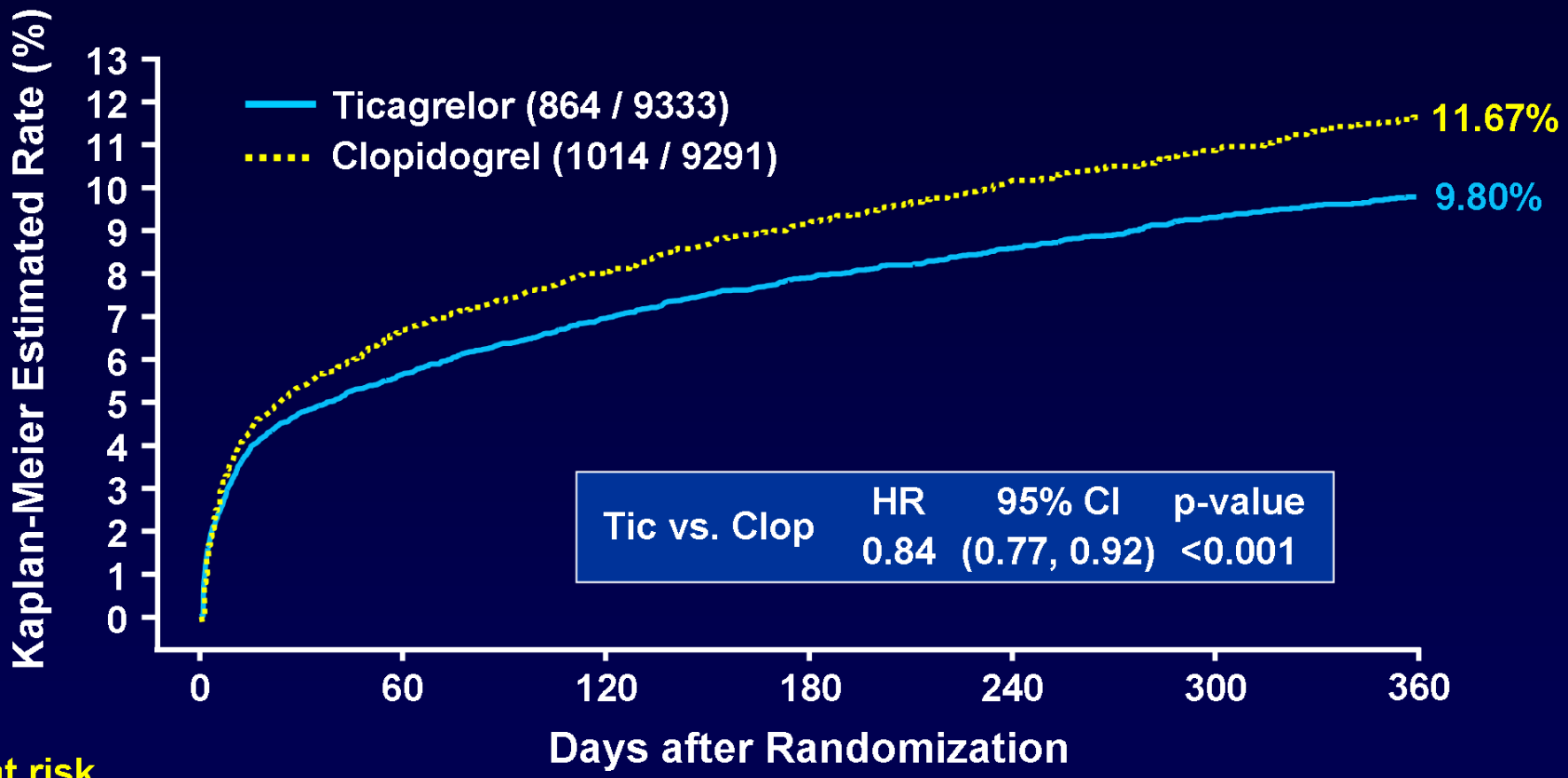


PLATO: Patient Disposition in Study



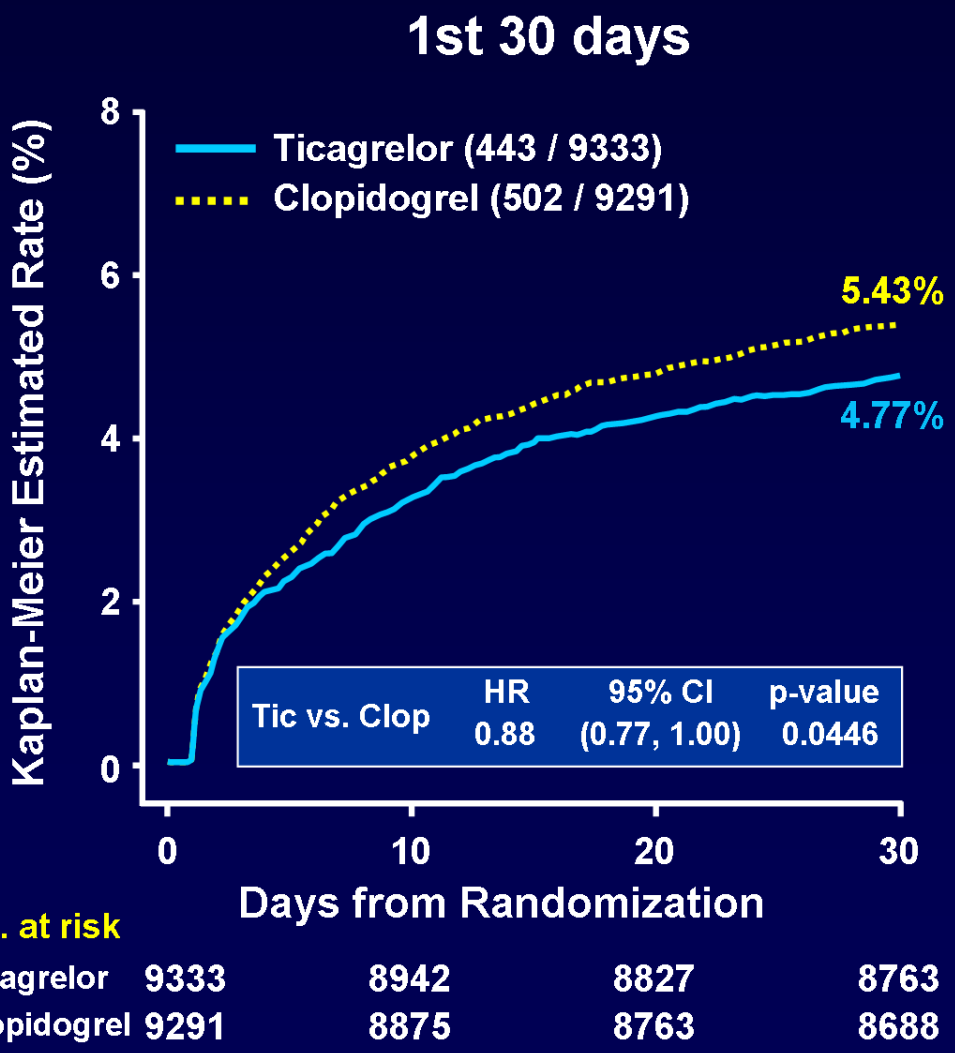
5 Patients Lost to Follow-up

KM % Estimate of Time to First Primary Efficacy Event (Composite of CV Death, MI or Stroke)



No. at risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6743	5096	4074

Ticagrelor Benefit Maintained Throughout Year



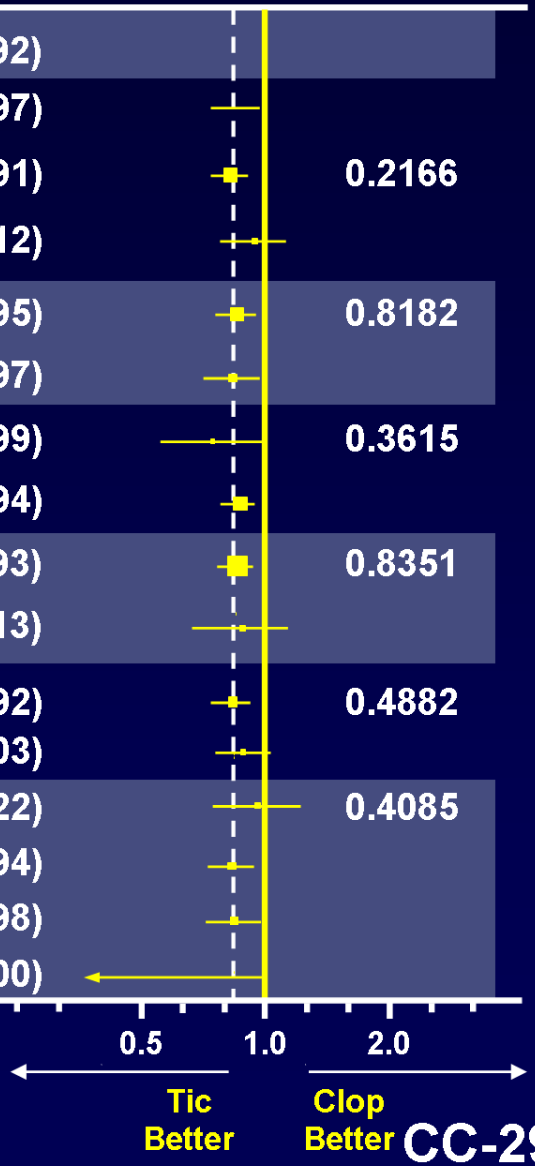
From Randomization to:	HR	ARR (%)
Day 30	0.88	0.6
Day 60	0.84	1.0
Day 90	0.86	1.0
Day 120	0.86	1.1
Day 180	0.85	1.3
Day 360	0.84	1.9

Ticagrelor: Consistency of Treatment Effect

All patients	Ticagrelor (n=9333)	Clopidogrel (n=9291)	HR for (95% CI)	*P*-value
Primary objective, n (%) CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77-0.92)	0.0003
Secondary objectives, n (%) Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77-0.92)	0.0001
CV death + MI + stroke + ischemia + TIA + arterial thrombotic events	1290 (14.6)	1456 (16.7)	0.88 (0.81-0.95)	0.0006
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75-0.95)	0.0045
CV death	353 (4.0)	442 (5.1)	0.79 (0.69-0.91)	0.0013
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91-1.52)	0.2249
Total death	399 (4.5)	506 (5.9)	0.78 (0.69-0.89)	0.0003

Ticagrelor: Efficacy Across Patient Subgroups

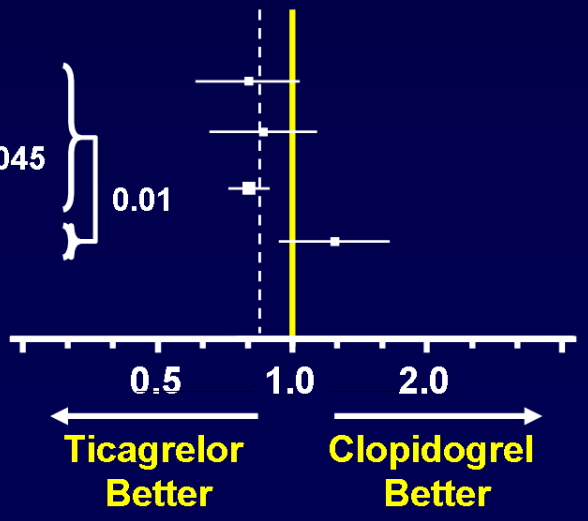
Characteristic		Total Patients	KM% at Month 12 Tic	KM% at Month 12 Clop	HR (95% CI)	Interaction *P-value*
Overall Treatment Effect		18624	9.8	11.7	0.84 (0.77, 0.92)	
Age	< 65 years	10643	7.2	8.5	0.85 (0.74, 0.97)	
	< 75 years	15744	8.6	10.4	0.82 (0.74, 0.91)	0.2166
	≥ 75 years	2878	16.8	18.3	0.94 (0.78, 1.12)	
Sex	Male	13336	9.2	11.1	0.85 (0.76, 0.95)	0.8182
	Female	5288	11.2	13.2	0.83 (0.71, 0.97)	
Body Weight	< 60 kg	1312	13.1	17.3	0.75 (0.56, 0.99)	0.3615
	≥ 60 kg	17256	9.5	11.2	0.86 (0.78, 0.94)	
Prior Non-hemorrhagic Stroke /TIA	Yes	17462	9.2	11.1	0.84 (0.76, 0.93)	0.8351
	No	1152	19.0	20.8	0.87 (0.66, 1.13)	
Diabetes Mellitus	No	13962	8.4	10.2	0.83 (0.74, 0.92)	0.4882
	Yes	4662	14.1	16.2	0.88 (0.76, 1.03)	
Final Diagnosis	Uns. Angina	3112	8.6	9.1	0.96 (0.75, 1.22)	0.4085
	NSTEMI	7955	11.4	13.9	0.83 (0.73, 0.94)	
	STEMI	7026	8.5	10.1	0.84 (0.72, 0.98)	
	Other	489	9.1	14.7	0.58 (0.34, 1.00)	



Ticagrelor Effect Across Geographic Region

- 31 prespecified subgroup tests conducted
- No adjustment for multiplicity
- Indication of qualitatively different outcome in NA region
- Results in NA appear to be driven by US: HR 1.27 (0.92, 1.75)

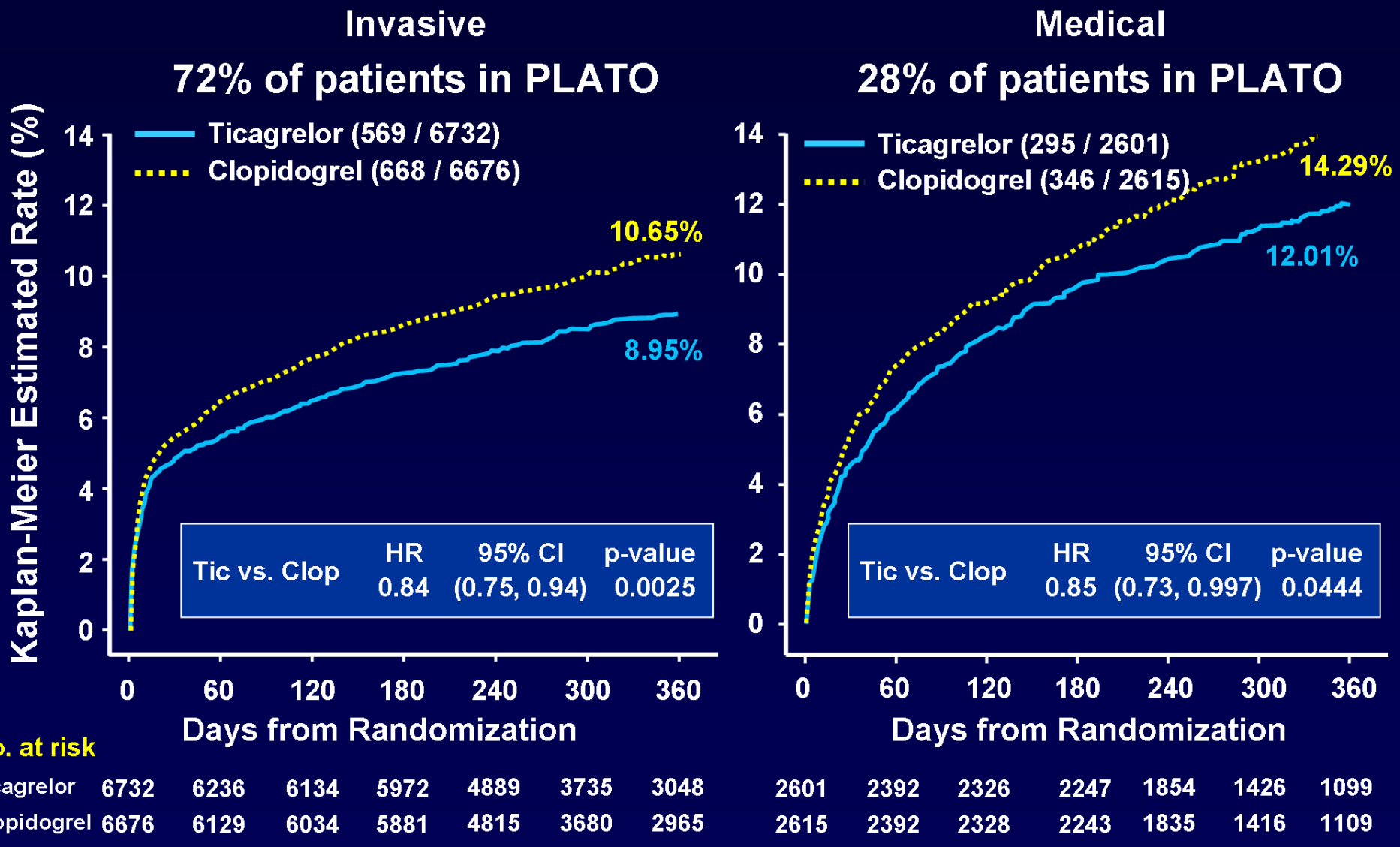
Characteristic	Total Patients	# of Events Tic	# of Events Clop	HR (95% CI)	Interaction p-value
Geographic Region					
Asia / Australia	1714	95	116	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	91	104	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	576	712	0.80 (0.72, 0.90)	
North America	1814	102	82	1.25 (0.93, 1.67)	0.01



PLATO: PK and PD Do Not Differ by Region

- **Population-PK analysis**
  - Post hoc analysis: ticagrelor exposure similar US / Non-US
- **PD: PLATO sub-study: US vs. UK**
  - Multiple PD measures, including IPA: similar results
- **US efficacy results not explained by regional differences in PK or PD**

Ticagrelor: Superior Efficacy for Intended Invasive and Medical Management



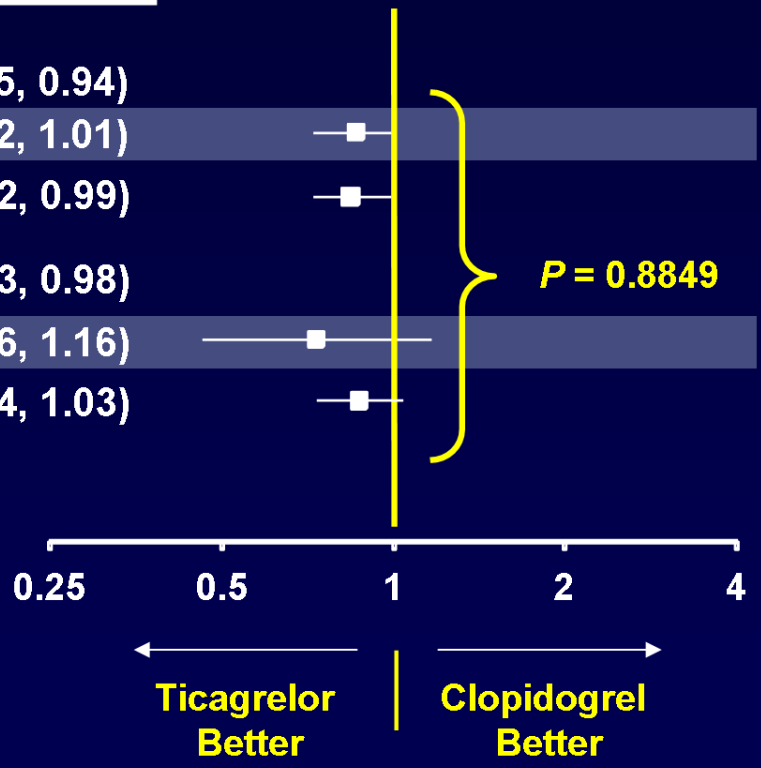
No. at risk

Ticagrelor	6732	6236	6134	5972	4889	3735	3048
Clopidogrel	6676	6129	6034	5881	4815	3680	2965

Ticagrelor	2601	2392	2326	2247	1854	1426	1099
Clopidogrel	2615	2392	2328	2243	1835	1416	1109

PLATO: Invasive and Medically Managed Subgroups by Final Diagnosis

Characteristic	Event (Total Patient) Ticagrelor	Clopidogrel	HR (95% CI)
Invasive	569 (6732)	668 (6676)	0.84 (0.75, 0.94)
STEMI	250 (3278)	293 (3297)	0.86 (0.72, 1.01)
NSTEMI / UA	301 (3240)	349 (3191)	0.84 (0.72, 0.99)
Medically Managed	295 (2601)	346 (2615)	0.85 (0.73, 0.98)
STEMI	31 (218)	44 (233)	0.73 (0.46, 1.16)
NSTEMI / UA	255 (2314)	293 (2322)	0.87 (0.74, 1.03)



PLATO: Stent Thrombosis

Evaluated in Patients with any Stent During the Study

	Ticagrelor (n=5640)	Clopidogrel (n=5649)	HR (95% CI)	*P*-value
Stent thrombosis, n (KM %)				
Definite	71 (1.3)	106 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118 (2.2)	158 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, definite	155 (2.9)	202 (3.8)	0.77 (0.62–0.95)	0.01

PLATO: Follow-up for Endpoint Events

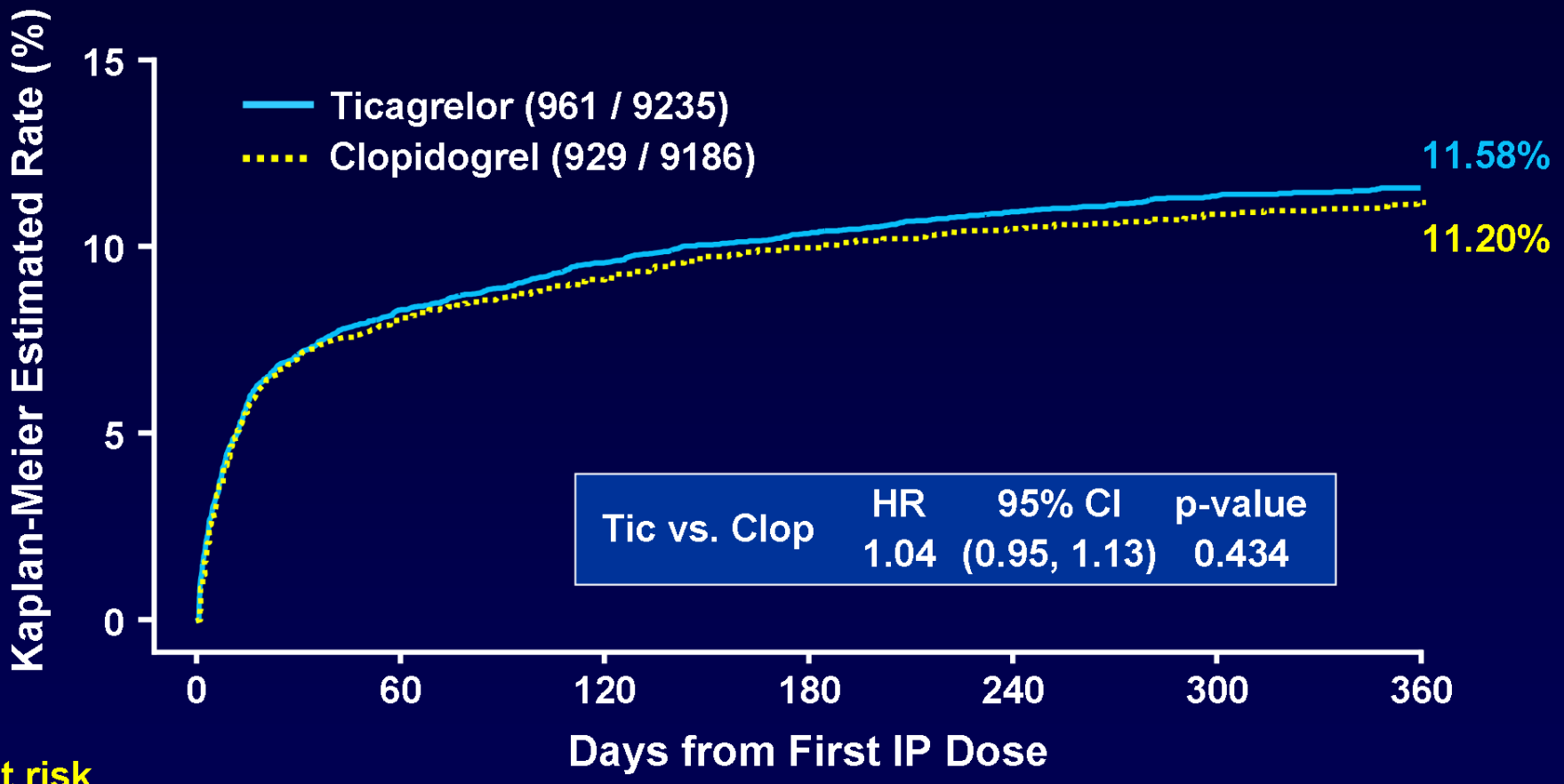
- Vital Status known for 99.97% (all but 5 patients)
- 91% patients achieved target duration CV event follow up (6-12 months)
- 8.9% did not achieve target and had median follow up 50 days
  - More than ¼ of these (2.4%) had withdrawn consent
  - Shortfall in target: 6-7% of patient-years
  - Estimate 50 non-fatal MIs or non-fatal strokes unobserved
- Sensitivity analysis including these events: Small effect on primary endpoint result

CV Event Follow-up Sensitivity Analysis

Non-fatal MI + Non-fatal Stroke (Unobserved)	HR among new events	Ticagrelor events	Clopidogrel events	Overall new HR	P-value
50	1.6	31	19	0.863	0.00125
	10	46	4	0.889	0.010
	>10	50	0	0.897	0.017

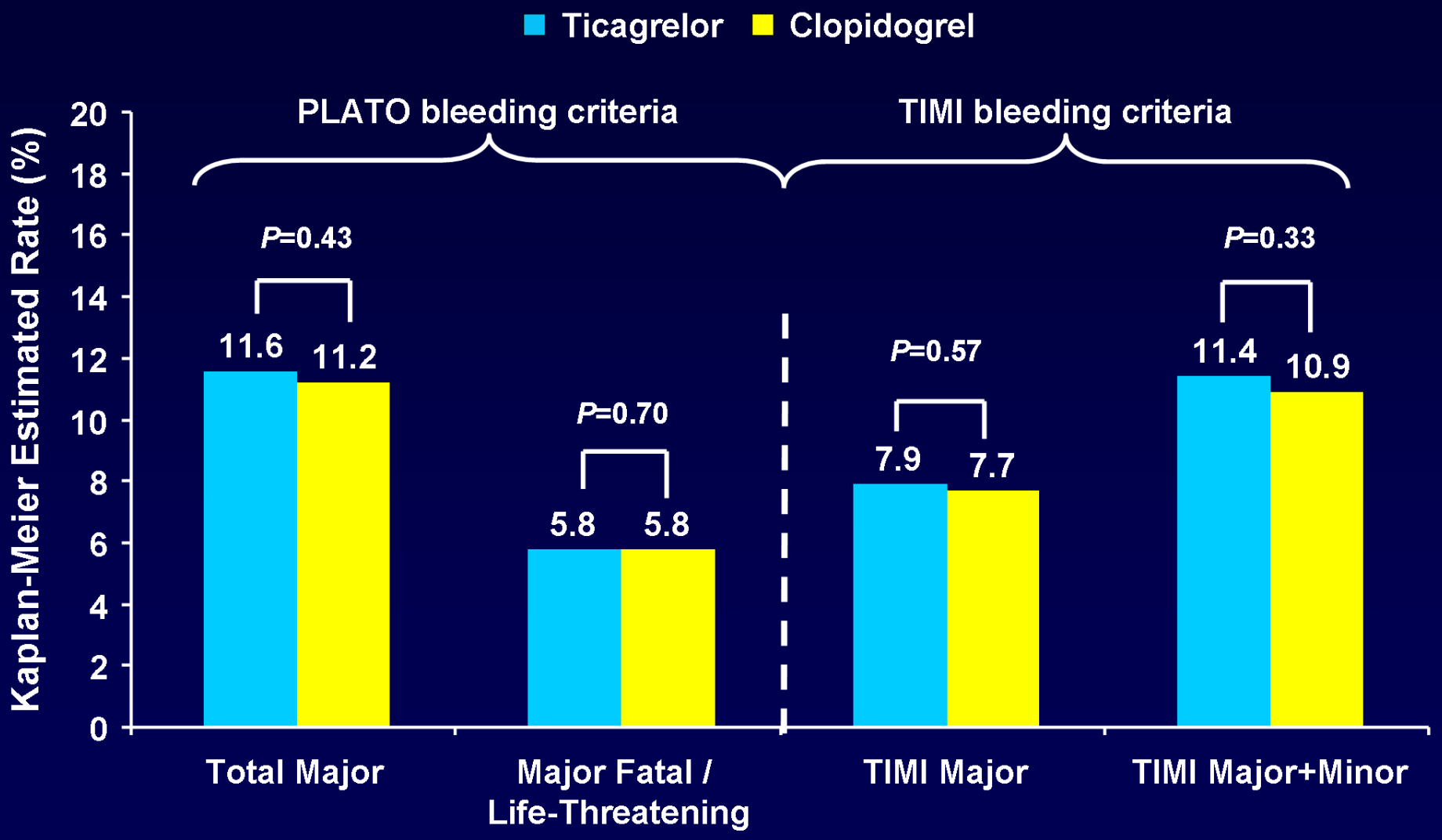
Bleeding

PLATO: Time to Major Bleeding Event (Primary Safety Endpoint)

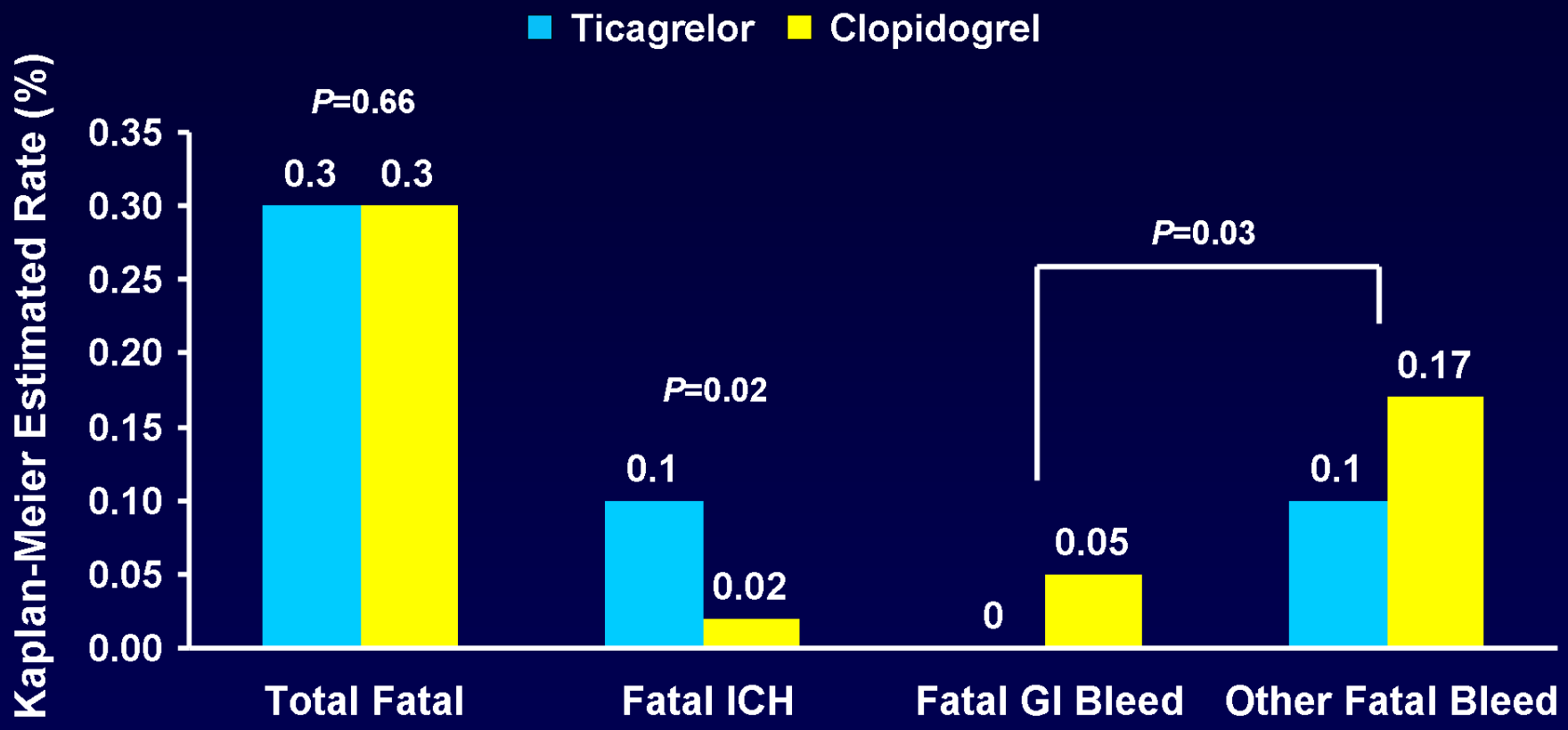


No. at risk							
Ticagrelor	9235	7246	6826	6545	5129	3783	3433
Clopidogrel	9186	7305	6930	6670	5209	3841	3479

PLATO: PLATO and TIMI Bleeding Criteria



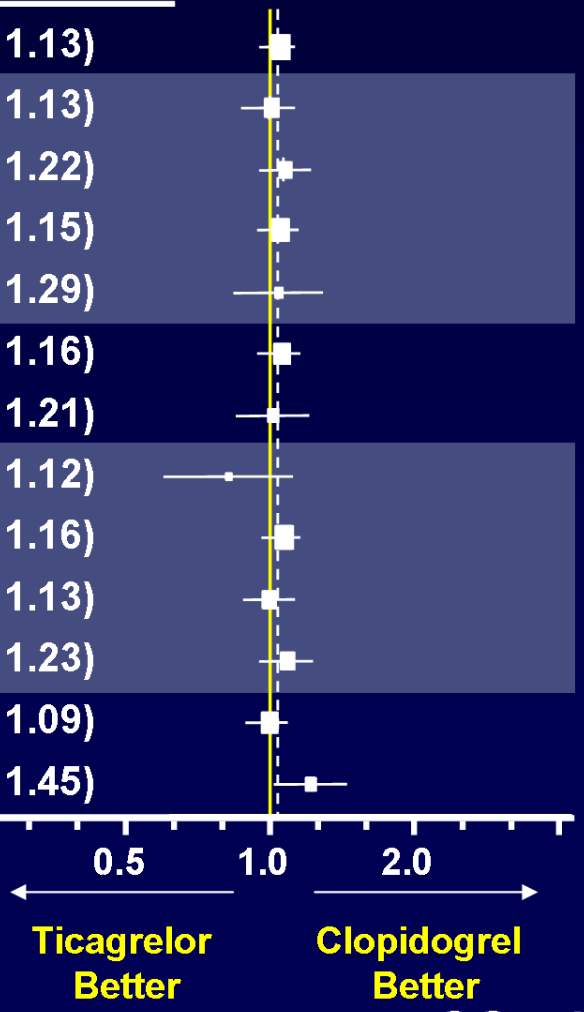
PLATO: Fatal Bleeding



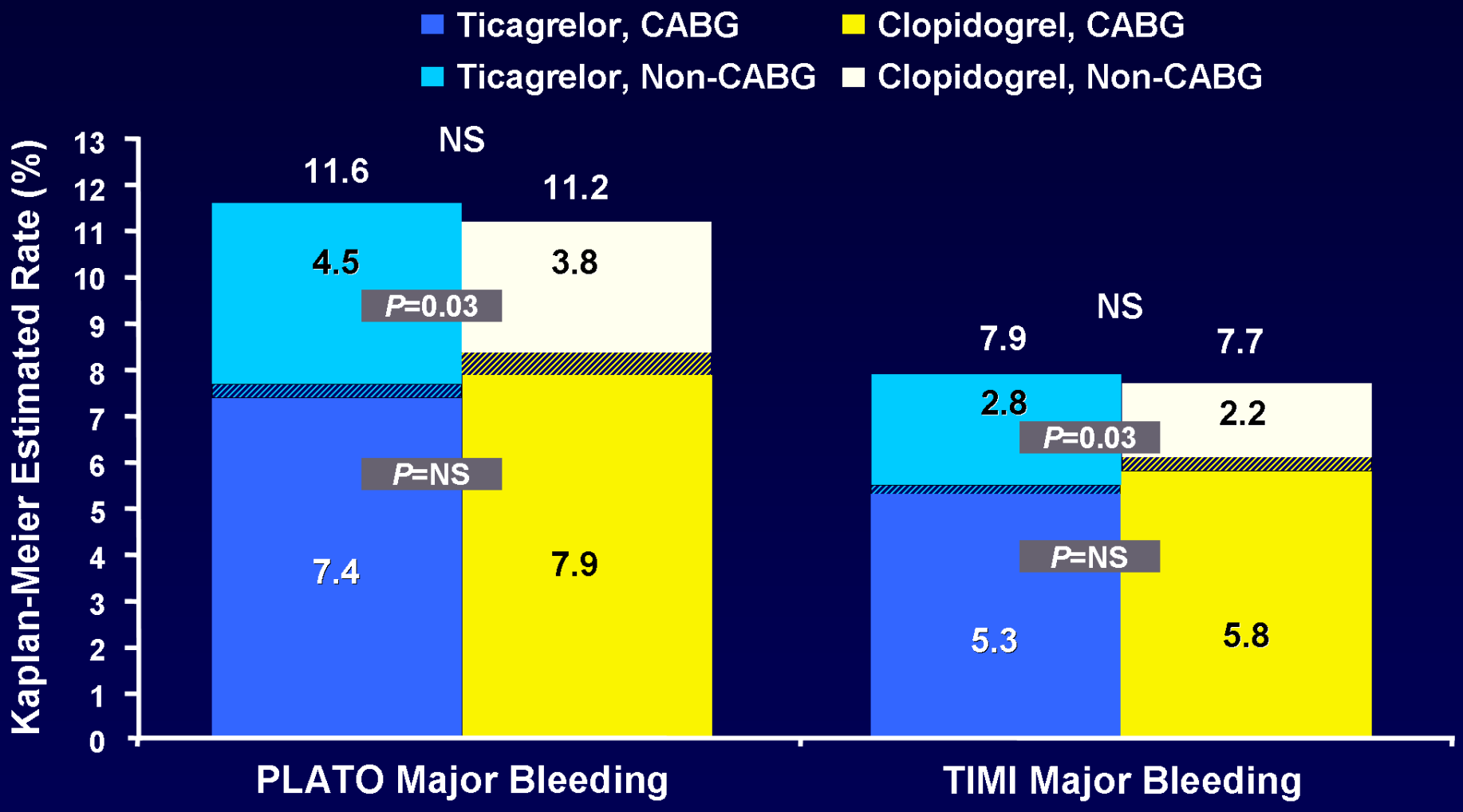
Ticagrelor (N=9235)	20	11	0	9
Clopidogrel (N=9186)	23	2	5	16

PLATO: Similar Major Bleeding Across Many Patient Subgroups

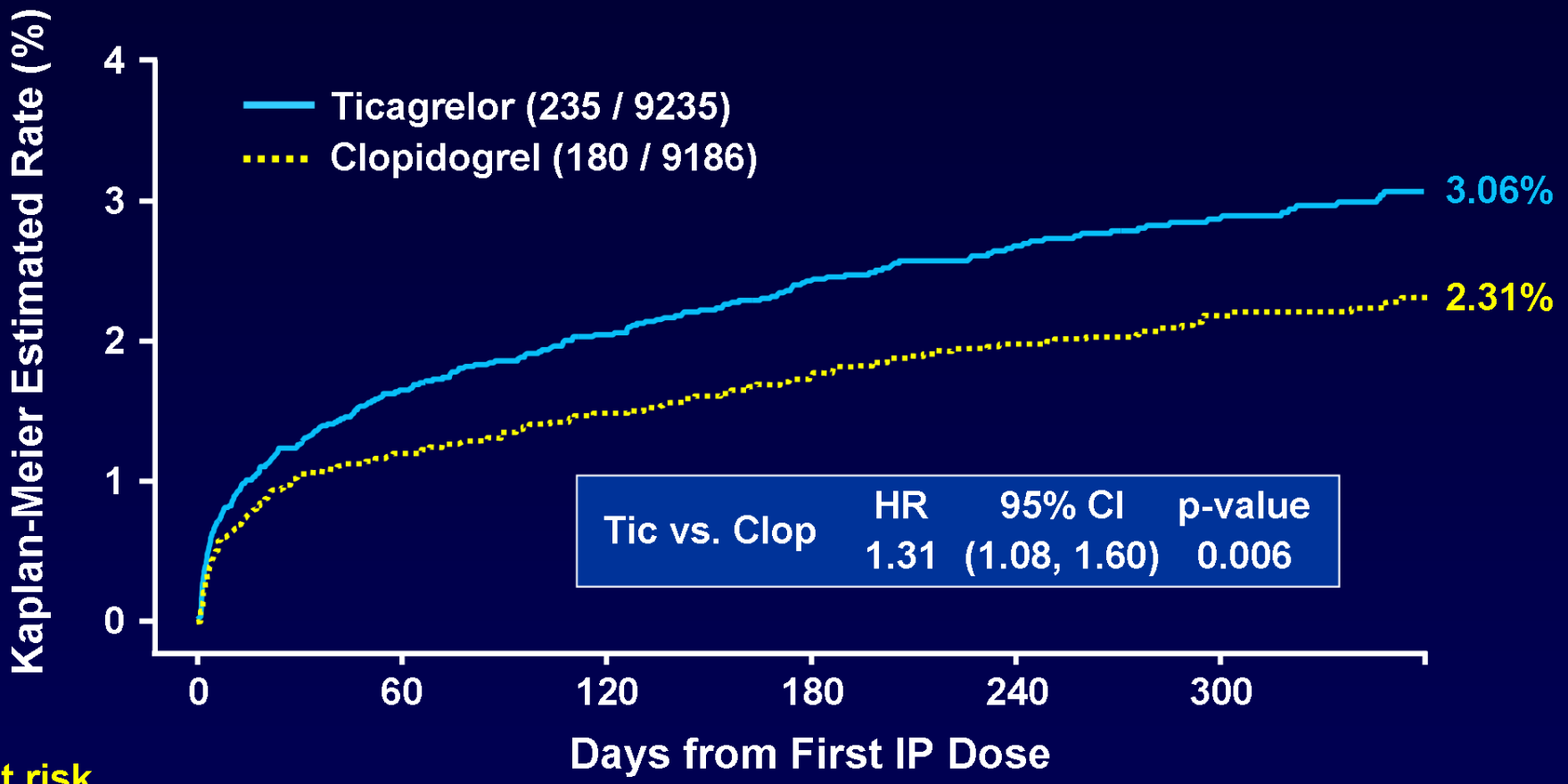
Characteristic		Total Patients	KM % at Month 12 Ticagrelor	Clopidogrel	HR (95% CI)
Major Bleeding		18421	11.6	11.2	1.04 (0.95, 1.13)
Age Group	<65 years	10528	9.5	9.5	1.00 (0.87, 1.13)
	≥65 years	7892	14.4	13.6	1.07 (0.95, 1.22)
	<75 years	15574	11.1	10.8	1.04 (0.94, 1.15)
	≥75 years	2846	14.2	13.3	1.04 (0.84, 1.29)
Sex	Male	13184	11.9	11.4	1.05 (0.94, 1.16)
	Female	5237	10.7	10.5	1.01 (0.85, 1.21)
Weight Group	<65 kg	1296	12.6	15.2	0.82 (0.60, 1.12)
	≥65 kg	17086	11.6	10.9	1.06 (0.96, 1.16)
	<80 kg	8959	11.7	11.0	0.99 (0.88, 1.13)
	≥80 kg	9423	11.4	10.5	1.08 (0.95, 1.23)
BMI Group	<30 kg/m^2	13229	11.6	11.6	0.99 (0.89, 1.09)
	≥30 kg/m^2	5121	11.6	10.0	1.21 (1.02, 1.45)



PLATO: CABG vs. Non-CABG Major Bleeding



PLATO: Time to Non-Procedural Major Bleeding



No. at risk							
Ticagrelor	9235	7641	7247	6979	5496	4067	3698
Clopidogrel	9186	7718	7371	7134	5597	4147	3764

Bleeding Events: Similar Pattern in US and Non-US

Adverse effect	US		Non-US	
	Ticagrelor 90 mg bid N=682	Clopidogrel 75 mg qd N=675	Ticagrelor 90 mg bid N=8553	Clopidogrel 75 mg qd N=8511
Major bleeding	77 (11.3%)	74 (11.0%)	884 (10.3%)	855 (10.0%)
Major + Minor	101 (14.8%)	92 (13.6%)	1238 (14.5%)	1123 (13.2%)
Non-procedural Major bleeding	20 (2.9%)	17 (2.5%)	215 (2.5%)	163 (1.9%)
Non-procedural Major + Minor bleeding	35 (5.1%)	28 (4.1%)	422 (4.9%)	304 (3.6%)

PLATO: Total Major Bleeding with Ticagrelor Similar to Clopidogrel

- **No difference in total major bleeding**
- **More major non-CABG, including non-procedural, bleeding**
- **More fatal ICH but fewer extracranial fatal bleeds**
- **No difference in fatal or life-threatening bleeding**

PLATO: Ticagrelor Provides Better Thrombotic Event Prevention without More Major Bleeding

- Reduced risk of composite of CV death, MI, or stroke compared to clopidogrel
- Primary endpoint driven by reduction in CV death and MI
- Reduction in stent thrombosis
- Benefit across a spectrum of ACS patients whether invasively or medically managed
- Consistent across multiple efficacy endpoints throughout 12 months
- Difference in total mortality parallels the benefits seen in CV death

Ticagrelor: Sponsor Presentation Plan

Introduction	Jonathan Fox, MD, PhD Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	Lars Wallentin, MD, PhD Professor of Cardiology Director Uppsala Clinical Research Center University Hospital, Uppsala, Sweden
PLATO: Design and Results	Robert A Harrington, MD Professor of Medicine Duke University School of Medicine Director, Duke Clinical Research Institute
Ticagrelor Safety Profile	**Kristen K Buck, MD** **Director, Clinical Development** **AstraZeneca**
PLATO: North America	Kevin J Carroll, BSc, MSc, FRSS VP Statistics and Chief Statistician AstraZeneca
Benefit and Risk of Ticagrelor	Robert A Harrington, MD

Ticagrelor: Adverse Event Profile Generally Similar to Clopidogrel

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Any AE	6714 (72.7)	6398 (69.6)
Mild	5655 (61.2)	5292 (57.6)
Moderate	3322 (36.0)	3073 (33.5)
Severe	1019 (11.0)	1061 (11.6)
Any SAE	1864 (20.2)	1866 (20.3)
SAE with outcome of Death	218 (2.4)	285 (3.1)
Leading to study drug discontinuation	687 (7.4)	500 (5.4)
SAE	259 (2.8)	218 (2.4)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Adverse Event Profile Generally Similar to Clopidogrel

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Any AE	6714 (72.7)	6398 (69.6)
Mild	5655 (61.2)	5292 (57.6)
Moderate	3322 (36.0)	3073 (33.5)
Severe	1019 (11.0)	1061 (11.6)
Any SAE	1864 (20.2)	1866 (20.3)
SAE with outcome of Death	218 (2.4)	285 (3.1)
Leading to study drug discontinuation	687 (7.4)	500 (5.4)
SAE	259 (2.8)	218 (2.4)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Adverse Event Profile Generally Similar to Clopidogrel

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Any AE	6714 (72.7)	6398 (69.6)
Mild	5655 (61.2)	5292 (57.6)
Moderate	3322 (36.0)	3073 (33.5)
Severe	1019 (11.0)	1061 (11.6)
Any SAE	1864 (20.2)	1866 (20.3)
SAE with outcome of Death	218 (2.4)	285 (3.1)
Leading to study drug discontinuation	687 (7.4)	500 (5.4)
SAE	259 (2.8)	218 (2.4)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Safety Topics

- Dyspnea
- Cardiac arrhythmias and conduction abnormalities
- Uric acid
- Renal effects

Ticagrelor: Safety Topics

- **Dyspnea**
- **Cardiac arrhythmias and conduction abnormalities**
- **Uric acid**
- **Renal effects**

Ticagrelor: Dyspnea Reported More Frequently

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Patients with at least 1 event	1270 (13.8)	721 (7.8)
MedDRA Preferred Term		
Dyspnea	1104 (12.0)	598 (6.5)
Dyspnea exertional	176 (1.9)	127 (1.4)
Dyspnea at rest	9 (0.1)	3 (<0.1)
Nocturnal dyspnea	8 (0.1)	4 (<0.1)
Dyspnea paroxysmal nocturnal	6 (0.1)	5 (0.1)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Most Reports of Dyspnea Mild to Moderate

Category (Includes 5 Dyspnea Preferred Terms)	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Dyspnea AE	1270 (13.8)	721 (7.8)
Mild	890 (9.6)	505 (5.5)
Moderate	413 (4.5)	218 (2.4)
Severe	35 (0.4)	18 (0.2)
Dyspnea SAE	69 (0.7)	39 (0.4)
Death	1 (<0.1)	1 (<0.1)
Dyspnea AE leading to study drug discontinuation	79 (0.9)	13 (0.1)
Dyspnea SAE leading to study drug discontinuation	10 (0.1)	1 (<0.1)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Most Reports of Dyspnea Mild to Moderate

Category (Includes 5 Dyspnea Preferred Terms)	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Dyspnea AE	1270 (13.8)	721 (7.8)
Mild	890 (9.6)	505 (5.5)
Moderate	413 (4.5)	218 (2.4)
Severe	35 (0.4)	18 (0.2)
Dyspnea SAE	69 (0.7)	39 (0.4)
Death	1 (<0.1)	1 (<0.1)
Dyspnea AE leading to study drug discontinuation	79 (0.9)	13 (0.1)
Dyspnea SAE leading to study drug discontinuation	10 (0.1)	1 (<0.1)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Most Reports of Dyspnea Mild to Moderate

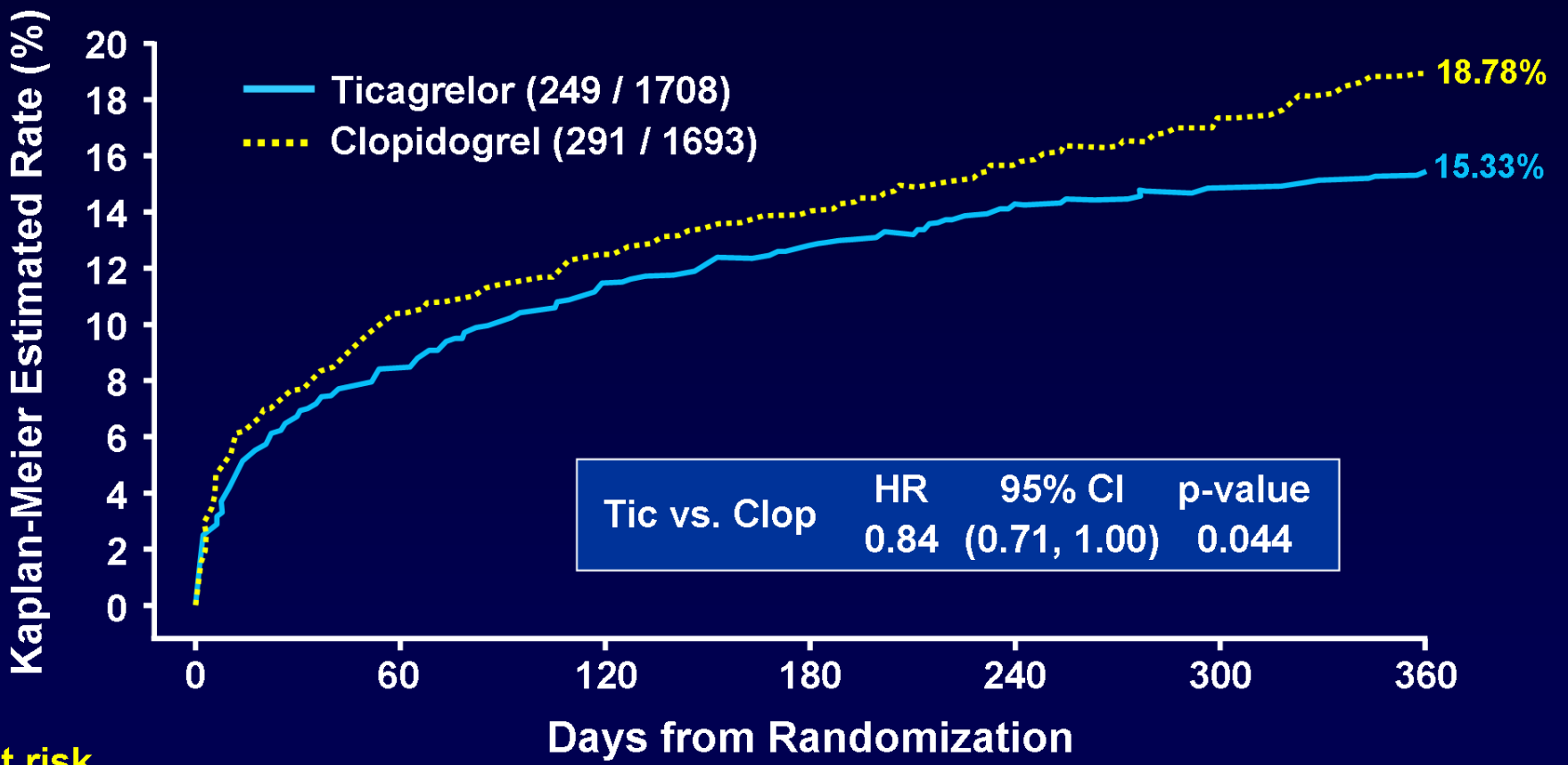
Category (Includes 5 Dyspnea Preferred Terms)	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Dyspnea AE	1270 (13.8)	721 (7.8)
Mild	890 (9.6)	505 (5.5)
Moderate	413 (4.5)	218 (2.4)
Severe	35 (0.4)	18 (0.2)
Dyspnea SAE	69 (0.7)	39 (0.4)
Death	1 (<0.1)	1 (<0.1)
Dyspnea AE leading to study drug discontinuation	79 (0.9)	13 (0.1)
Dyspnea SAE leading to study drug discontinuation	10 (0.1)	1 (<0.1)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: No Changes in Pulmonary Function

- Two Phase 1 studies (healthy elderly volunteers, volunteers with asthma or COPD)
- Cardiopulmonary assessments in DISPERSE2 and ONSET/OFFSET
- Pulmonary Function substudy in PLATO

Ticagrelor: Efficacy Maintained in Patients with History of COPD/Asthma/HF at Baseline



No. at risk

Ticagrelor	1708	1526	1466	1415	1150	880	712
Clopidogrel	1693	1489	1444	1391	1121	845	675

PLATO Safety Analysis Set

Dyspnea Associated with Ticagrelor

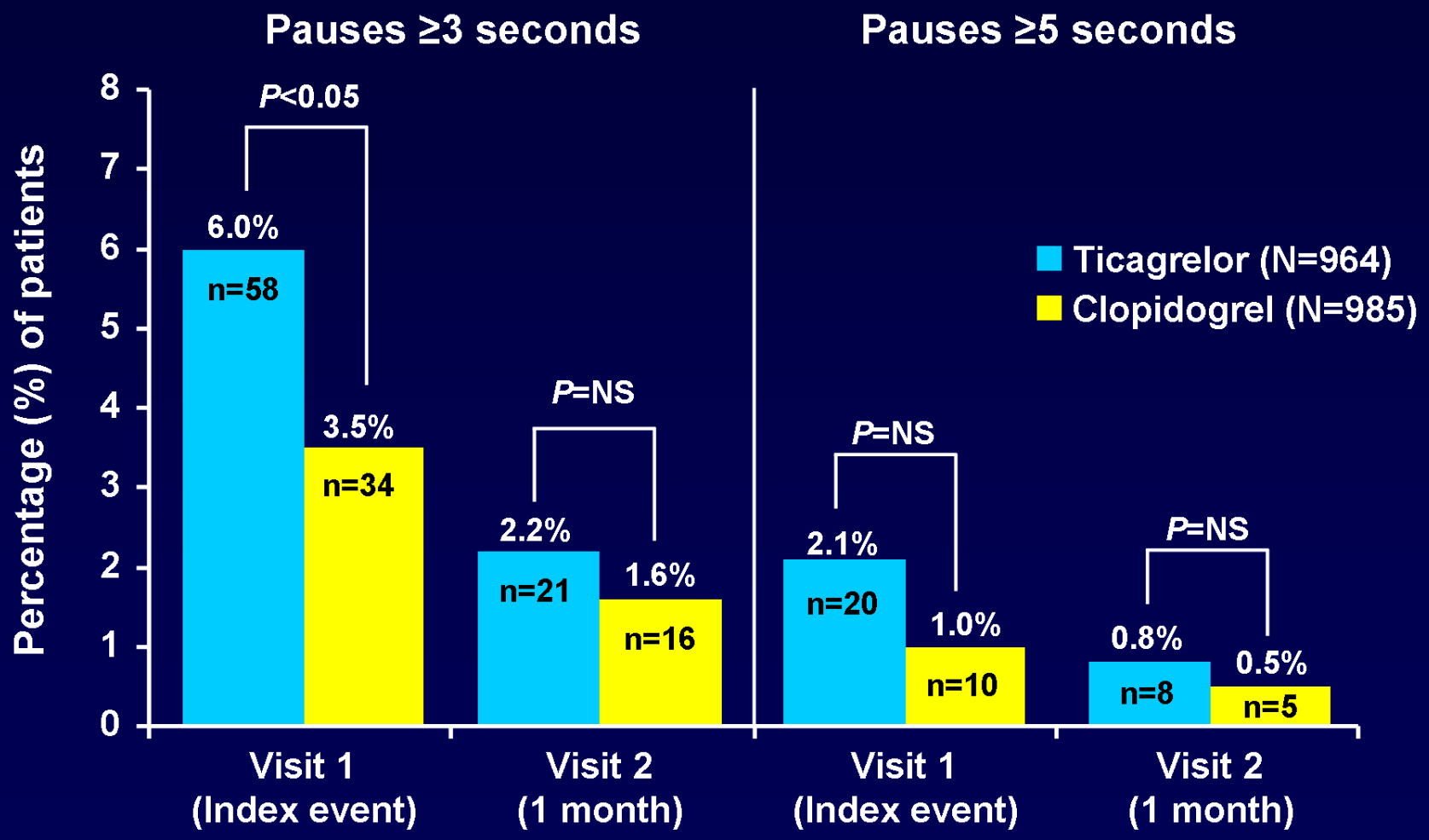
- Usually mild to moderate
- No measured changes in pulmonary function
- Patients with baseline cardiopulmonary disease were not at an increased relative risk of dyspnea
- Risk factors for dyspnea were similar between treatment groups
- 9 in 1000 patients discontinued ticagrelor due to dyspnea
- Benefit of ticagrelor is maintained in patients at risk for dyspnea and those who experience dyspnea

Ticagrelor: Safety Topics

- Dyspnea
- **Cardiac arrhythmias and conduction abnormalities**
- Uric acid
- Renal effects

Ticagrelor: More Patients with Ventricular Pauses than Clopidogrel

- **PLATO Holter Substudy**



Ticagrelor: No Increase in Adverse Clinical Consequences in Patients with ≥3 Second Pauses

- **PLATO Holter Substudy**

	Ticagrelor 90 mg bid N = 89	Clopidogrel 75 mg qd N = 62
Patients with at least 1 symptomatic AE	9	12
Bradycardia/bradyarrhythmia	4	4
Cardiac arrest	2	2
Atrioventricular block complete	1	3
Atrioventricular block second degree	1	1
Hypotension	1	3
Syncope	1	1
Dizziness	0	2
Orthostatic hypotension	0	1

PLATO: Composite Primary Endpoint in Patients With a Ventricular Pause ≥3 Seconds

- **PLATO Holter Substudy**

	Ticagrelor 90 mg bid			Clopidogrel 75 mg qd		
Patients	N	Patients with event n (%)	KM%	N	Patients with event n (%)	KM%
With ventricular pauses ≥3 seconds	89	11 (12.4%)	11.3%	62	15 (24.2%)	24.5%

PLATO: Cardiac Arrhythmias Similar

	Ticagrelor 90 mg bid N = 9235 % of patients	Clopidogrel 75 mg qd N = 9186 % of patients
Cardiac Arrhythmia AEs (HLGT)	14.2	14.6
Atrial fibrillation	4.2	4.6
Bradycardia	2.9	2.9
Ventricular tachycardia	2.0	2.1
Ventricular fibrillation	0.8	1.0
Cardiac Arrhythmia SAEs (HLGT)	2.6	2.9
Cardiac Arrhythmia Discontinuations due to AEs (HLGT)	0.6	0.7

HLGT – Higher Level Group Term

PLATO: Cardiac Arrhythmias Similar

	Ticagrelor 90 mg bid N = 9235 % of patients	Clopidogrel 75 mg qd N = 9186 % of patients
Cardiac Arrhythmia AEs (HLGT)	14.2	14.6
Atrial fibrillation	4.2	4.6
Bradycardia	2.9	2.9
Ventricular tachycardia	2.0	2.1
Ventricular fibrillation	0.8	1.0
Cardiac Arrhythmia SAEs (HLGT)	2.6	2.9
Cardiac Arrhythmia Discontinuations due to AEs (HLGT)	0.6	0.7

HLGT – Higher Level Group Term

Ticagrelor: Cardiac Arrhythmias and Conduction Abnormalities Summary

- More Holter-detected ventricular pauses with ticagrelor compared to clopidogrel
- Ventricular pauses did not translate into an increase in clinically significant outcomes
- In the overall PLATO population, no imbalance in cardiac arrhythmia events
- Benefit of ticagrelor is maintained in patients who experience bradyarrhythmias inclusive of ventricular pauses

Ticagrelor: Safety Topics

- Dyspnea
- Cardiac arrhythmias and conduction abnormalities
- **Uric acid**
- Renal effects

PLATO: Mean Serum Uric Acid Over Time

	Ticagrelor 90 mg bid		Clopidogrel 75 mg qd	
Timepoint	n	Mean (SD) mg/dL	n	Mean (SD) mg/dL
Visit 1 (baseline)	4642	5.77 (1.630)	4624	5.81 (1.591)
Visit 2	4901	6.36 (1.759)	4870	5.97 (1.563)
Visit 3	4494	6.44 (1.743)	4496	6.04 (1.602)
Visit 4	4021	6.42 (1.747)	3998	6.01 (1.578)
Visit 5	229	6.41 (1.534)	222	6.10 (1.625)
Visit 6	3652	6.37 (1.739)	3642	6.00 (1.554)
30 day Follow-up	3595	5.95 (1.559)	3546	6.01 (1.593)

On-treatment
PLATO Safety Laboratory Analysis Set

PLATO: Uric Acid-Related Adverse Events

	Ticagrelor 90 mg bid N = 9235 n (%)	Clopidogrel 75 mg qd N = 9186 n (%)
Patients with at least 1 event	195 (2.1)	164 (1.8)
MedDRA Preferred Term		
Gout	59 (0.6)	58 (0.6)
Hyperuricemia	42 (0.5)	19 (0.2)
Calculus urinary	21 (0.2)	24 (0.3)
Blood uric acid increased	18 (0.2)	12 (0.1)
Joint swelling	17 (0.2)	18 (0.2)
Nephrolithiasis	16 (0.2)	23 (0.3)
Gouty arthritis	15 (0.2)	6 (0.1)
Gout + Gouty arthritis	73 (0.8)	63 (0.7)

Note: Table contains PTs with frequency of ≥0.2% in Ticagrelor group
On-treatment

Ticagrelor: Safety Topics

- Dyspnea
- Cardiac arrhythmias and conduction abnormalities
- Uric acid
- **Renal effects**

PLATO: Mean Serum Creatinine Over Time

Visit schedule		Ticagrelor 90 mg bid N	Ticagrelor 90 mg bid Mean creatinine mg/dL Mean (SD)	Clopidogrel 75 mg qd N	Clopidogrel 75 mg qd Mean creatinine mg/dL Mean (SD)
Visit 1	Index Event	4641	0.98 (0.31)	4624	0.98 (0.32)
Visit 2	1 month	4901	1.06 (0.35)	4870	1.04 (0.32)
Visit 3	3 months	4494	1.05 (0.33)	4496	1.03 (0.33)
Visit 4	6 months	4022	1.05 (0.33)	3998	1.04 (0.32)
Visit 5	9 months	229	1.08 (0.33)	222	1.03 (0.25)
Visit 6	12 months	3652	1.07 (0.41)	3643	1.04 (0.31)
	30 day follow-up	3595	1.06 (0.37)	3545	1.05 (0.34)

On-treatment
PLATO Safety Laboratory Analysis Set

Ticagrelor: More Renal-related AEs

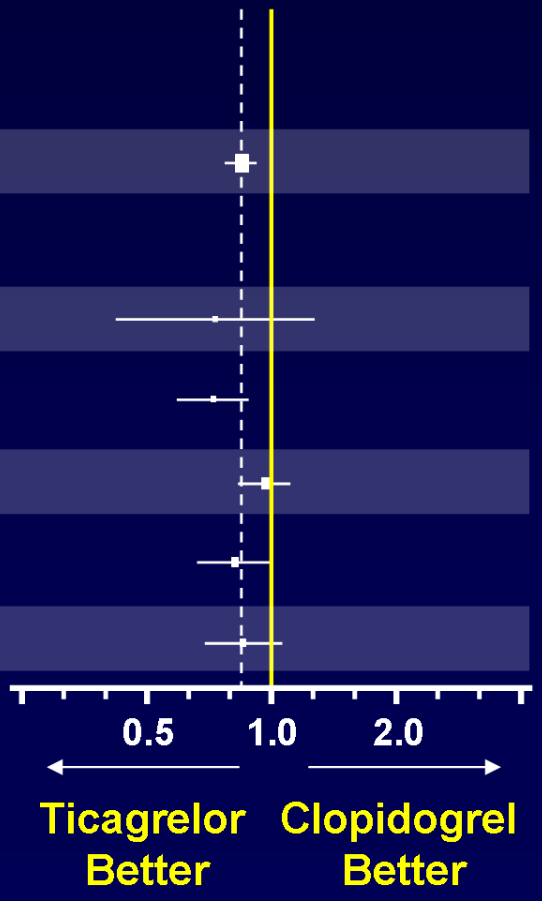
	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Renal-related AE	449 (4.9)	345 (3.8)
Renal-related SAE	73 (0.8)	60 (0.7)
SAEs other than death	71 (0.8)	57 (0.6)
Deaths	2 (<0.1)	4 (<0.1)
Renal-related AE leading to permanent discontinuation of study drug	15 (0.2)	14 (0.2)
SAE leading to permanent discontinuation of study drug	4 (<0.1)	8 (0.1)
New onset dialysis	39 (0.4)	31 (0.3)

On-treatment
PLATO Safety Analysis Set

Ticagrelor: Efficacy Maintained in Patients with Baseline Renal Impairment

Adjudicated Primary Clinical Endpoint by Baseline Renal Function

	Total Patients	KM at Month 12 Tic	KM at Month 12 Clop	HR (95% CI)
Overall Treatment Effect				
Primary Endpoint	18624	9.8	11.7	0.84 (0.77, 0.92)
Baseline Renal Function				
Severe (<30 ml/min)	181	27.1	36.6	0.73 (0.42, 1.27)
Moderate (30 - <60 ml/min)	2402	15.8	21.5	0.72 (0.59, 0.88)
Mild (60 - <90 ml/min)	7088	10.2	10.9	0.96 (0.83, 1.11)
Normal (≥90 ml/min)	5582	6.5	8.0	0.81 (0.66, 0.99)
Unknown	3371	9.4	11.0	0.85 (0.69, 1.06)



PLATO Full Analysis Set

Ticagrelor: Renal Effects Summary

- Small increases from baseline in serum creatinine in both treatment groups
- No excess of important renal-related adverse outcomes with ticagrelor, including dialysis or death irrespective of baseline renal function
- Benefit from ticagrelor, including reduced CV mortality, in patients with baseline renal impairment and in those patients with creatinine increases > 30% consistent with overall trial result

Ticagrelor: Safety Summary

- **Identified safety topics do not substantially add to the background morbidity in the ACS population**
  - **Dyspnea**
  - **Cardiac arrhythmias and conduction abnormalities**
  - **Uric acid**
  - **Renal effects**
- **Adverse effects associated with ticagrelor are clinically manageable**

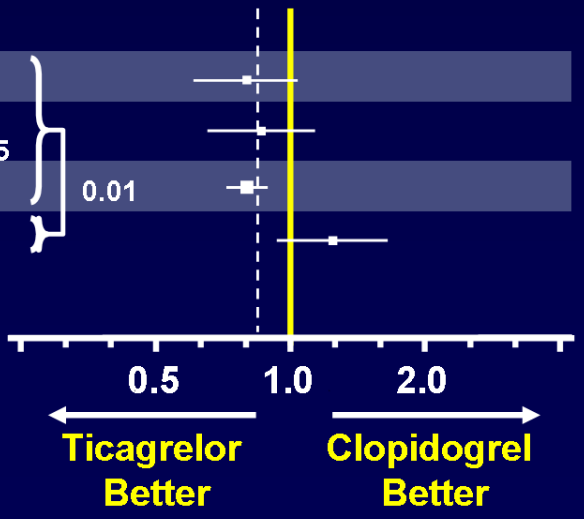
Ticagrelor: Sponsor Presentation Plan

Introduction	Jonathan Fox, MD, PhD Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	Lars Wallentin, MD, PhD Professor of Cardiology Director Uppsala Clinical Research Center University Hospital, Uppsala, Sweden
PLATO: Design and Results	Robert A Harrington, MD Professor of Medicine Duke University School of Medicine Director, Duke Clinical Research Institute
Ticagrelor Safety Profile	Kristen K Buck, MD Director, Clinical Development AstraZeneca
PLATO: North America	**Kevin J Carroll, BSc, MSc, FRSS** **VP Statistics and Chief Statistician** **AstraZeneca**
Benefit and Risk of Ticagrelor	Robert A Harrington, MD

PLATO: Ticagrelor Effect Apparently Inconsistent Across Geographic Regions

- 31 pre-specified subgroup tests conducted for consistency
- No α-level adjustment for multiplicity
- Indication of qualitatively different outcomes by region
- Results in NA appear to be driven by US: HR 1.27 (0.92, 1.75)

Characteristic	Total Patients	KM at Month 12 Tic	KM at Month 12 Clop	HR (95% CI)	Interaction p-values
Geographic Region					
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



PLATO: These Data Give Rise to a Critical Question

- **Does this statistical finding represent a real difference in the efficacy of ticagrelor relative to clopidogrel across geographic regions, or is it rather a chance finding, possibly due to the high number of subgroups analyzed?**

PLATO: Possible Explanations for the US Observation

1. Systematic issues in trial conduct at US sites
2. Play of chance
3. Difference between US and Non-US populations in important baseline characteristics or aspects of clinical management

1. PLATO: Do Systematic Issues in Trial Conduct at US Sites Explain the US Observation?

- No evidence of systematic issues in conduct
- Mislabeled drug product ruled out:
  - Batch numbers, randomization codes, IVRS data checked
  - PK samples showed ticagrelor patients received ticagrelor
- Conduct at US sites investigated
  - Interviews with site personnel disclosed no quality issues
  - US had smaller study centers, but no quality issues

2. PLATO: Could the US Observation Be Due to Play of Chance?

- **Yes**
  - **Chance alone cannot be ruled out as the explanation for the US result**
- **Observed treatment-by-region interaction is of marginal statistical significance**
  - **One of 31 descriptive interaction tests**
  - **In the absence adjustment for multiplicity, the likelihood of spurious, chance findings is increased**
  - **Adjustment for multiplicity would render the interaction p=NS**
- **Switching of just one event in the NA cohort from ticagrelor to clopidogrel would render the regional interaction p=NS**

3. PLATO: Are There Imbalances in Baseline Characteristics or Clinical Management That Might Explain the US vs Non-US Regional Interaction?

Factors evaluated in exploratory analyses

- Race
- Index event
- Weight#
- Troponin
- BMI #
- Age #
- Compliance
- ASA at rand.
- Invasive or med man
- Smoking status
- Waist circumference
- ACE at rand.
- NSAID at rand.
- Gender
- CCB at rand.
- Time index to 1st dose #
- CYP3A at rand.
- Heparin use
- PCI <24h of rand.
- Lipid low at rand.
- Stent use
- ARB at rand.
- BB at rand.
- PPI at rand.
- GPI at rand.
- Pre index anti-plat.
- Diabetes hist.
- Prior MI
- Prior CABG
- Prior PCI
- Cath lab access
- Clop loading dose
- TIMI risk score
- ASA loading dose
- ASA maintenance dose #

- # Some factors defined in different ways, e.g age: <65 vs ≥ 65 and age <75 vs ≥ 75.
- ASA dose defined for patients who had (i) at least 5 days or (ii) at least 2 days of ASA; and (iii) as agreed with FDA, for patients with at least 1 maintenance dose to avoid the biasing influence of high ASA loading dose.
- ASA loading dose considered separately.

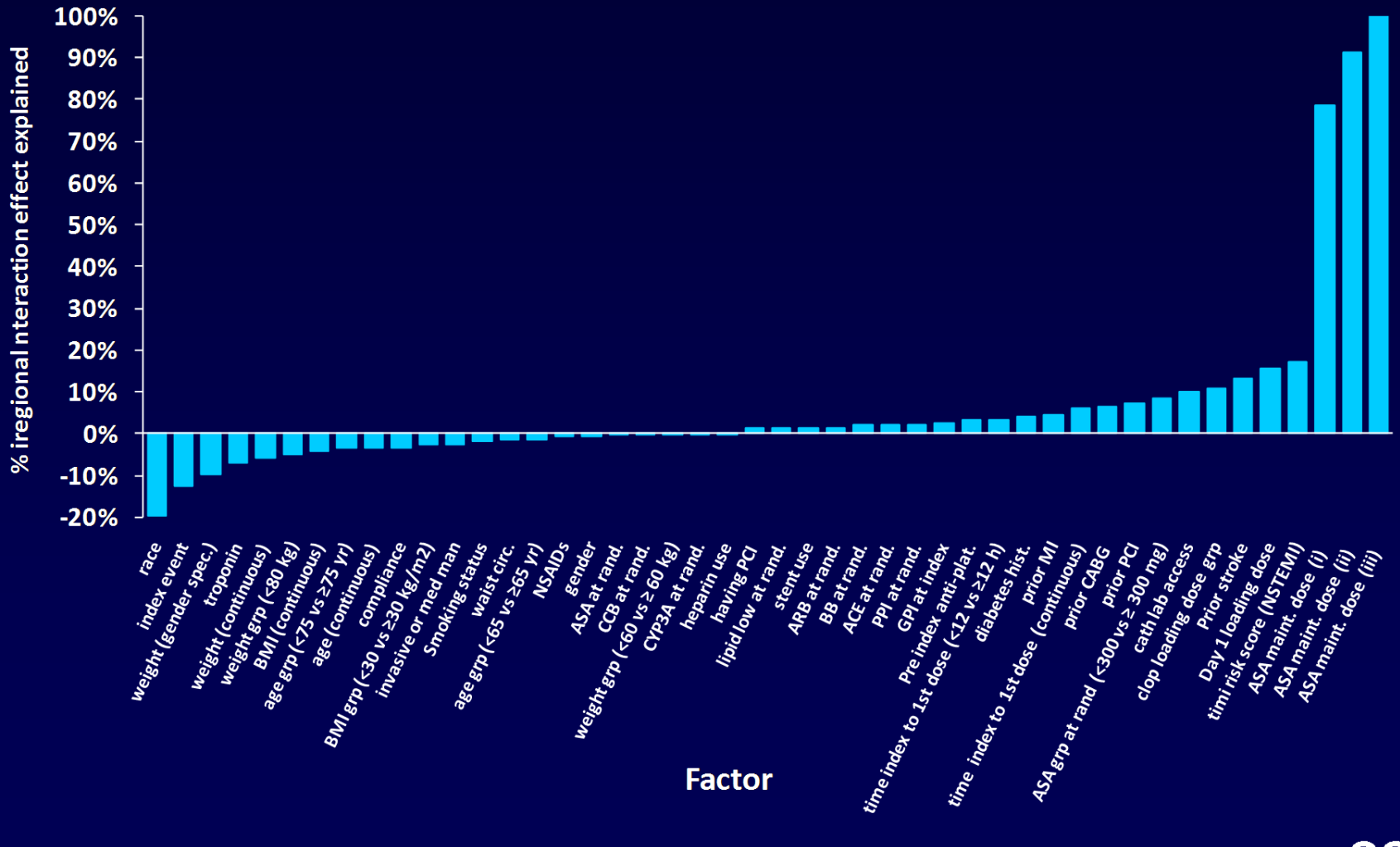
PLATO: What Kind of Factors or Patient Characteristics Might Explain the US vs Non-US Result?

- **To explain a meaningful fraction of the US/Non-US interaction, a factor is needed that simultaneously:**
  - **(i) has a strong qualitative interaction with randomized treatment for the primary endpoint and**
  - **(ii) is strongly imbalanced between US and Non-US settings**

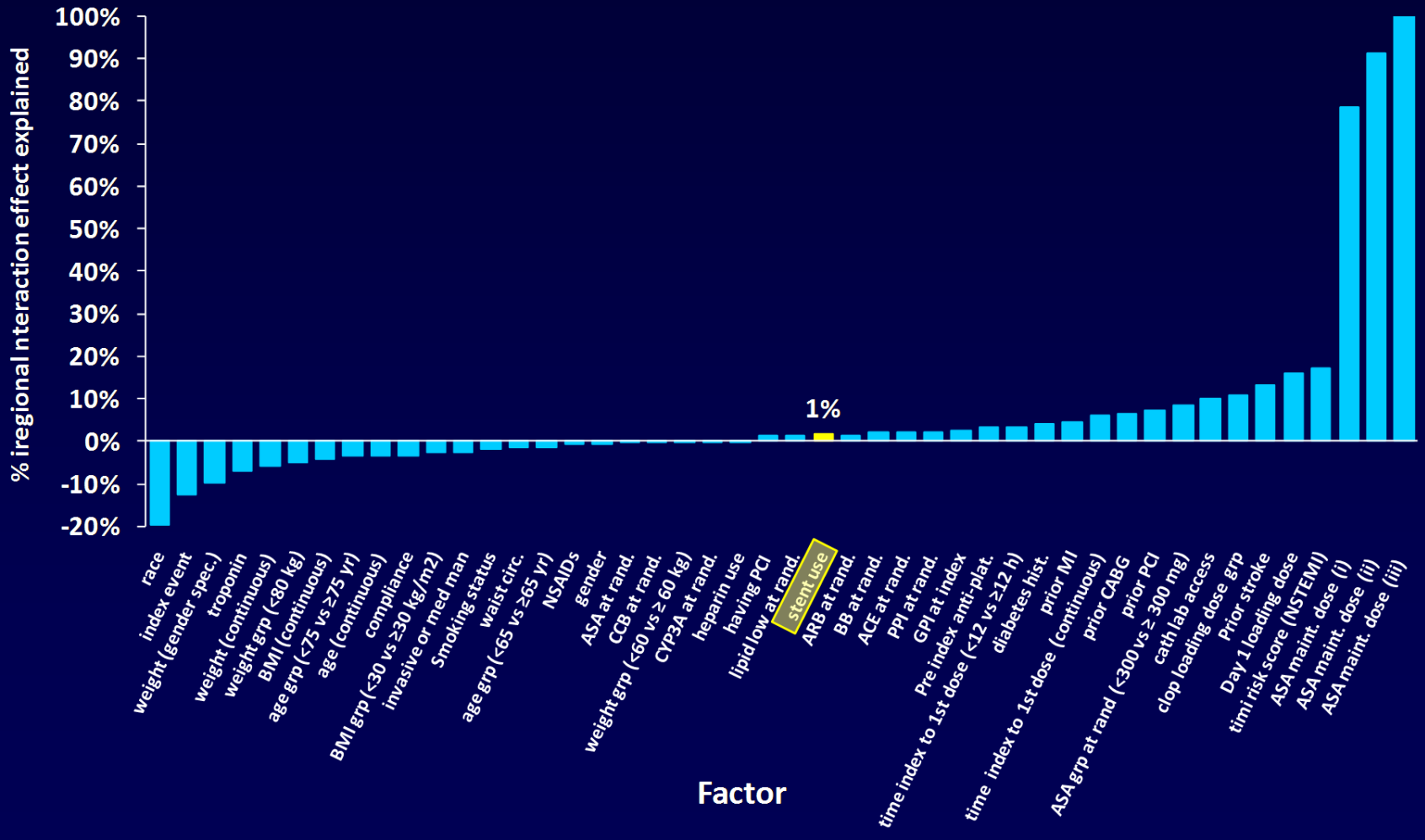
- **Weakly imbalanced prognostic factors will likely not be sufficient to explain the US result**

- **Visual inspection for imbalances of clinical concern needs to be supported by an objective and statistically rigorous analysis of the data**

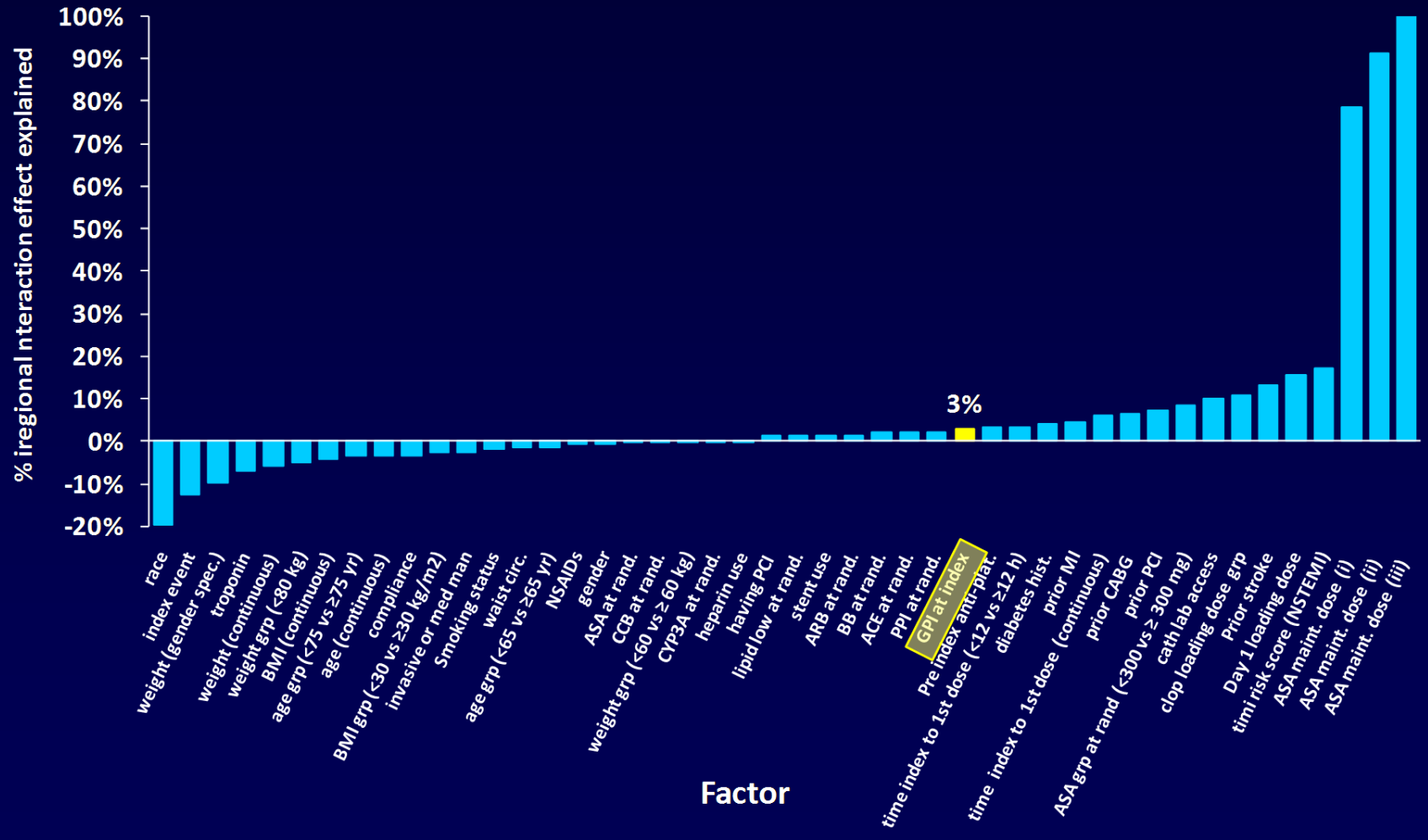
PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy



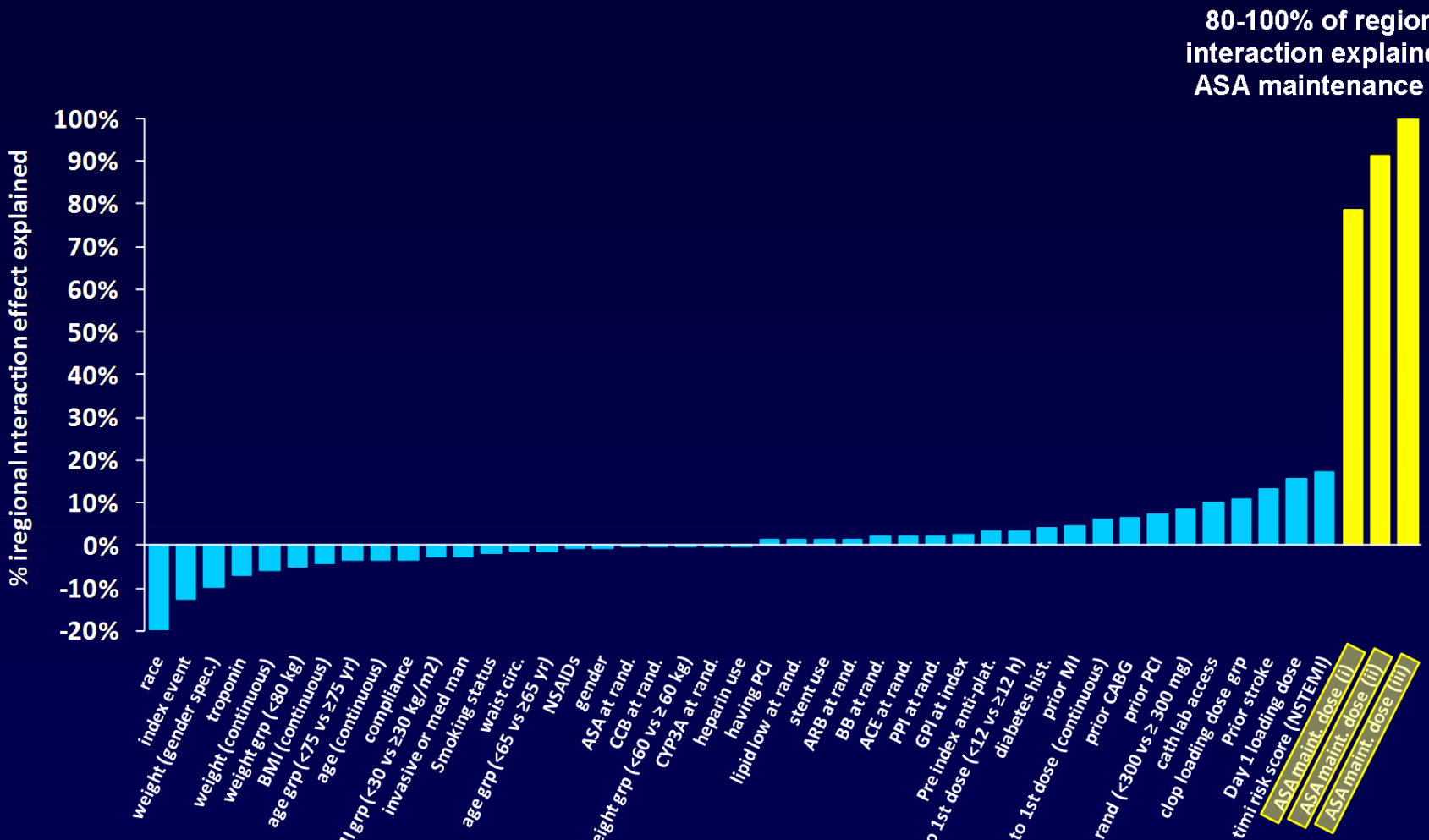
PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy



PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy

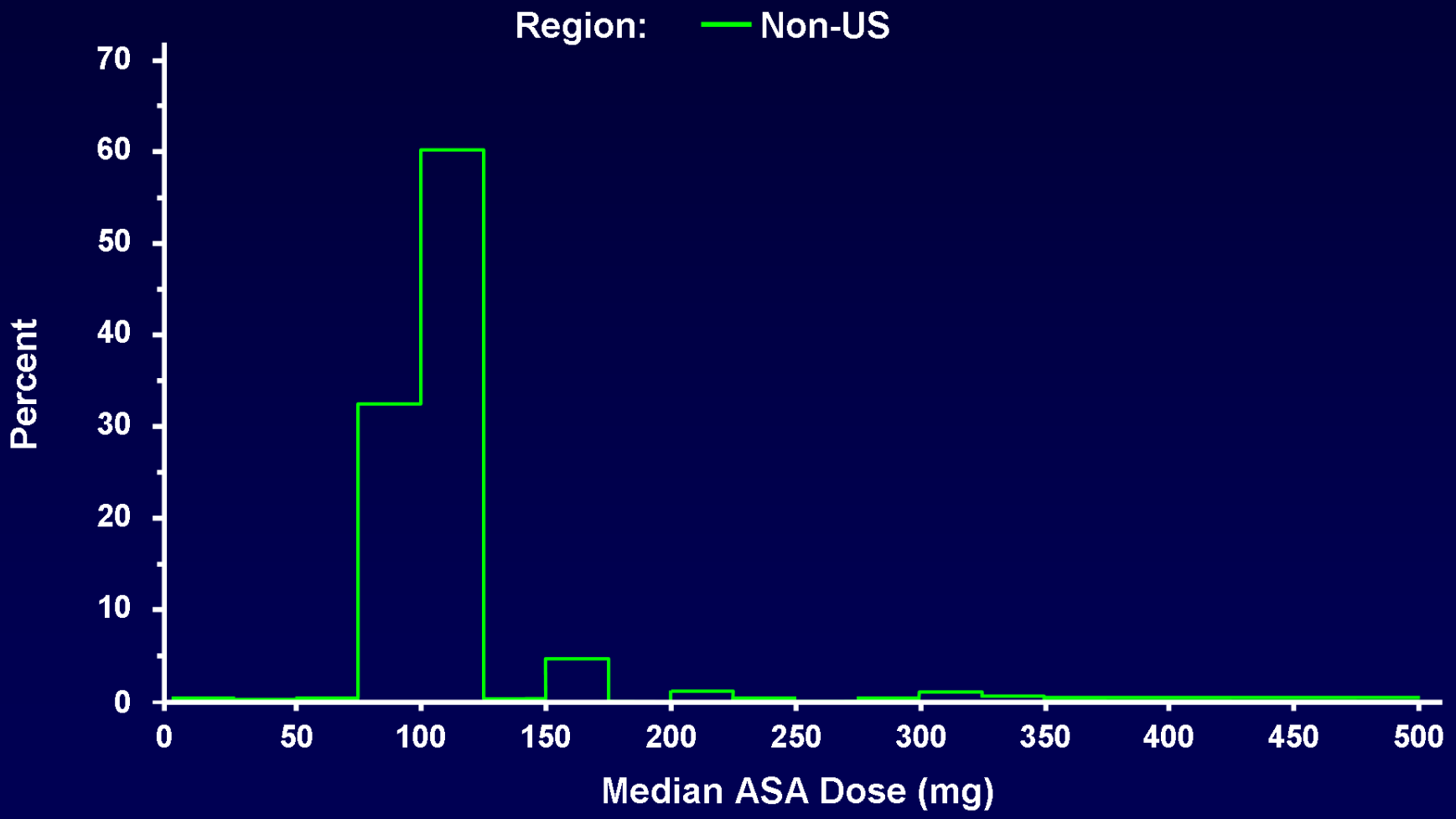


PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy

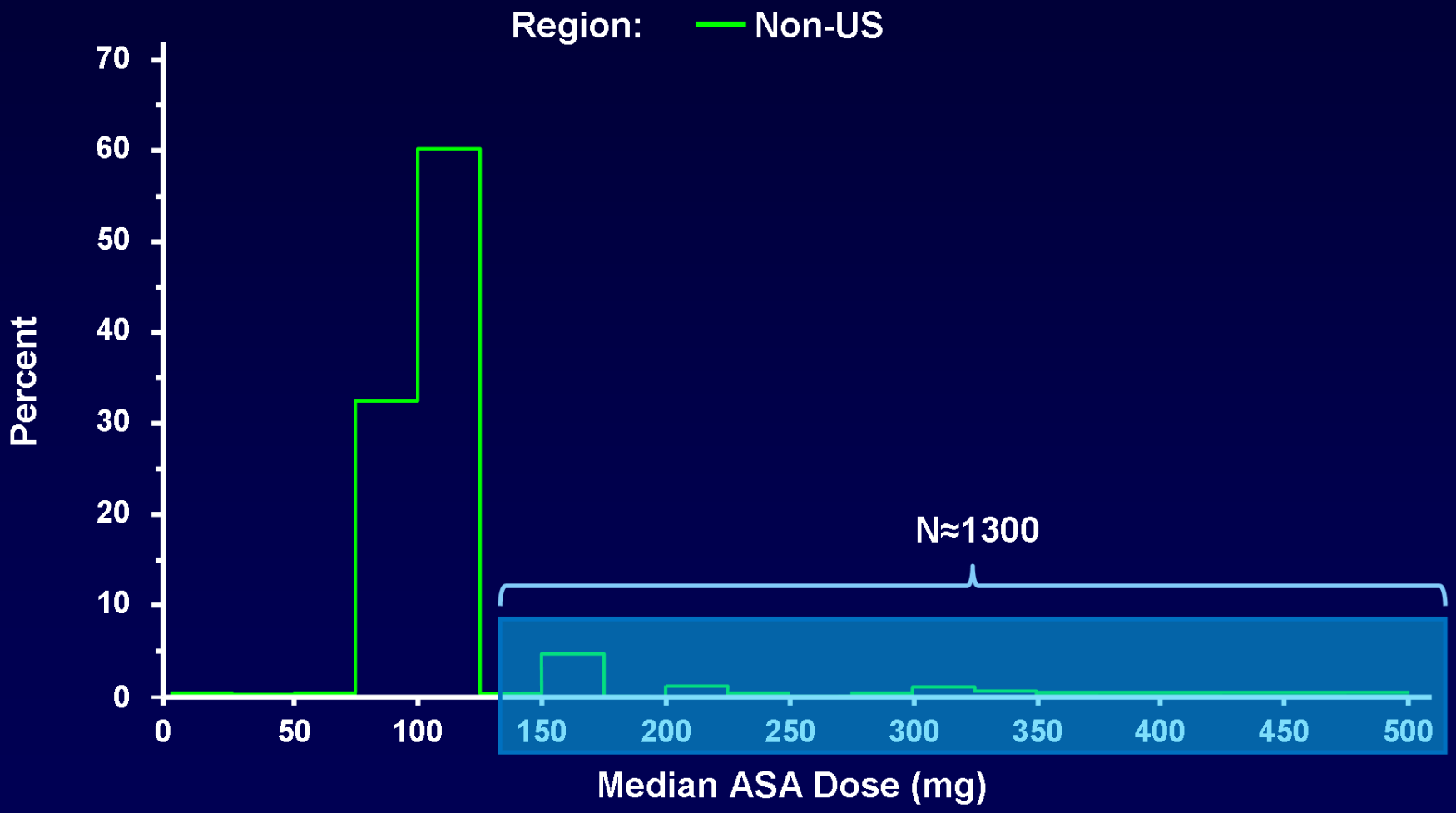


CC-87

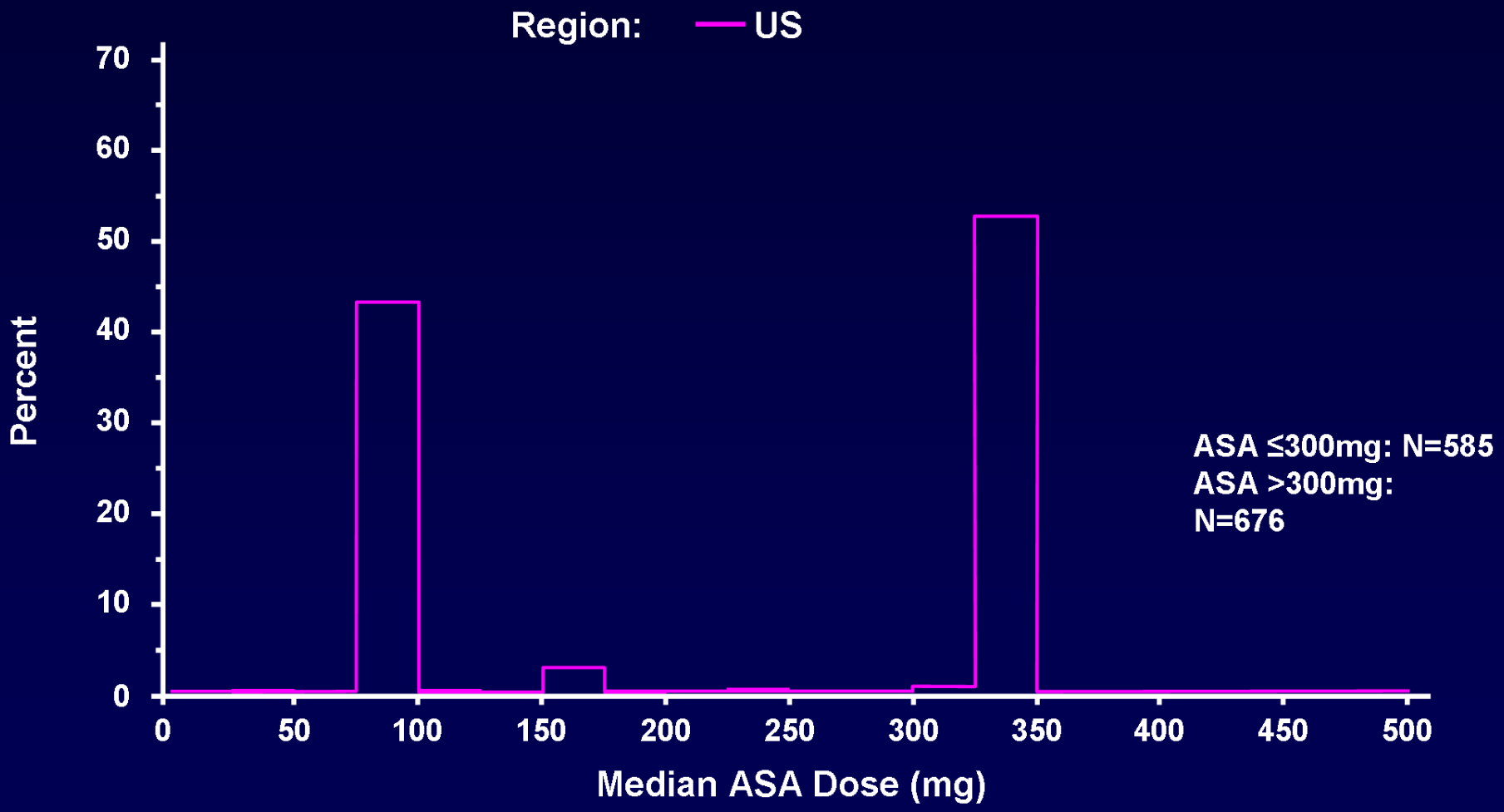
PLATO: ASA Dose Distribution Differs Between Regions



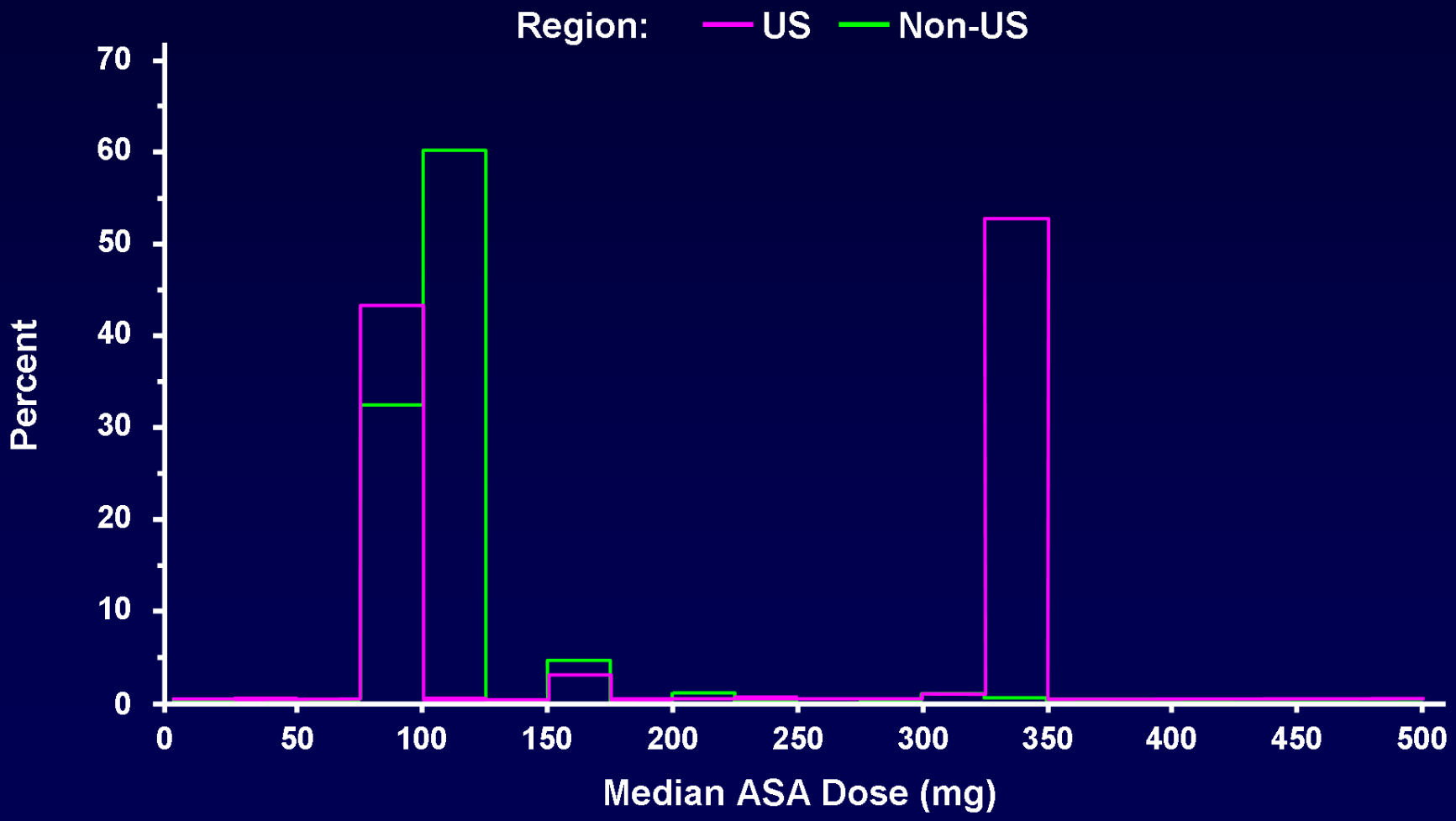
PLATO: ASA Dose Distribution Differs Between Regions



PLATO: ASA Dose Distribution Differs Between Regions

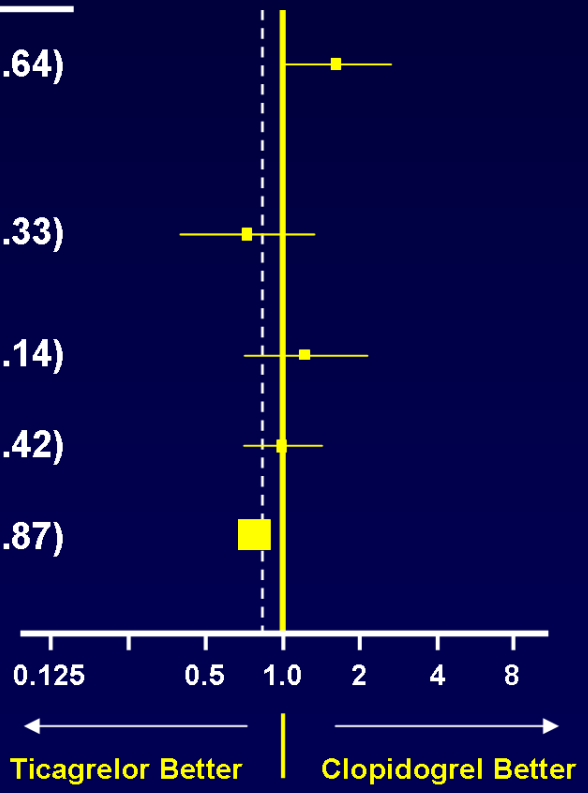


PLATO: ASA Dose Distribution Differs Between Regions



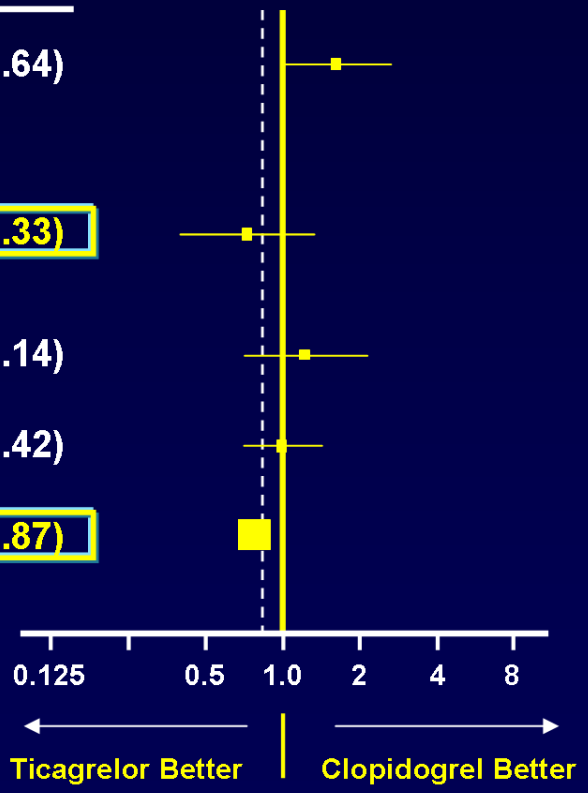
PLATO: Similar Pattern of Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US

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)



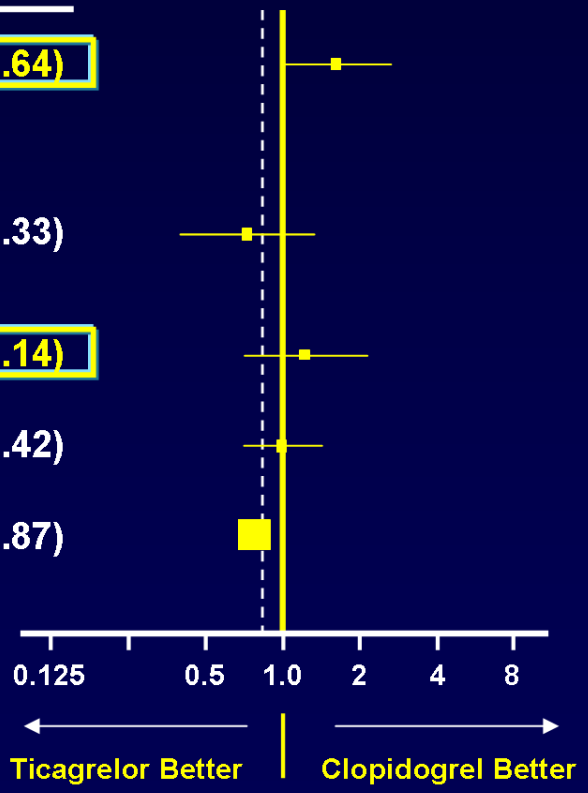
PLATO: Similar Pattern of Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US

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)



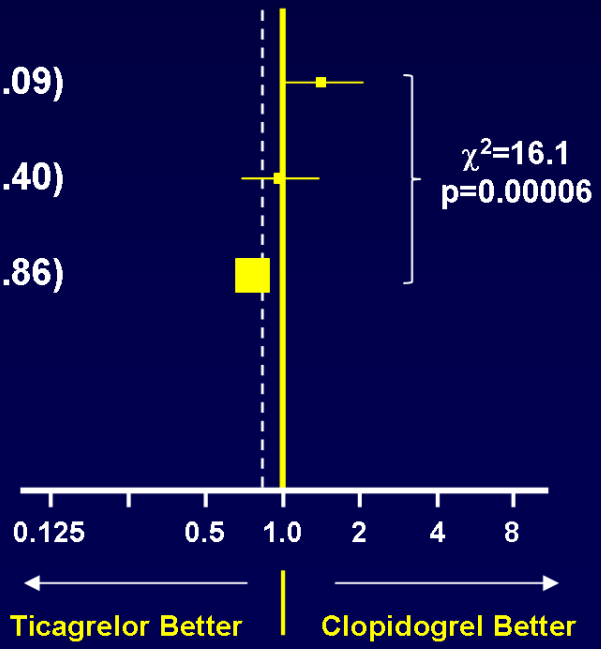
PLATO: Similar Pattern of Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US

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)



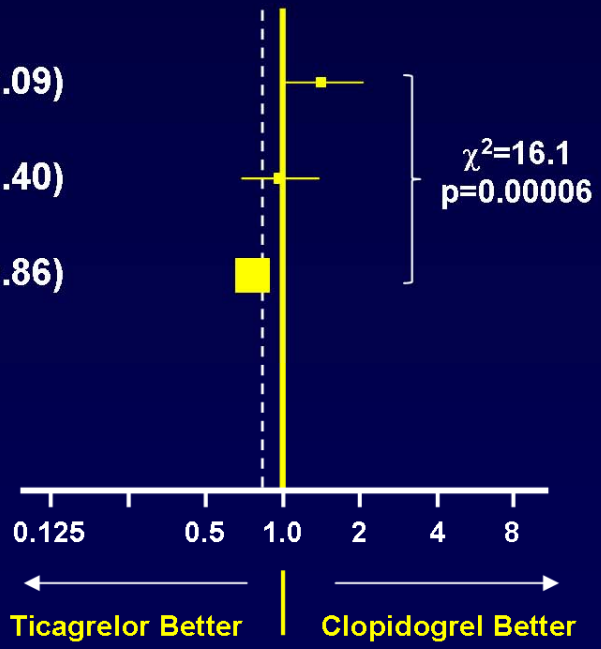
PLATO: The Regional Interaction is Explained by an Interaction with ASA Maintenance Dose

ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
Overall					
≥300	464	68	492	50	1.45 (1.01, 2.09)
>100 – <300	525	64	527	65	0.99 (0.70, 1.40)
≤100	7733	565	7706	723	0.77 (0.69, 0.86)

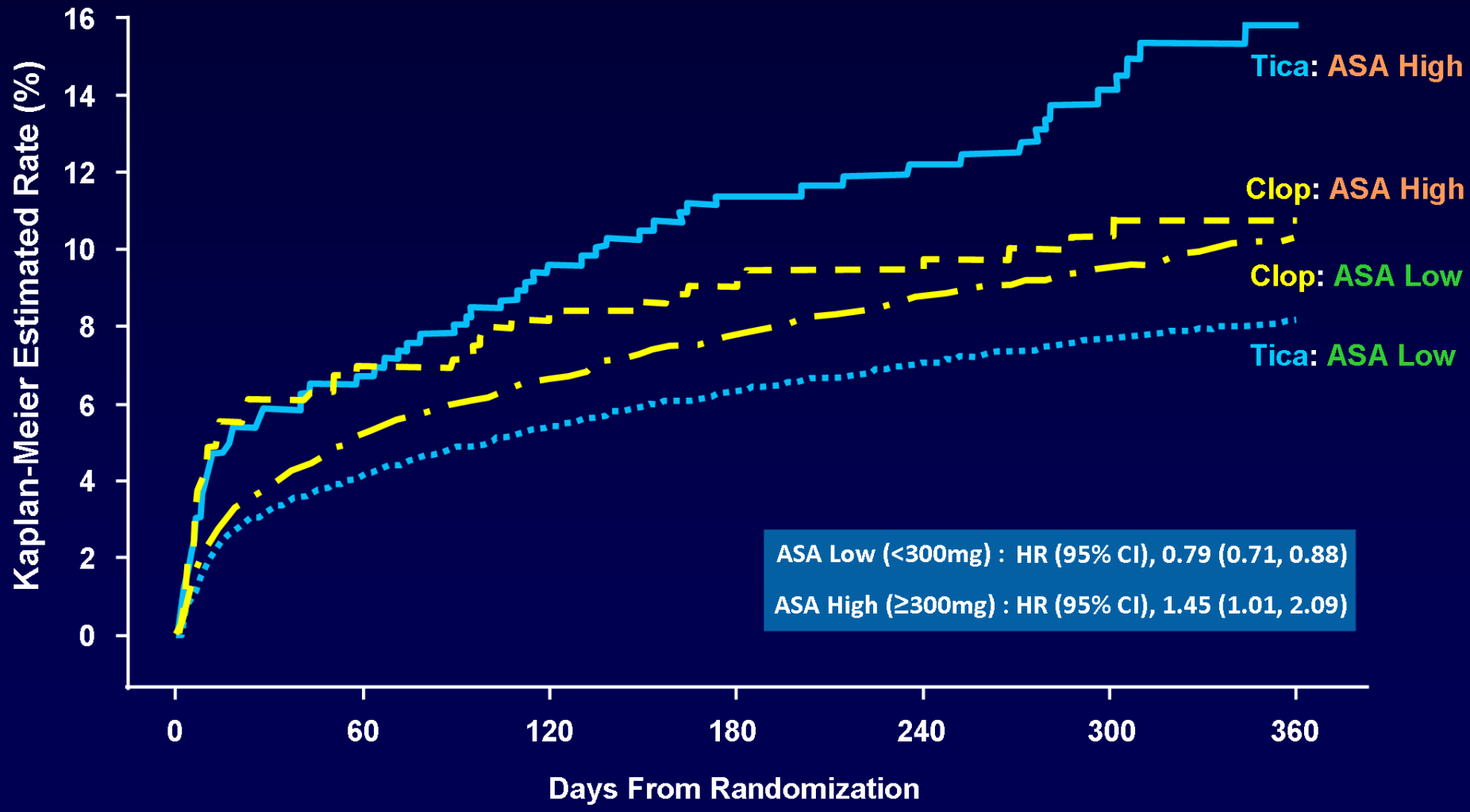


PLATO: The Regional Interaction is Explained by an Interaction with ASA Maintenance Dose

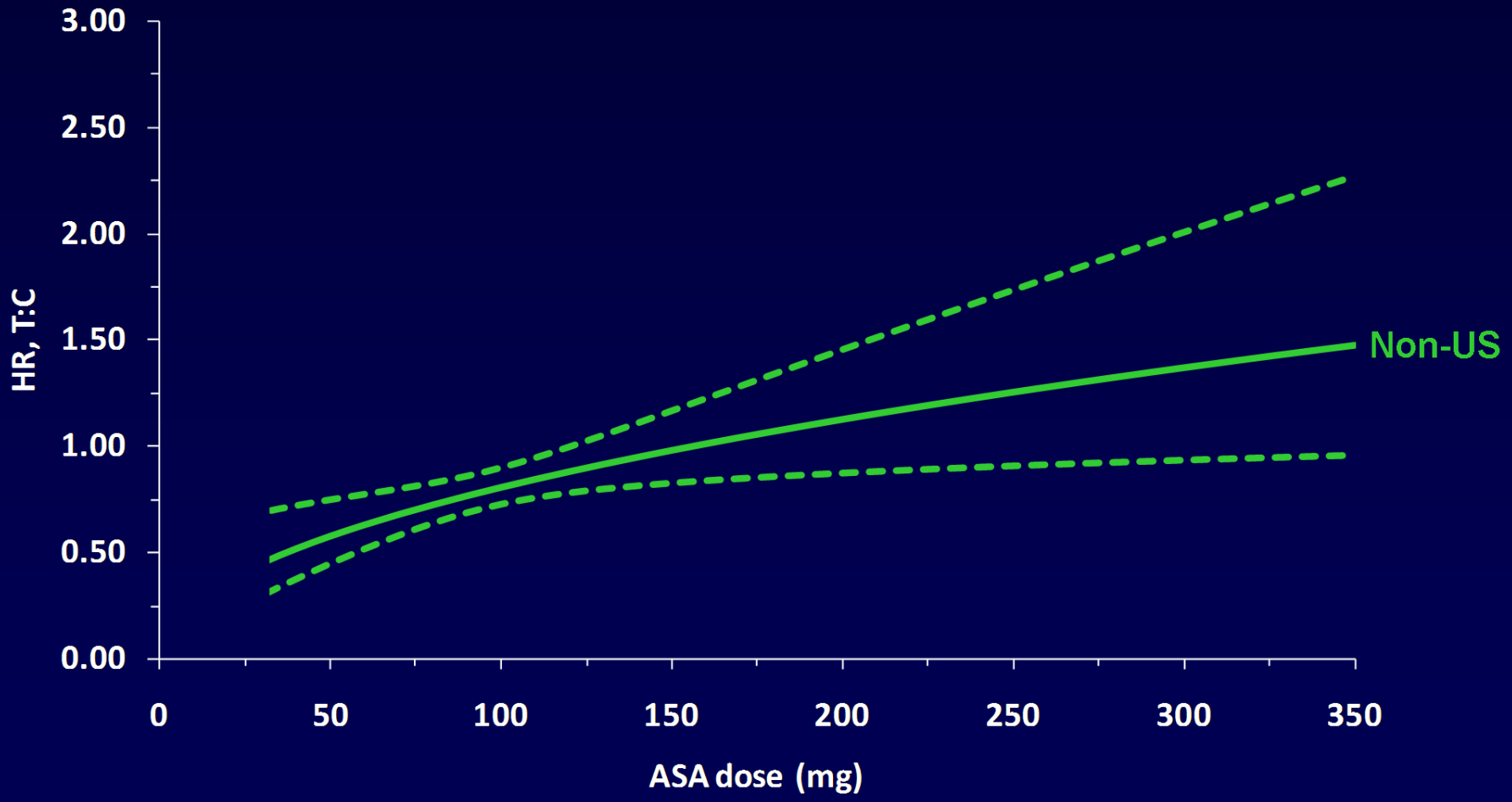
ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
Overall					
≥300	464	68	492	50	1.45 (1.01, 2.09)
>100 – <300	525	64	527	65	0.99 (0.70, 1.40)
≤100	7733	565	7706	723	0.77 (0.69, 0.86)



PLATO: The Treatment Effect is Strongly Dependent on ASA Maintenance Dose

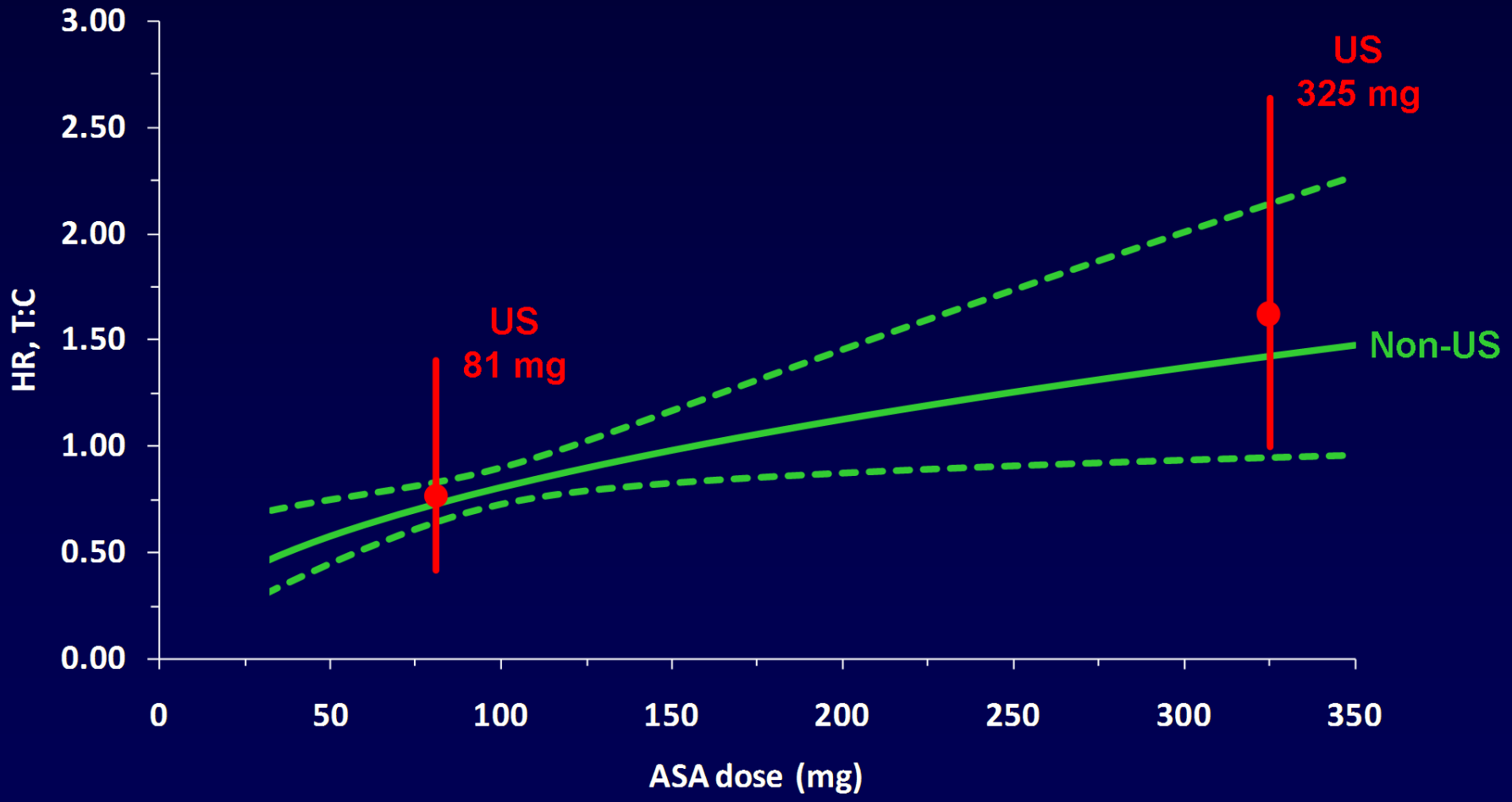


The Relationship Between ASA Maintenance Dose and Treatment Effect is seen in Non-US patients

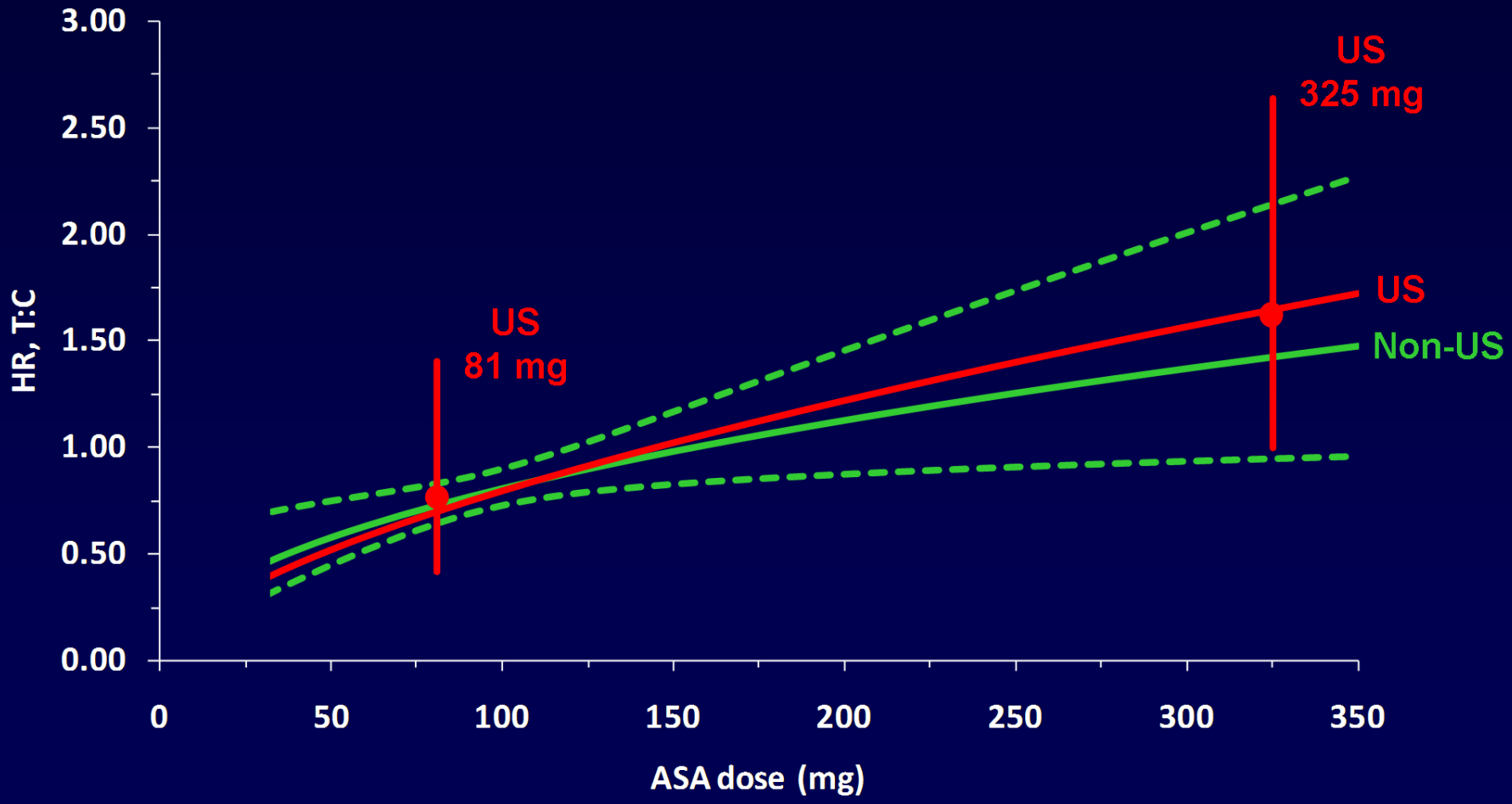


CC-98

And This Closely Reflects That Seen In US Patients



And This Closely Reflects That Seen In US Patients



CC-100

PLATO: How Robust is the Relationship Between ASA Maintenance Dose and Treatment Effect?

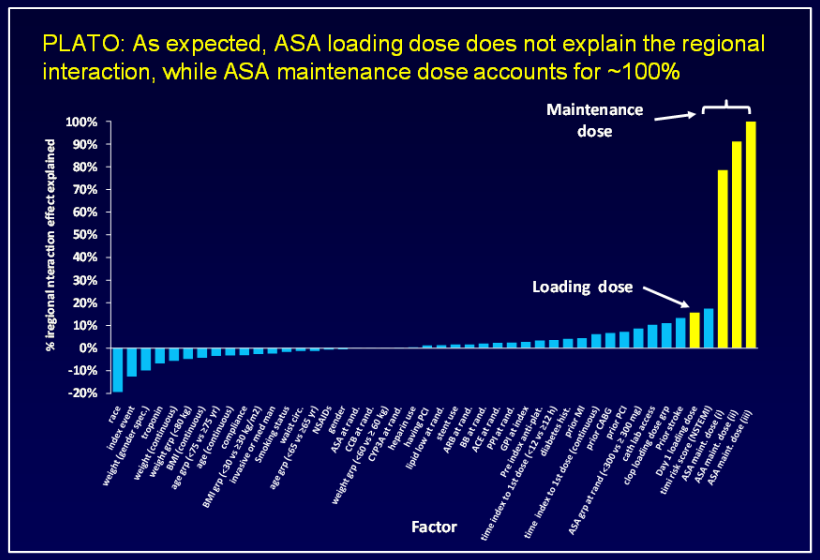
1. **Does it rely on a small number of Non-US patients taking high dose ASA?**

- **Interaction with ASA dose is profound, χ^2=16.1, p=0.00006**
- **~1,300 Non-US patients plus ~700 US patients with >100mg ASA**
- **Significant relationship persists even if higher ASA doses removed**

PLATO: How Robust is the Relationship Between ASA Maintenance Dose and Treatment Effect?

2. What is the influence of the initial ASA loading dose?

- Distinct aspect of patient management considered separately from the outset
- Loading dose high in both US and Non-US – little likelihood to explain the regional interaction
- Maintenance dose differs between US and Non-US
- Duration of maintenance dose varies between patients



- Correct to examine loading and maintenance doses separately

PLATO: How Robust is the Relationship Between ASA Maintenance Dose and Treatment Effect?

3. Do multiplicity issues take away the ASA interaction?

- **Analyses are exploratory**
- **At p=0.00006, strength of ASA x treatment interaction would comfortably beat the most stringent of multiplicity adjustments**

PLATO US Observation: Summary of Statistical Evaluation

- PLATO met its primary endpoint, demonstrating ticagrelor has superior efficacy to clopidogrel in the treatment of patients with ACS
- A qualitative regional interaction was observed, driven by a difference between the US and Non-US regions
- Issues related to trial conduct have been ruled out
- Chance cannot be entirely ruled out as explanation
- Extensive evaluation of the data revealed ASA maintenance dose was strongly imbalanced across US and Non-US regions, and statistically accounted for 100% of the observed interaction
- Data suggest the regional interaction is, in fact, an interaction with ASA maintenance dose
- When ticagrelor is administered with low-dose ASA, a positive treatment effect is seen in both US and Non-US regions

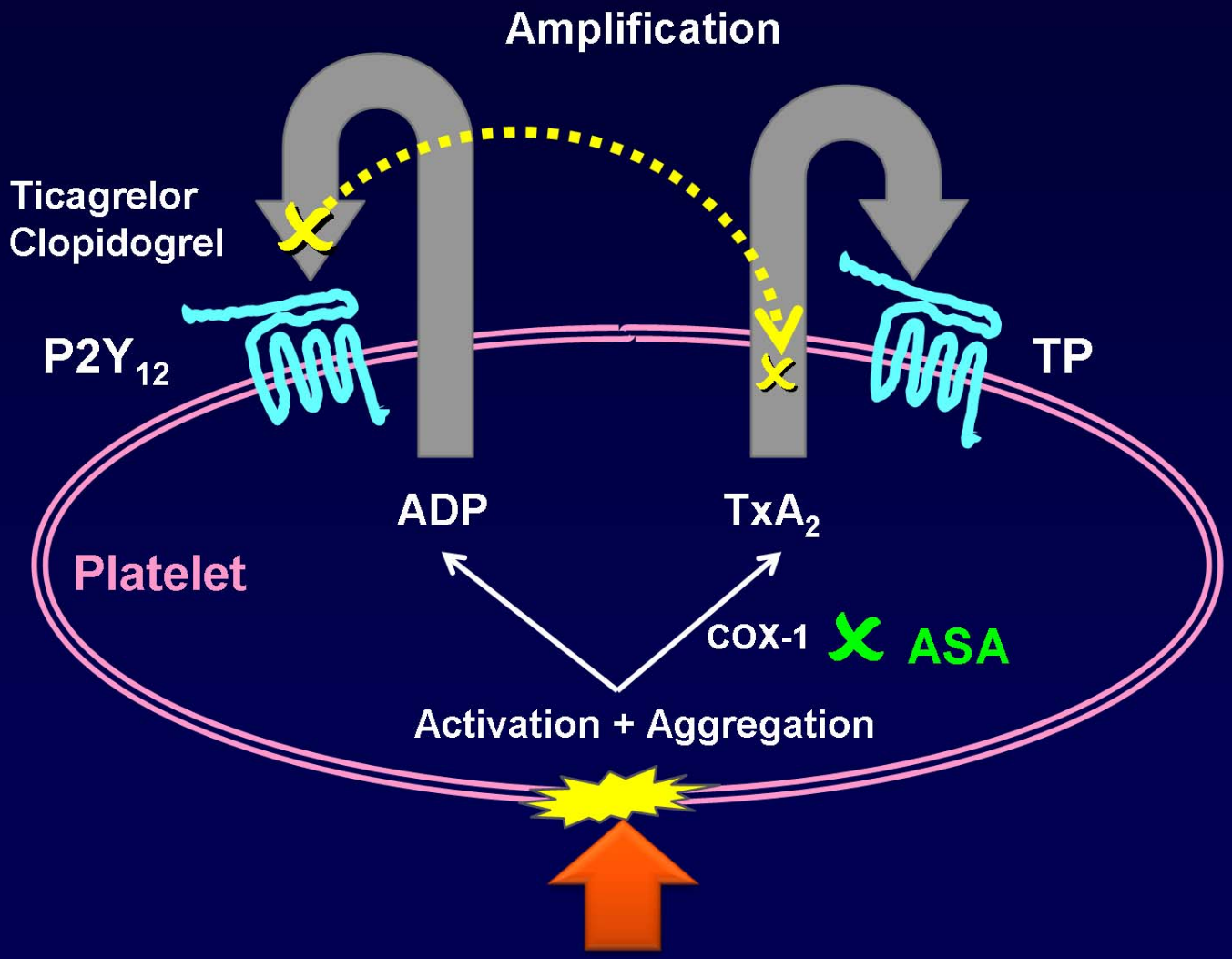
Ticagrelor: Sponsor Presentation Plan

Introduction	Jonathan Fox, MD, PhD Vice President, Clinical Development AstraZeneca
Rationale for Ticagrelor Development and the PLATO Trial	Lars Wallentin, MD, PhD Professor of Cardiology Director Uppsala Clinical Research Center University Hospital, Uppsala, Sweden
PLATO: Design and Results	Robert A Harrington, MD Professor of Medicine Duke University School of Medicine Director, Duke Clinical Research Institute
Ticagrelor Safety Profile	Kristen K Buck, MD Director, Clinical Development AstraZeneca
PLATO: North America	Kevin J Carroll, BSc, MSc, FRSS VP Statistics and Chief Statistician AstraZeneca
Benefit and Risk of Ticagrelor	Robert A Harrington, MD

PLATO ASA Analysis: Clinical Implications

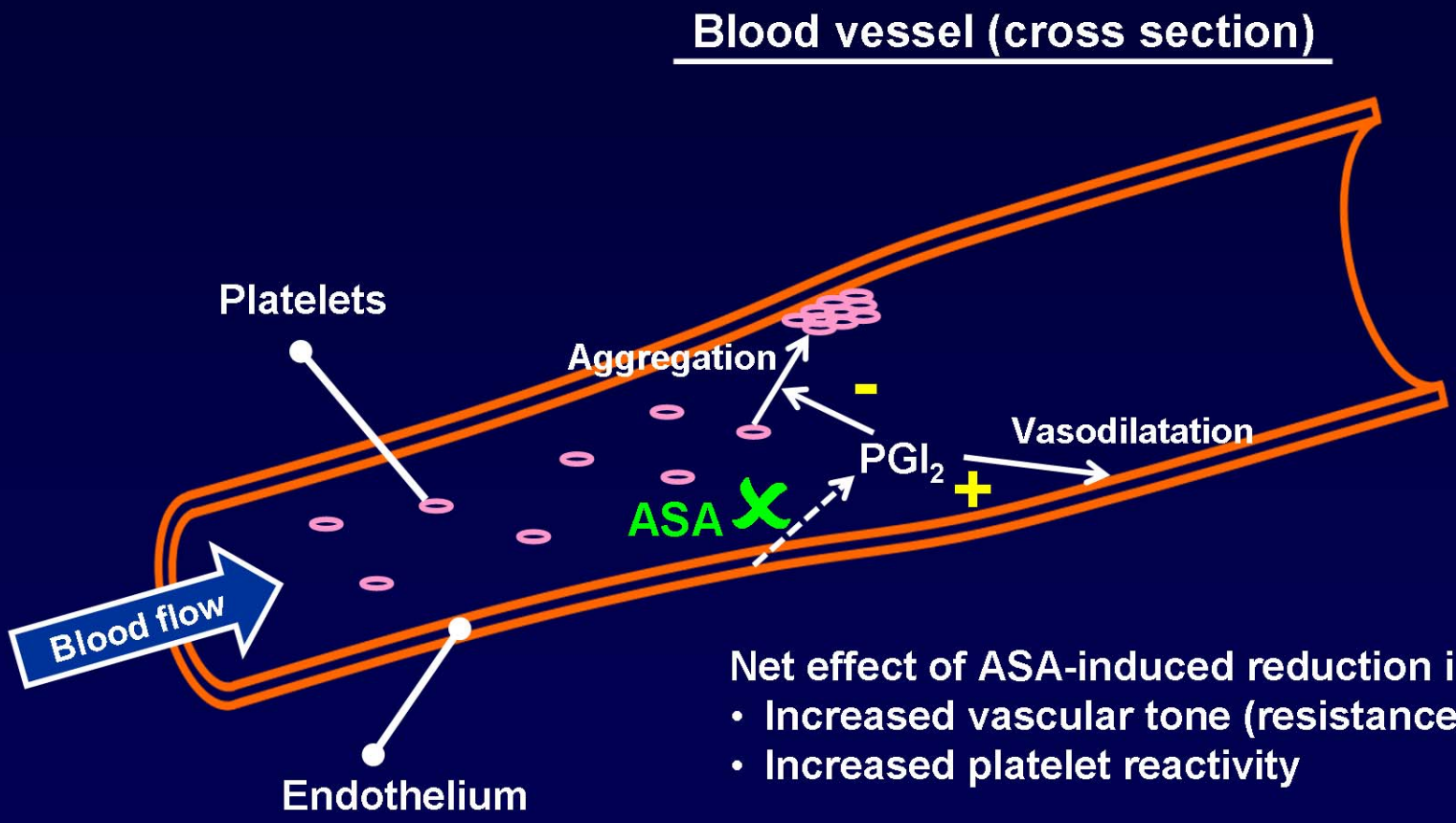
- Analysis shows efficacy is modified by ASA dose
- Optimal dose of ASA not established in prior trials
- Dose-related effects of ASA on prostanoids
  - Low dose: predominantly antagonizes TxA_2
  - High dose: also inhibits endothelial prostacyclin
- These effects may also be altered in the presence of different levels of $P2Y_{12}$ blockade

Effects of P2Y12 Inhibitors and ASA on Two Amplification Pathways of Platelet Activation: ADP and TxA_2



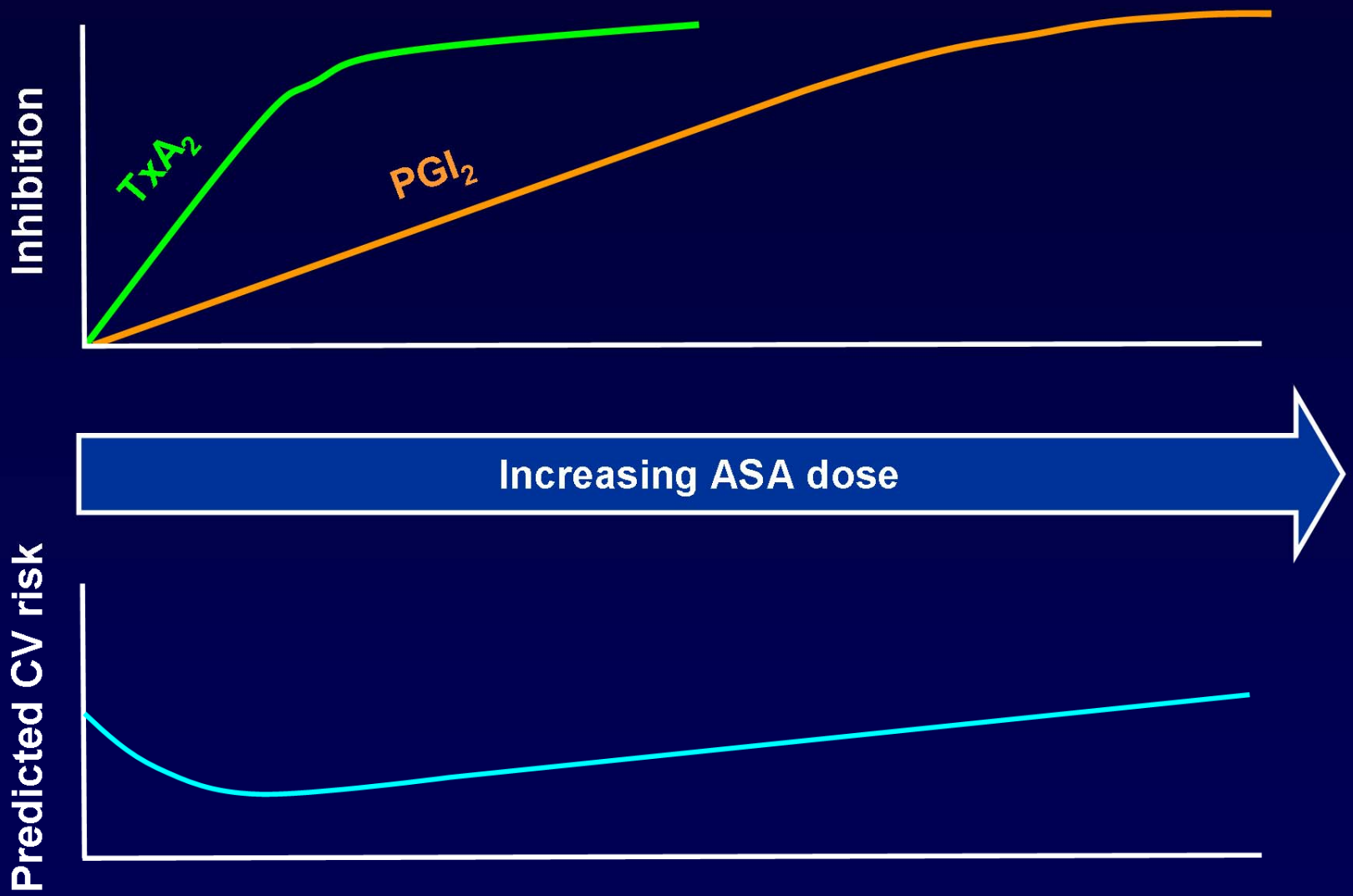
CC-107

ASA-Related Effects via Inhibition of Endothelium-Released PGI_2



Net effect of ASA-induced reduction in PGI_2
- Increased vascular tone (resistance)
- Increased platelet reactivity

Dose Dependent ASA Effects on TxA_2 and PGI_2 Inhibition and Potential Clinical Relevance



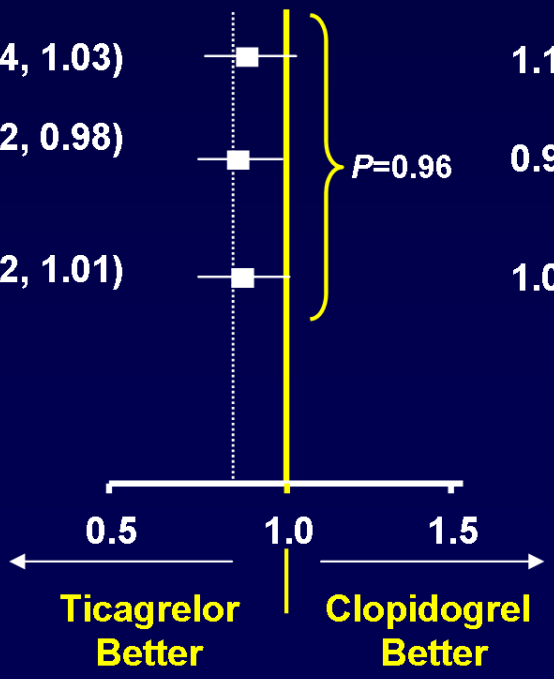
CC-109

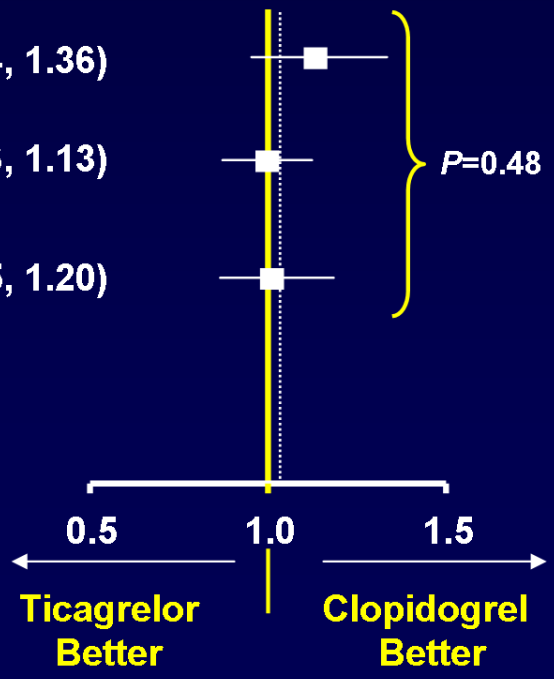
PLATO ASA Analysis: Clinical Implications

- The overall PLATO result, that ticagrelor reduced major CV events compared to clopidogrel, including CV mortality, is robust
- ASA is well established for secondary prevention, however the optimal ASA dose has not been determined
  - Most data observational
  - Limited randomized data, inconclusive
  - Low dose ASA sufficient to confer clinical benefit
  - High dose may be deleterious regarding bleeding risk
- PLATO protocol recommended, and 92% used, low maintenance dose ASA
- Ticagrelor is superior to clopidogrel when used with low dose ASA and informs the recommendation for effective use of ticagrelor

PLATO: Efficacy and Bleeding by Final Diagnosis

Subset	Efficacy HR (95% CI)	Major Bleeding HR (95% CI)
Entire Cohort	0.84 (0.77, 0.92)	1.04 (0.95, 1.13)
UA/NSTEMI:		
Medical Management	0.87 (0.74, 1.03)	1.13 (0.94, 1.36)
Invasive Management	0.84 (0.72, 0.98)	0.99 (0.86, 1.13)
STEMI:		
Invasive Management	0.86 (0.72, 1.01)	1.01 (0.85, 1.20)





CC-111

PLATO and ACS: One Syndrome and One Study

- One clinical trial for one clinical syndrome caused by atherosclerotic plaque rupture
- PCI is urgent in STE, but invasive management and PCI is used in many NSTE patients
- Dual anti-platelet therapy is used early in STEMI and NSTEMI
- PLATO was designed based on clinical presentation of ACS patients

Generalizability of the PLATO Trial

- Broad ACS population randomized pre-catheterization
  - Based on initial ECG: STE or NSTE
  - Declared intent for invasive or medically managed
  - All but lowest-risk patients and thrombolysis patients
- Initiated dual antiplatelet treatment promptly, consistent with widespread standard of care
- Allowed preloading or prior maintenance clopidogrel
- PLATO study population reflects US ACS population

Ticagrelor: Summary of Benefits

- Reduction in composite of CV death, MI or stroke: 16% RRR, 1.9% ARR (p=0.0003) – NNT = 54
- CV death benefit: 21% RRR, 1.1% ARR (p=0.001)
- Reduction in stent thrombosis
- Applicable to the broad ACS patient population
- Applicable across many patient subgroups and secondary endpoints
- Treatment effect constant over duration of study

Ticagrelor: Summary of Risks

- Bleeding compared to clopidogrel
  - No difference in total major bleeding
  - More major non-CABG, including non-procedural, bleeding
  - More fatal ICH but fewer extracranial fatal bleeds
  - No difference in fatal or life-threatening bleeding
- Dyspnea
  - More frequent with ticagrelor (not cardiac in origin; not COPD)
  - 9 of 1000 patients discontinued treatment
  - History, physical exam usually suffice to exclude treatable cause
- No increased risk for elderly, women, or low body weight subgroups

Ticagrelor: Therapeutic Considerations

Based on PLATO, use of ticagrelor instead of clopidogrel for 12 months in 1,000 patients admitted to hospital for acute coronary syndrome would result in:

Benefits

- 14 fewer deaths
- 11 fewer myocardial infarctions
- 6–8 fewer cases with stent thrombosis

Risks

- 6 major non-CABG bleeds
  - No increase in fatal/ life-threatening bleeds
- 9 discontinuations due to dyspnea

Cardiovascular and Renal Drugs Advisory Committee Meeting

BRILINTA (ticagrelor)

AstraZeneca

July, 2010

CC-117

Potential Follow-on Study

- Large, multi-national randomized, double-blind, double-dummy study
- Stable coronary artery disease patients
- Greater than 12 months from ACS
- Background of ASA 70-150 mg daily
- Ticagrelor vs placebo
- Primary outcome composite: CV death, MI, stroke
- Including a large US cohort of patients (~25%)

Cardiovascular and Renal Drugs Advisory Committee Meeting

BRILINTA (ticagrelor)

AstraZeneca

July, 2010

CC-119