

Ticagrelor: Sponsor Presentation Plan

Introduction

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Rationale for Ticagrelor Development
and the PLATO Trial

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PLATO: Design and Results

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Ticagrelor Safety Profile

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PLATO: North America

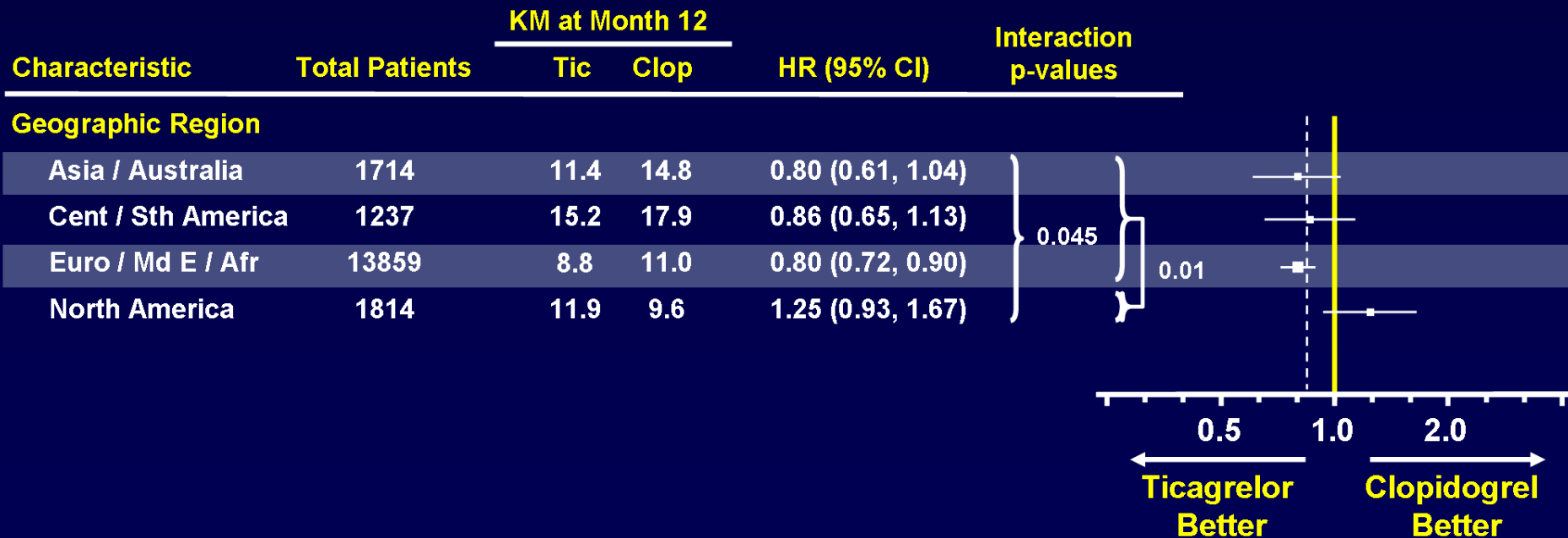
Kevin J Carroll, BSc, MSc, FRSS
VP Statistics and Chief Statistician
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Benefit and Risk of Ticagrelor

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)



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

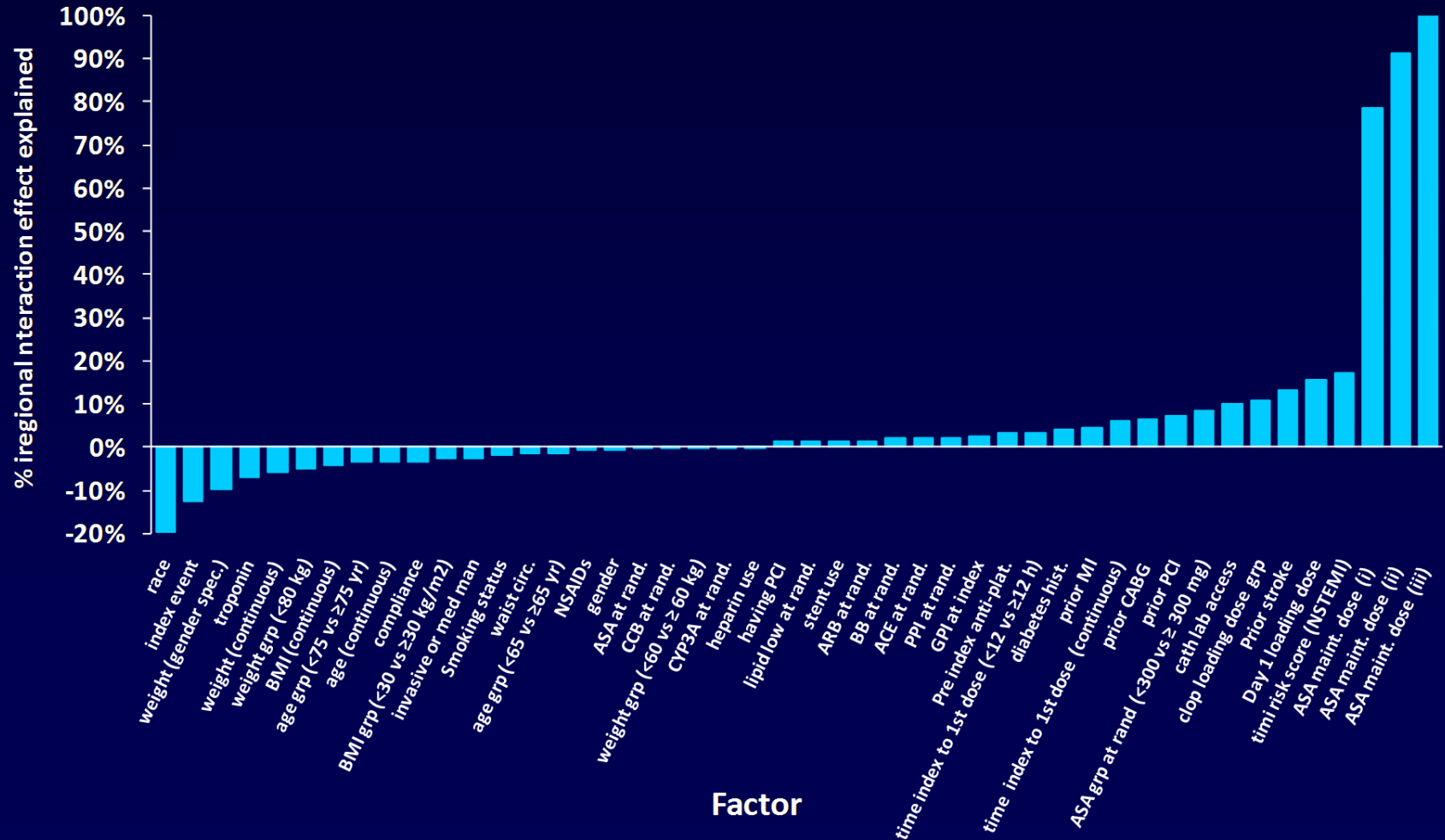
- Race
- Index event
- **Weight#**
- Troponin
- **BMI #**
- **Age #**
- Compliance
- ASA at rand.
- Invasive or med man
- Smoking status
- Waist circumference
- ACE at rand.
- NSAID at rand.
- Gender
- CCB at rand.
- **Time index to 1st dose #**
- CYP3A at rand.
- Heparin use
- PCI <24h of rand.
- Lipid 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.

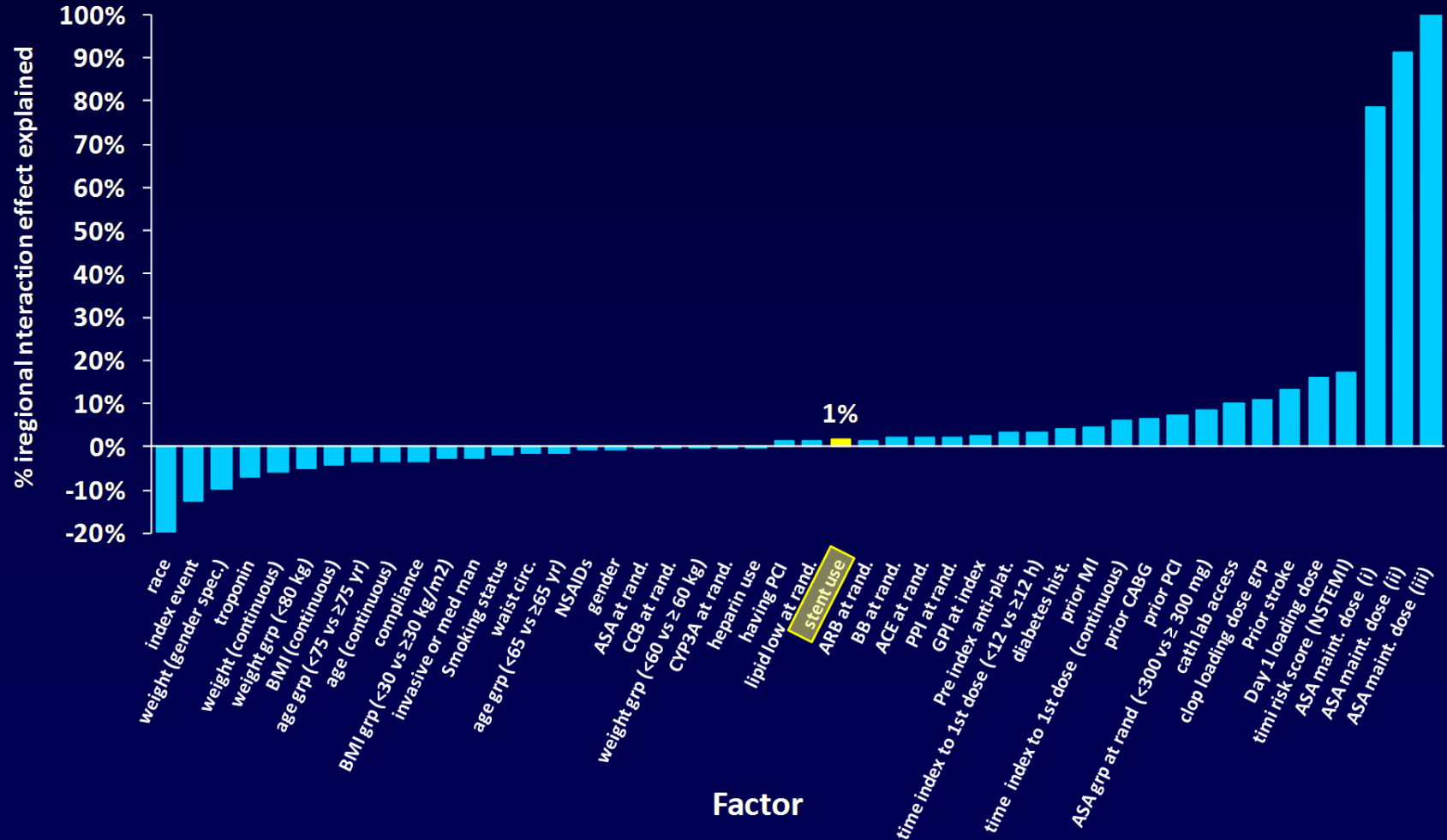
PLATO: What Kind of Factors or Patient Characteristics Might Explain the US vs Non-US Result?

- 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

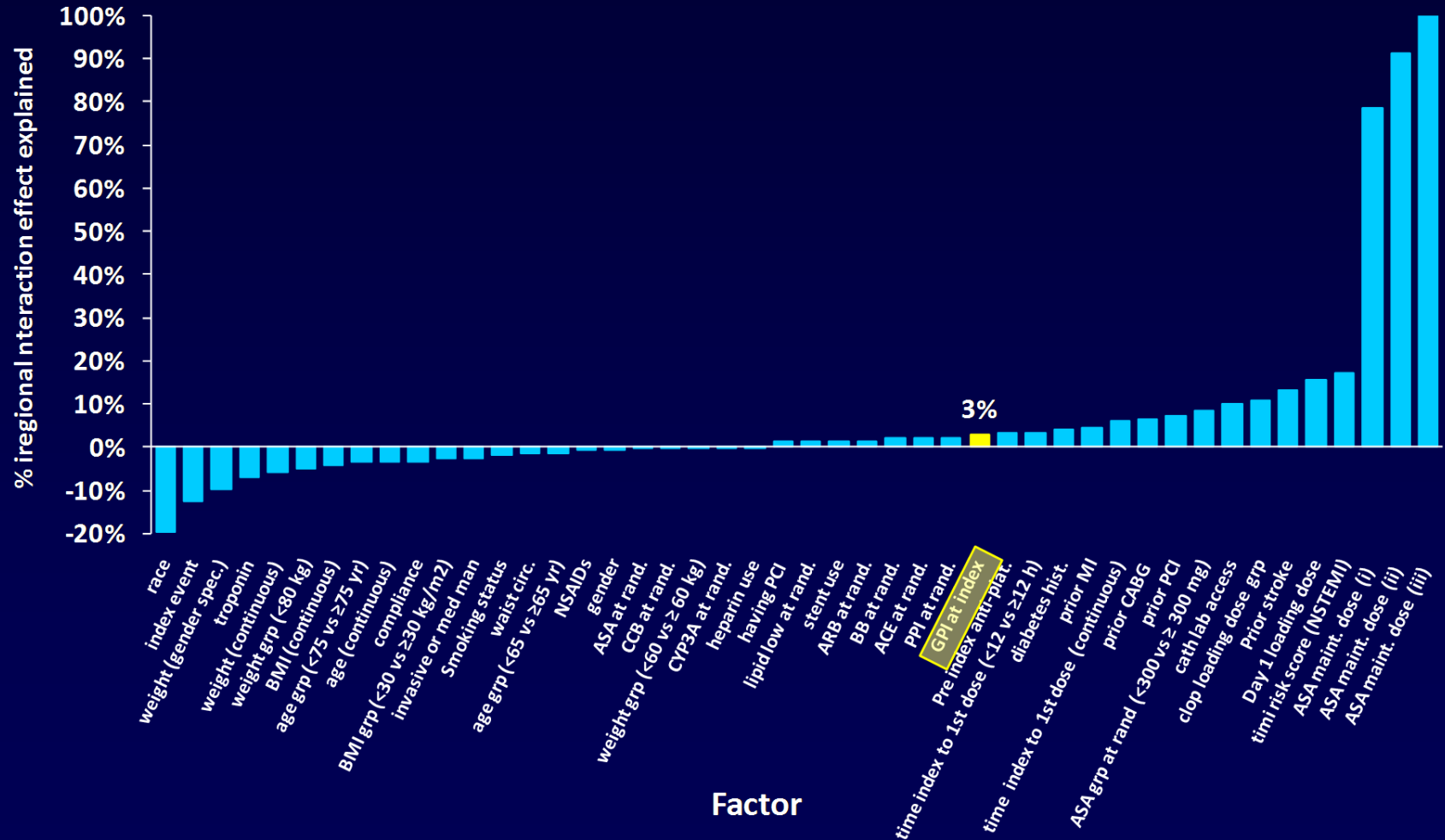
PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy



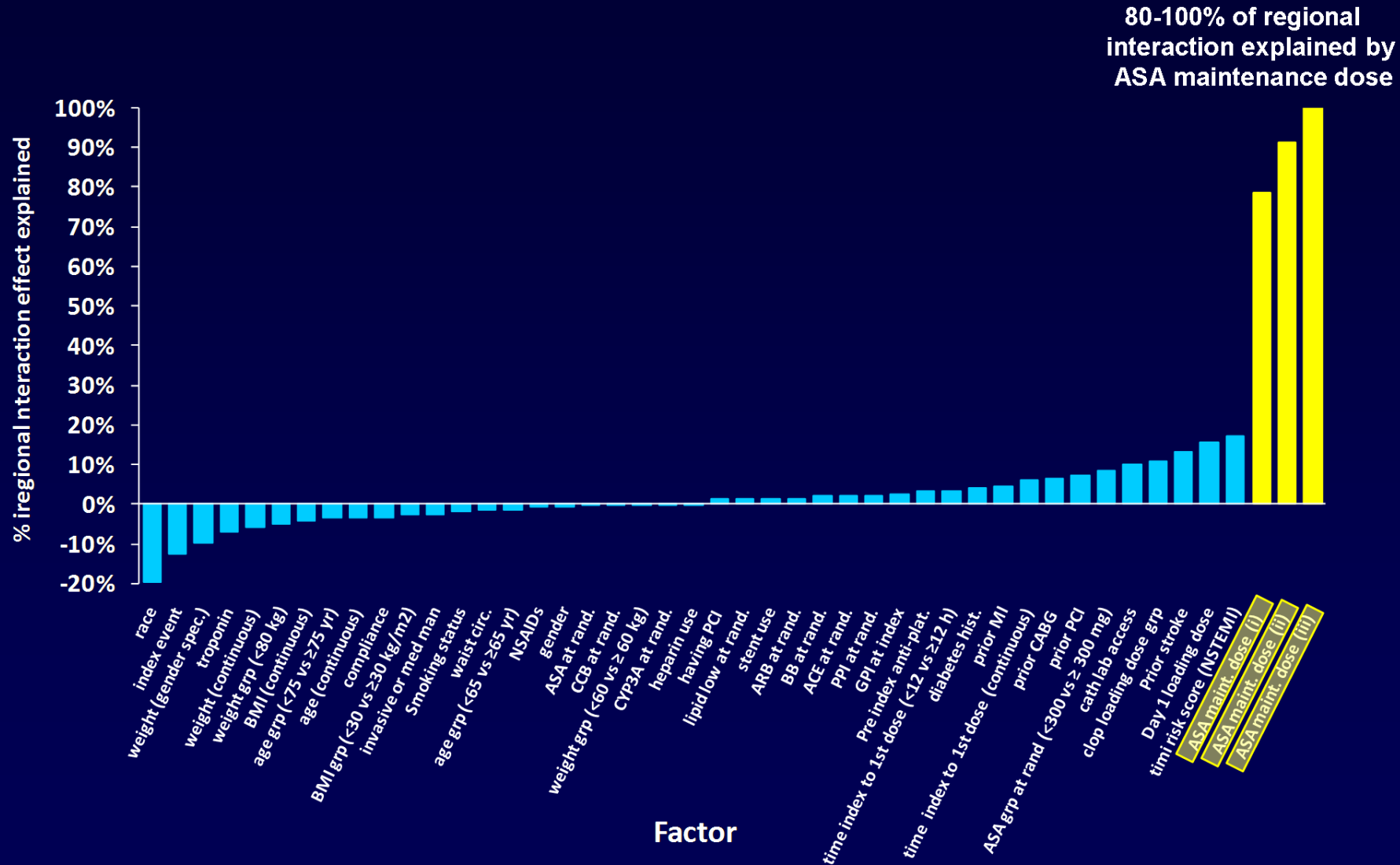
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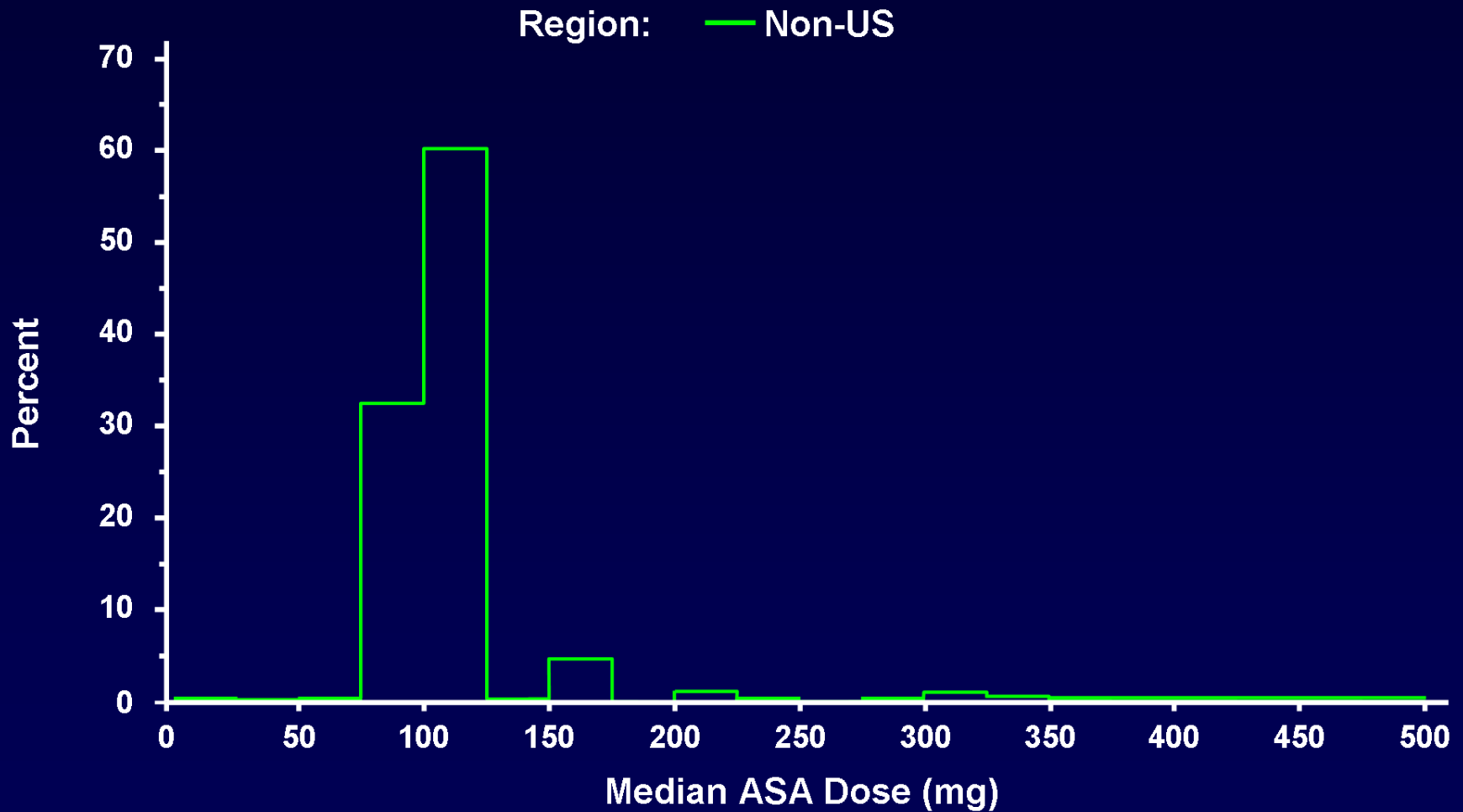
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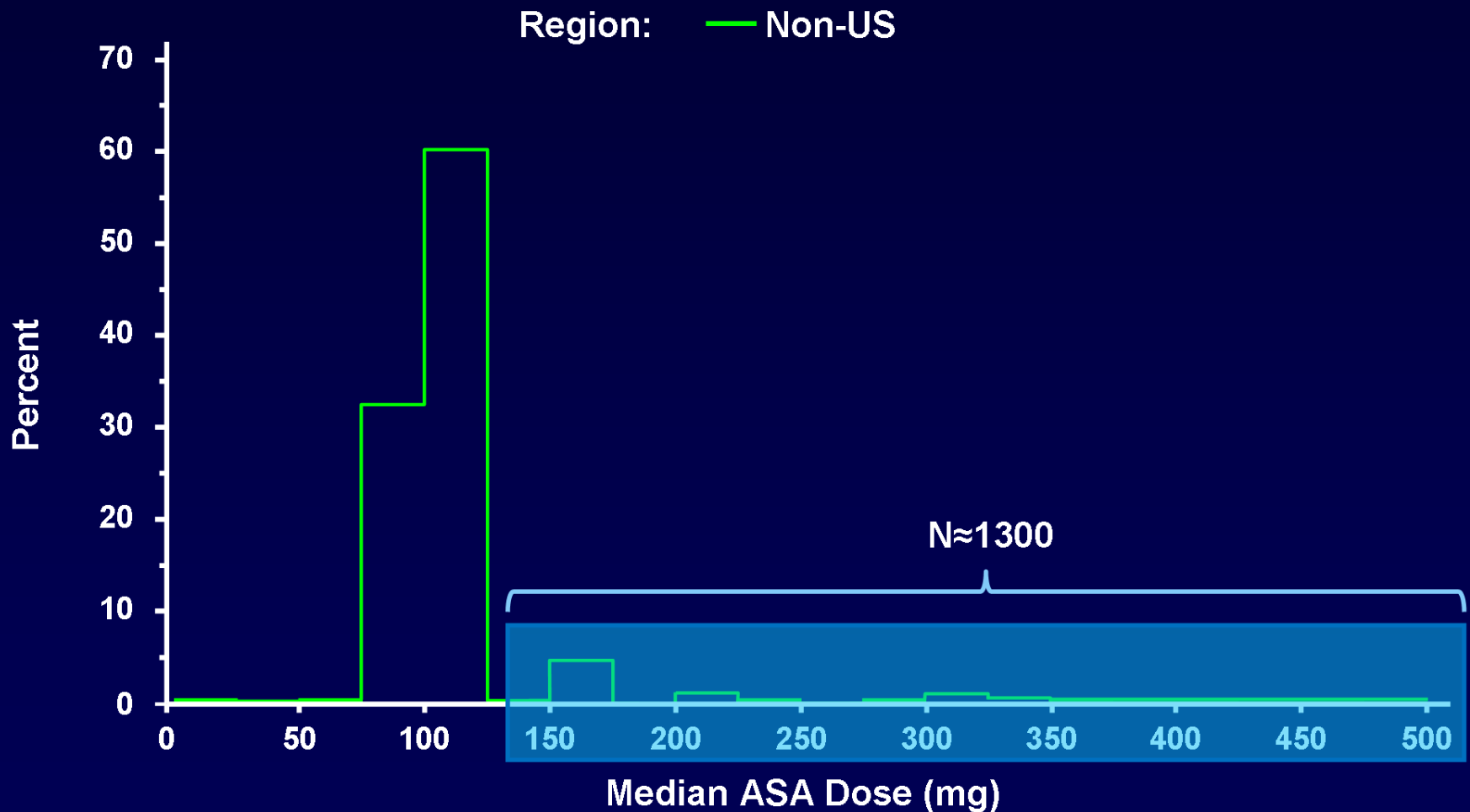
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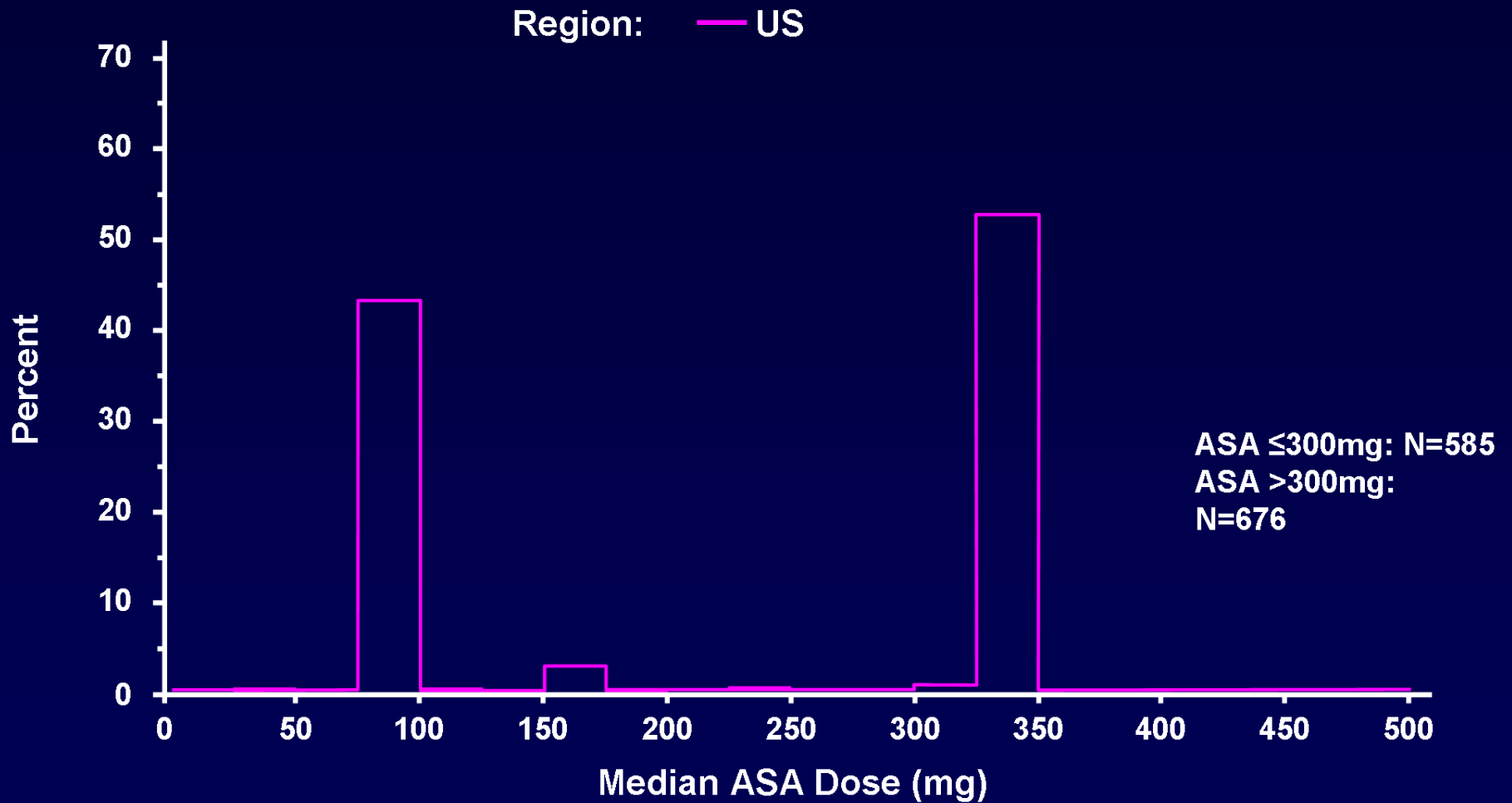
PLATO: ASA Dose Distribution Differs Between Regions



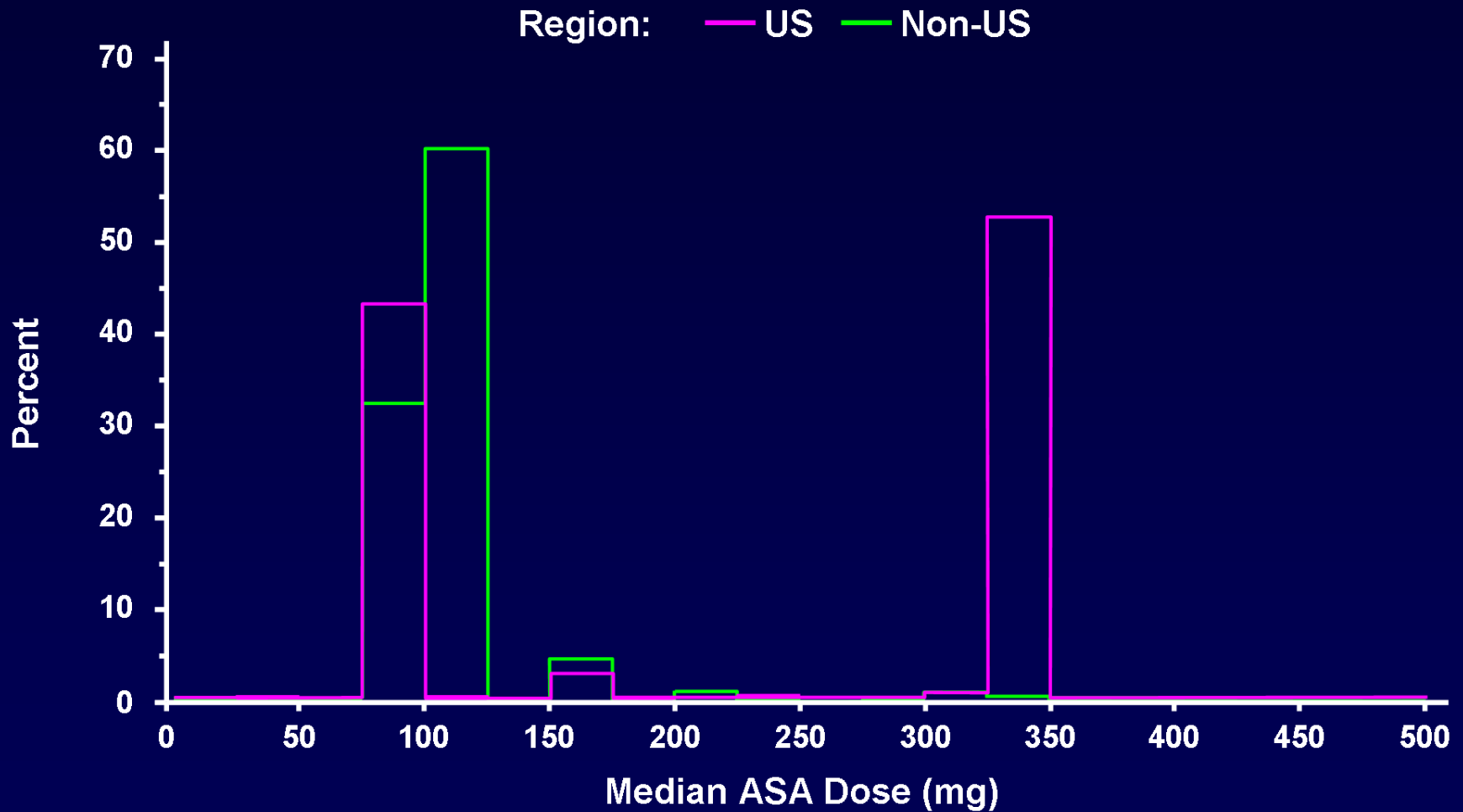
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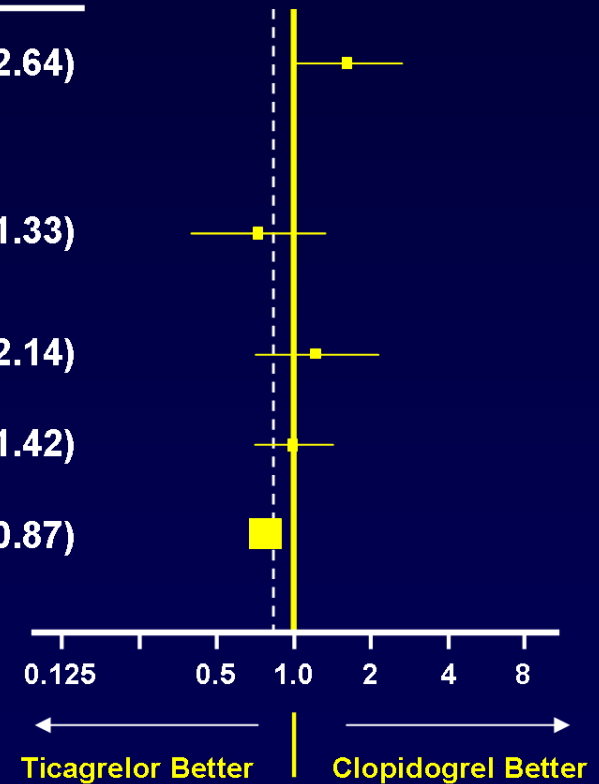


PLATO: ASA Dose Distribution Differs Between Regions

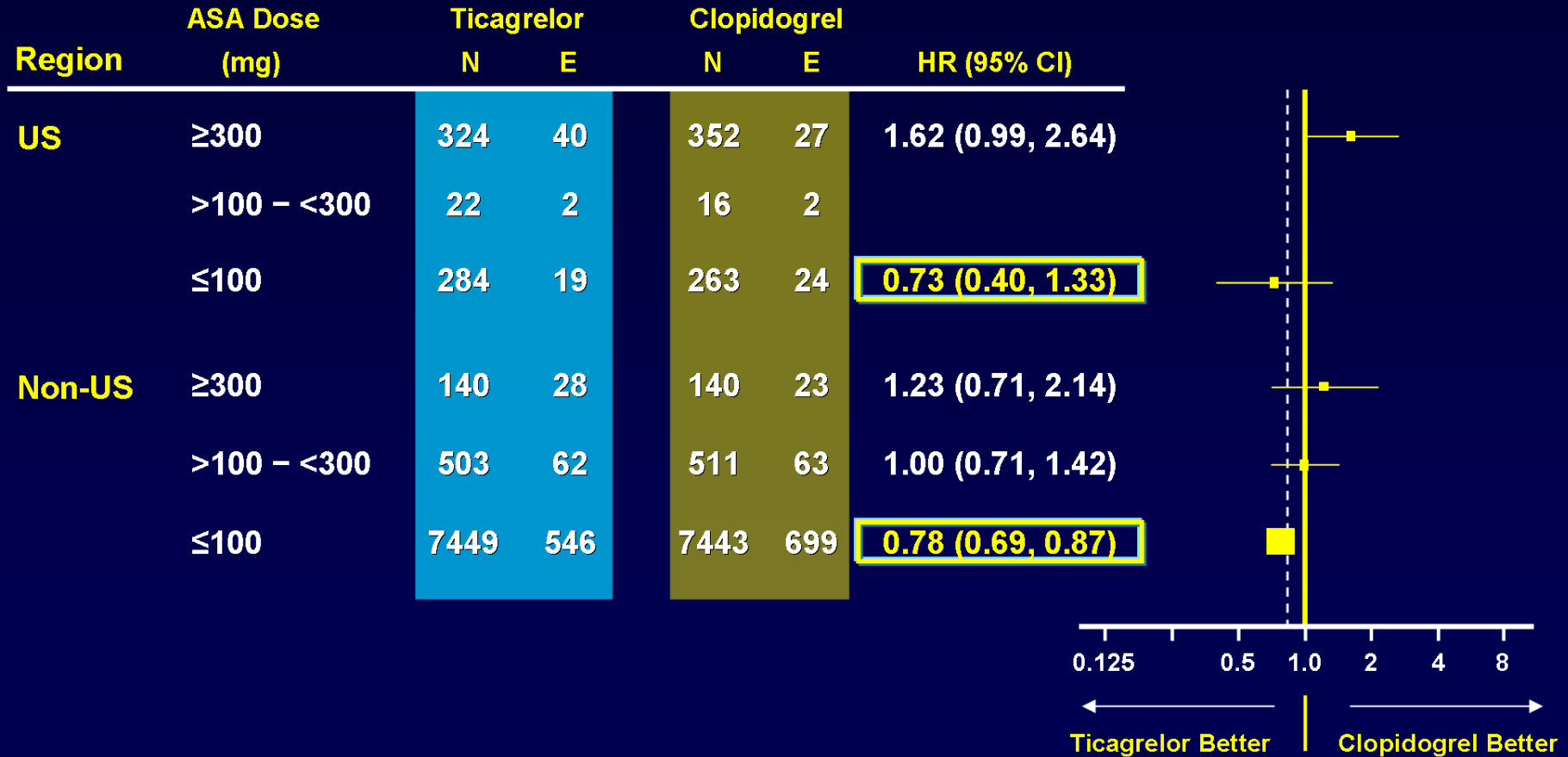


PLATO: Similar Pattern of Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US

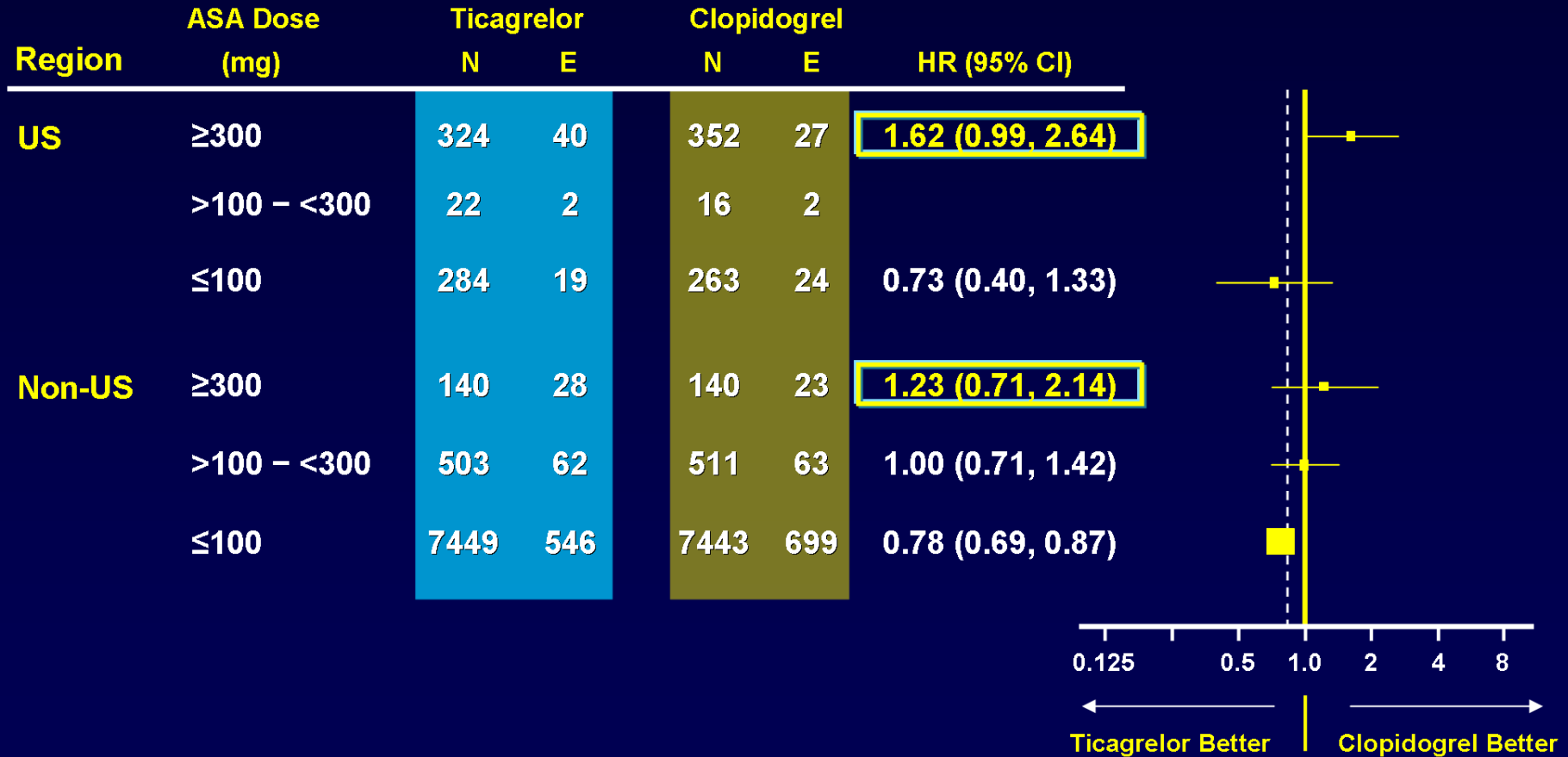
Region	ASA Dose (mg)	Ticagrelor		Clopidogrel		HR (95% CI)
		N	E	N	E	
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100 – <300	22	2	16	2	
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100 – <300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



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



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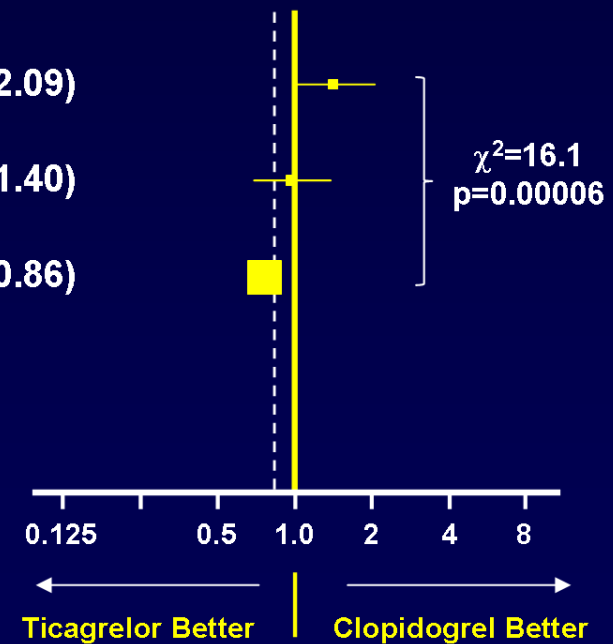


PLATO: The Regional Interaction is Explained by an Interaction with ASA Maintenance Dose

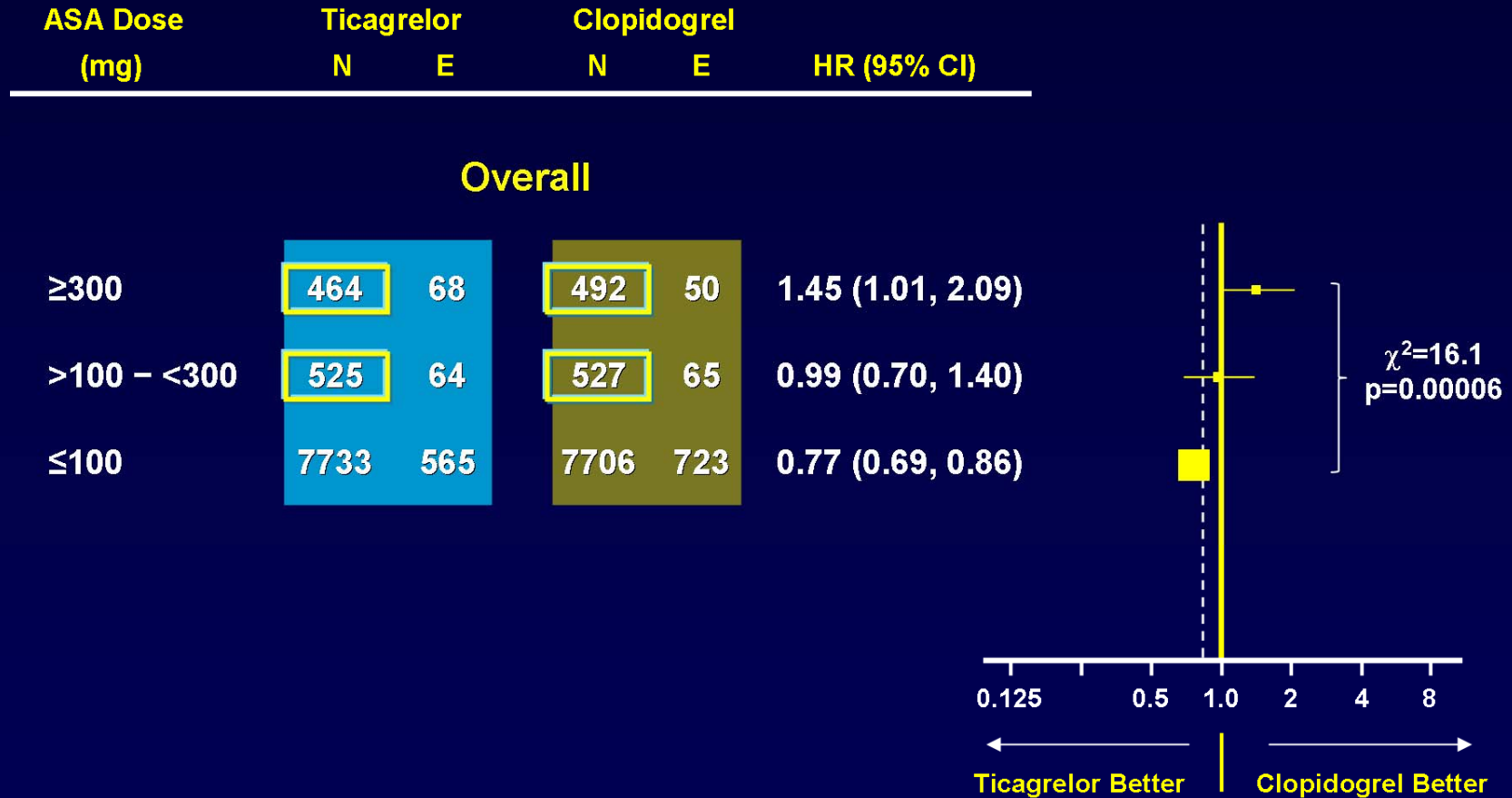
ASA Dose (mg)	Ticagrelor		Clopidogrel		HR (95% CI)
	N	E	N	E	

Overall

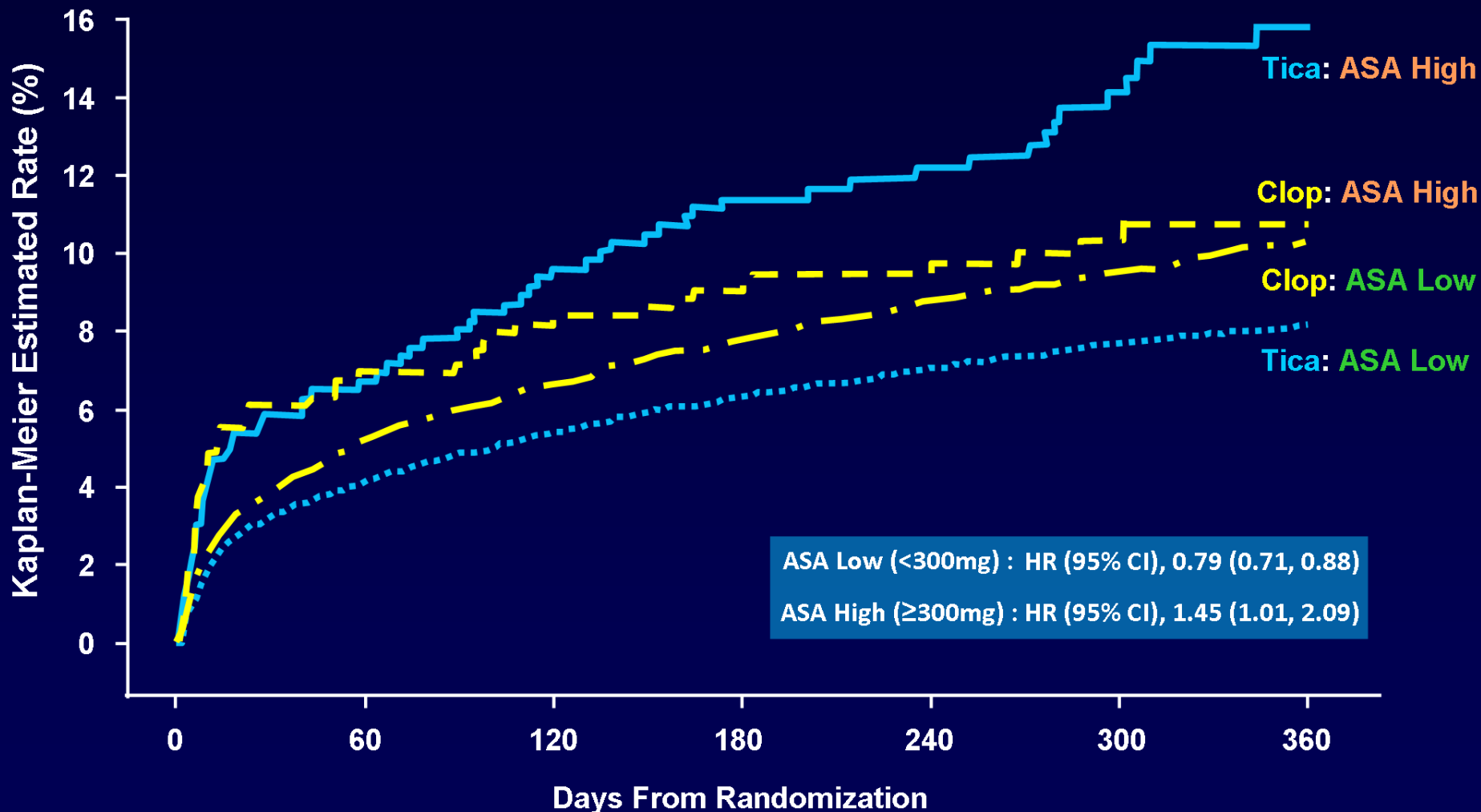
≥300	464	68	492	50	1.45 (1.01, 2.09)
>100 - <300	525	64	527	65	0.99 (0.70, 1.40)
≤100	7733	565	7706	723	0.77 (0.69, 0.86)



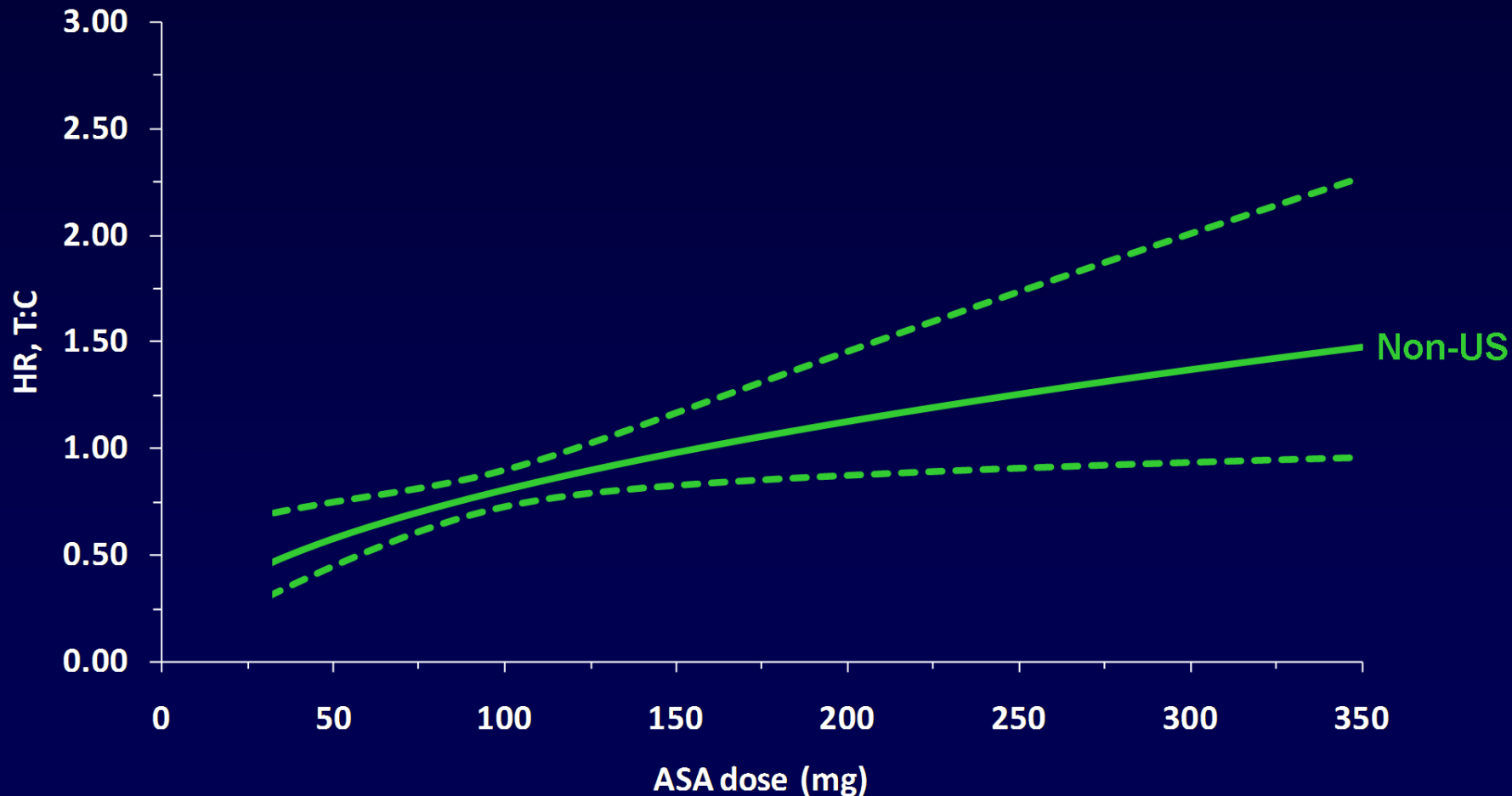
PLATO: The Regional Interaction is Explained by an Interaction with ASA Maintenance Dose



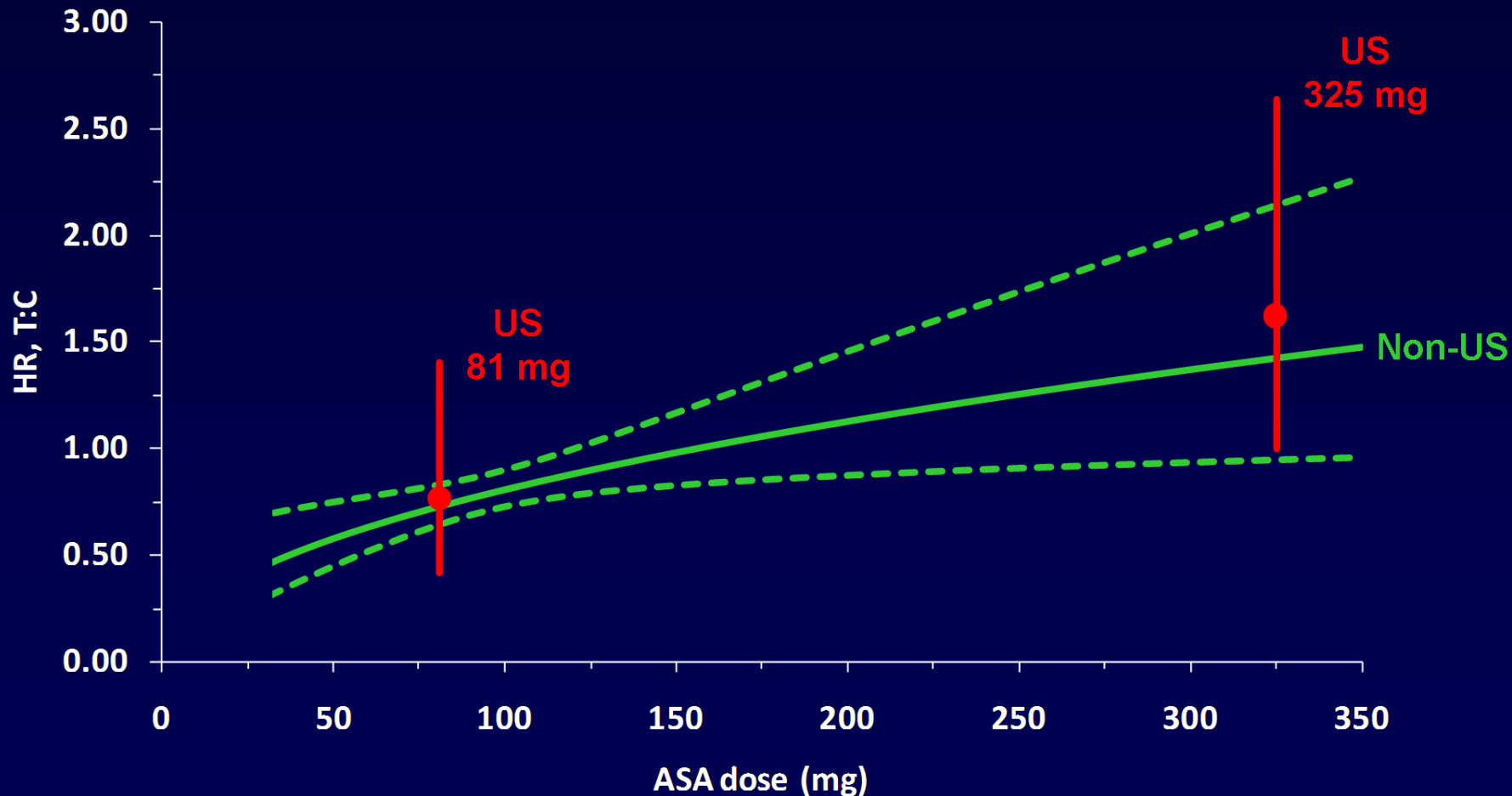
PLATO: The Treatment Effect is Strongly Dependent on ASA Maintenance Dose



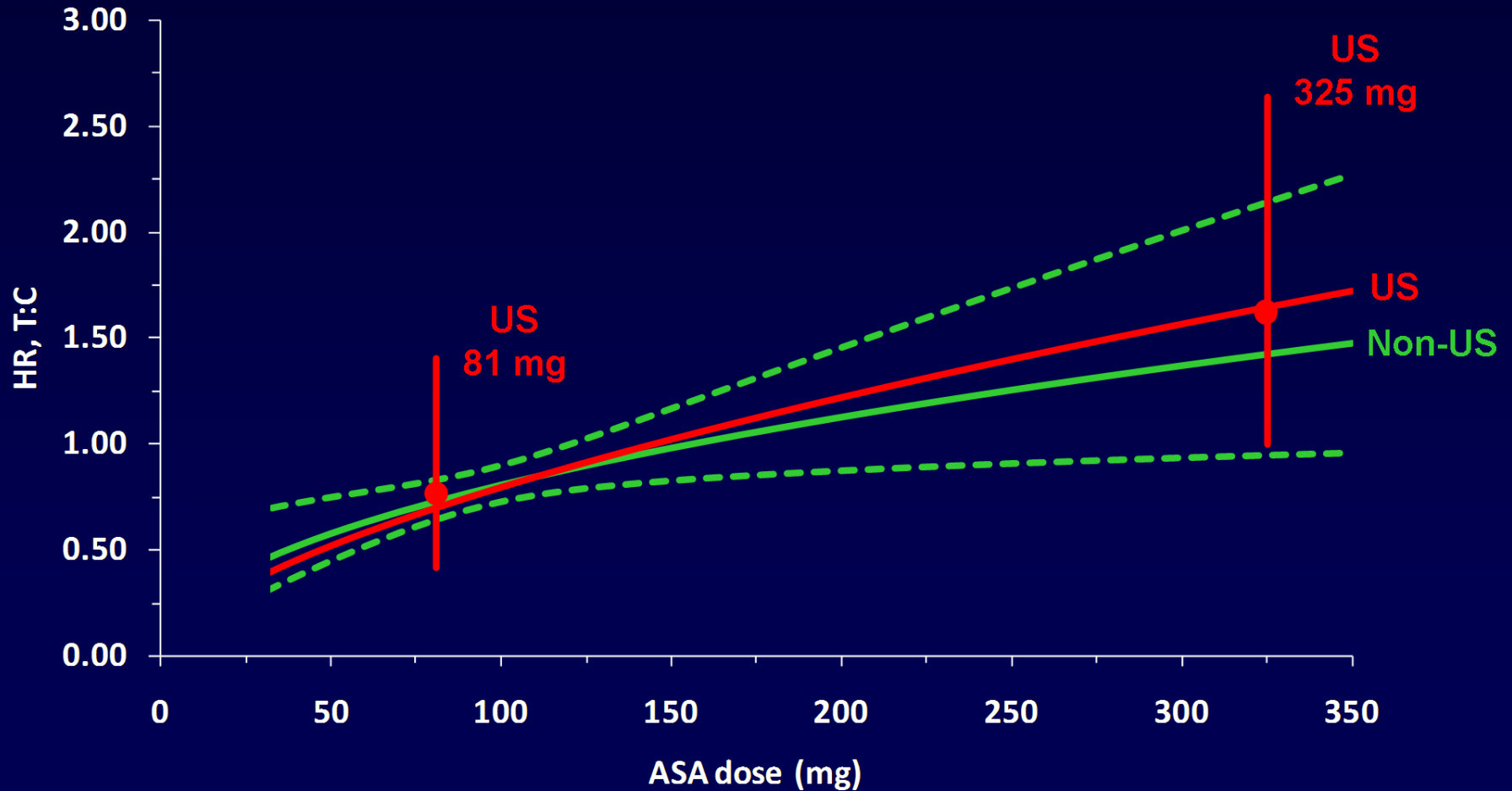
The Relationship Between ASA Maintenance Dose and Treatment Effect is seen in Non-US patients



And This Closely Reflects That Seen In US Patients



And This Closely Reflects That Seen In US Patients



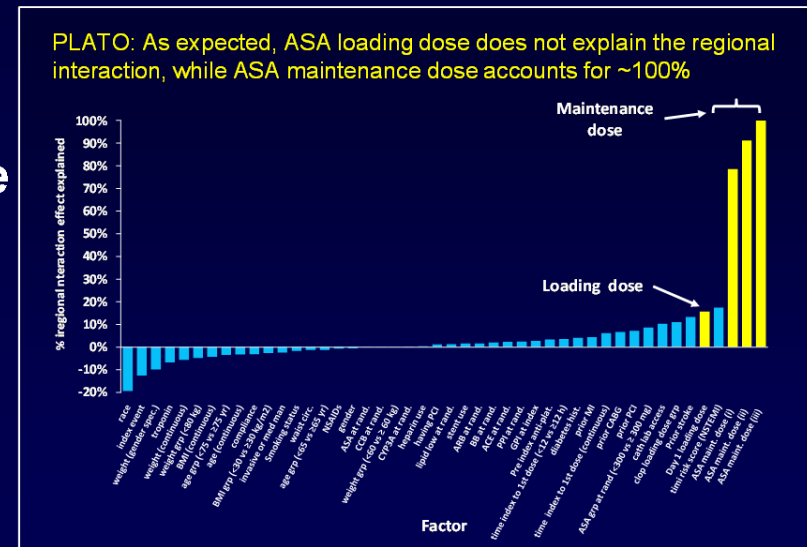
PLATO: How Robust is the Relationship Between ASA Maintenance Dose and Treatment Effect?

1. Does it rely on a small number of Non-US patients taking high dose ASA?
 - Interaction with ASA dose is profound, $\chi^2=16.1$, $p=0.00006$
 - ~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**