Integration of Knowledge from Late Phase Trials to Support Regulatory Decisions

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Outline

- Motivation for learning while confirming
- Case study
  - Ticagrelor
- Summary

Learn While Confirming

- **The understandable focus of commercial drug development on confirmation, as this immediately precedes and justifies regulatory approval, has led, in my view, to a parallel intellectual focus that slights learning. The predictable result … is that clinical drug development is often inefficient and inadequate.**
- ***Phase 3/4*. Although learning is not the primary goal of this phase, it is a most important subsidiary one. Because confirming, the primary purpose of this phase, must not be compromised, one must learn while confirming, not instead of confirming.**
- **The most obvious reason is that at no earlier stage is it possible to study as large a number and as wide a variety of patients as in phase 3/4. …Thus, important "learning" about the response surface for purposes of appropriate labeling will either take place at this stage or will not occur at all.**
- **The most important reason to learn while confirming, however, is none of the above. It is because confirmation sometimes fails. …What is needed at this point to plan future action is a diagnosis: why did the confirmation fail? Only if there are learning-oriented features to the study can this question be answered.**

Learning versus confirming in clinical drug development, Lewis B Sheiner, CPT, 1997

Comments from FDA Officials

- ***"Pharmacometrics brings much-needed quantitative, mechanistic reasoning to the clinical review process. Use of modeling and simulation can fill in the huge gaps left by even the most comprehensive development program, and can save less informative programs. As we continue to synthesize clinical data using pharmacometric techniques, we will advance the science of drug development in ways we have not anticipated. I will continue to support pharmacometrics in CDER"--Janet Woodcock, Director, CDER***

- ***"One of the most important benefits of pharmacometric analyses is providing insight into dose-response/concentration-response by using blood levels collected (population PK), together with patient effects to relate blood level to response, providing potentially richer data than the D/R data from the fixed dose D/R studies (where patients, despite the dose assignment, experience a range of drug concentrations)"--Robert Temple, Deputy Director for Science, CDER***

- ***"At NDA review, exploration of exposure response relationships can complement planned analyses, providing supportive evidence of effectiveness, and helping with decisions relating to choice of dosing regimens to approve"--Norman Stockbridge, Director, Division of Cardiovascular and Renal Products***

Mission of Office of Clinical Pharmacology and Biopharmaceutics

- **To assure that an individual patient receives the right drug, in the right dose at the right time and in the right dosage form.**

MANUAL OF POLICIES AND PROCEDURES (MaPP):
Clinical Pharmacology and Biopharmaceutics Review Template
Originator: Office of Clinical Pharmacology and Biopharmaceutics
Effective Date: 04/27/04

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm073007.pdf

Mission of Office of Clinical Pharmacology

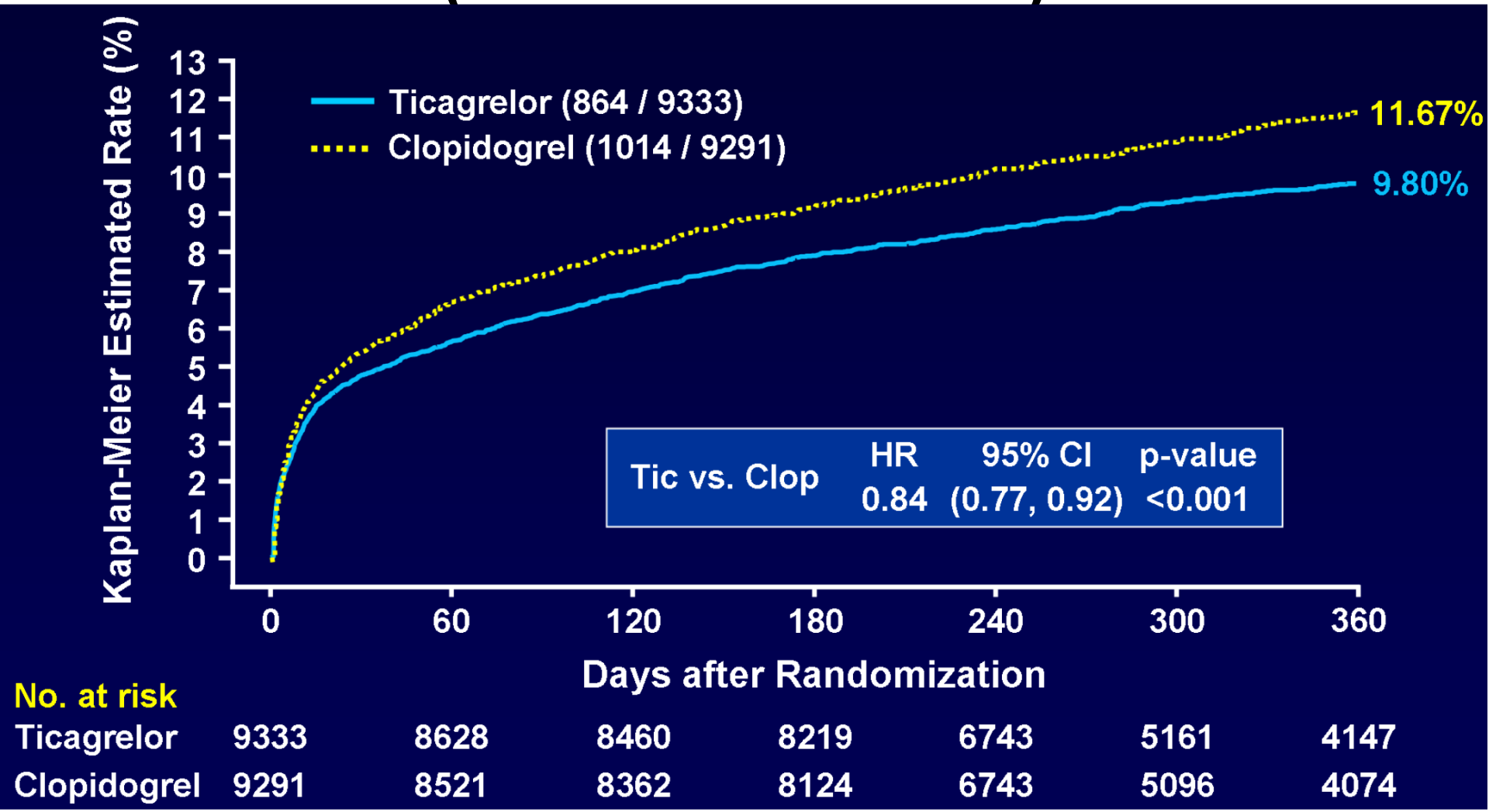
Our Mission

- To play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles
- To promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle

Case Study: Ticagrelor

- **Indication: reduction of thrombotic events in acute coronary syndrome patients**
- **Mechanism of action: selective and reversible P2Y12 ADP-receptor antagonist**
- **Dose: loading dose of 180 mg and maintenance dose of 90 mg BID plus aspirin**
- **Phase 3 trial: superiority compared to clopidogrel 75 mg QD**
- **Regulatory dilemma: opposite results in US vs non-US even though overall results positive**

Overall Efficacy Results
(CV death+MI+Stroke)



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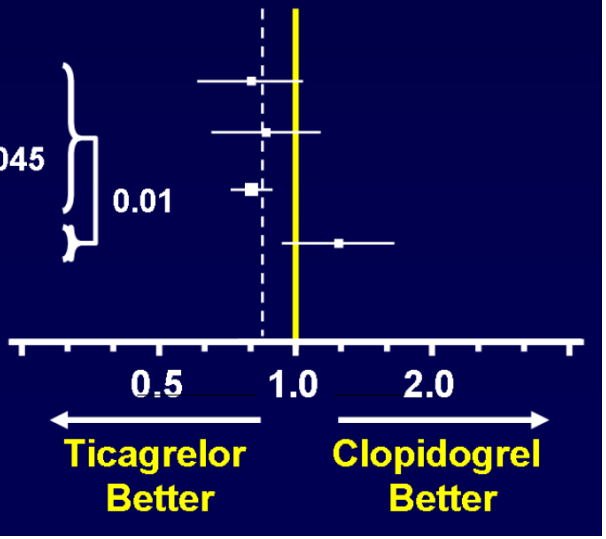
Efficacy Across Regions

78% of North America patients are from US

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



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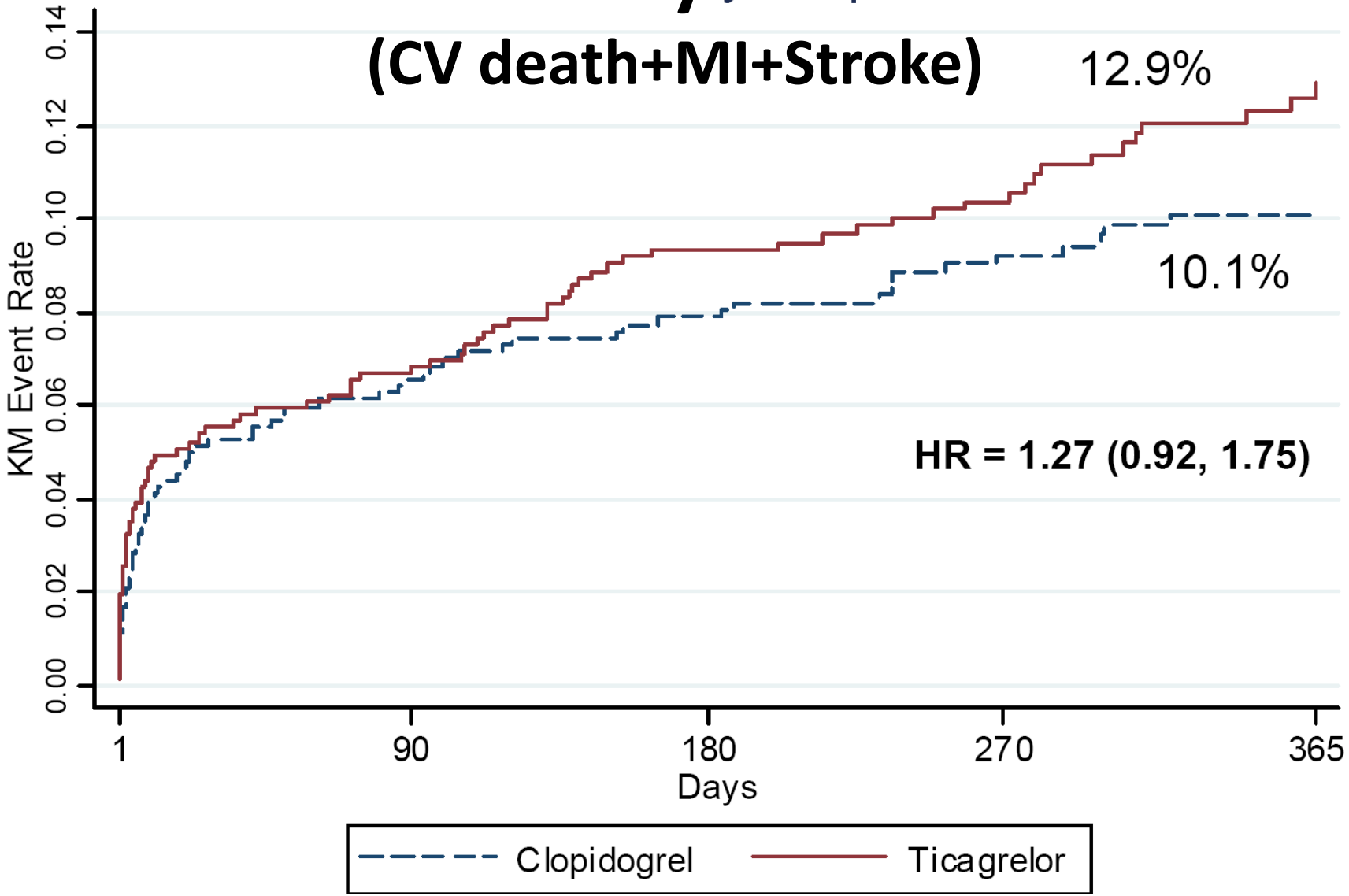
Efficacy in US

(CV death+MI+Stroke)



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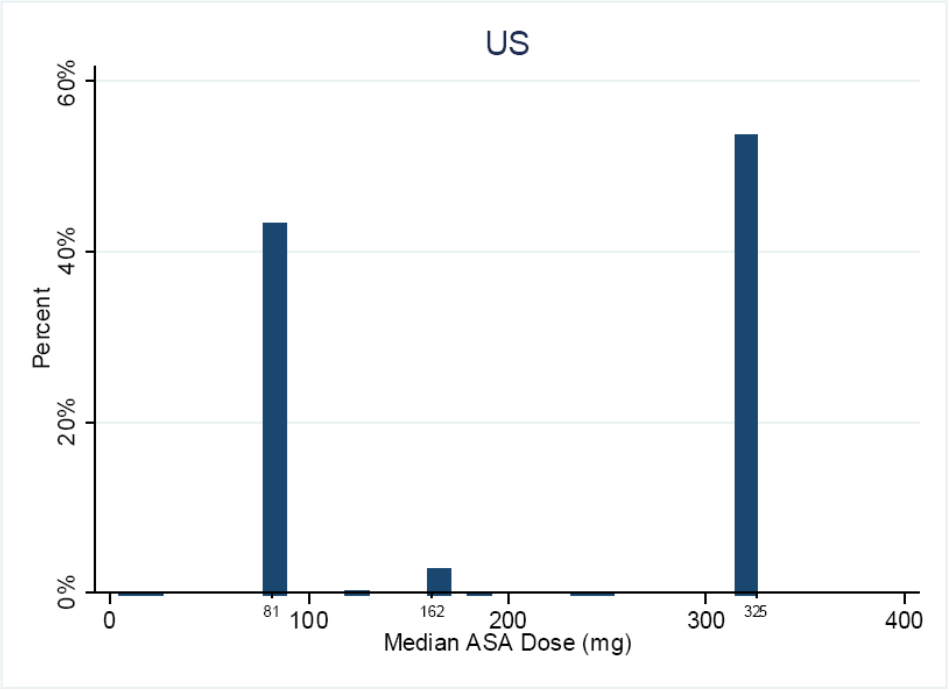
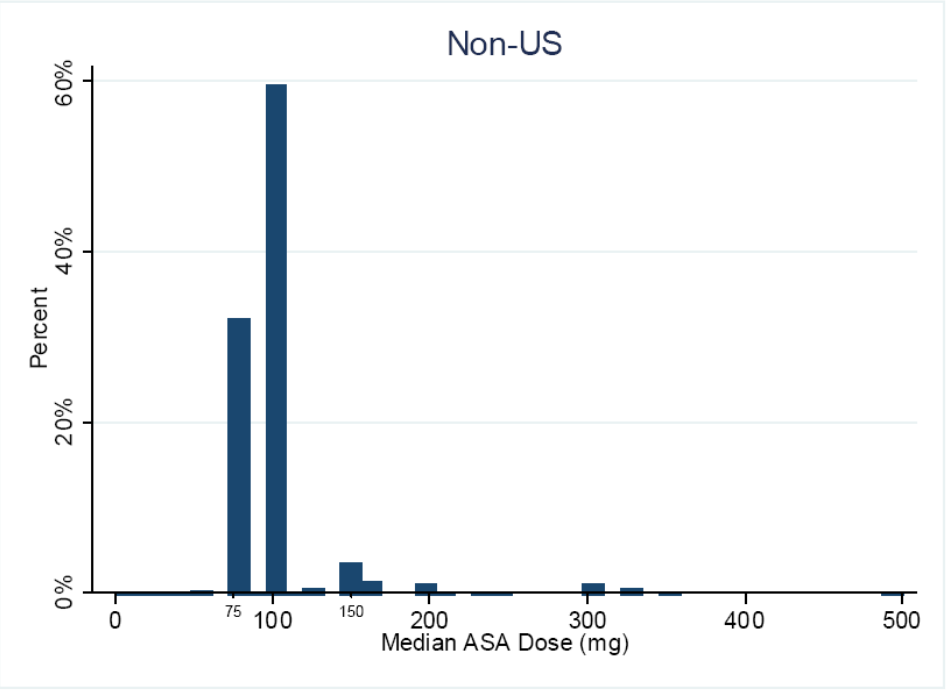
PK and PD Similar

- **Population PK analysis**
  - **Ticagrelor exposure similar between US and non-US**
- **PD: US vs UK**
  - **Multiple PD measurement, including IPA: similar results**
- **US efficacy results not explained by regional differences in PK or PD**

ASA Dose Distribution Differs between Regions





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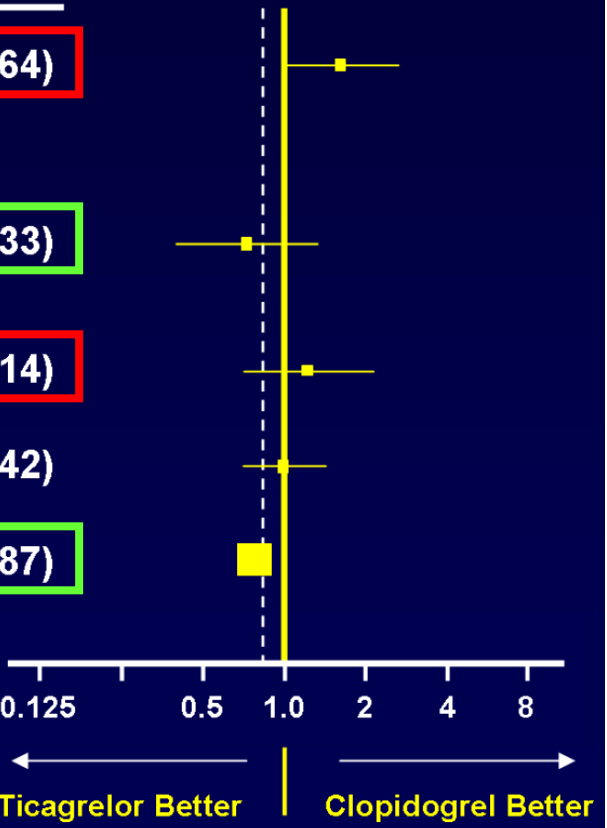
Similar Pattern of Effect vs ASA Dose in US and non-US

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)



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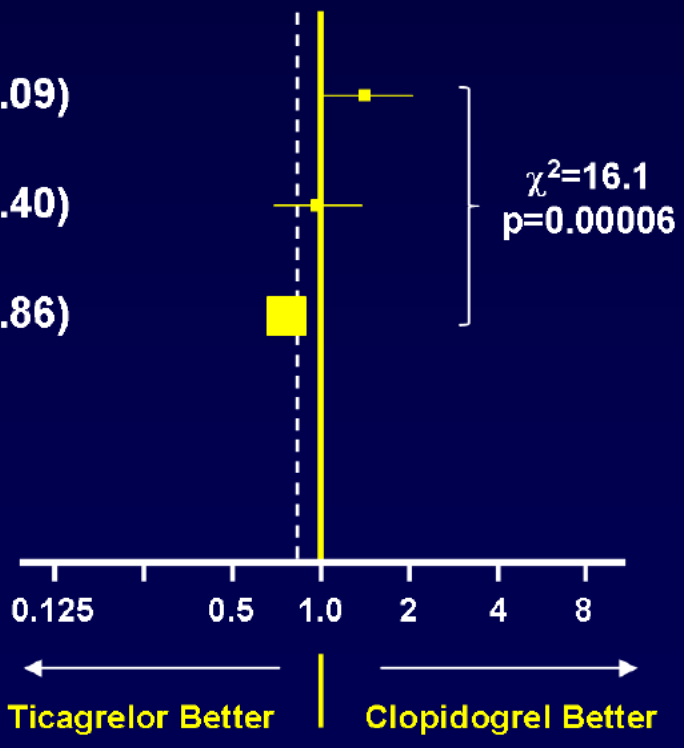
Regional Efficacy Interaction Is Explained by Interaction with ASA Dose

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)



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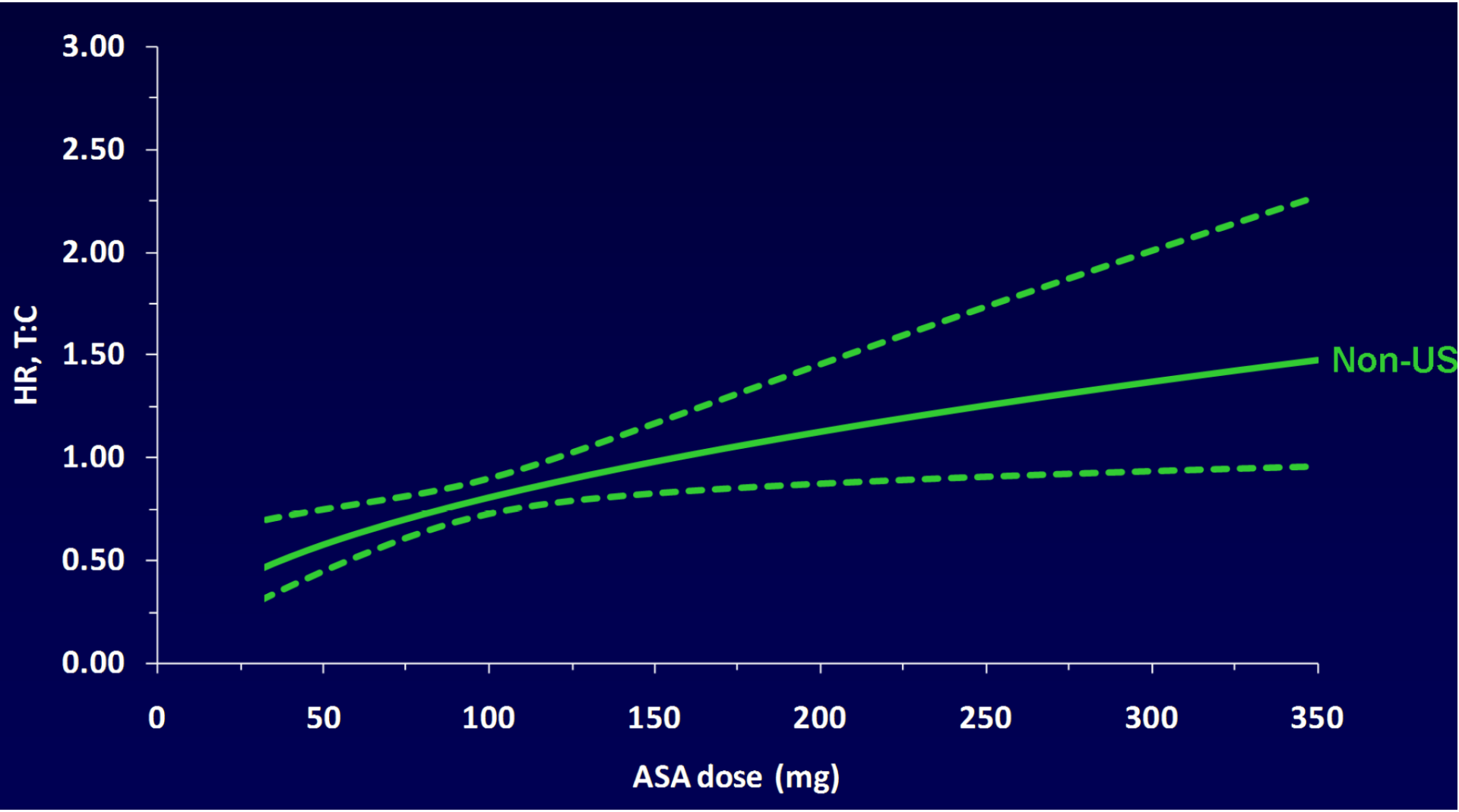
Hazard Ratio vs ASA Dose in non-US Patients



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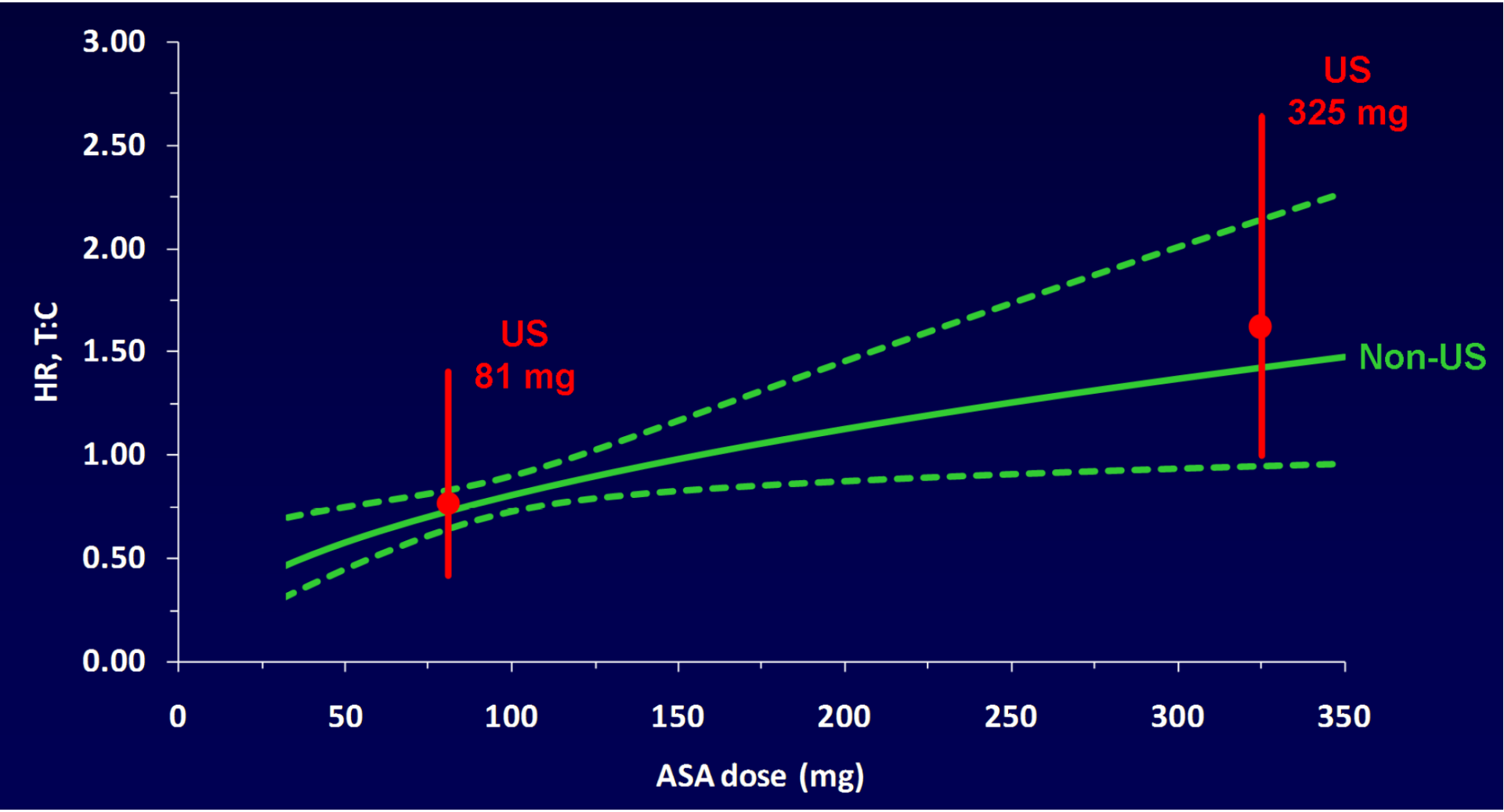
Consistency between Non-US and US Patients



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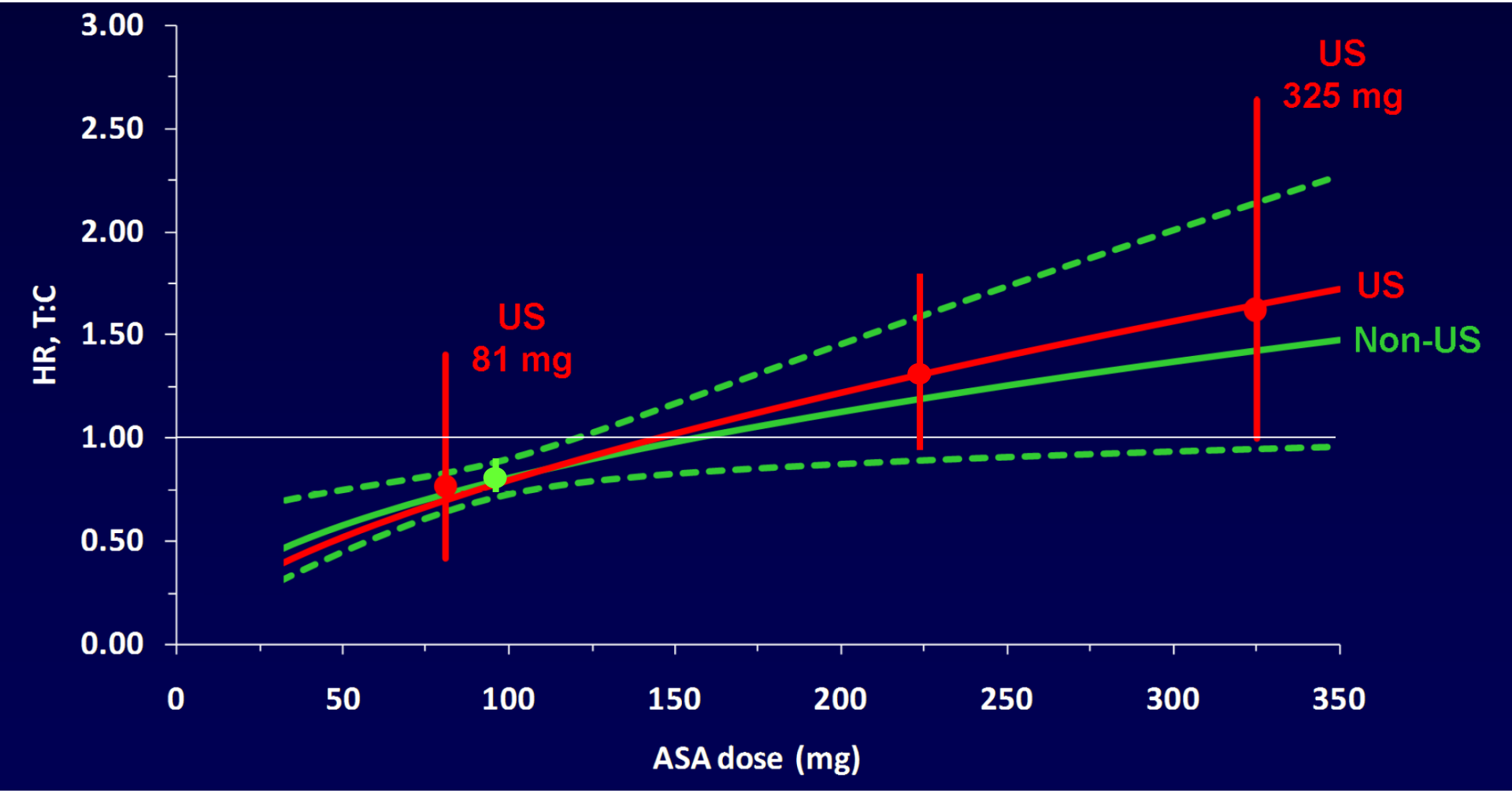

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FDA's Final Decision

- **Final approved regimen: 180 mg loading dose and 90 mg BID maintenance dose for ticagrelor + 325 mg loading dose and 75-100 mg maintenance dose for ASA**
  - **Warning: Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day**
- **Similar ASA dose-efficacy relationship across regions was established**
- **Post hoc bridging analysis served as the foundation for approval and dose recommendation**
- **Precedent was set with important implication for future international trials**

Summary

- **Precision medicine or personalized medicine is the core of clinical pharmacology**
- **Valuable knowledge can be learned from confirmatory trials**
- **Rigorous analyses led to**
  - **Rational dosing regimen**
  - **Unnecessary trials avoided**
  - **Faster access of medication for patients**
- **Routine practice in drug development and regulatory review**

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