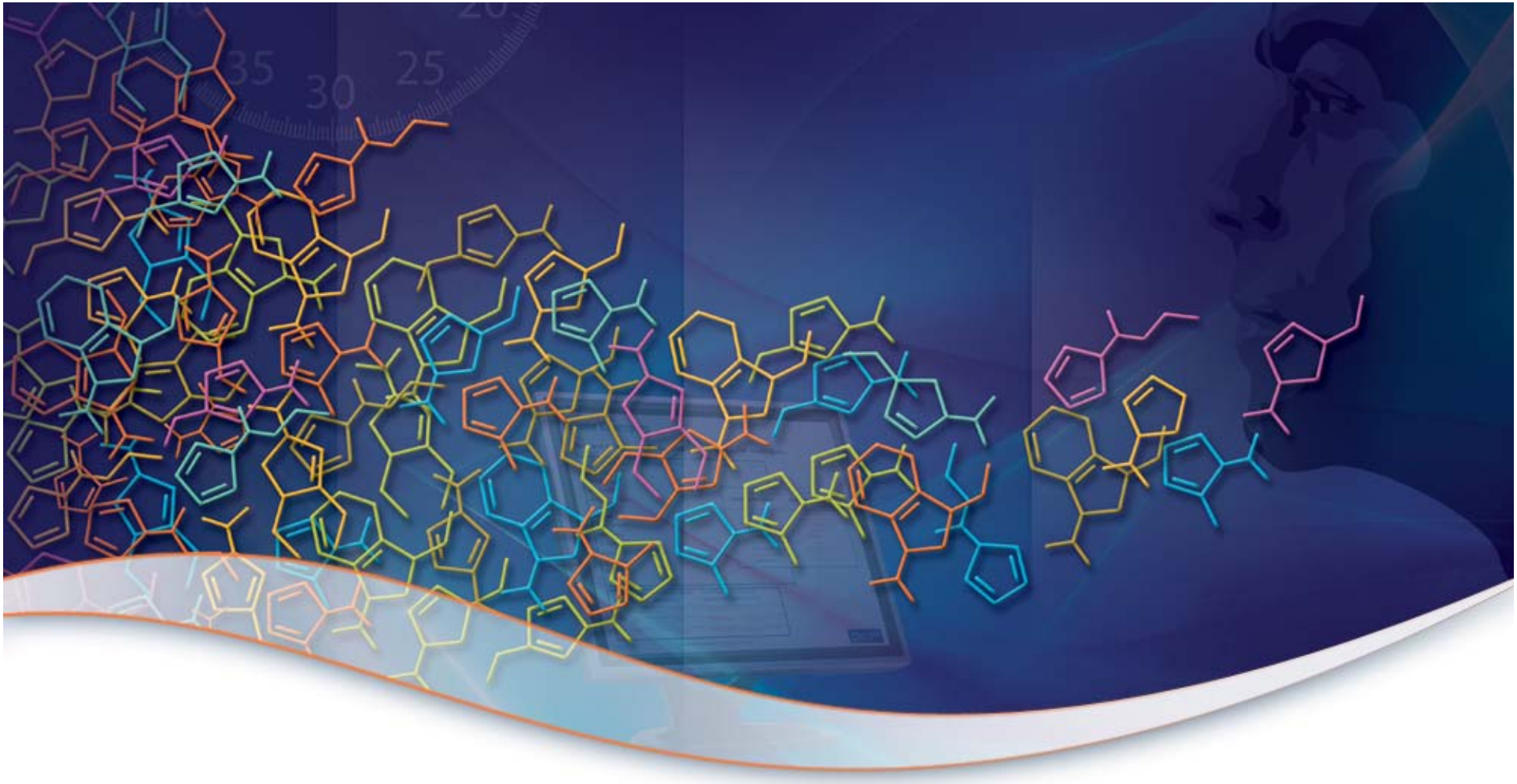

Do We Really Need Another Anti-platelet?

(Making Better Decisions Through Modeling and Simulation)

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A case study

Factor Xa Inhibitor for the Management of Thromboembolic Diseases

Presented at:

Drug Development Boot Camp
September 10, 2010
Weill Cornell Medical College, New York, NY
http://www.cctec.cornell.edu/events/boot-camp/drug-development/

The Problem

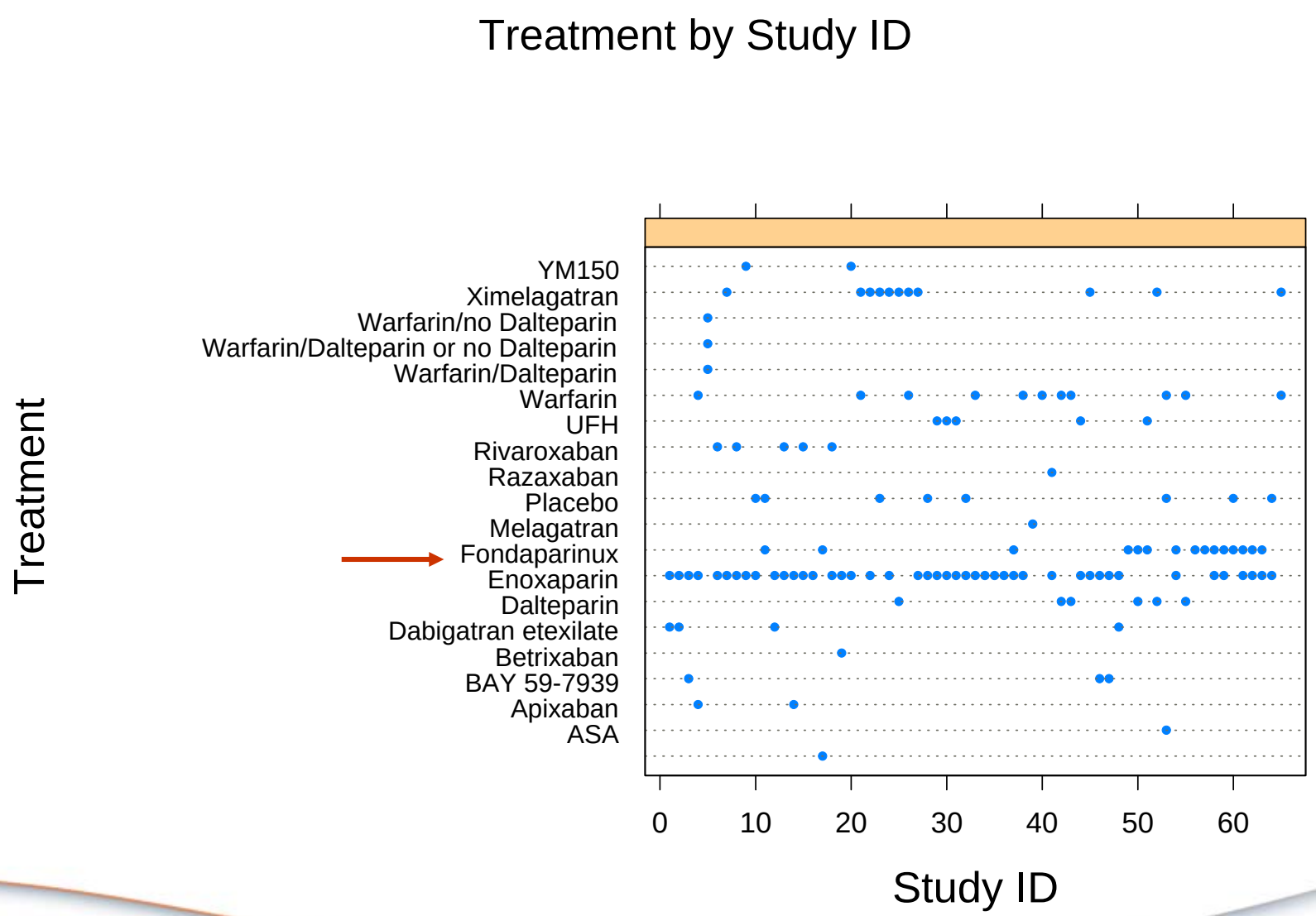
Following completion of pre-clinical phase, clinical development team is to decide which of several compounds to move forward to Phase I

One compound under consideration is a factor Xa (Fxa) inhibitor for the management of thromboembolic diseases

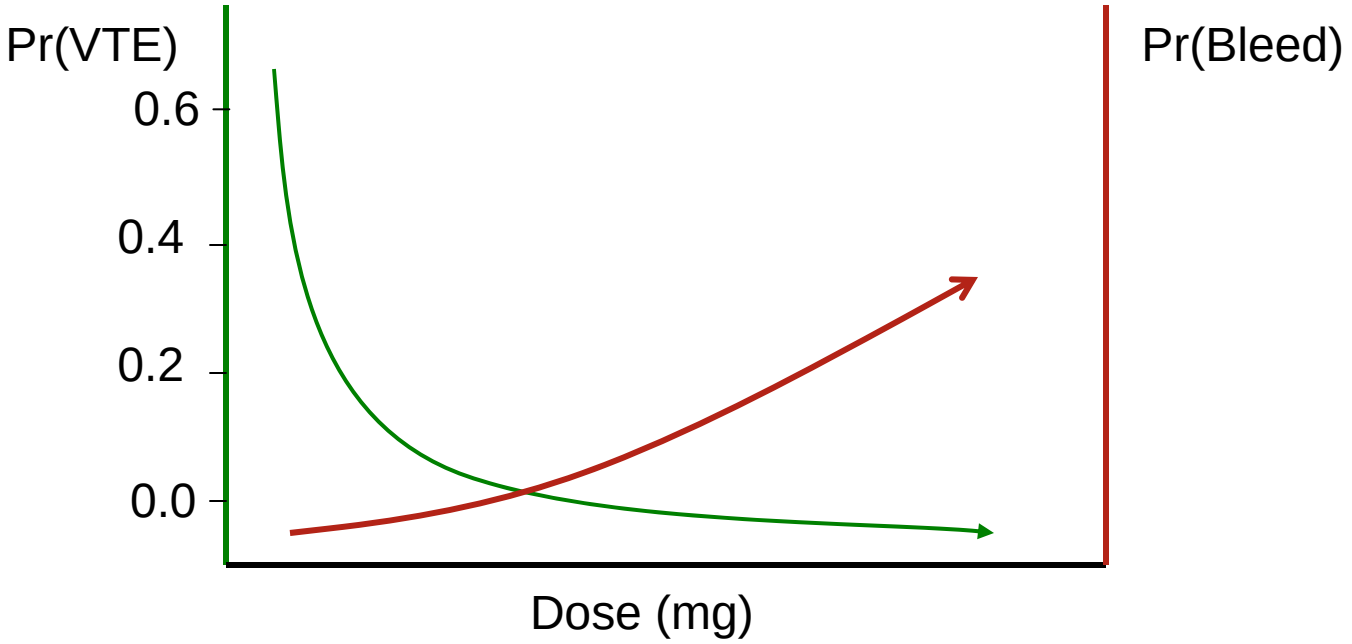
Prevention of venous thromboembolic events (VTE) subsequent to hip or knee replacement is one major application of Fxa inhibitor as well as long term use for the prevention cardiovascular events following acute coronary syndrome.

Can this compound be an alternative to Warfarin and a serious competitor to enoxaparin (Lovenox®) and fondaparinux (Arixtra®)?

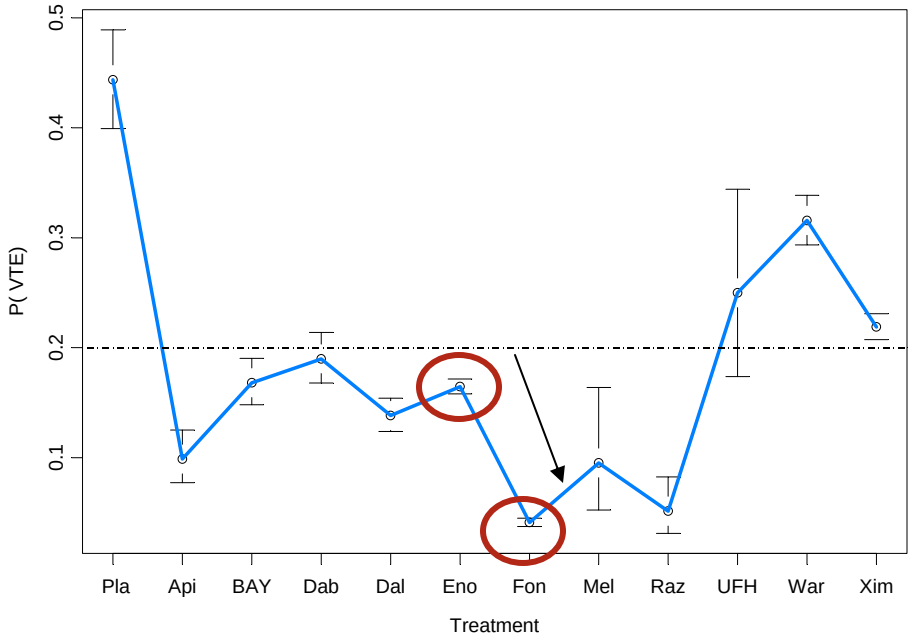
Competitive landscape is over-crowded and extensively investigated (Enoxaparin 44 studies) allowing comprehensive model building and comparison between treatments

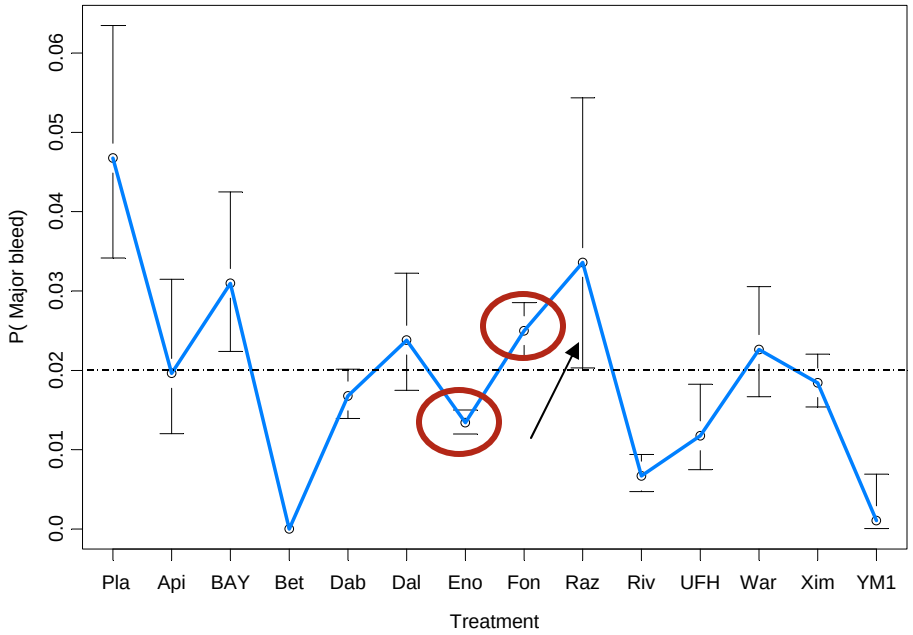


Objective: Minimize Venous Thromboembolic Events (VTE), while maintaining a small chance of bleed episodes



Proportions of VTE and major bleed (P(VTE)) suggest different Efficacy/Safety profiles for Enoxaparin and Fondaparinux





Fondaparinux has Higher P(VTE) but lower P(bleed) than Enoxaparin

Issues to Consider

- How useful and applicable is animal data to human?
- Is it possible to predict biomarker levels in human?
- What are commonly used methods and how predictive are they?
- What factors that influence biomarker levels in human?
- The drug is cleared by kidney, how relevant is this information?
- What subject demographics/characteristics are of potential concern?
- Which biomarker is indicative of clinical outcome?
- How useful is literature data in deciding on how and when to continue with development?

Why Modeling and Simulation

1. Introduction
   - M&S is a Systematic and Accountable Process
2. The Application of M&S to Guide Development of a Direct Factor Xa Inhibitor: A change in Paradigm
   - Use and Value of Meta Analysis

M&S is a Systematic and Accountable Process

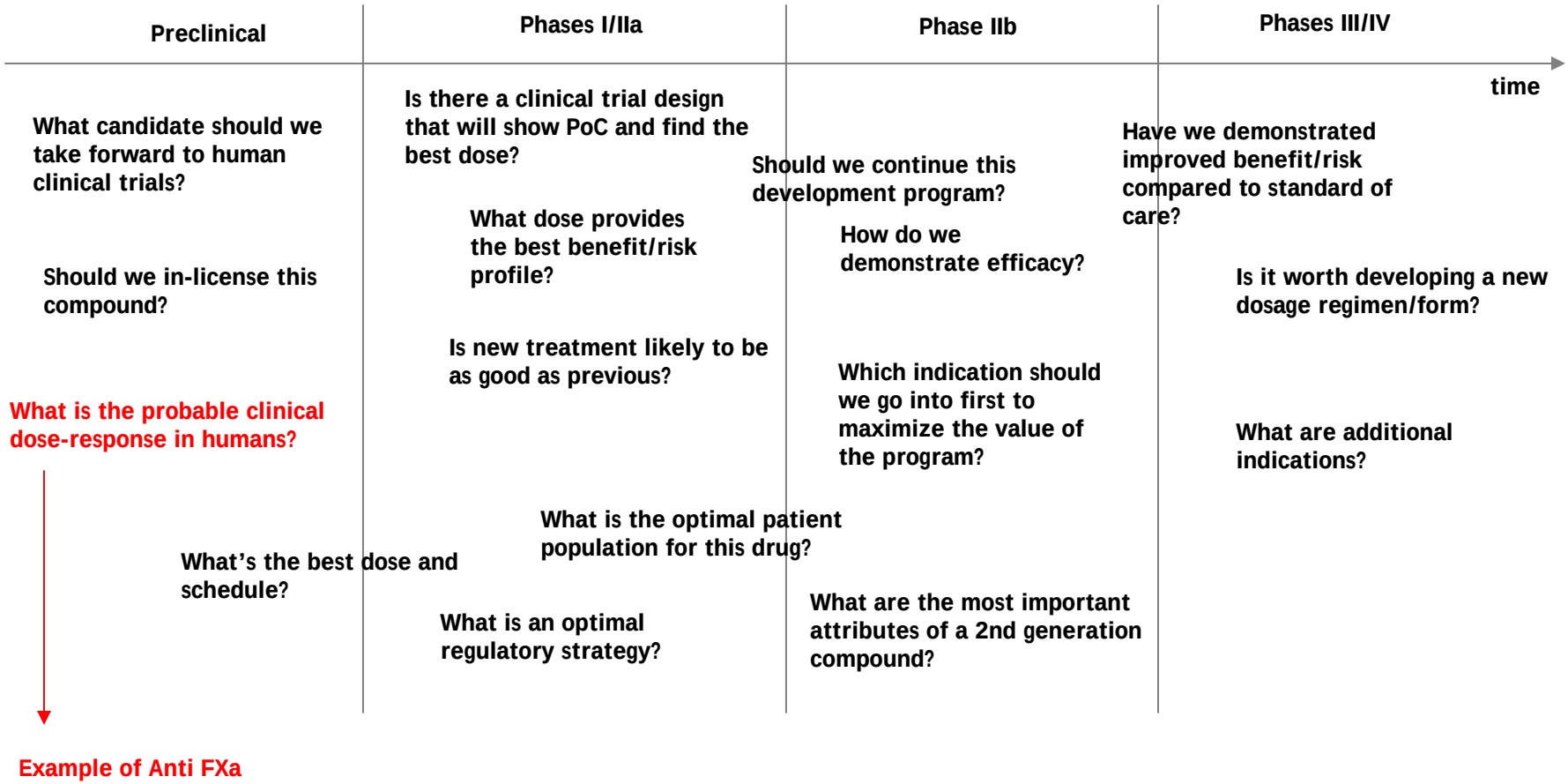
Modeling Steps

- **Define** drug development decisions in terms of program value
- **Explore** all the **proprietary** data that is relevant to your decisions
- **Augment** proprietary data with relevant **public** data
- **Build** a mathematical, quantitative model of the state of **knowledge**
- **Qualify** model against data and **assumptions** used in model building

Simulation Steps

- **Simulate/project** outcomes resulting from various possible decision scenarios using model
- **Quantify and** qualify the most likely outcome

Use Modeling and Simulation to Address Drug Development Decisions Across All Phases



Compound Background

CS-3030 is an oral, direct Factor Xa (FXa) inhibitor for the management of thromboembolic diseases.

Prothrombin time (PT) prolongation is known to be mediated by FXa inhibition

A PT International Normalized Ratio (INR) of 2-3 fold is considered a safe and effective anticoagulant range, therefore,

- **Determination of anti-FXa activity and PT provide a basis and a practical guide for driving the drug development process towards dose selection**

Reference: Rohatagi, S., Haworth, S.J., Ezzet, F., Kastrissios, H. Model Based Development of a Direct Factor Xa Inhibitor. ACoP, Tucson, Arizona, March 2008

Method (using pre-clinical data + Literature information)

Establish PK/PD models for

- a range of CS-3030 doses (10 to 320 mg),
- regimens (single dose, once daily (QD) and twice daily (BID))
- bioavailability fractions (4.5 to 50%)

Influences of patient demographics and laboratory values were investigated on response to CS-3030.

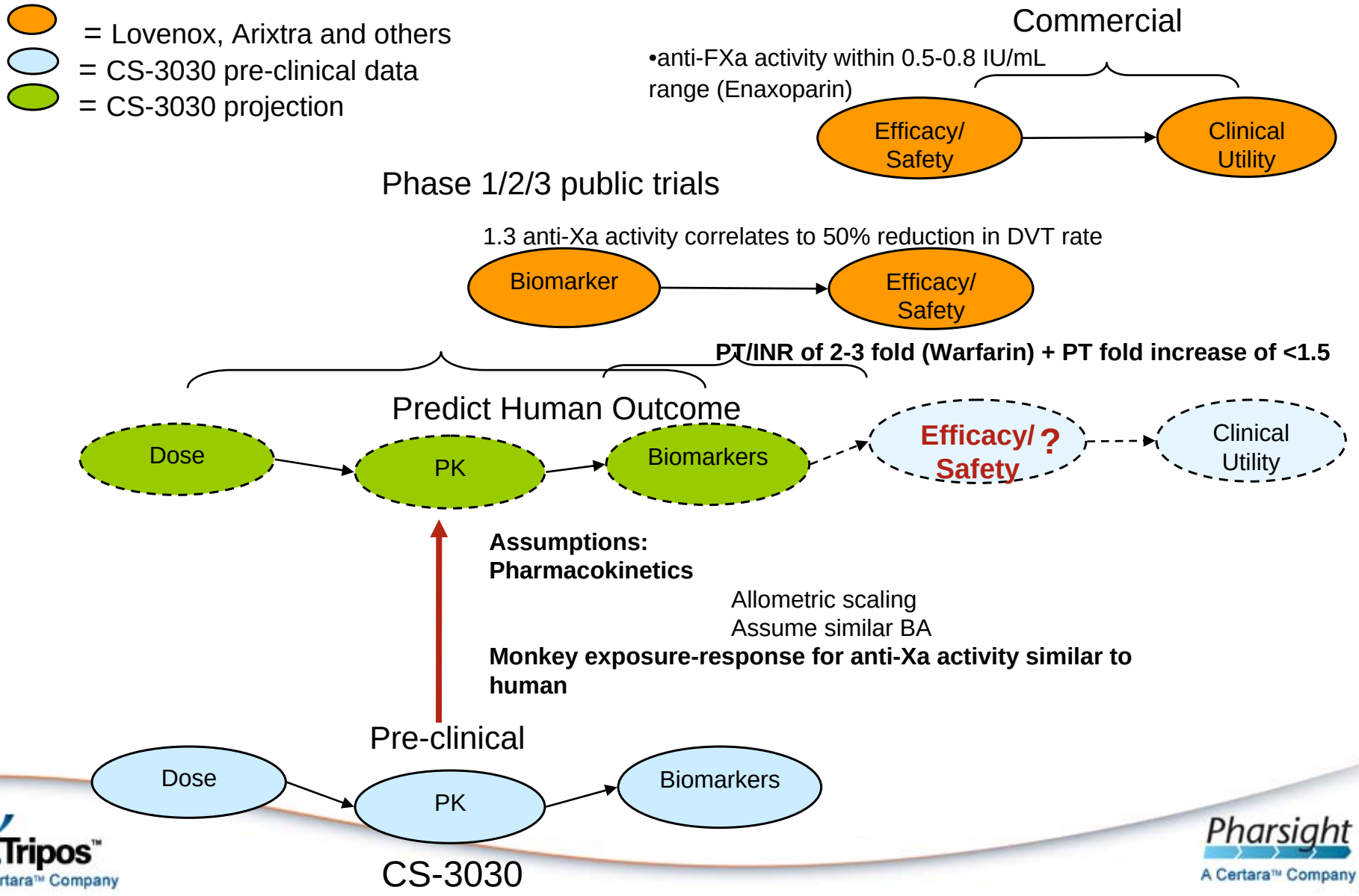
Criteria:

- Anti-FXa activity within 0.5-0.8 IU/mL range (based on enoxaparin)
- 2- to 3-fold increase in PT (based on warfarin).

Comparison of clinical events was made using publicly available literature for three comparators: warfarin, enoxaparin (Lovenox®) and fondaparinux (Arixtra®).

Model Based Drug Development Schema of a Factor Xa Inhibitor

Projecting Efficacy and Safety profile can begin as early as pre-clinical using biomarkers from animal



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Animal (monkey) Pharmacokinetic

information are available:

- Absorption rate = 0.75 1/h
- Volume/F = 7.6 L
- Clearance/F=0.5 L/h/kg
- F = 0.09

Assuming drug concentration is driver of clinical response

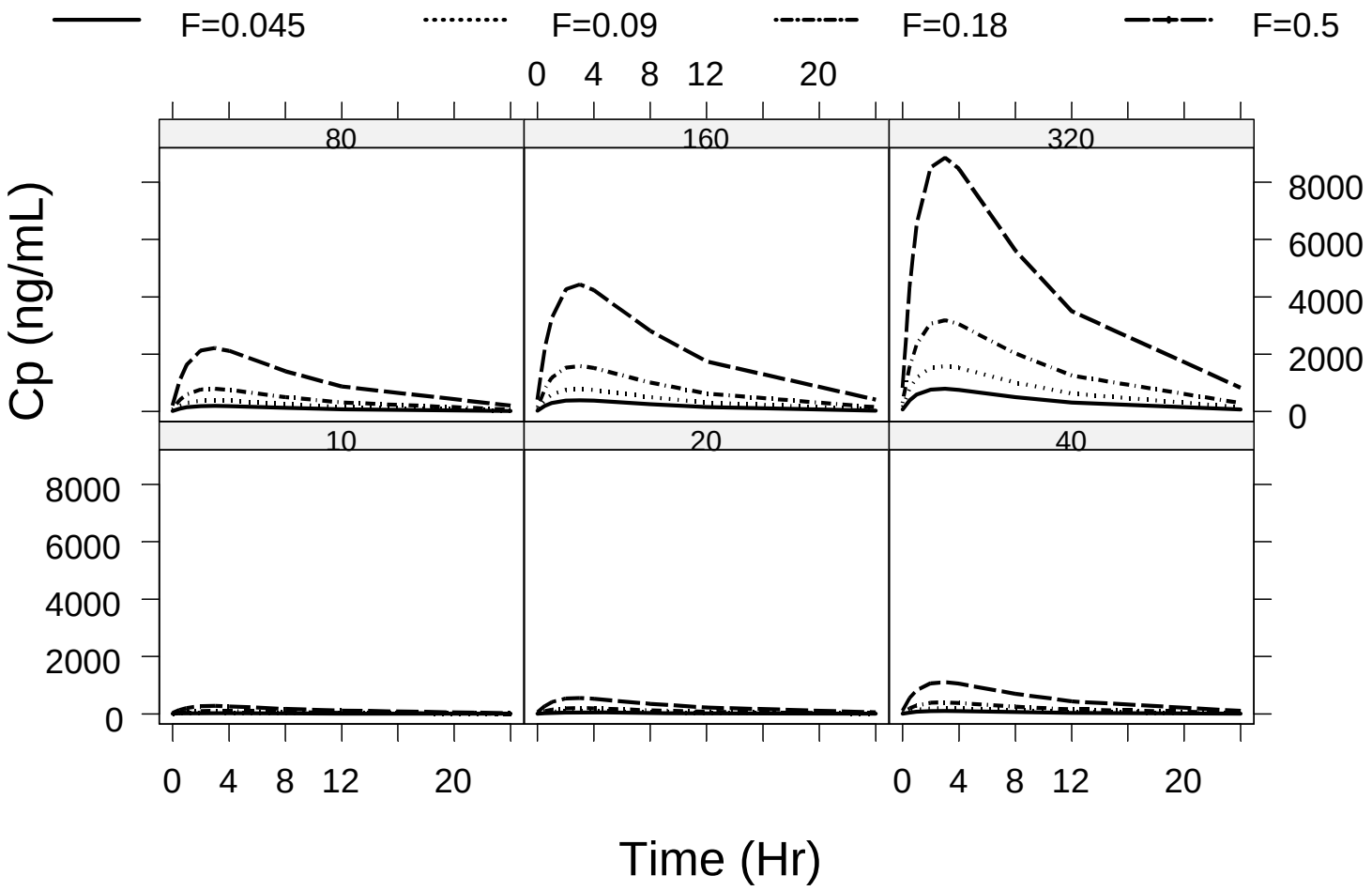
Obtain Simulated PK Profiles in Humans Using Allometric Scaling from Monkey PK

$CL = a\ WT^{0.782}$ ← **Allometric Scaling**

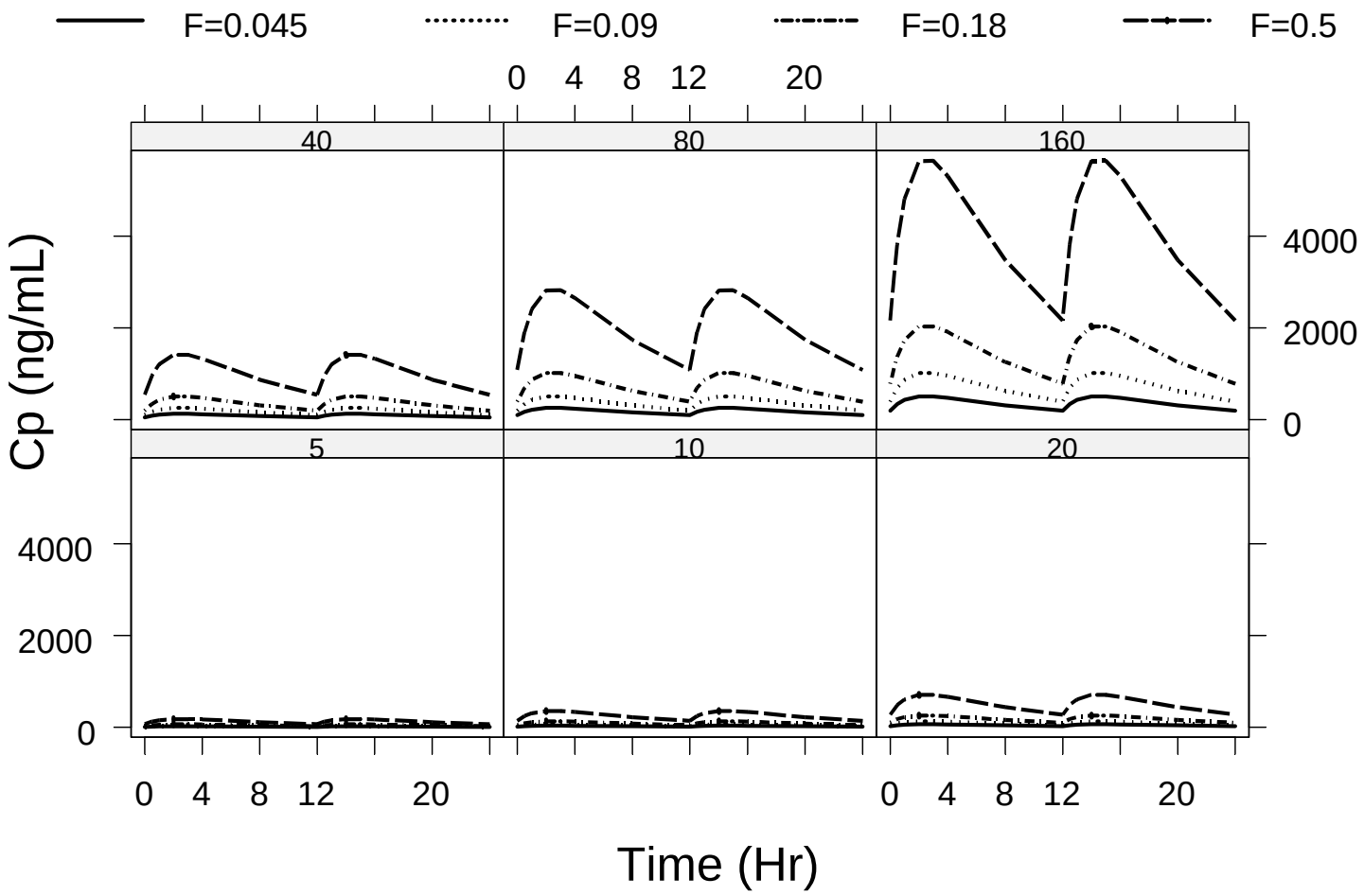
$V = b\ WT$

Parameter	Monkey	Projected Human
k_a	0.75 h^{-1}	0.75 h^{-1}
V/F	7.6 L	151 L
CL/F	0.5 L/h/kg	18.2 L/h

Simulated PK Profiles in Humans (QD) under a range of bioavailability Fractions for a range of dose levels

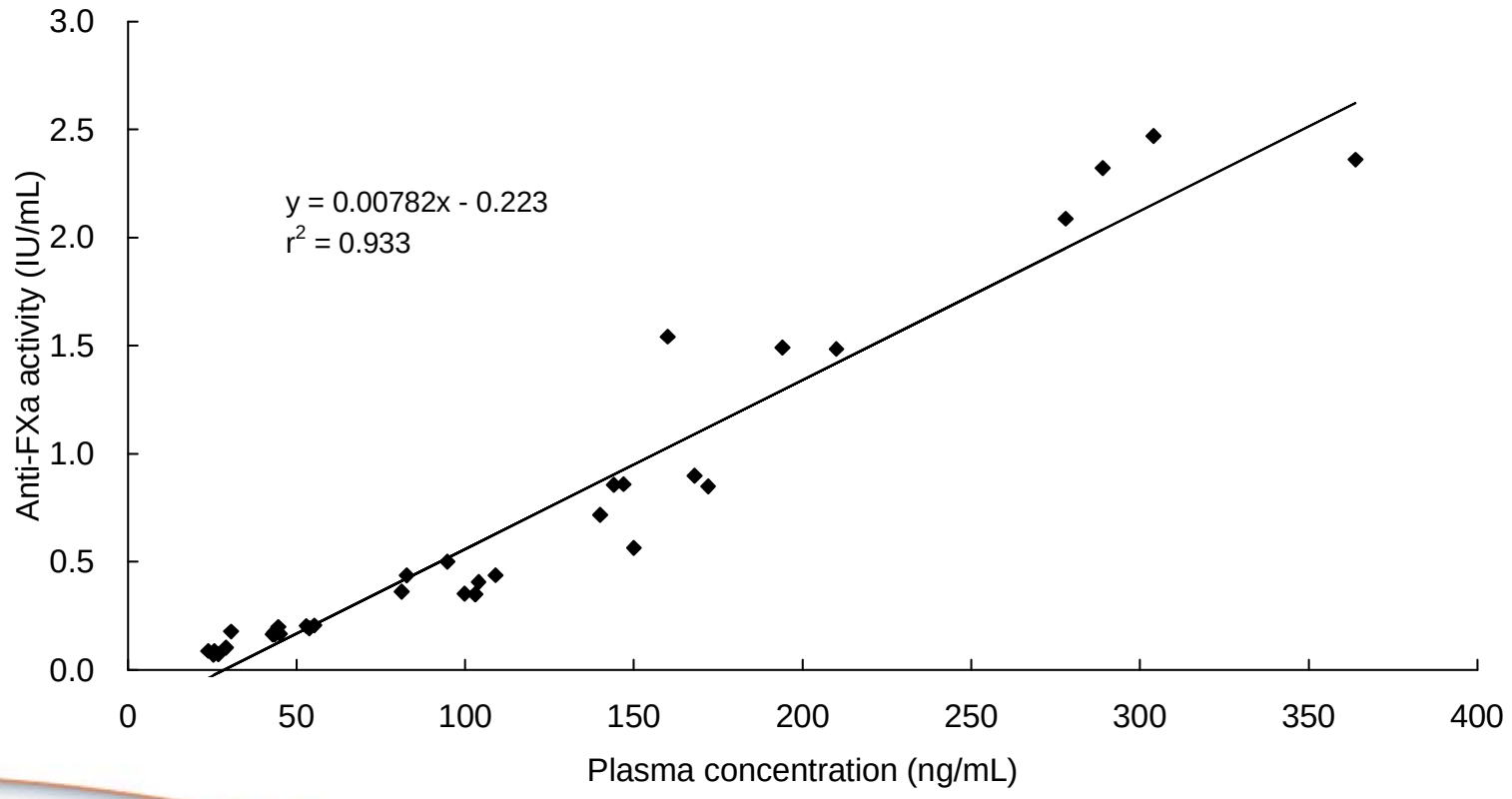


Simulated PK Profiles in Humans (BID) under a range of bioavailability Fractions for a range of dose levels



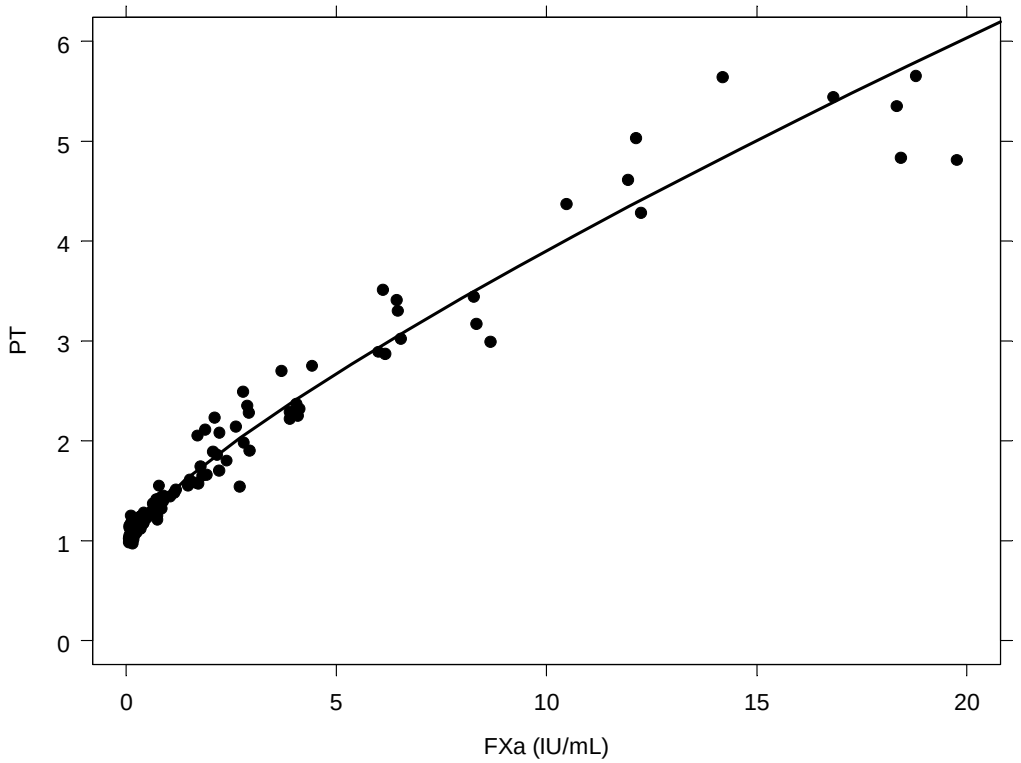
Establish animal biomarker models: Anti-FXa

Anti-FXa = 0.008 Cp – 0. 2



Establish animal biomarker models: Prothrombin Time (PT)

$$PT = 1 + 0.47\ (\text{Anti-FXa})^{0.8}$$



$$\text{Thus, } PT = 1 + 0.47 \bullet (\ 0.008 \times Cp - 0.2\ )^{0.8}$$

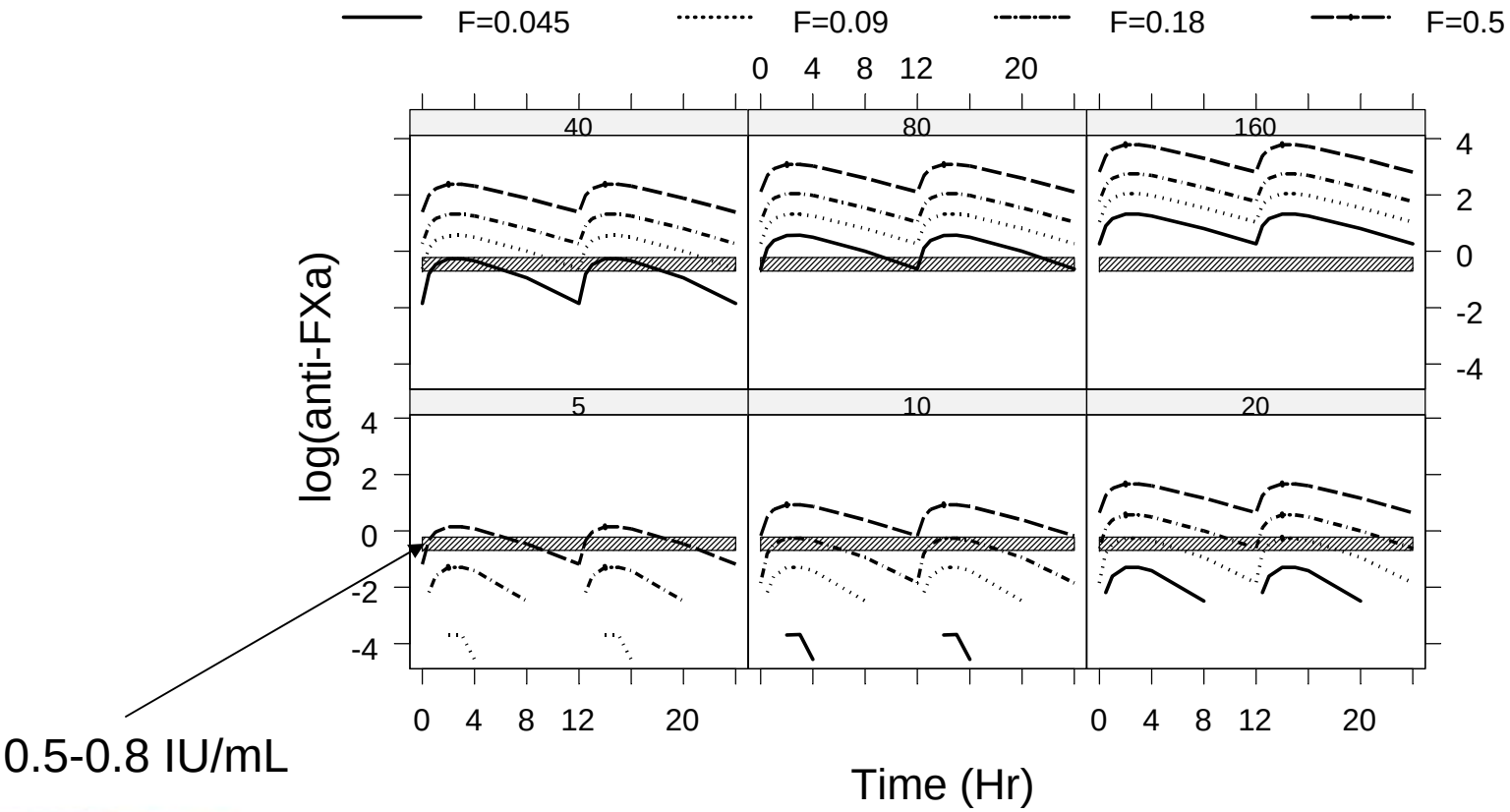
Other PT-FXa relationship?

Pro-thrombin Ratio

- In human, a PT International Normalized Ratio (INR) of 2-3 fold is considered a safe and effective anticoagulant range

Establish human biomarker models: Anti-Fxa Projected from animal model

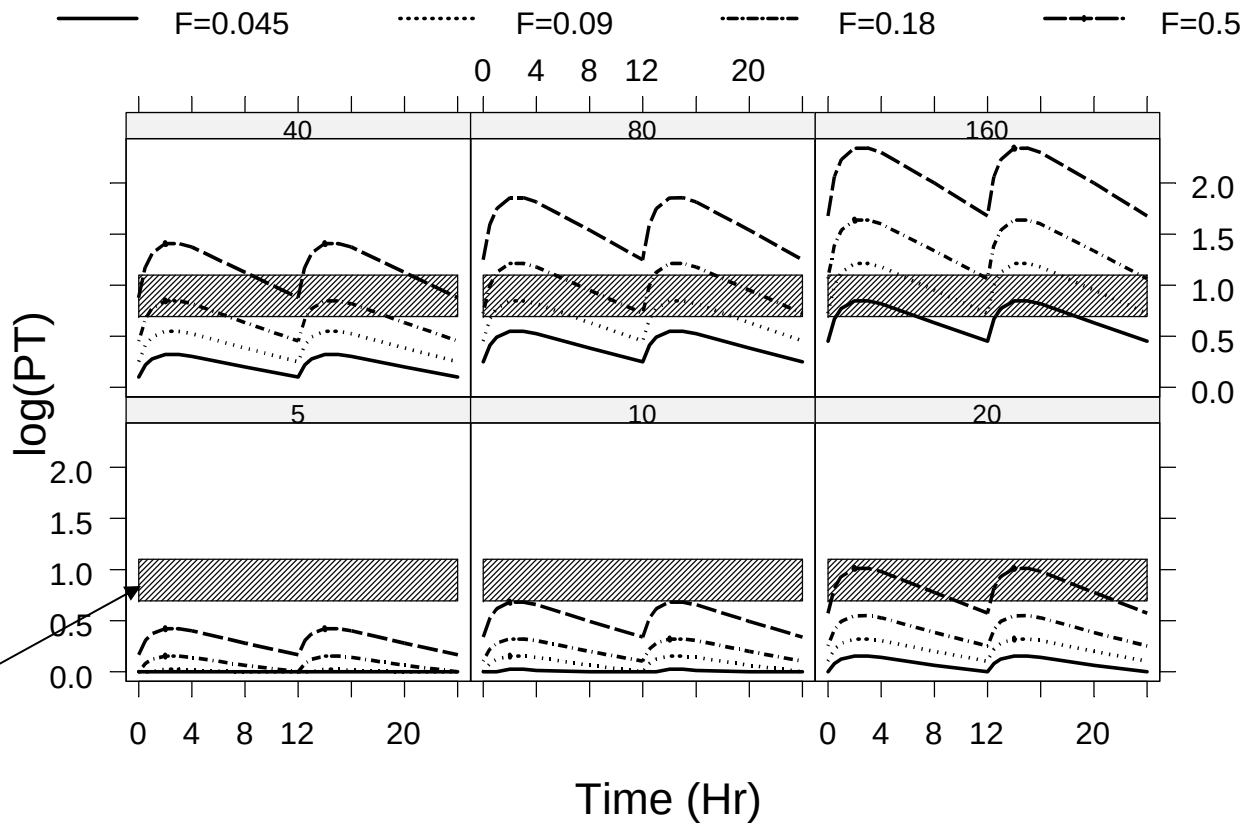
Using,
Anti-FXa = 0.008 Projected Cp – 0. 2



Establish human biomarker models: PT Projected from animal model

Using,

$PT = 1 + 0.47 \bullet (0.008 \times \text{Projected Cp} – 0.2)^{0.8}$



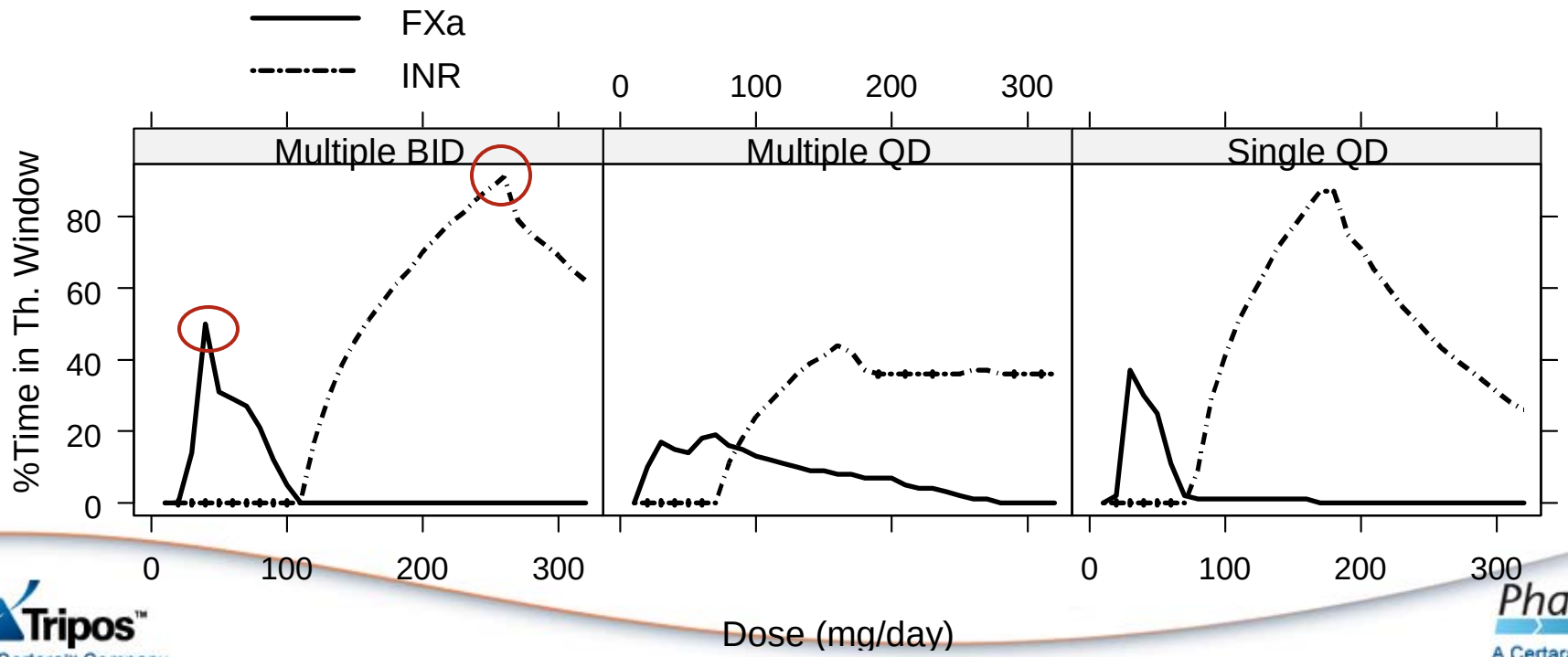
2-3 fold

Better coverage
If PT in human > PT in Animal

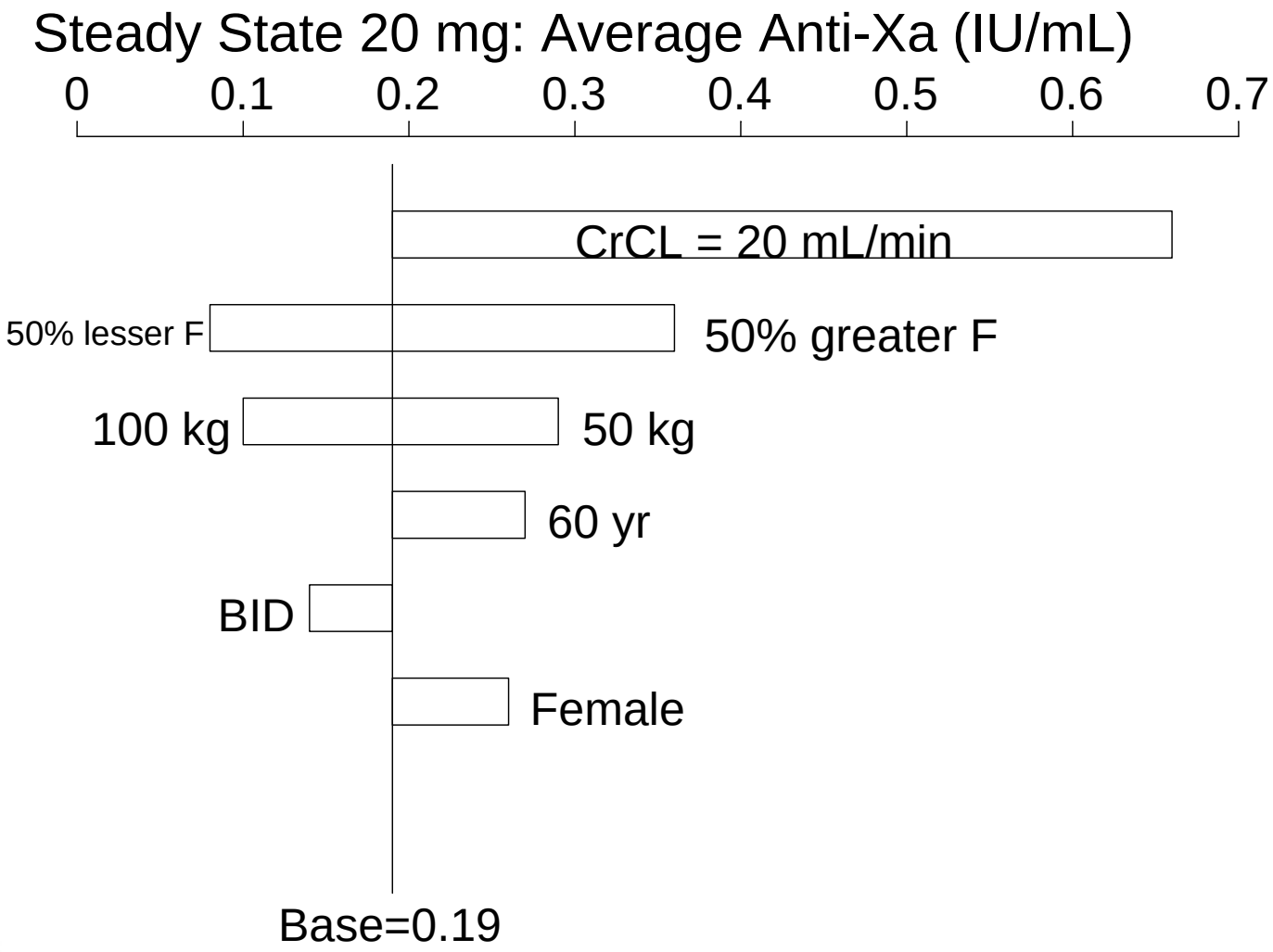
Percent of Time Responses are within the Targeted Ranges for FXa Activity or INR For a Range of Dosage Regimens

No one dose met the dual criteria of anti-FXa activity and PT response. Rather, target levels were achieved only partially over the dosing interval

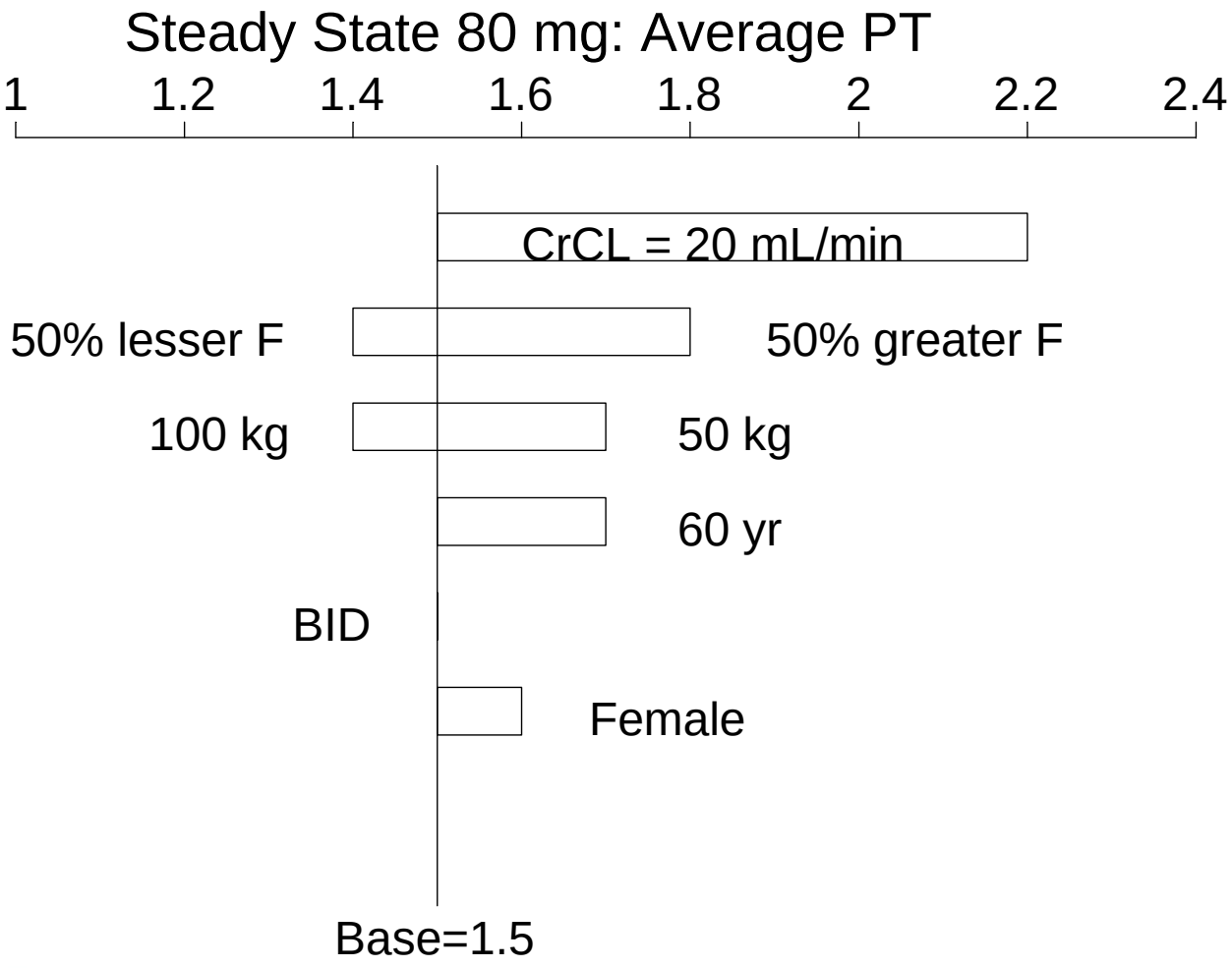
For BID, the largest proportion of time within the anti-FXa activity range was estimated to be 50% for a dose of 40 mg.
Similarly, the largest proportion of time within the INR range was estimated to be 88% but at a higher dose of 250 mg



Explore Influence of subject characteristics on biomarkers: Anti-FXa



Explore Influence of subject characteristics on biomarkers: PT



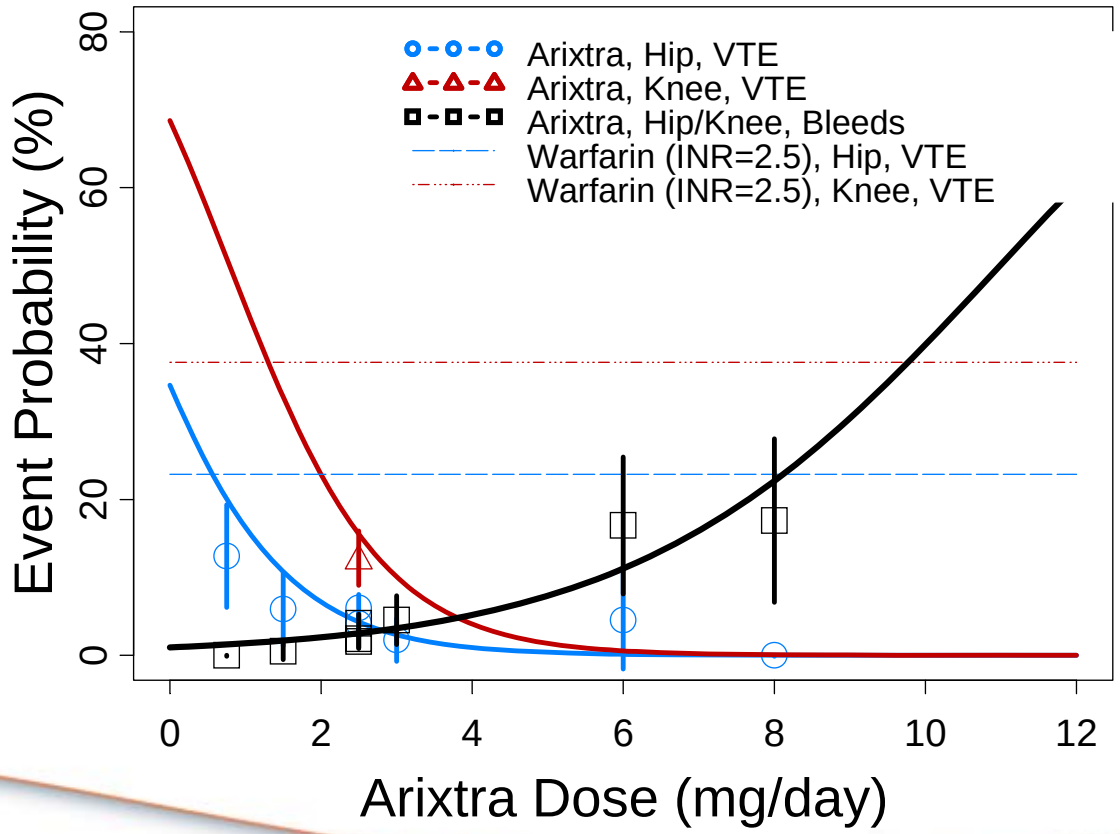
Characterize drug attributes of Competitor treatments using public literature

- Arixtra (Fondaparinux)

  P(Hip VTE)=-0.63 – 0.99 • dose

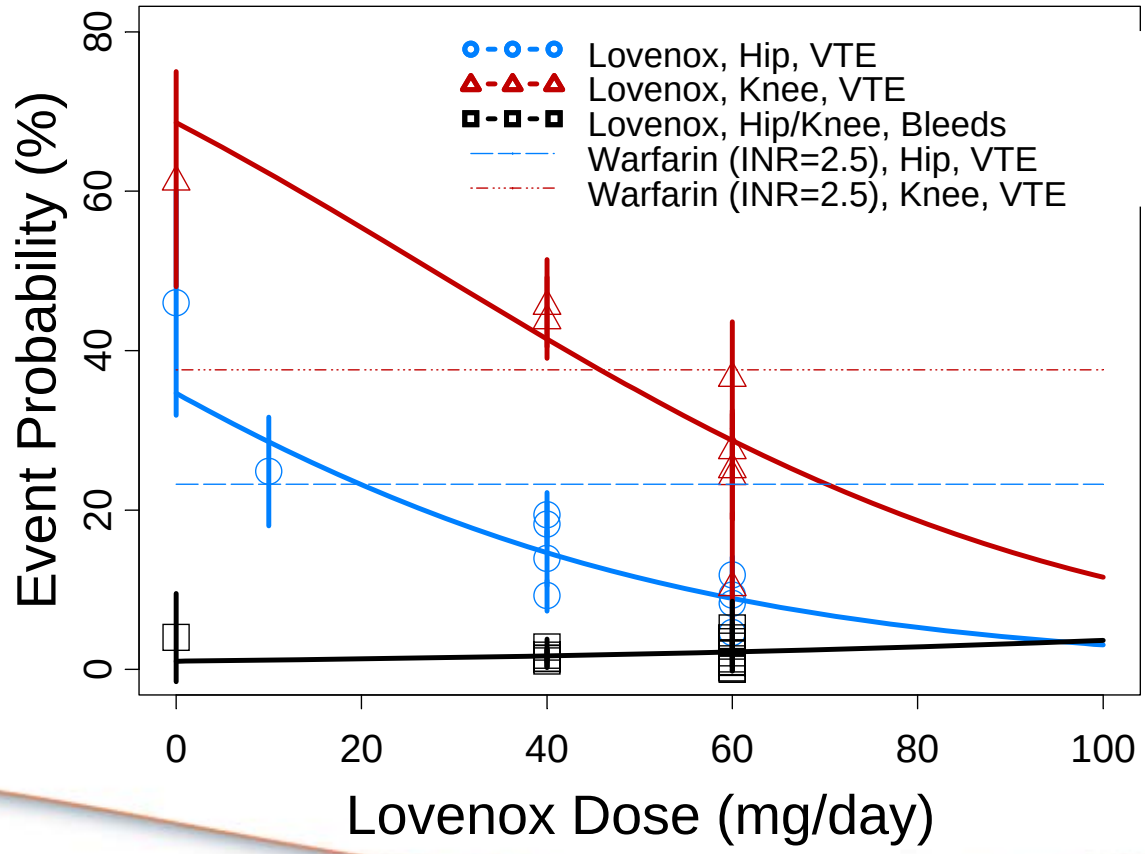
  P(Knee VTE)=-0.78 – 0.99 • dose

  P(Bleed)=-0.46 + 0.42 • dose



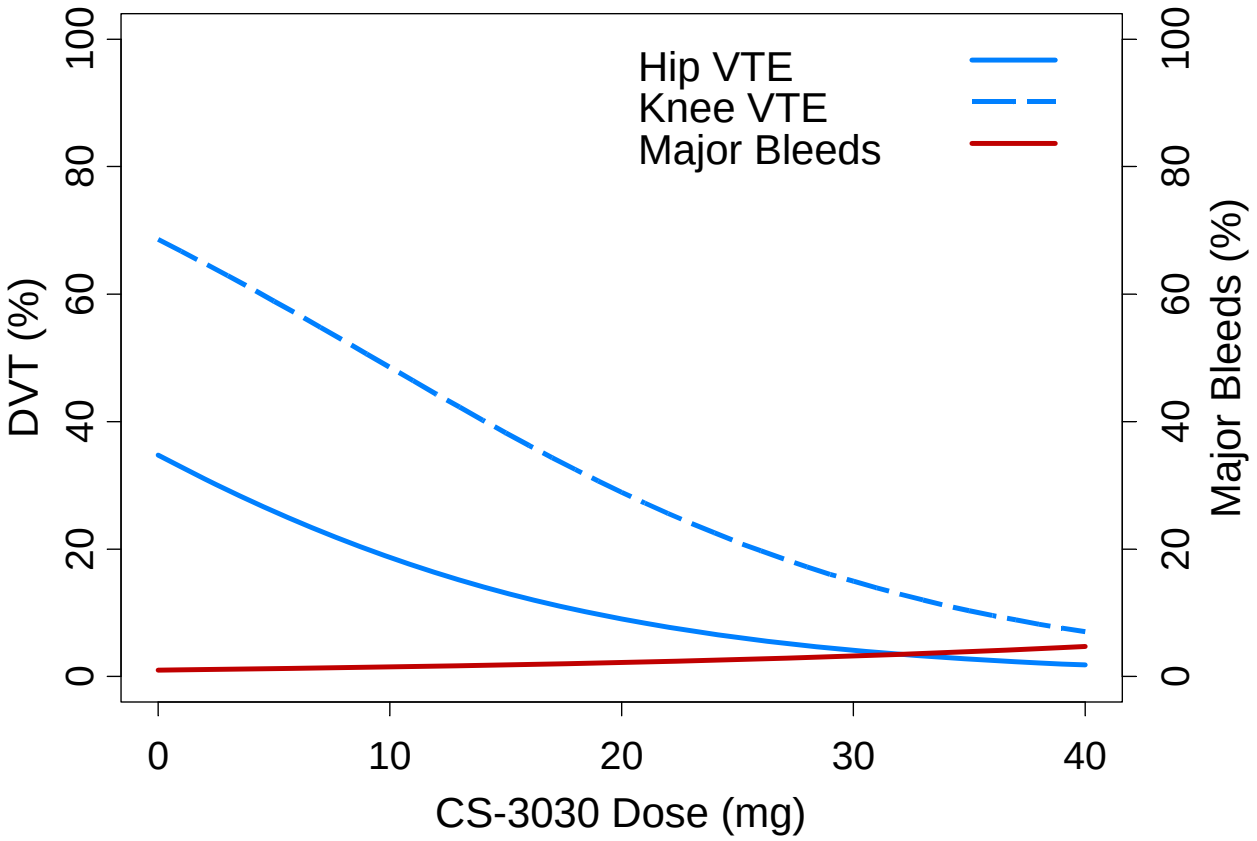
Characterize drug attributes of Competitor treatments using public literature

- Lovenox (Enoxaparin)
  P(HipVTE)=-0.63 – 0.028 • dose
  P(KneeVTE)=-0.78 – 0.028 • dose
  P(Bleed VTE)=-0.46 + 0.013 • dose



Projected efficacy and safety
Assuming a relative potency of CS-3030 to be 3 times that of Enoxaparin (Lovenox®) for anti-Xa activity

Suggesting CS-3030 up to 40 mg/day is similar to enoxaparin up to 100 mg/day.



Probability(event)=f(b.dose),
For CS-3030,
Probability(event)= f(w.b.dose),
w = anti-FXa activity of a 1 mg CS-3030/ anti-FXa activity of 1 mg Enoxaparin.

Summary

Integration of animal data and public literature allowed human PK-PD to be projected under certain plausible assumptions and scenarios.

Human projections for CS-3030 identified dosing regimens which provided similar efficacy and safety profiles to that of comparators

M&S was used to

- Optimize the Phase 1 program to reduce uncertainty and test assumptions such as bioavailability and variability
- Estimate the likely quality of Phase 2 dose-response during Phase 1 planning
- Quantify the effect of covariates, the magnitude and sources of uncertainty, and key assumptions

Conclusion

Despite limitations due to data quality and assumption, the approach should help

- **Quantify and leverage** knowledge for development purposes by
  - Providing **objective comparisons** between treatments
  - Permit **exploration of study design** alternatives to guide further development
  - Permit evaluation of **likelihood of achieving** viable target responses **utilizing short term data** from early efficacy studies
  - Provide a **forum** for discussion and allow **open communication** within project teams