

Is There A Role For Pharmacokinetic/Pharmacodynamics Guided Dosing For Novel Anticoagulants?

The Heart House, Washington, DC, 3 December 2015

What evidence is there that variable clinical responses to PK parameters exist for NOACs? What conclusions can we draw from these data?

Review of data from *edoxaban*

Michele Mercuri, MD, PhD, FAHA

Daiichi Sankyo for SAVAYSA[®] / LIXANA[®] (*edoxaban*)

Disclosures

- **Employment**
 - Yes
 - Entity: Daiichi Sankyo Pharma Development, Daiichi Sankyo, Inc.
 - Compensation: Significant (>\$10K or 5%)
- **Ownership Interest**
 - Stock option equivalent is part of the compensation plan
- **Research Grant or Other Research Support**
 - None
- **Speakers' Bureau**
 - No speaking engagements to disclose
- **Honoraria**
 - No honoraria to disclose.
- **Consultant or Advisory Board**
 - No consultant or advisory relationship to disclose
- **Expert Witness**
 - No expert testimony to disclose

Outline

- Which PK/PD factors are associated with bleeding and thrombotic events?
- What patient factors are associated with stroke/thrombotic events?
- What is the extent of intra-individual PK variability?
- Can PK/PD be used as a guide for dosing?

Question N. 1

Which PK/PD factors are associated with bleeding and thrombotic events?

***edoxaban* Pharmacokinetic and Pharmacodynamic Profiles “*what do we know?*”**

edoxaban has been extensively tested *in vitro*, *ex vivo*, in healthy volunteers and in patients with Atrial Fibrillation and Venous Thrombo-Embolicism as well in those who underwent various orthopedic surgeries

ENGAGE AF-TIMI 48

Time to First Event Modeling

- **Parametric time-to-event analysis** (Exponential, Weibull or Gompertz distributed times-to-event evaluated)
- warfarin and *edoxaban* **treatments modeled separately**
- **Stepwise covariate model (SCM)** building ($p < 0.05$ forward, $p < 0.05$ backwards) for warfarin arm, backwards ($p < 0.05$) for *edoxaban* arm
- Two exposure response models (C_{\min} and C_{av}) for each efficacy and safety endpoint

In collaboration with the University of Uppsala and the Pharmetheus Group

ENGAGE AF-TIMI 48

Risk Factors Included in Exposure Response Analyses

Risk Factor	Efficacy	Safety
Age (as continuous value)	X	X
Age ≥ 75	X	X
Female sex X	X	
Body weight	X	X
Congestive heart failure	X	X
Hypertension requiring medication	X	X
Diabetes mellitus	X	X
Prior stroke or TIA	X	X
Composites of CHADS ₂ scores (CHADS ₂ 2-3 vs 4-6)	X	X
Anemia		X
History of any bleeding		X
Serum creatinine ≥ 1.5 mg/dL or CrCL		X
History of cancer		X
Prior stroke		X
VKA-naïve vs VKA-experienced	X	X
Concomitant use of aspirin or antiplatelet agent		X
Concomitant use of NSAID	X	X
Ethnicity	X	X
Race	X	X
Diuretics	X	
Dyslipidemia	X	
Concomitant use lipid lowering therapy	X	

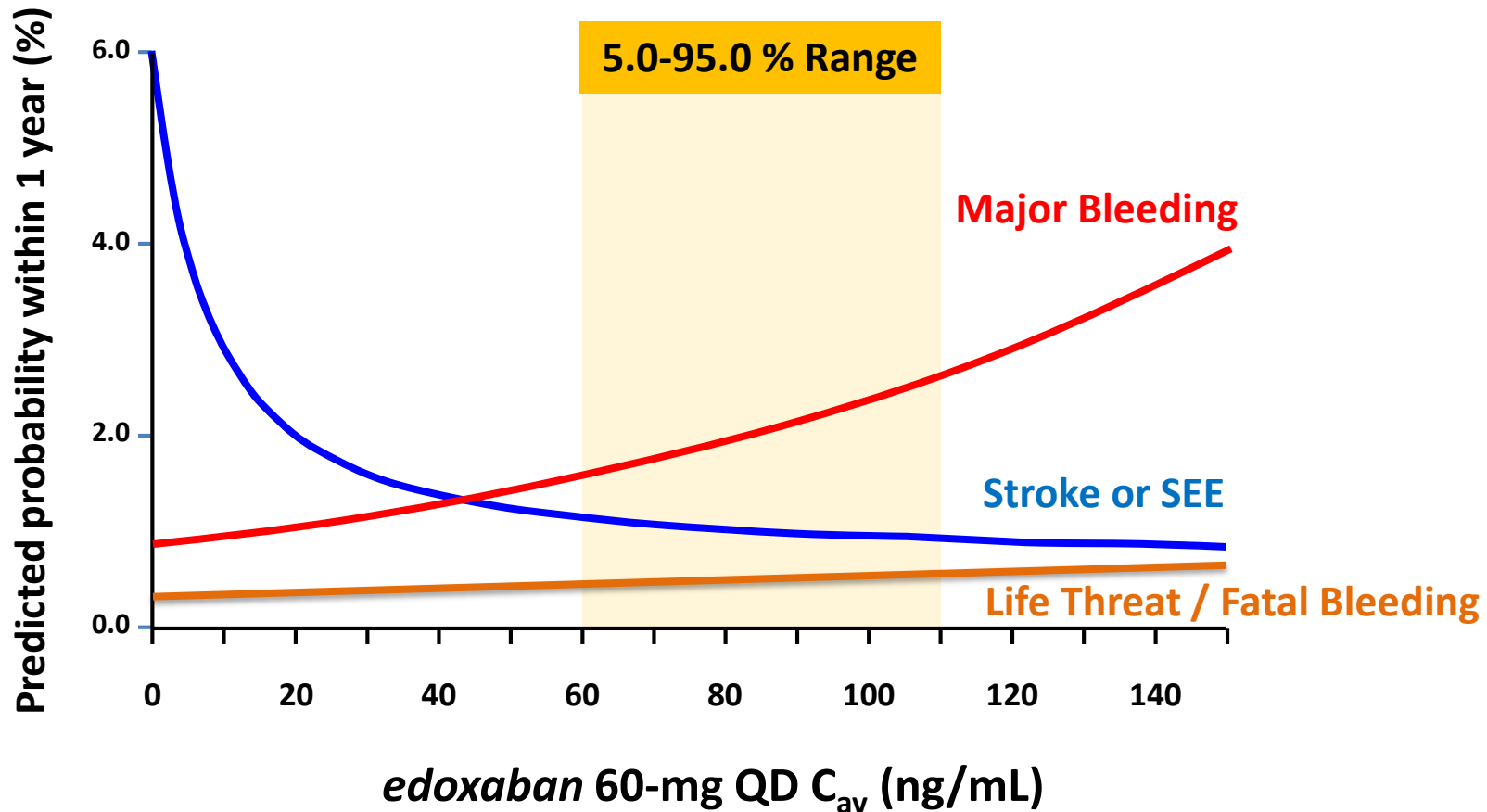
In collaboration with the University of Uppsala and the Pharmetheus Group

Which PK/PD factors are associated with bleeding and thrombotic events?

**Average Drug Concentration (C_{av})
could be used to adequately describe
the “exposure-response” relationship
in the Phase 3 Program**

THE ENGAGE AF – TIMI 48 TRIAL

Average Concentration vs. Clinical Outcomes

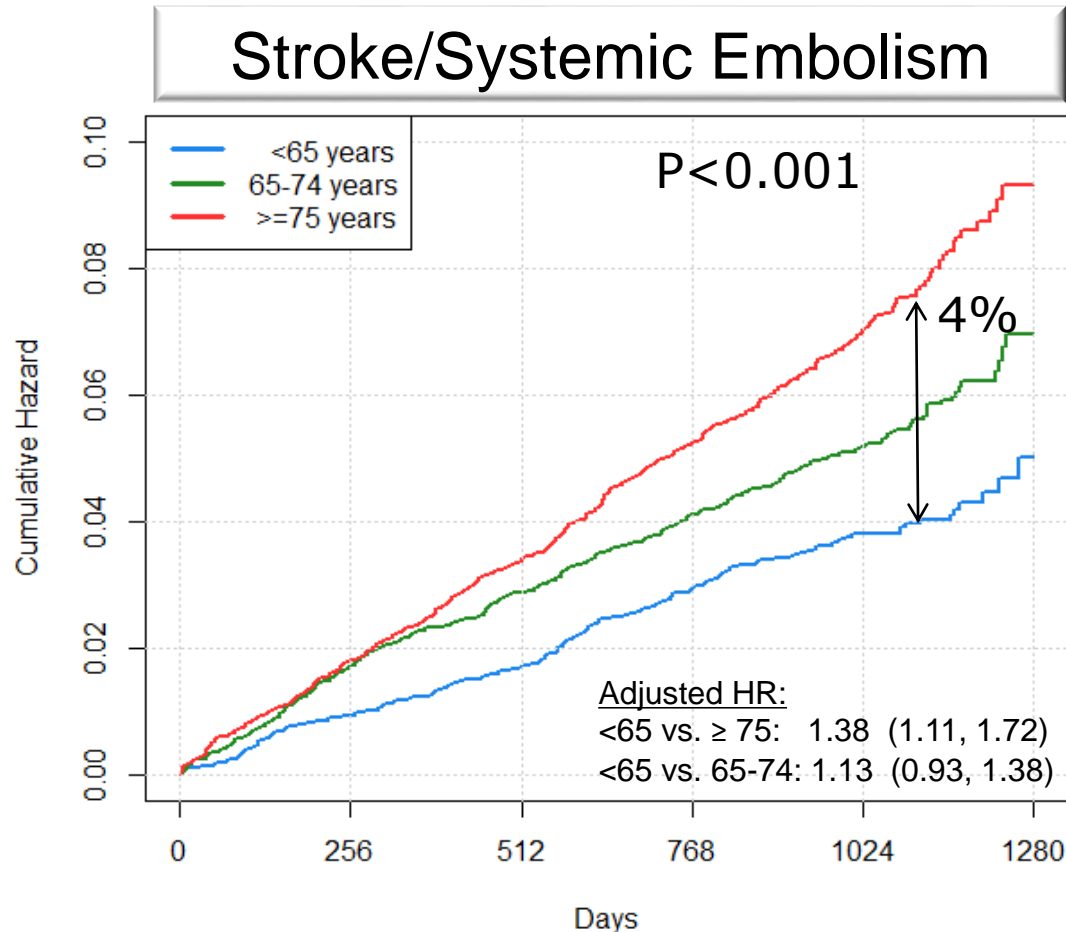


Predicted outcomes using ~10,000 samples from ~5,000 ENGAGE AF – TIMI 48 patients

Question N. 2

What patient factors are associated with stroke/thrombotic events?

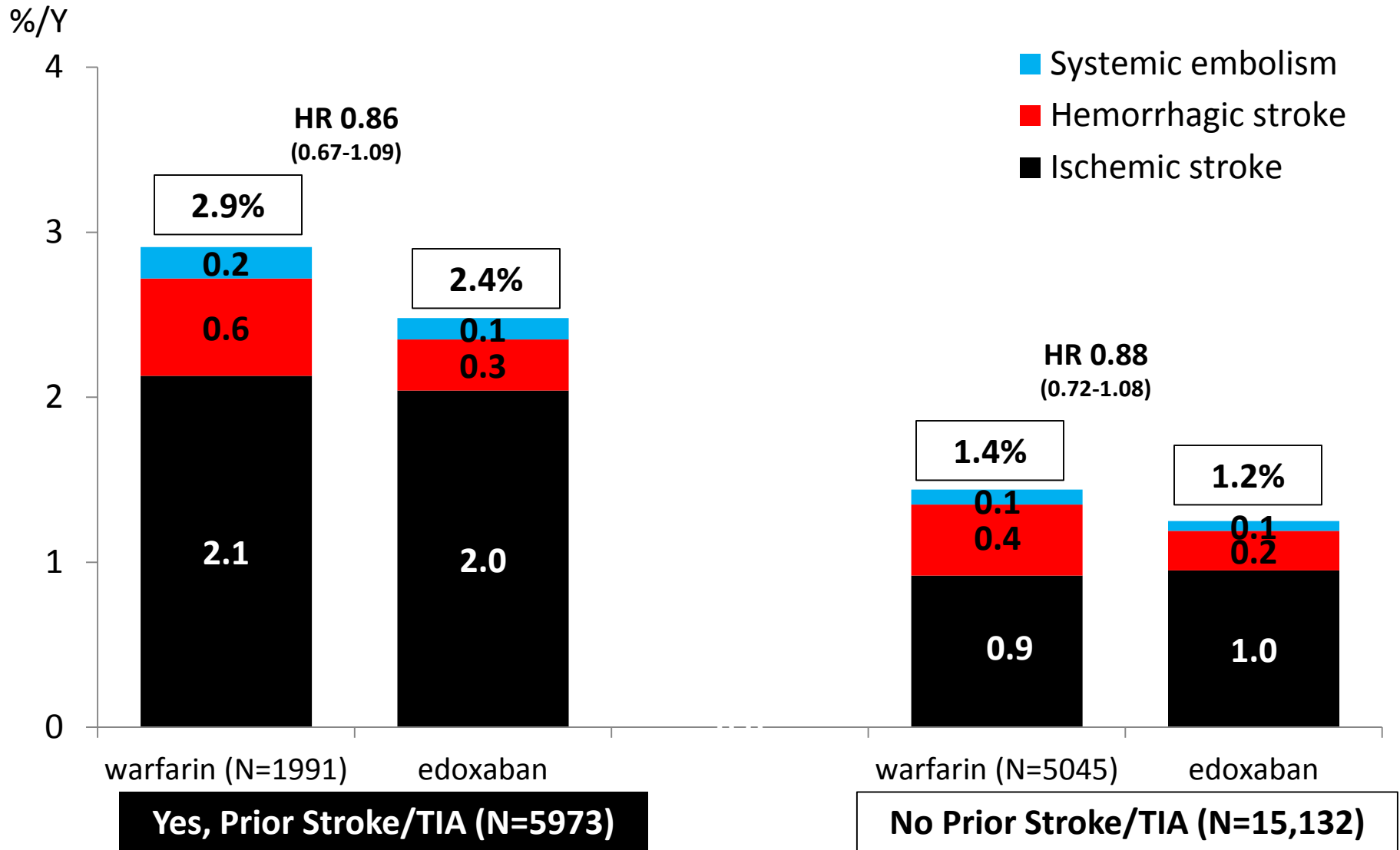
Observed Cumulative Hazard Rates (All Patients)



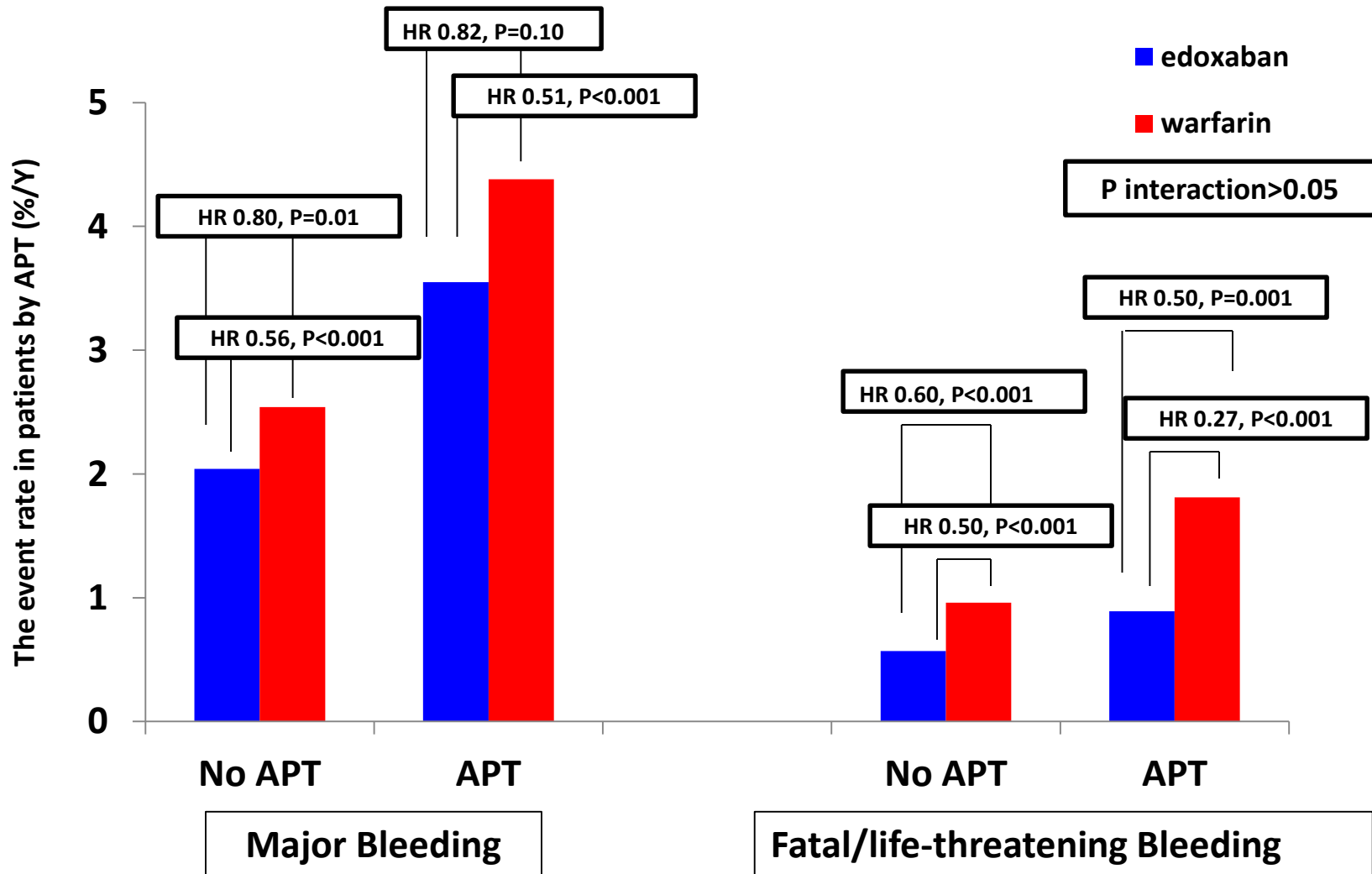
Adjusted for weight, gender, HTN, Dyslipidemia, DM, Smoking, Prior PCI, Prior stroke or TIA, Congestive HF, treatment arms, type of AF, CrCl, Race, Region, History of increased risk of falling, History of neuropsychiatric, and dose reduction

Adapted from Kato et al., AHA 2014; Courtesy of the TIMI Study Group

Stroke/TIA history is associated with a Higher Incidence of Vascular Events

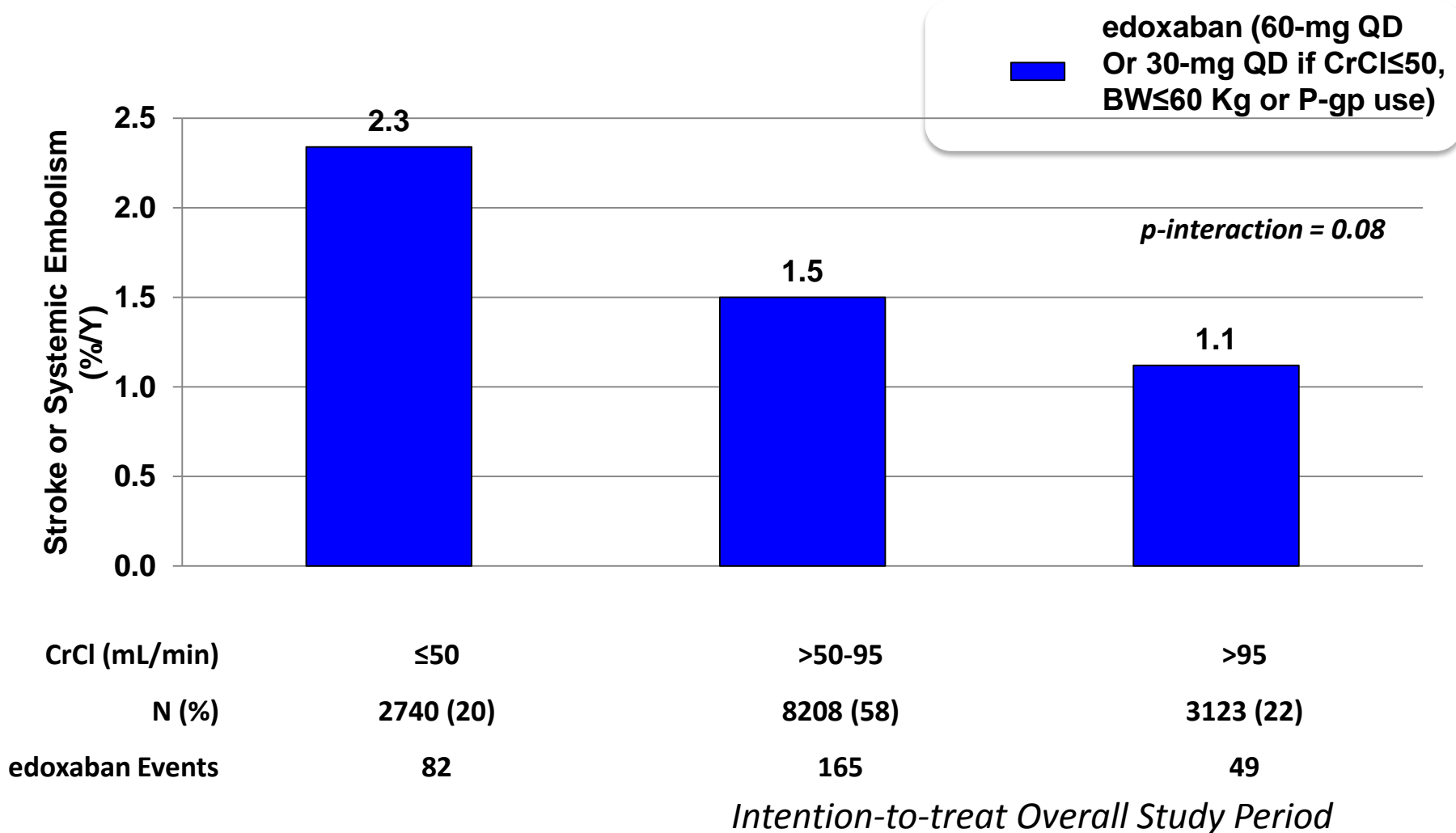


Antiplatelet (ATP) use increases the risk of bleeding



Adapted from Xu et al, AHA 2014; Courtesy of the TIMI Study Group

Stroke/Systemic Embolism by Exploratory Creatinine Clearance Subgroup

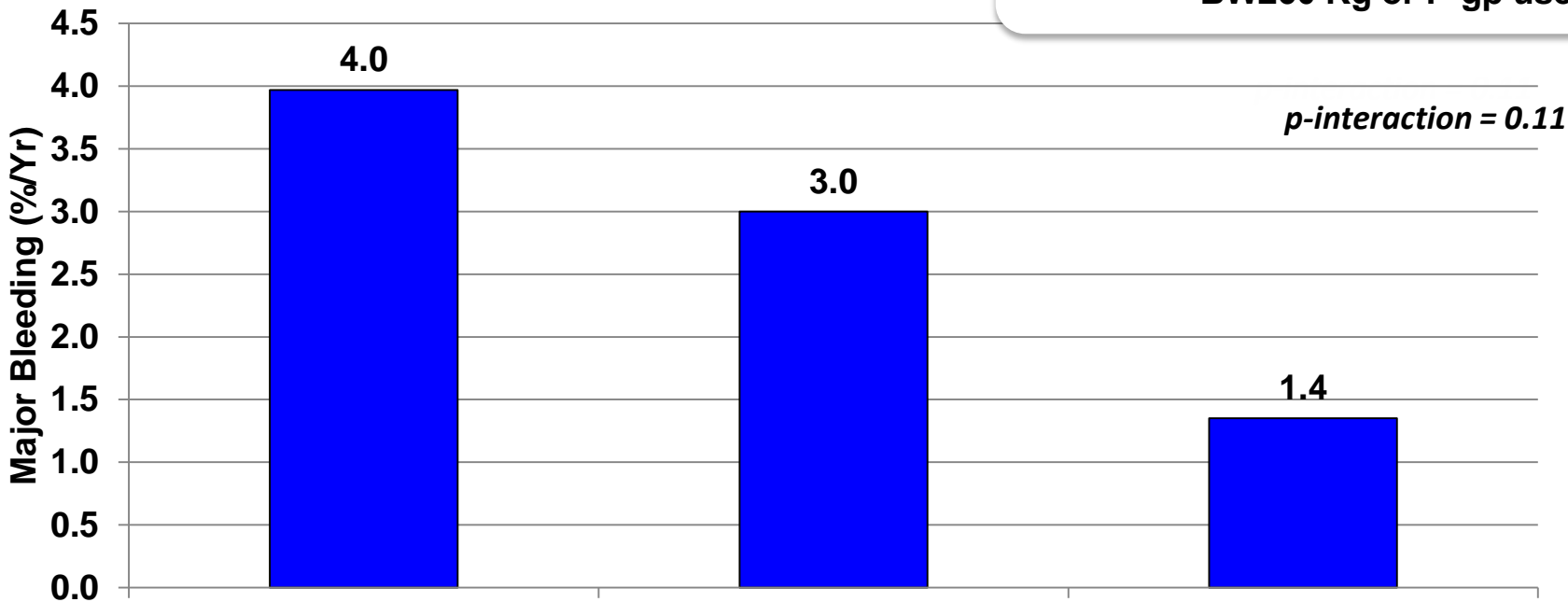


Adapted from Bohula et al, AHA 2015; Courtesy of the TIMI Study Group

Major Bleeding by Exploratory Creatinine Clearance Subgroup



edoxaban (60-mg QD
Or 30-mg QD if CrCl ≤ 50,
BW ≤ 60 Kg or P-gp use)



CrCl (mL/min)	≤50	>50-95	>95
N (%)	2728(20)	8177 (58)	3119 (22)
edoxaban Events	100	267	51

Safety Population On Treatment Period

Question N. 3

**What is the extent of intra-individual
PK variability?**

ENGAGE AF – TIMI 48: Pop-PK Modeling Estimated Intra-individual (Inter-occasion) Variability

PK parameter	Inter-occasion variability (% CV)
Apparent oral clearance (CL/F)	9.78
Absorption rate constant (Ka)	101
Apparent volume of central compartment (Vc/F)	26.9

Question N. 4

Can PK/PD be used as a guide for dosing?

Despite the good knowledge acquired from the *edoxaban* registration program, many critical questions remain to be answered.

PK measurements are impractical for clinical use outside controlled clinical trials due to technical complexity, intra- and inter-patients' variability, and the key role of specific clinical characteristics on PK data interpretation.

Standardization of methodology is lacking and shall be established before this approach can be further considered for wide clinical use.

Daiichi Sankyo continues to work with the large *edoxaban* PK/PD dataset, and to explore the possible use of other more common coagulation tests to further the available data interpretation, and to guide future hypothesis testing

Summary

- 1. Several PK/PD factors are associated with thrombotic and bleeding events**
 - Drug concentrations, Renal function/Age
- 2. Several patient factors are associated with thrombotic and bleeding events**
 - History of Stroke/TIA, Renal function/Age, Concomitant use of APT
- 3. PK measurements are still rather impractical for clinical use outside controlled clinical trials due to technical complexity, patients' variability, and the key role of specific clinical characteristics on PK data interpretation**
- 4. Daiichi Sankyo continues to work with the large *edoxaban* PK/PD dataset, and to explore the possible use of alternative coagulation tests to further the available data interpretation and to guide future hypothesis testing**