

The Role of Pharmacokinetic and Pharmacodynamic Measurements in the Use of Direct Oral Anticoagulants

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**Session 4: Future Perspectives. What
Could Be Done? Industry Perspective.**

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Daiichi Sankyo for LIXIANA[®] (*edoxaban*)

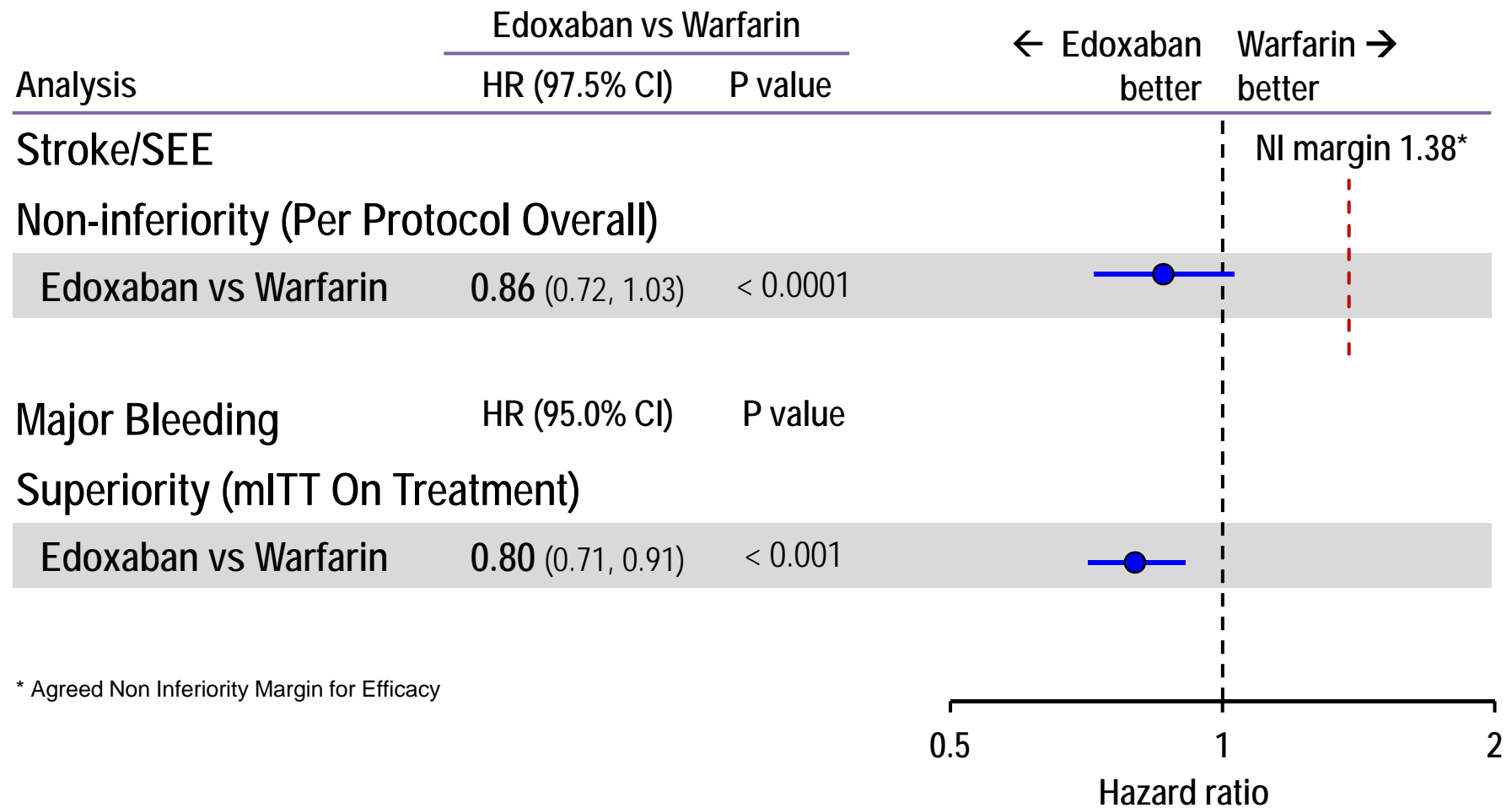
Outline

Four key relevant Daiichi Sankyo activities:

- 1. Analyses of the LIXIANA[®] PK database**
- 2. Development of LIXIANA[®] specific anti-Xa assay**
- 3. Development of anticoagulation test**
- 4. Enable PORTOLA and PEROSPHERE to develop reversing agents**

ENGAGE AF – TIMI 48

Primary Efficacy and Safety



Why Measure DOACs in Clinical Practice?

The Daiichi Sankyo's Perspective

Medical decision making in a few specific situations would be improved:

1. Life threatening bleeding
2. Trauma/surgery
3. Overdose
4. Thrombotic event requiring thrombolysis
5. Therapeutic compliance

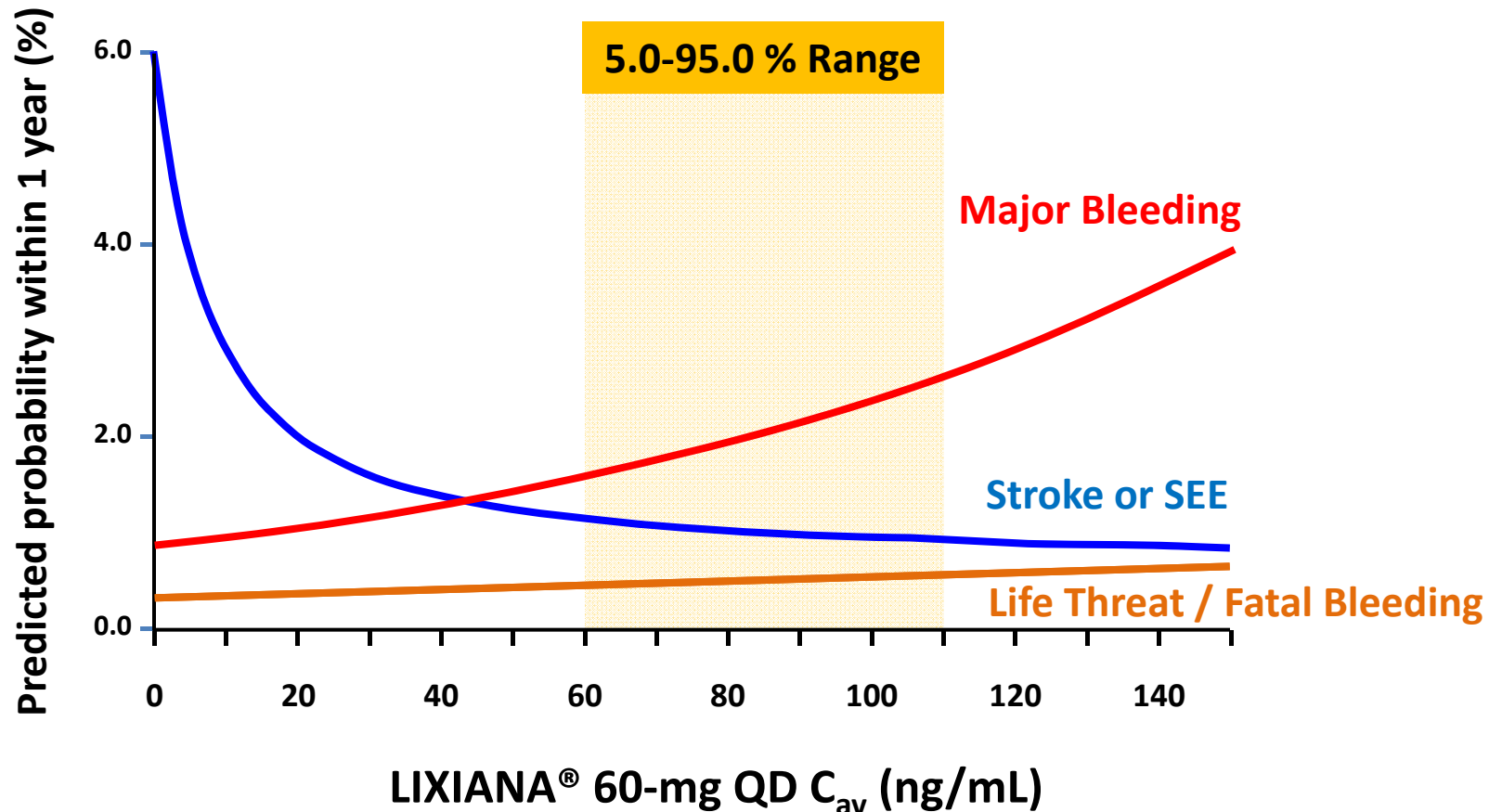
LIXIANA[®] Pharmacokinetic and Pharmacodynamic Profiles

“what do we know?”

LIXIANA[®] 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

Therapeutic Range (Average Concentration) vs. Clinical Outcomes

THE *ENGAGE AF – TIMI 48* TRIAL



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

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

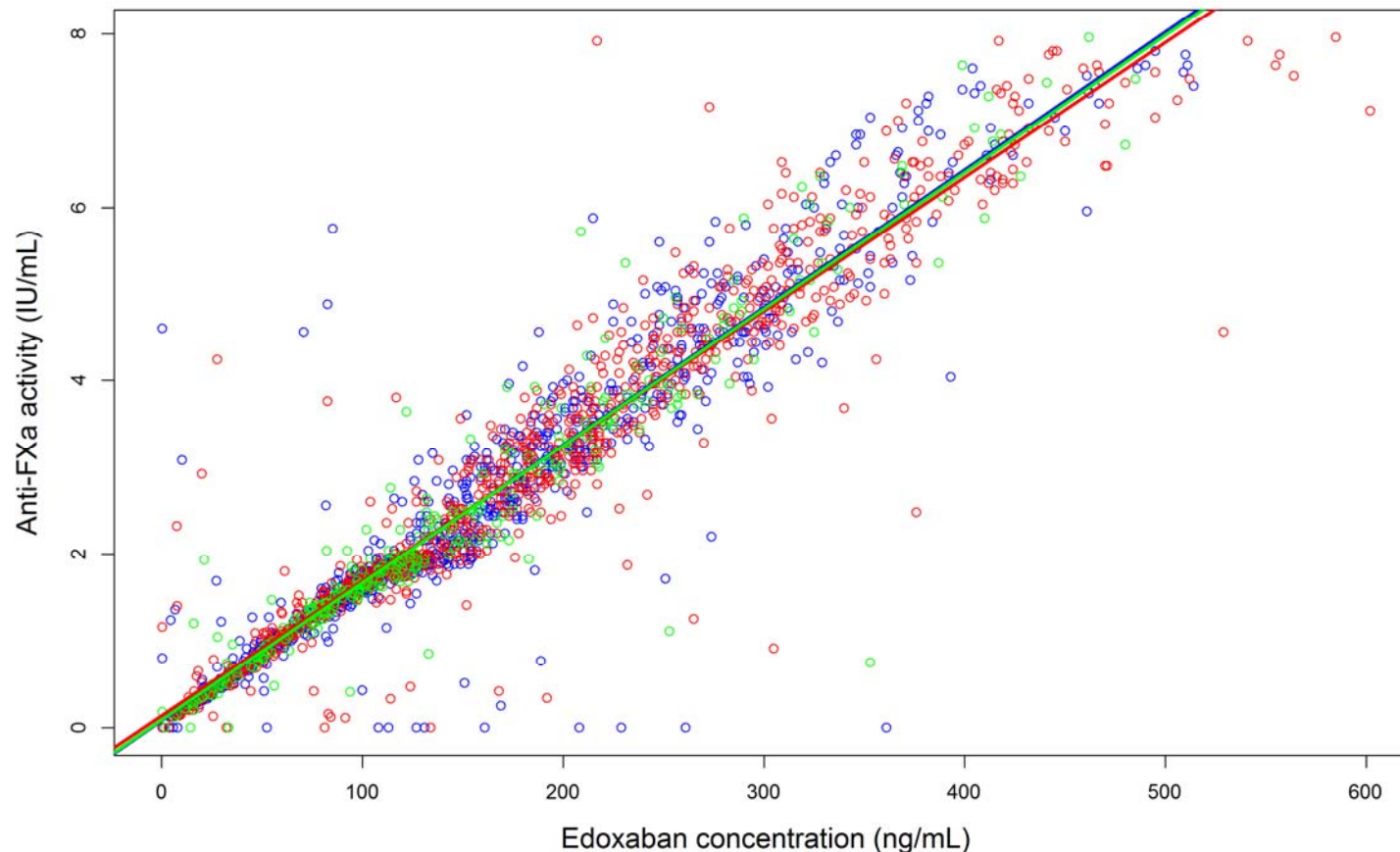
Daiichi Sankyo Activities -1-

Daiichi Sankyo continues to work with the large LIXIANA[®] PK dataset to further its interpretation and guide future hypothesis testing

What Measurements, Other Than PK Concentration, Could Be Considered?

Anti-Factor FXa Activity Increases Linearly and Correlates with LIXIANA® Concentration

The Phase 3 Population PK Study in AF



14, 014 AF Patients were randomized to receive LIXIANA®
~6,600 samples were analyzed at steady state pre- and post-dose

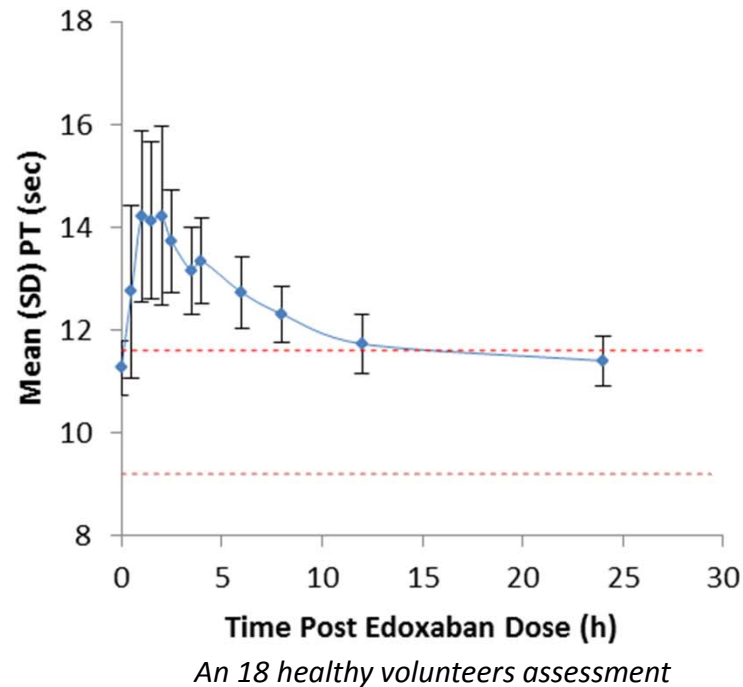
However, as it is for drug concentration, a single measurement of anti-Xa activity is Xa-inhibitor-specific, is sensitive to the time elapsed from administration, and requires integration of the inter-patients' variability related to specific clinical characteristics

Daiichi Sankyo Activities -2-

**Daiichi Sankyo is working with
STAGO to develop a LIXIANA[®]-
specific anti-Xa-based assay**

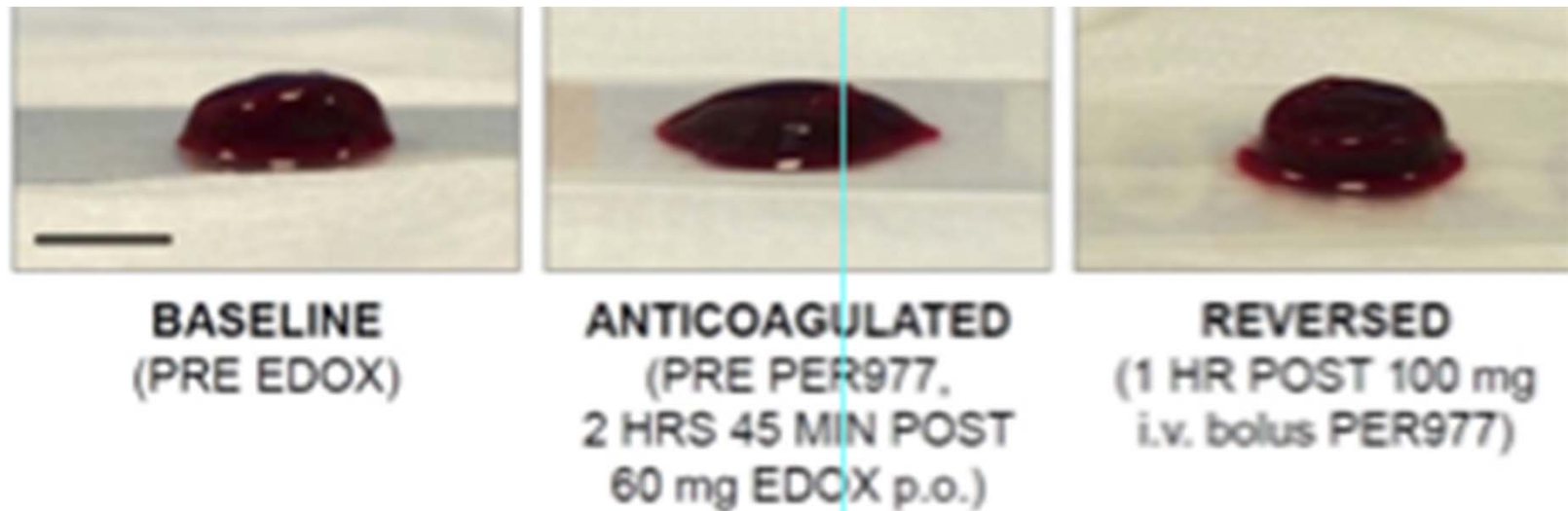
Several Common Anticoagulant Laboratory Tests Were Investigated PT emerged as potentially informative for clinical use

An elevated PT, in a patient who is on LIXIANA[®], indicates that the patient is anticoagulated



Under emergency conditions, one could use PT to establish whether the patient is anticoagulated with LIXIANA[®]

A Simple Coagulation Test Could Be Very Informative



Courtesy of PEROSPHERE, Inc.

Daiichi Sankyo Activities -3-

**Daiichi Sankyo is collaborating
with device manufacturers to
develop an appropriate
coagulation test**

Daiichi Sankyo's Current & Future Work

Four key relevant activities:

- 1. Continue to analyze the LIXIANA[®] PK database**
- 2. Complete the development of the STAGO LIXIANA[®] specific anti-Xa activity assay**
- 3. Continue to search for an anticoagulation test for LIXIANA[®]**
- 4. Continue to work with PORTOLA and PEROSPHERE to develop reversing agents for LIXIANA[®] to be added to the already available 4-factor Prothrombin Complex Concentrates**