

*Drug and disease models in drug development: better
knowledge, better decisions, better drugs*

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Acknowledgements to many others

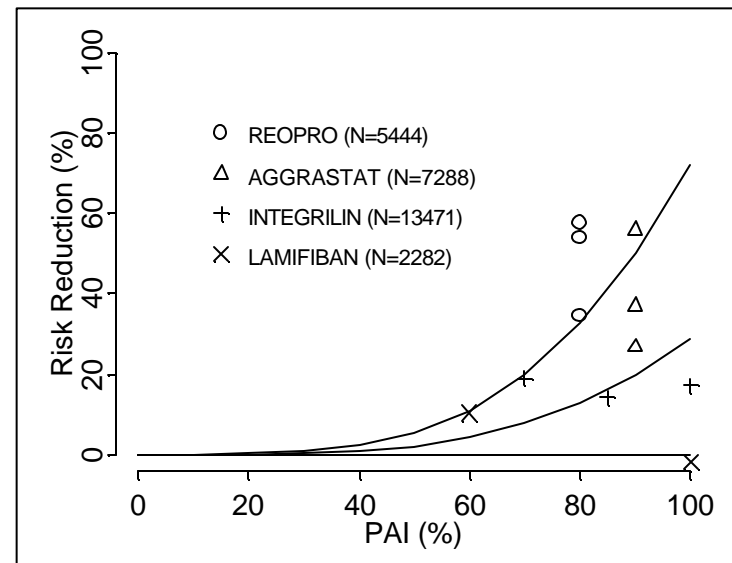
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My initial experiences suggested that models have fundamental value in integrating information.

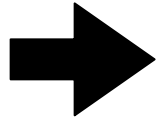
GPIIb/IIIa Phase II/III Strategy

18 March 1999



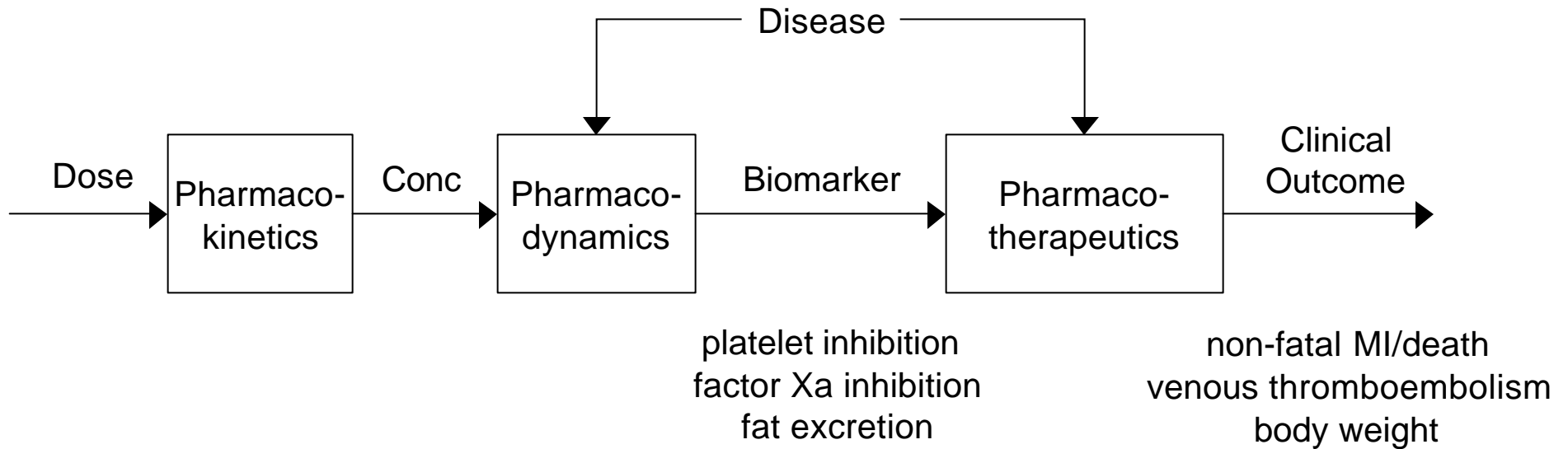
- Skipping Phase II provides greatest expected benefit, because of the cost of missing out on a “winner” or “blockbuster”. However, a failed Phase III trial will occur 40% of the time.
- Doing 500 subject Ph II and going forward with “blockbusters” cuts profits by 60%, but a failed Phase III trial will occur only 5% time.
- PK-PD-PT-PE modeling and simulation quantitate risk vs benefit to improve decision-making.

Agenda



- Introduction
- Method Overview
- Examples
- Conclusions

The purpose of this talk is to illustrate the value that models have for integrating information in drug development.



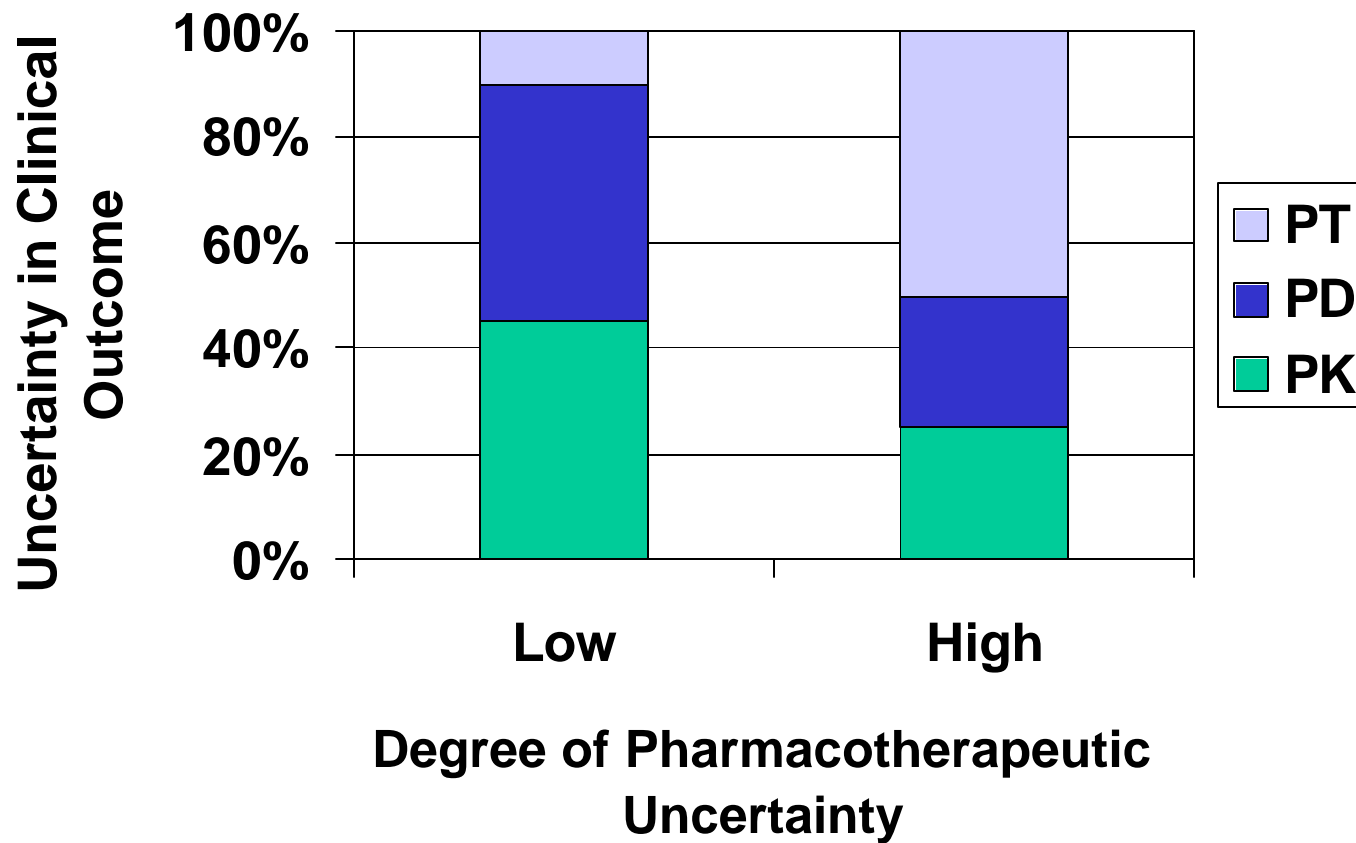
Framing

- Data sources are from the literature or from public websites up to the time of completion of the project.
- Modeling prior to Phase I, but in anticipation of Phase II/III
- Prospective modeling to make decisions, not just to describe data.

Integrating information with models is valuable when decisions involve linkage of separate pieces of information.

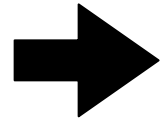
- Multiple drugs
 - Can we learn anything about Factor Xa dosing by looking at Enoxaparin.
- Multiple indications
 - Can we learn anything about Factor Xa dosing in prophylactic hip replacement by looking at prophylaxis for knee replacement?
- Biomarkers and clinical endpoints
 - What is the optimal level of LDL cholesterol? Weight loss? Blood pressure decrease?
- Go / No Go, and what dose?

Linking dose to clinical endpoint response, and understanding the key uncertainties focuses learning.



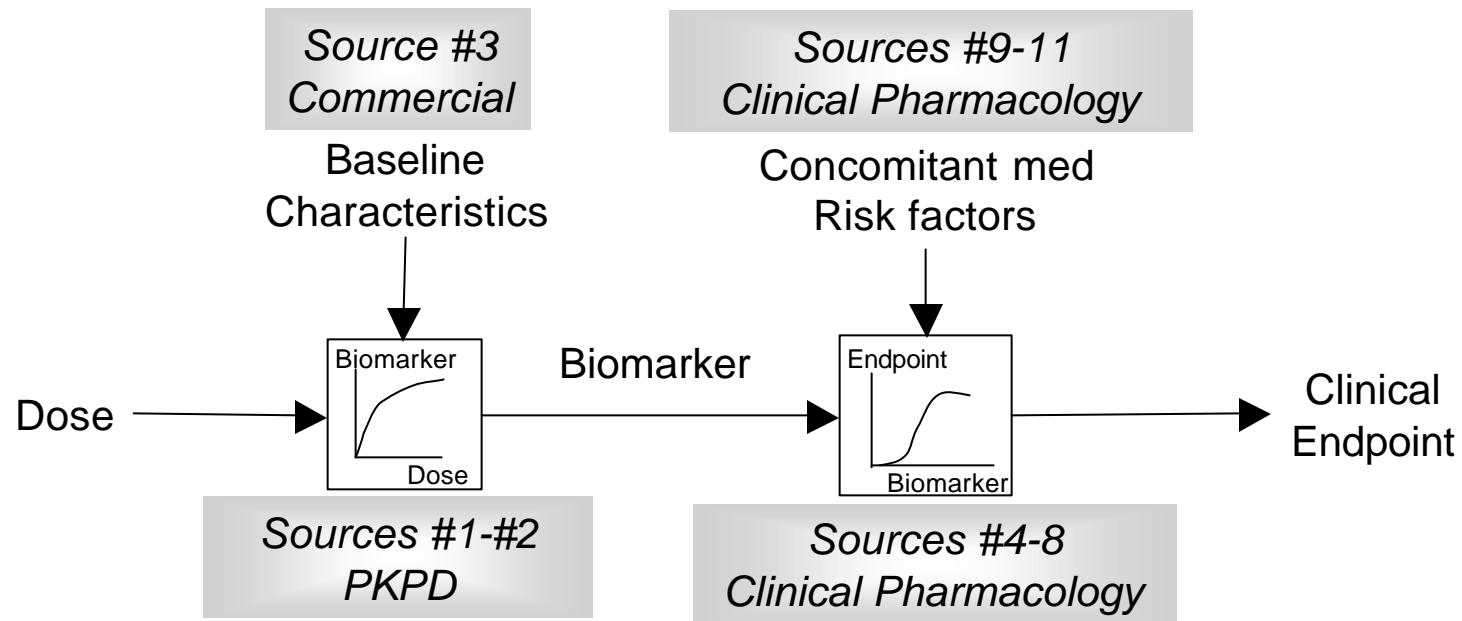
- Low pharmacotherapeutic uncertainty: focus on learning about PKPD in patients
- High pharmacotherapeutic uncertainty: additional early focus on learning about clinical outcome

Agenda



- Introduction
- Method Overview
 - Designing and displaying models
 - Interpreting data
- Examples
- Conclusions

Multidisciplinary teams design the model structure, select data sources, then fit the model to the data.



Model Requirements

- Predict endpoints of interest
- Handles key trial variables, e.g. dose, inclusion criteria, dropouts
- Reasonable structure and assumptions
- Model fit is consistent with data sources
- Data sources are adequate

Selection and interpretation of data sources requires clinical judgment. Close collaboration between clinical pharmacologists and modelers is key.

- Is patient response due to the protocol or to the drug?
- What factors might explain variability in results across trials?
- Example: Why do patients regain weight in long-term weight-loss trials? Is it adherence to diet, or a physiological control system?

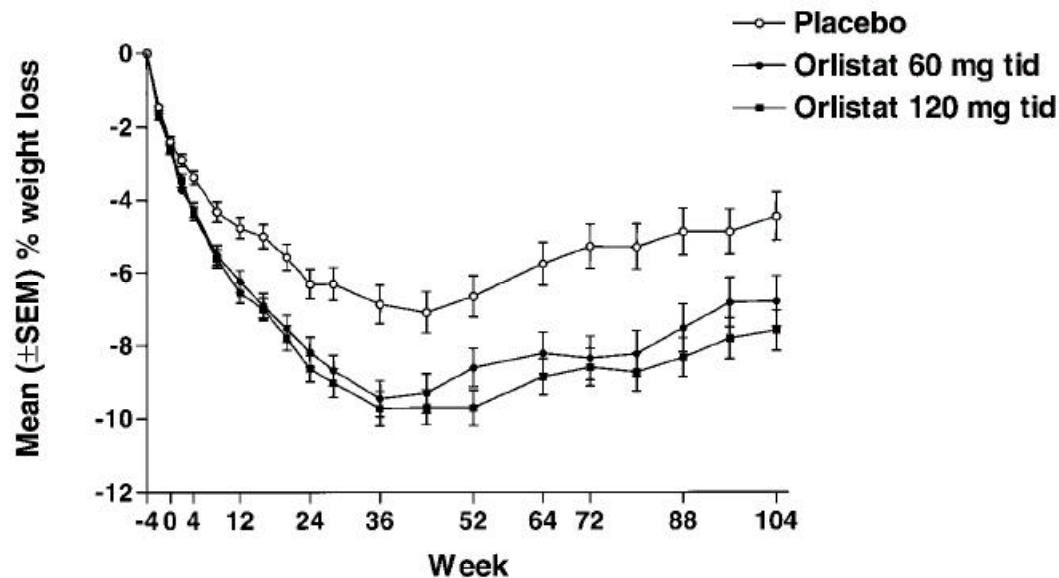
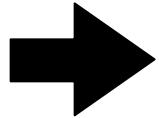


Figure 2: Mean percentage change (\pm SEM) from initial body weight during 2 years of treatment. ITT population.

Source: Rossner et al. Obes. Res. 2000

Agenda

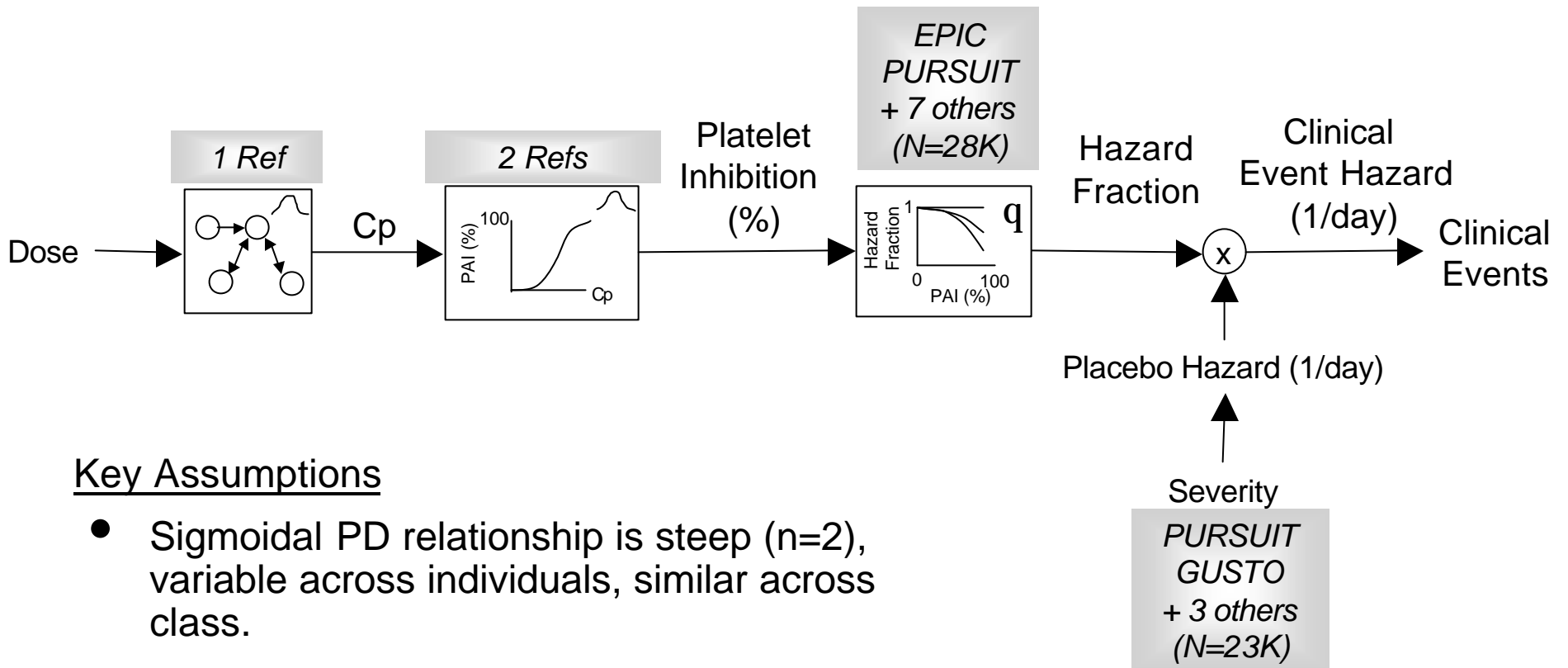
- Introduction
- Method Overview
- Examples
 - GPIIb/IIIa platelet inhibition and acute coronary syndromes
 - Overview
 - Model Structure and Assumptions
 - Model Fits to Data
 - Implications
 - Factor Xa inhibitors in deep vein thrombosis
 - Gastrointestinal lipase inhibitors in obesity
- Conclusions



GP1Ib/IIIa inhibitors have a valuable role in acute coronary syndromes.

- Acute coronary syndromes
 - Patients present with chest pain.
 - All are treated with aspirin, most undergo angiography, some undergo angioplasty
 - Discharged after 2-4 days.
 - Rate of clinical events (non-fatal MI/death) is approximately 10% over 30-days on standard therapy, mostly in the first 2-4 days. A 20% reduction in clinical events is considered to be medically relevant.
- Three approved iv GP1Ib/IIIa inhibitors
 - Inhibit platelet aggregation (PAI)
 - Patients are treated in-hospital; clinical benefit persists for 30-days.
- (Old) Application
 - Planning for a new iv/oral GP1Ib/IIIa inhibitor

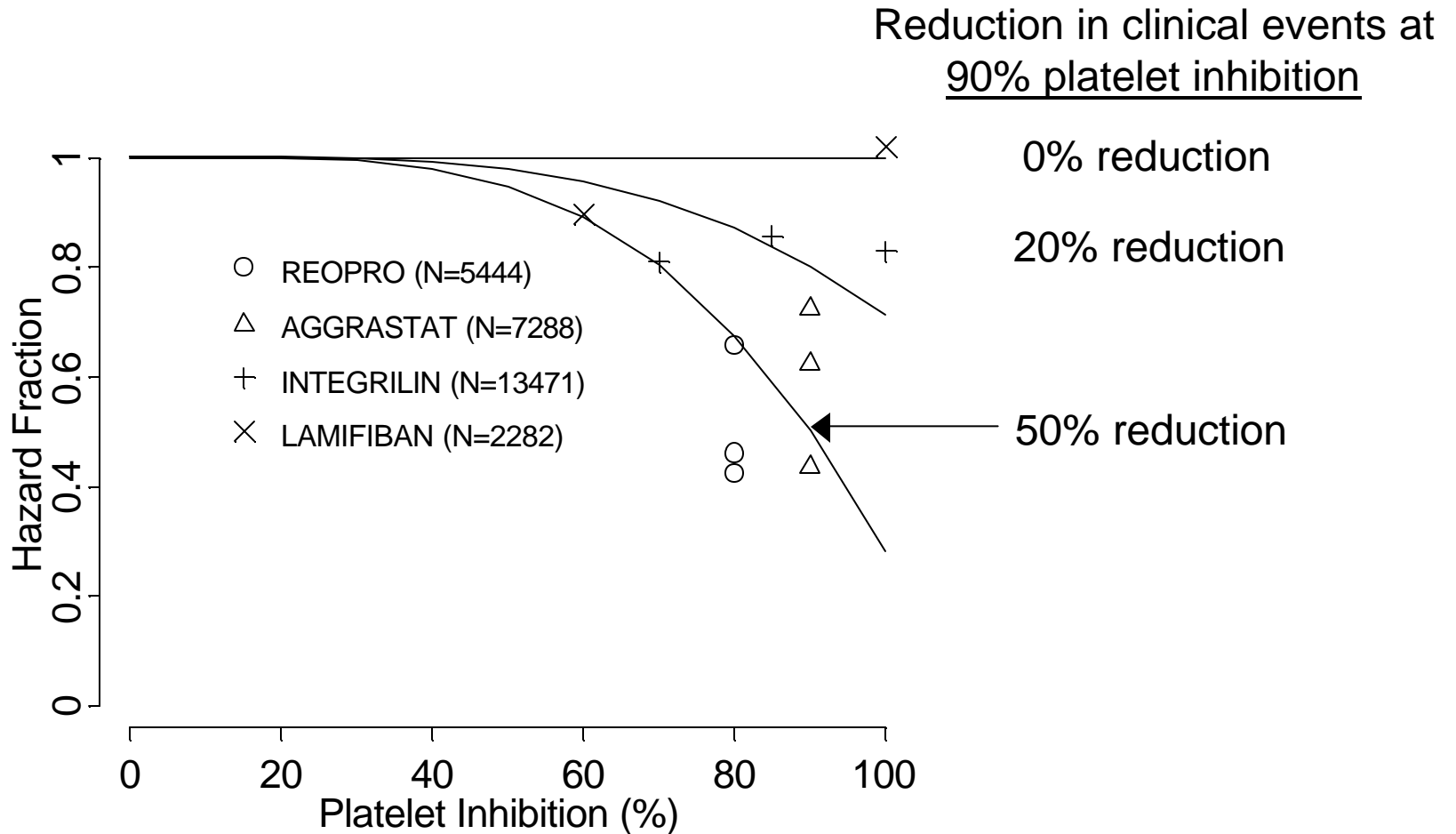
The GPIIb/IIIa model in acute coronary syndromes has PK, PD, and PT blocks.



Key Assumptions

- Sigmoidal PD relationship is steep (n=2), variable across individuals, similar across class.
- Reduction in the incidence of clinical events begins when platelet inhibition is near complete.

The relationship between GPIIb/IIIa platelet inhibition and hazard fraction (event reduction) is highly uncertain.



$$\text{Hazard fraction} = E_{max} \cdot \frac{PAI_{50}^n}{PAI^n + PAI_{50}^n}, \quad PAI_{50} = 90\%, \quad n=4$$

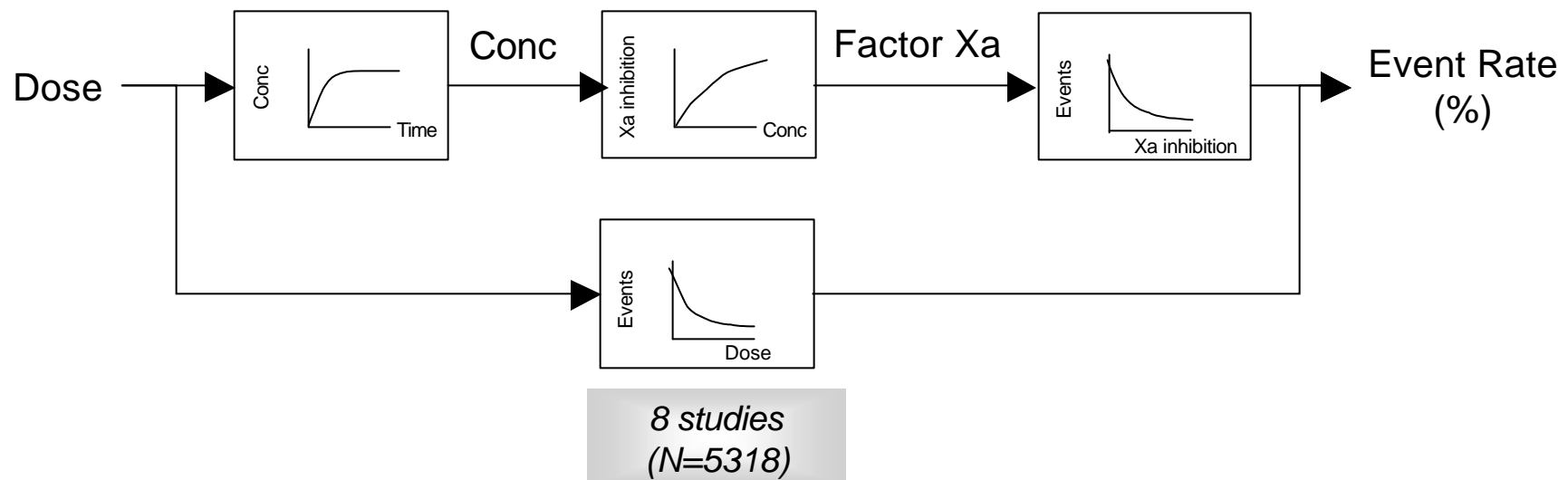
The pharmacotherapeutic model clarifies Phase II/III alternatives for a new GPIIb/IIIa antagonist in acute coronary syndromes.

- The model for antiplatelets
 - The pharmacodynamic relationship is fairly steep (n=2) and variable
 - The PT relationship is highly uncertain
- Application
 - Clinical trial simulation showed that a large Phase II program with 500 subjects could discriminate the 0% and 50% model to some degree, but not enough to justify the time spent in Phase II.
 - Possible Phase II focuses
 - Confirm platelet inhibition of the proposed regimen in patients
 - Explore safety on chronic treatment
 - But considerable risk in Phase III must be faced.
 - Take the risk
 - Wait for or begin planning research to resolve PT uncertainty
 - Group sequential Phase II

Prophylactic Factor Xa inhibition reduces DVT events in several types of orthopedic surgery with comparable incidence of bleeding to low molecular weight heparins.

- Prophylaxis for deep vein thrombosis in orthopedic surgery
 - Standard of care is low molecular weight heparins or warfarin.
 - LMWHs require less monitoring than warfarin, but require parenteral injections.
- Indirect factor Xa inhibition
 - Fondaparinux is approved for prophylaxis of deep vein thrombosis in orthopedic surgeries, and provides comparable risk/benefit to enoxaparin.
 - Fondaparinux binds to antithrombin, and selectively inhibits activated clotting factor Xa.
 - Fondaparinux has been investigated in Acute Coronary Syndromes.
- Application
 - Planning for a new direct Factor Xa inhibitor

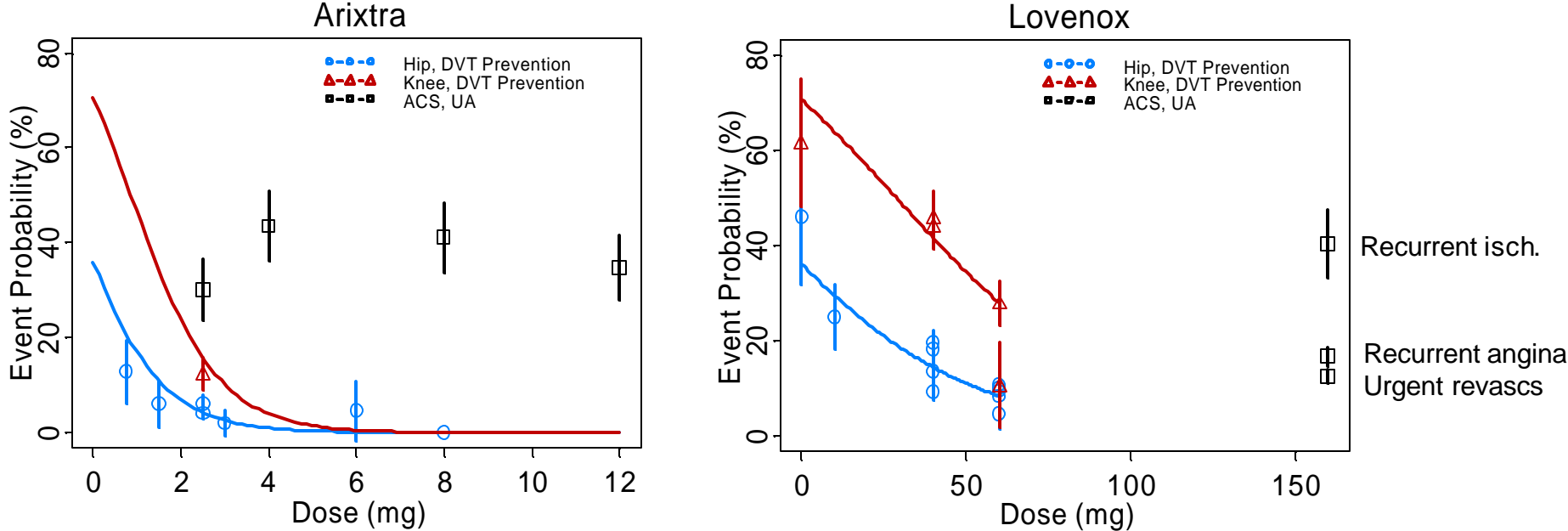
The model for fondaparinux has factor Xa inhibition as an intermediate variable. However because fondaparinux's factor Xa response is specific to fondaparinux, we consider the dose-response relationship only.



Key Assumptions

- Logistic dose-response model offset by potency for both enoxaparin and fondaparinux.
- Similar dose-response slopes in hip or knee prophylaxis, with different event rates on placebo.

Fondaparinux and enoxaparin show a consistent dose-related reduction in DVT prophylaxis for orthopedic surgeries, but not in ACS.



Event probability vs. dose for fondaparinux (left) and lovenox (right). DVT events are venous thromboembolism events. ACS events are a composite of death, non-fatal MI, and recurrent ischemia. The fitted curve is a logistic model with a separate intercept for hip (36%) or knee surgeries (70%), and separate slopes for fondaparinux (-1.0) and lovenox (-0.030) suggesting a 30-fold potency advantage in favor of fondaparinux.

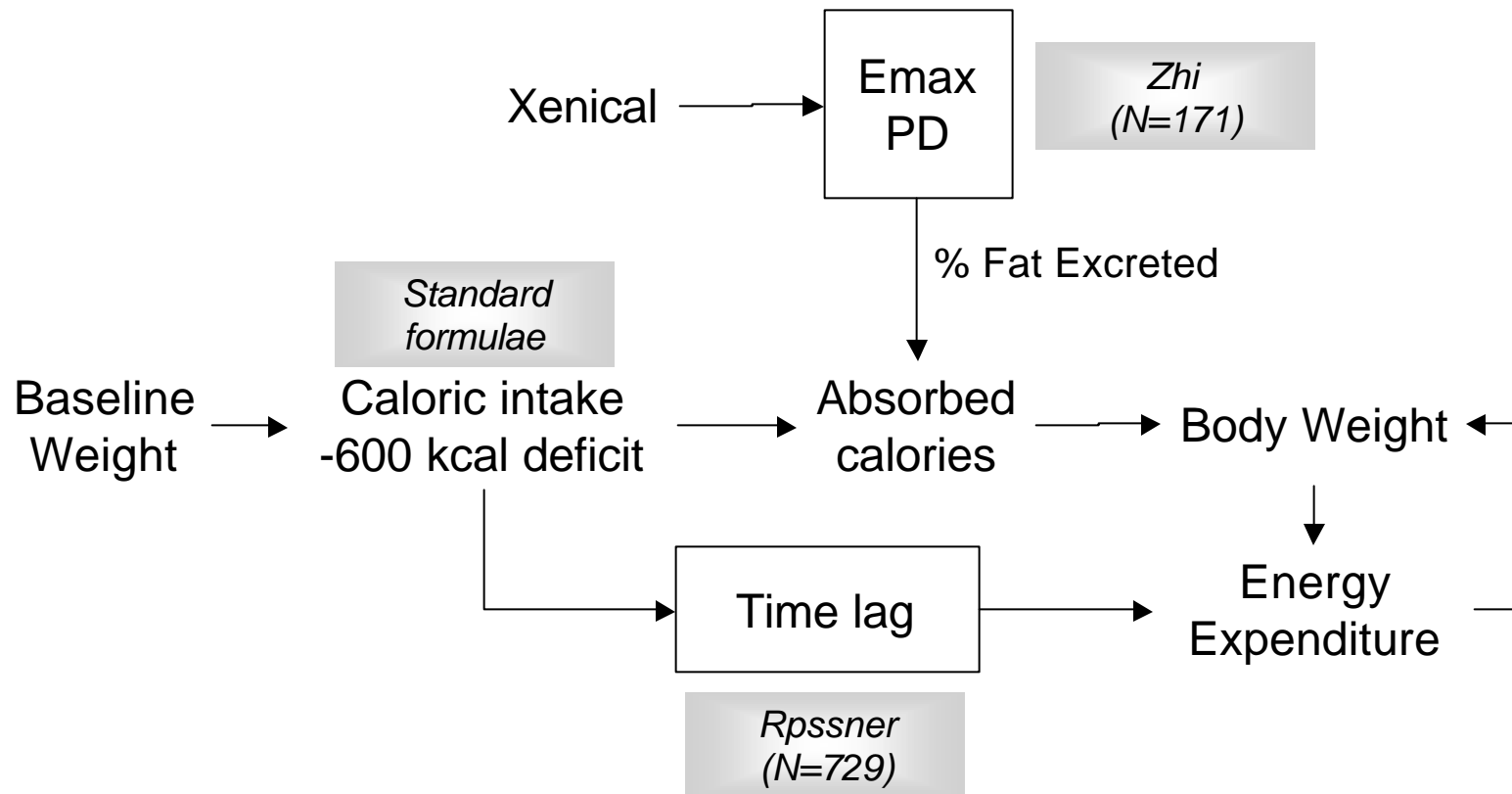
The modeling suggests possible Phase I/II activities for a new Factor Xa inhibitor.

- The model for anti-thrombotics
 - Arixtra is 30-fold more potent than Lovenox in DVT in prophylaxis for hip/knee surgery
 - No clear dose-response for ACS
- Development plans for a new factor Xa inhibitor
 - Phase I: Estimate relative potency to Arixtra (or Lovenox?), based on PKPD relationship. Requires pharmacodynamic calibration studies.
 - Phase II: Small dose-finding DVT study at Arixtra-like doses, to obtain max dose without increased bleeds.
 - Further modeling: Effect of dose-time.
 - Further investigation for dose-selection in ACS
 - Could very low doses still be effective?
 - Could frequent endpoint (recurrent ischemia) be insensitive to factor Xa inhibitors?

Orlistat inhibits dietary fat absorption and produces sustained weight loss over 2-years.

- Obesity is a prevalent major cardiovascular risk factor.
 - Conventional interventions such as diet and exercise have limited success in producing sustained weight loss.
 - Sibutramine and orlistat are approved anti-obesity drugs which reduce body weight by 5-10 kg over 1 year.
- Orlistat
 - Lipase inhibitor that blocks uptake of up to 30% of dietary fat.
 - When coupled with a low calorie diet, orlistat has maintained weight loss over 2 years relative to placebo. [Rossner et al. 2003]
 - 0, 60, 120 mg TID
 - 600 kcal deficit from estimated energy requirements, 30% in fat
 - Increase in caloric intake in year 2, if extensive weight loss in the last 3 months of year 1.
- Application
 - Planning for a new anti-obesity drug

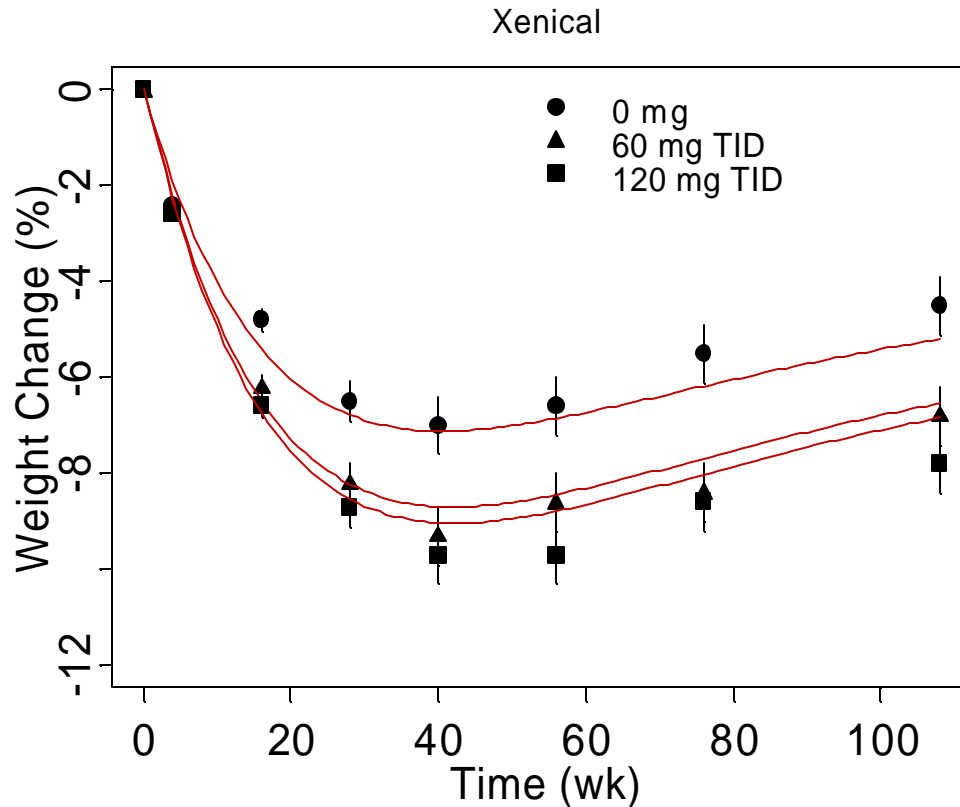
The obesity model accounts for the effect of changing body weight on energy expenditure, and assumes a delayed effect of decreased caloric intake on energy expenditure.



Key Assumption

- Energy expenditure is decreased in proportion to the reduction in caloric intake.

The model describes the rapid fall and gradual weight regain over two years.



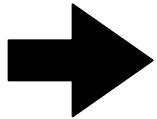
Mean percent weight change (SE) vs. time data are taken from the publication of Rossner et al. 2003. The curves represent the fit of the model at three doses. The estimated model parameters are as follows: $t_{1/2}$ of effect of caloric intake on energy expenditure is 15 weeks; proportionality factor relating change in energy expenditure to change in caloric intake is 0.85.

The model can be used to anticipate the effects of other types of anti-obesity drugs, such as appetite suppressants.

- The model for anti-obesity
 - The weight loss and regain for diet w/orlistat can be described by standard energy balance considerations, and an effect of the reduction in caloric intake on energy expenditure.
 - The model can be used to anticipate the results of diet, exercise, regimen, and alternate mechanisms of action.
- Development plans for a new anti-obesity drug
 - Sustained weight-loss may depend on inhibiting the link between caloric intake and energy expenditure.
 - Quantify this parameter in indirect calorimetry studies.

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Integrating information with models is valuable in clinical development:

- Capture data in a consistent intellectual framework
- Understand uncertainty in the pathway to the clinical endpoint
- Focus development strategy prior to Phase I and continuing throughout development
- Focus where more detailed experiments and models are needed.