Challenges and Opportunities for QSP in Drug Development and Regulatory Evaluation

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UF | CENTER FOR PHARMACOMETRICS & SYSTEMS PHARMACOLOGY

Three Objectives for Today's Talk

- Provide a brief overview of history & current state of MIDD approaches and their use in drug development & regulatory evaluation.
- Provide a perspective on current barriers to routine application of QSP models in drug development & regulatory evaluation
- Provide a perspective on what we should do next

Genesis of Terminology, Seminal Initiatives & Current State

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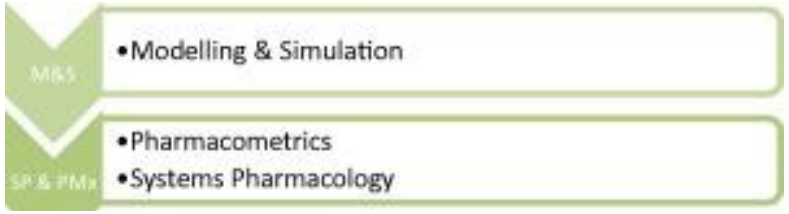
1990s



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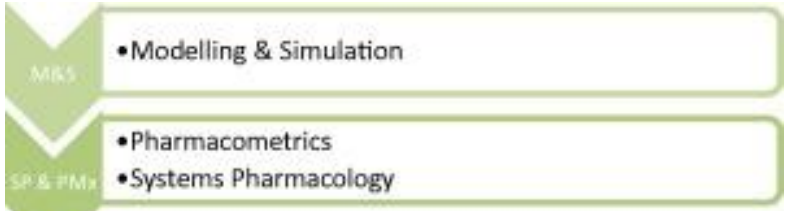

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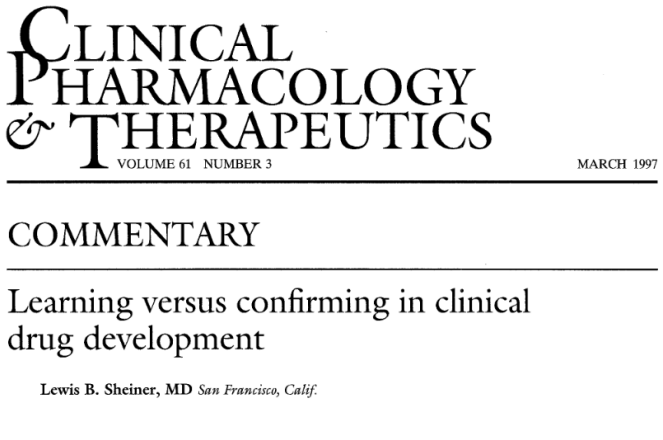
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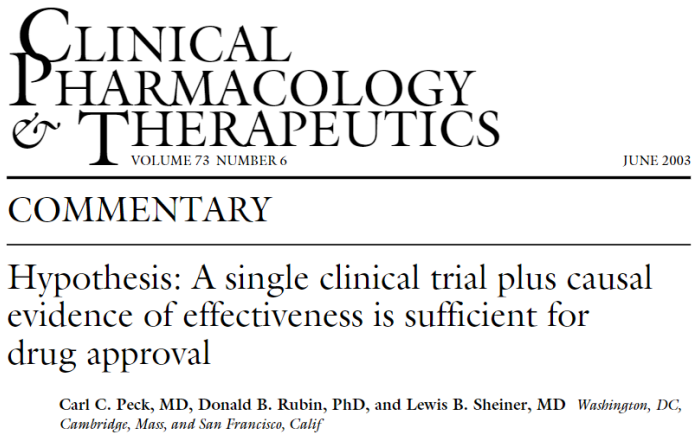
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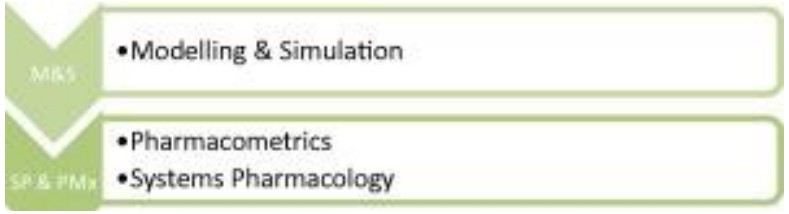

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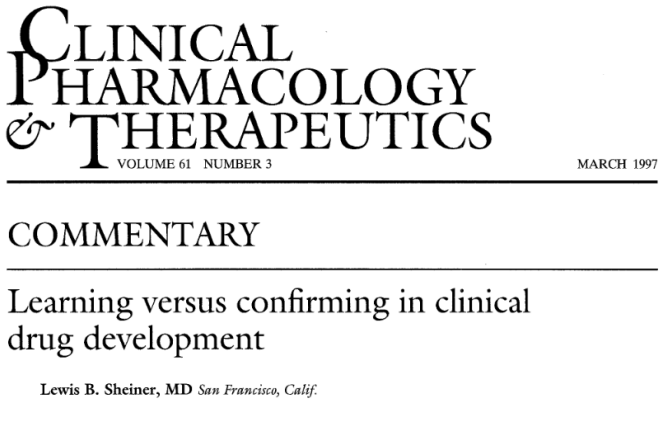
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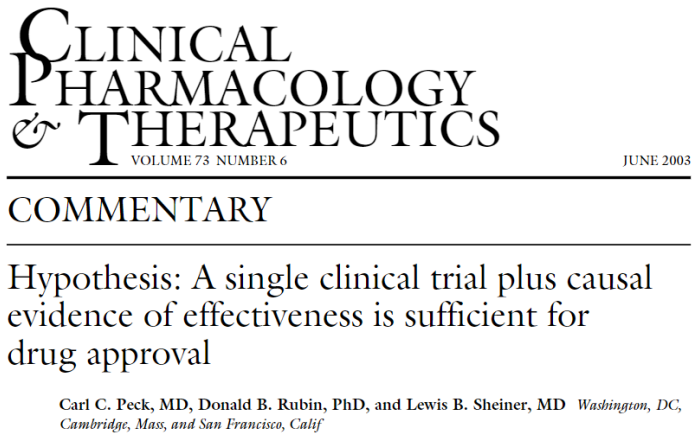
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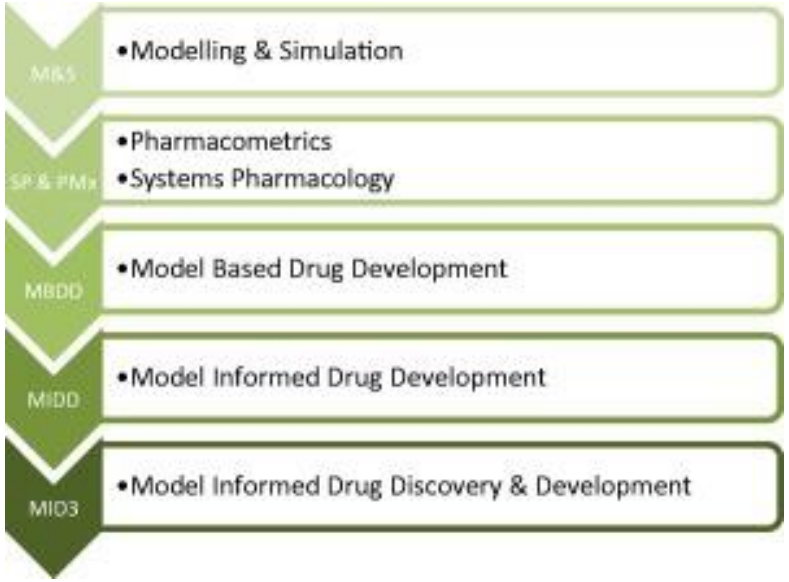

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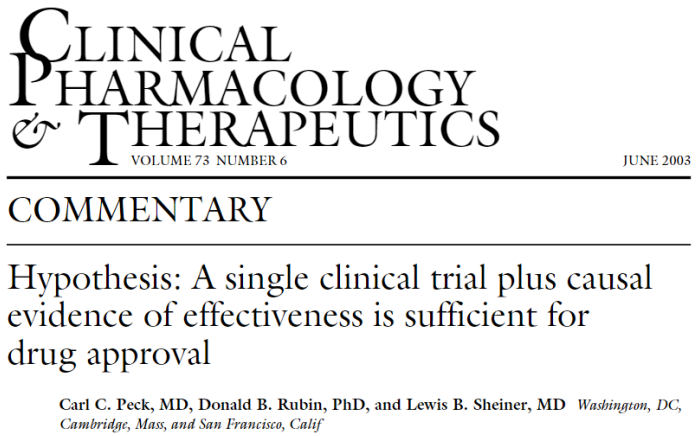
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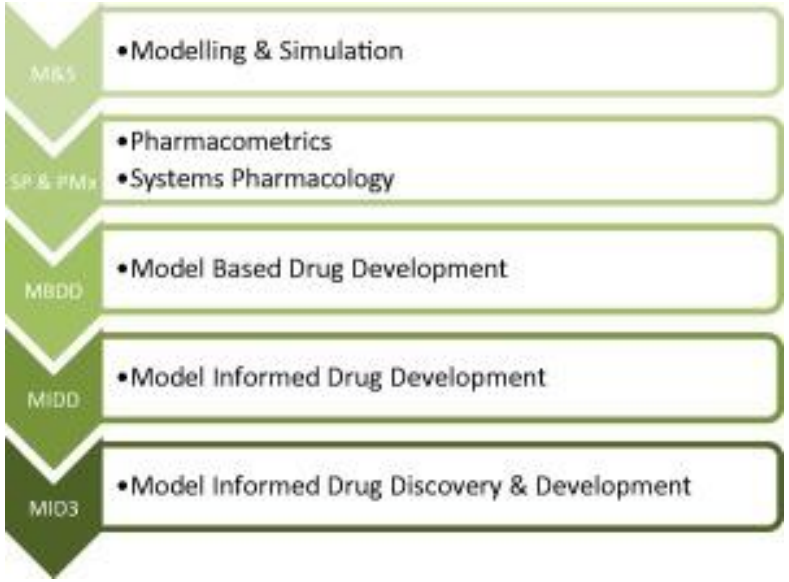

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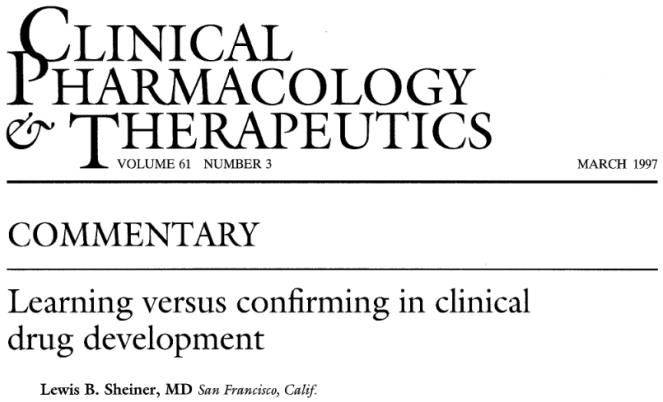
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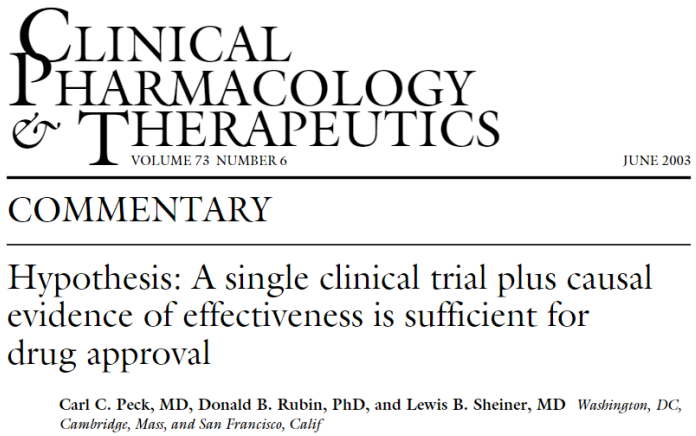
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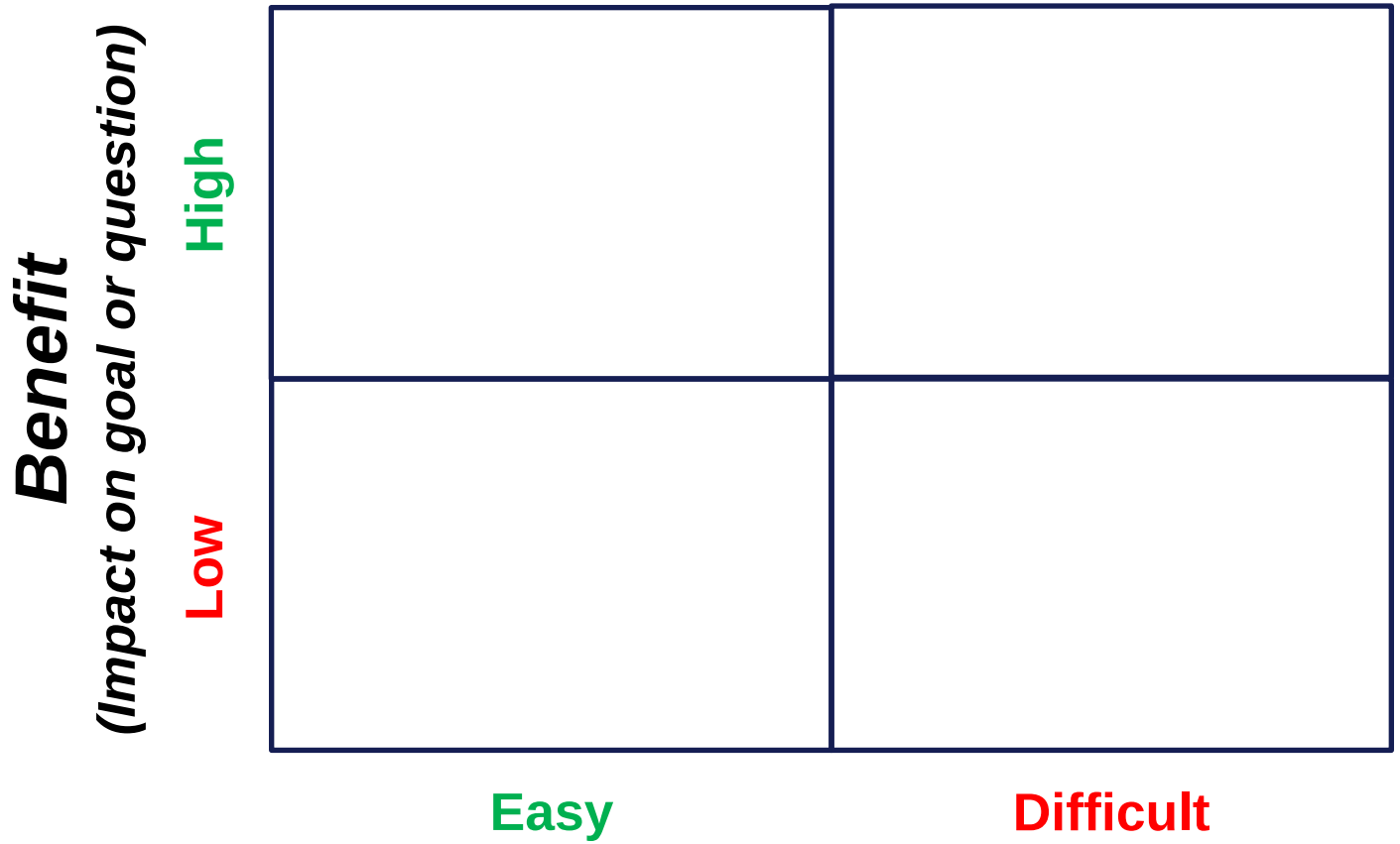
Value Proposition vs. Prioritization of MIDD Approaches: A 2023 Snapshot



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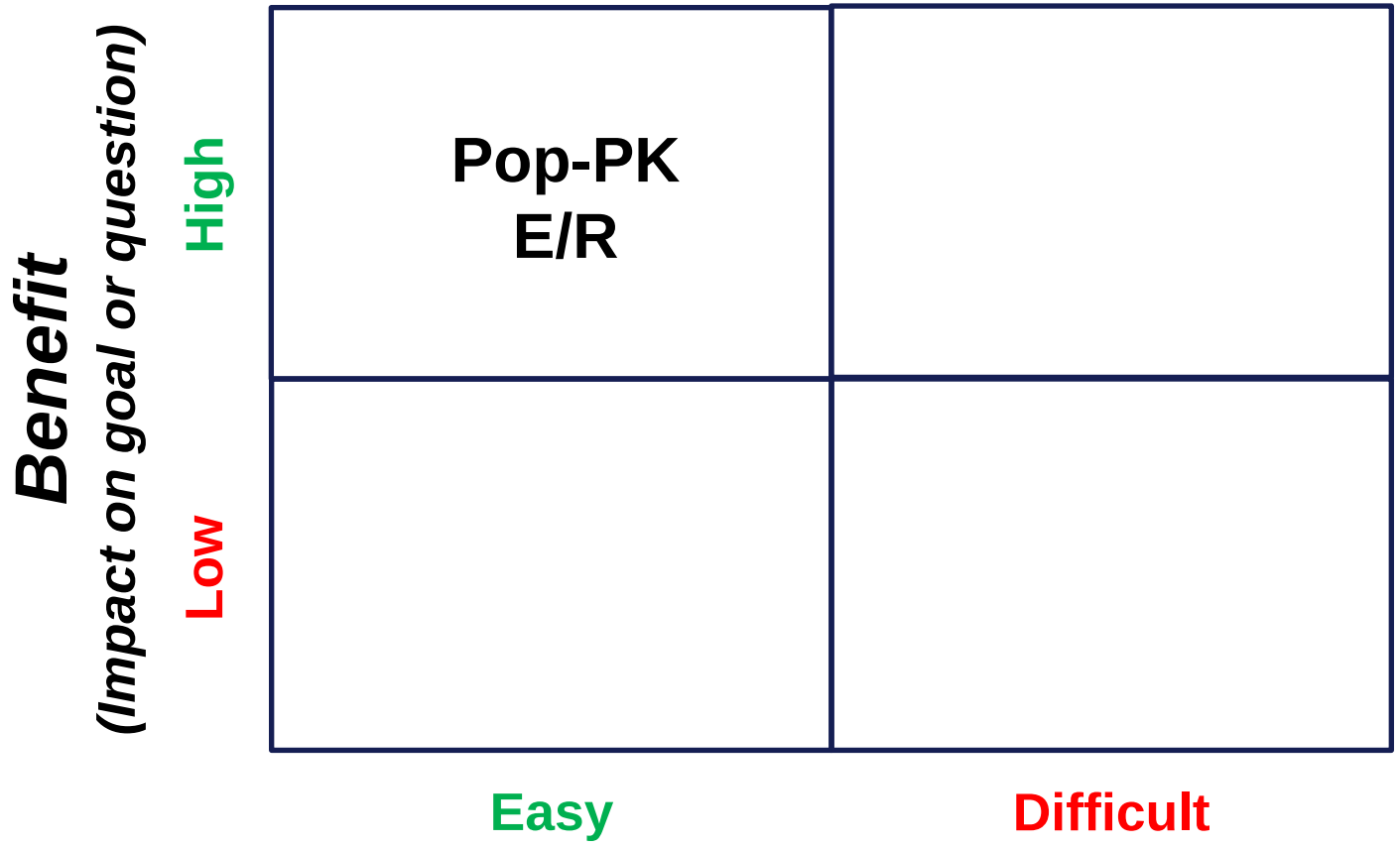

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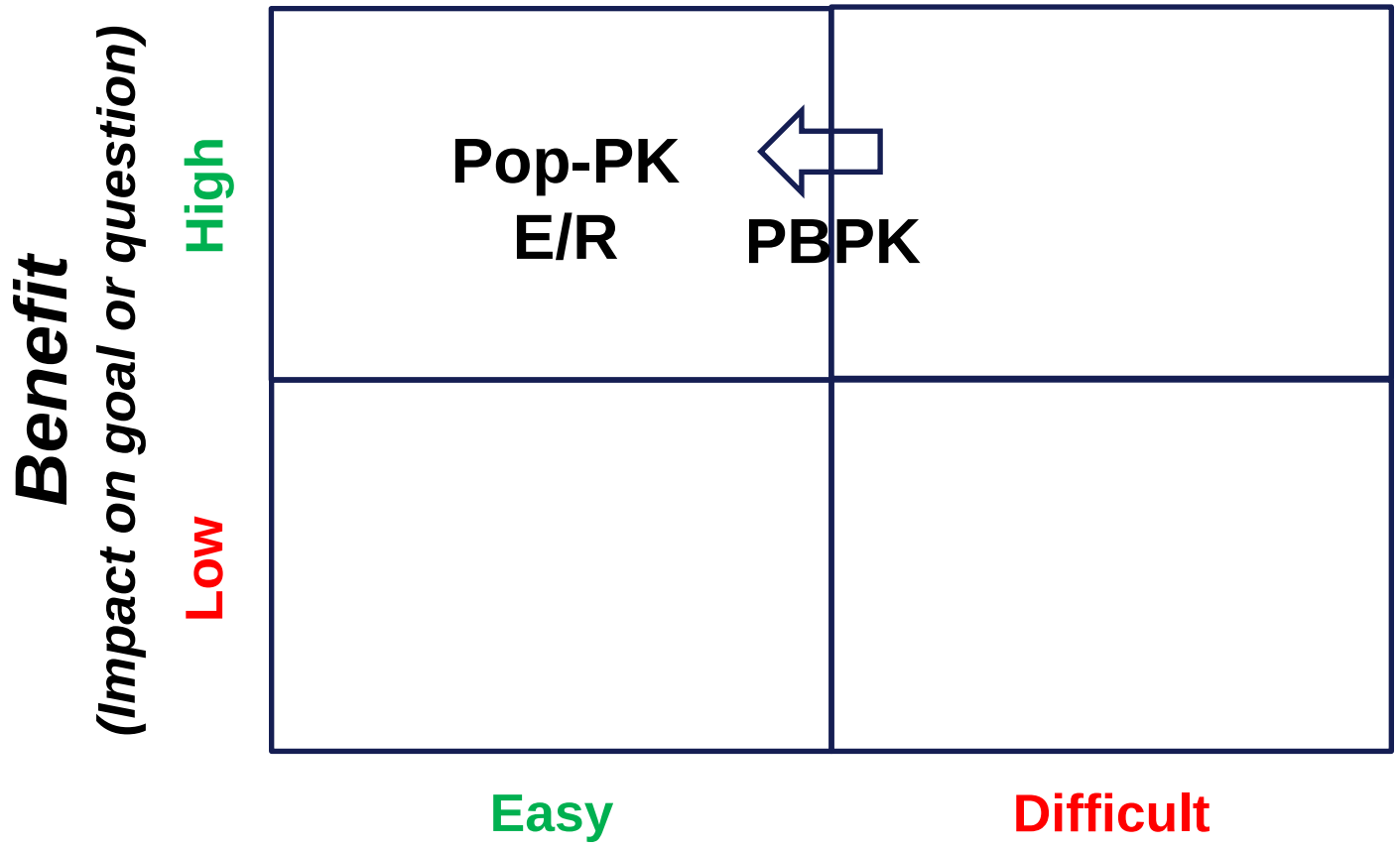

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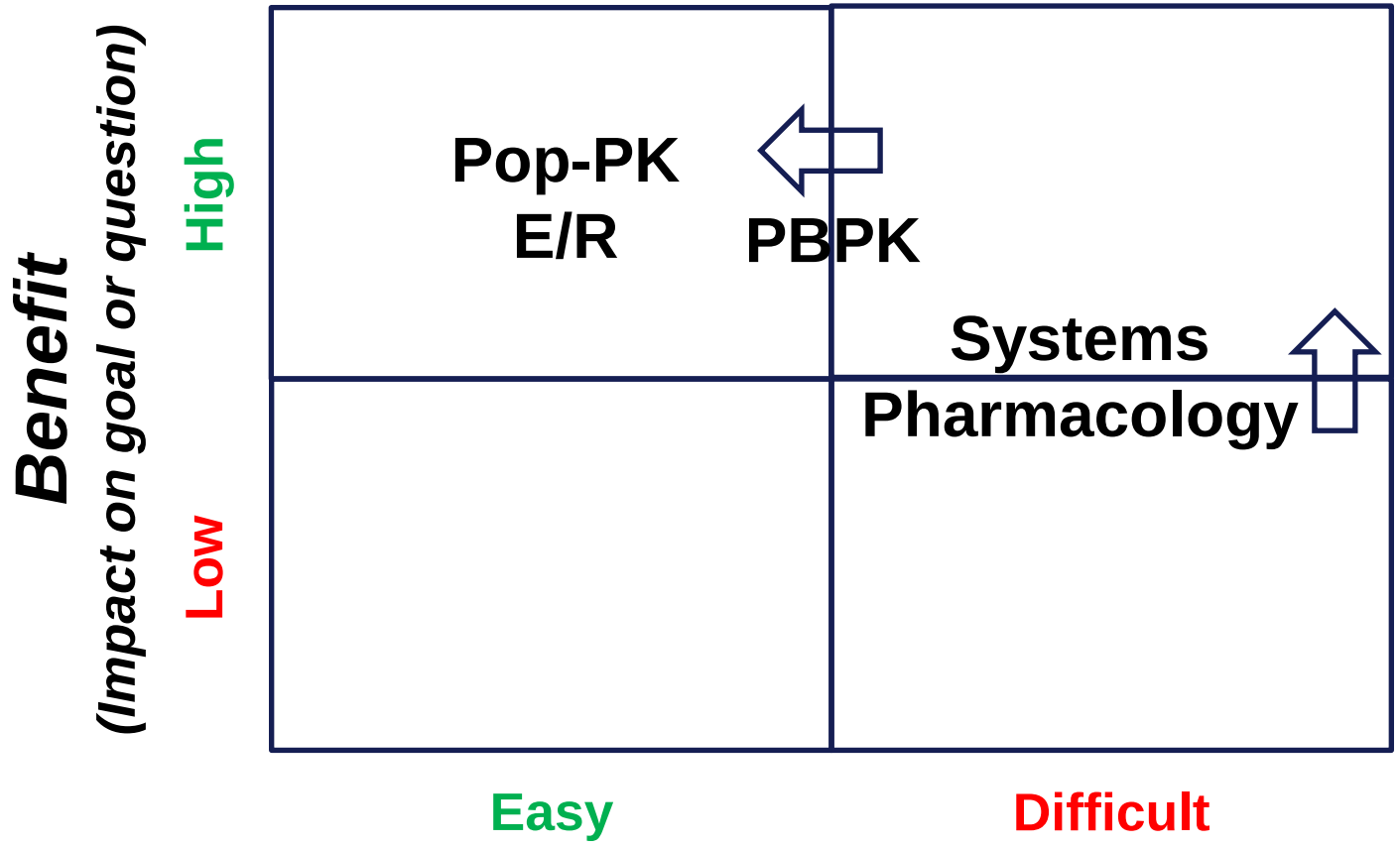

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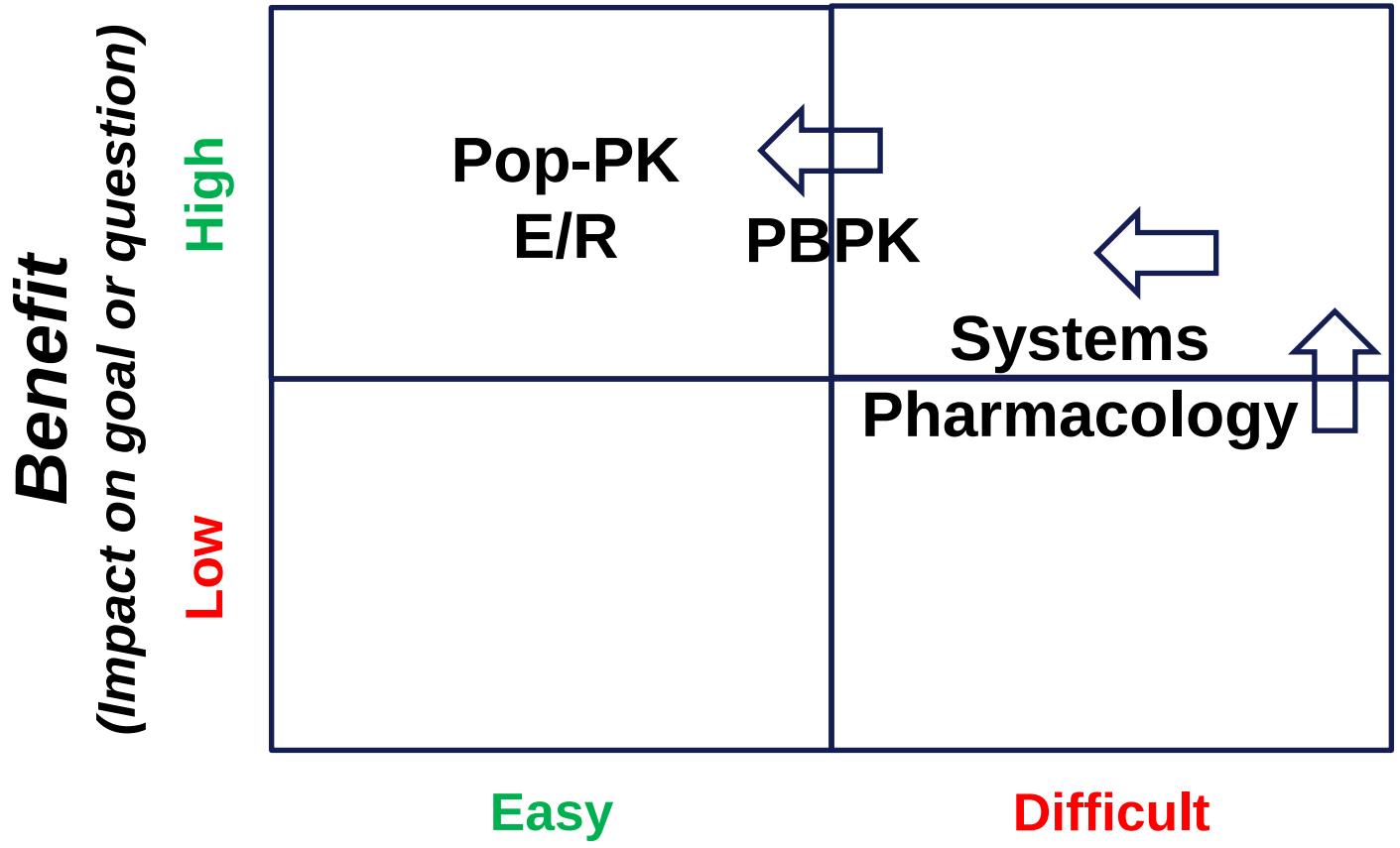
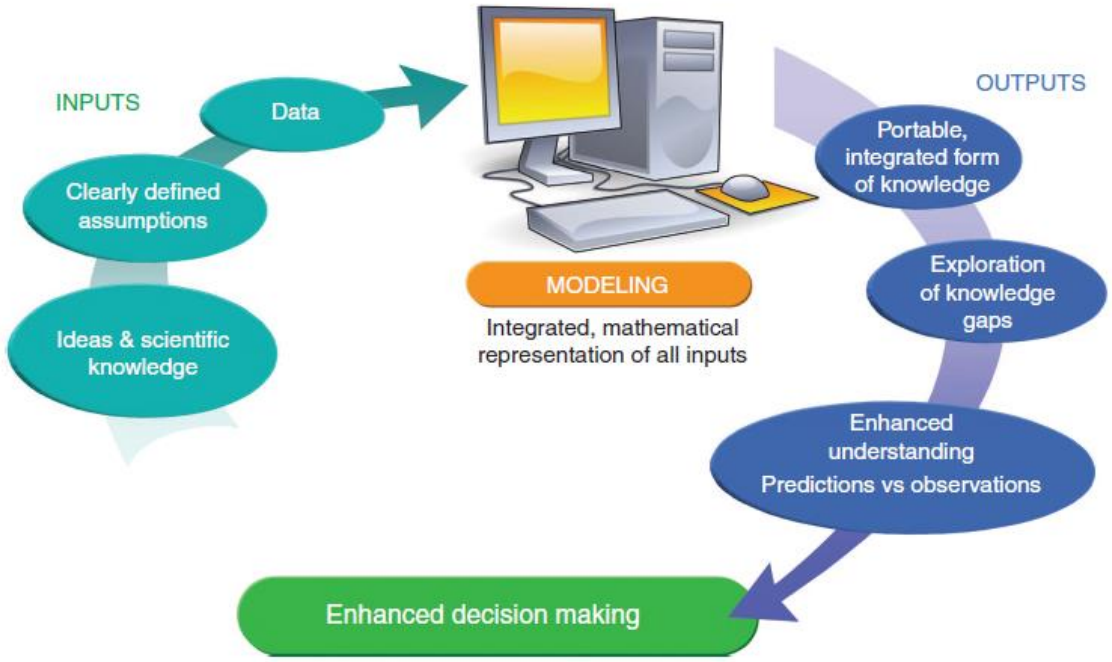


Current Barriers to Routine Application of QSP Models in Drug Development & Regulatory Evaluation: A Personal Perspective

- Perception matters
  - ✓ PBPK models are:
    - User-friendly black boxes
    - Click here, click there, click everywhere
  - ✓ QSP are:
    - Structurally complex
    - Require a lot of data
    - Have challenges with scaling to long-term endpoints/outcomes
    - Everyone has their own favorite model
- Modelers cannot seem to agree on tools, standards, and terminology so how are other stakeholders supposed to buy in?

Let's Go Back To The Idea Behind Modeling & Simulation



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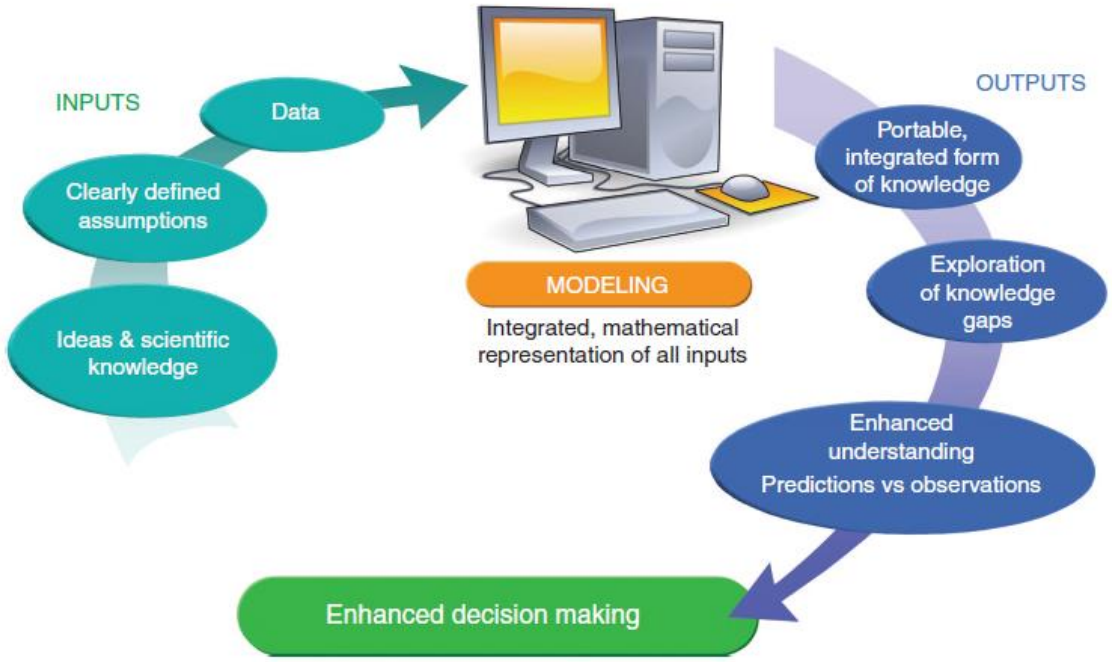

Three key questions that define the context of modeling and simulation:

1) What do we want to know?
2) How certain do we need to be?
3) What are we willing to assume?

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What Do We Want to Know?

Selecting the Right Tools for the Right Question

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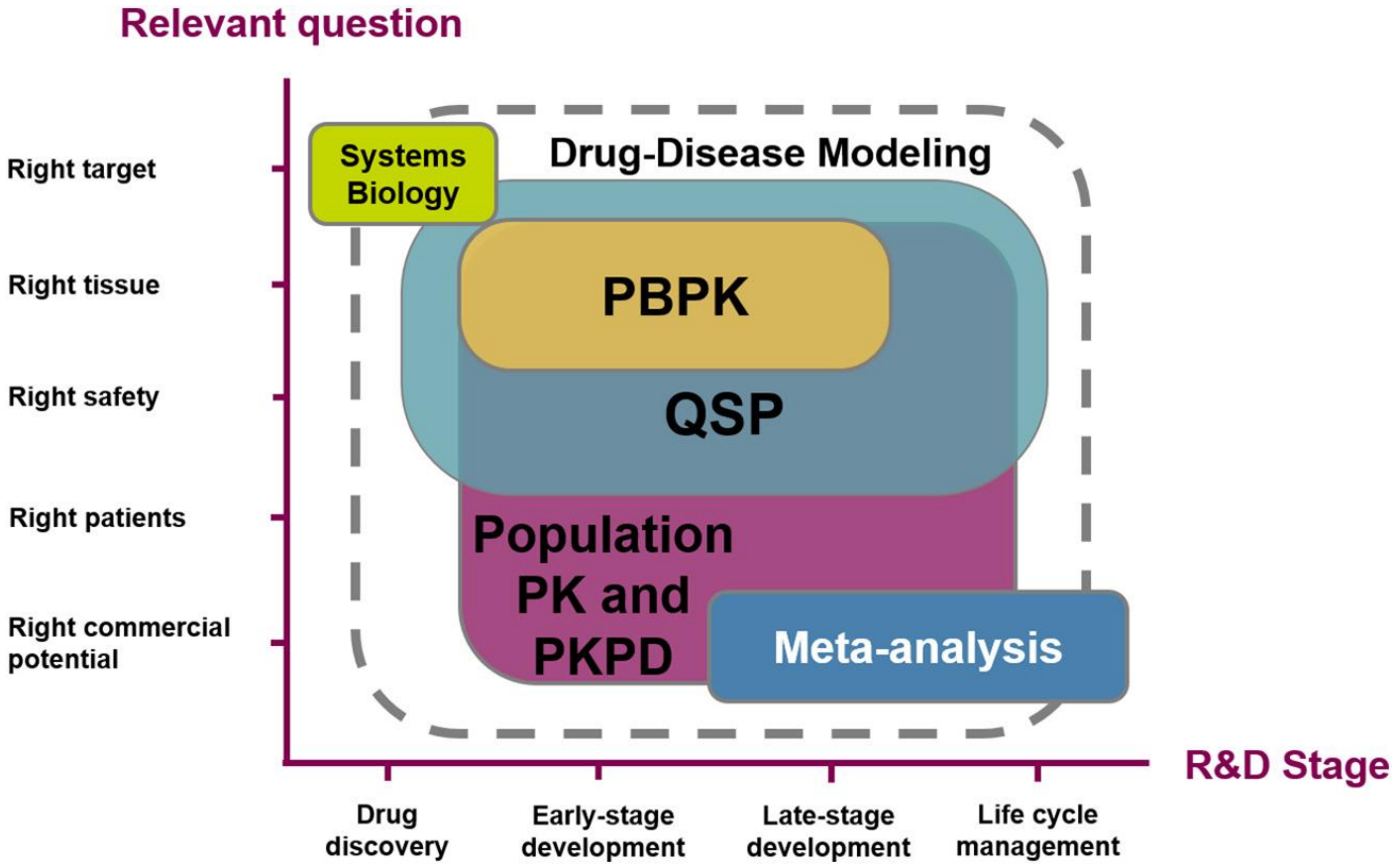

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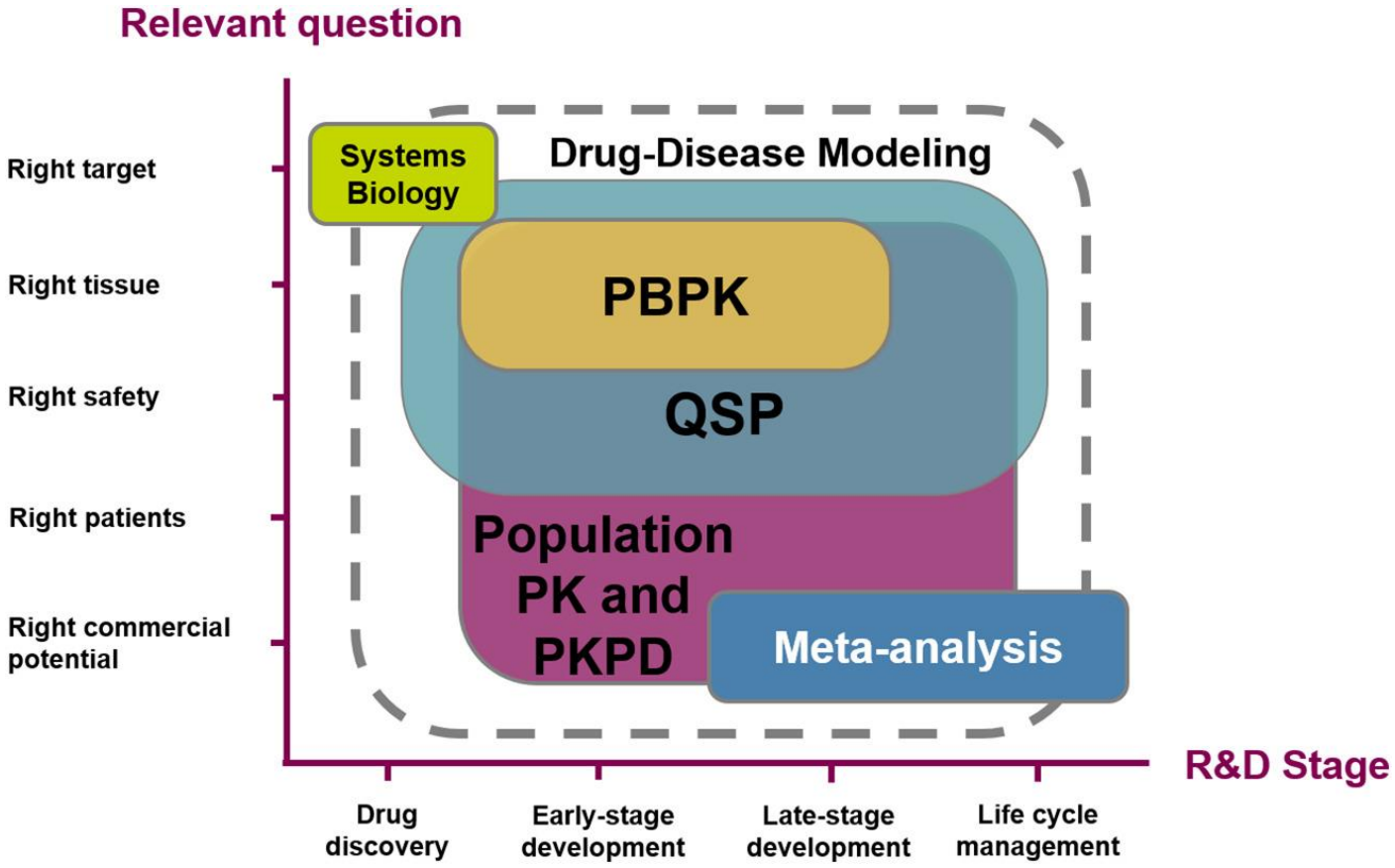

It's a modeling continuum, not a modeling competition!

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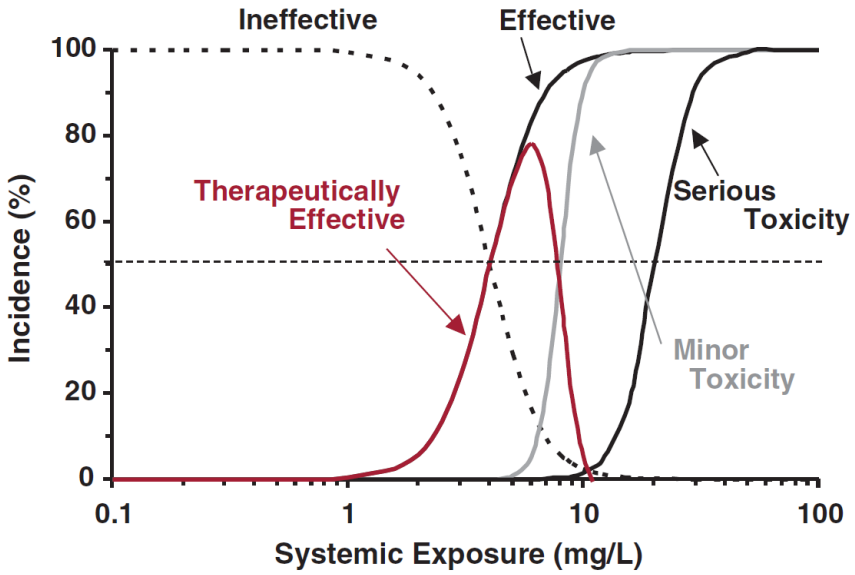
How Certain Do We Need to Be?

Impact of Variability in Exposure-Response



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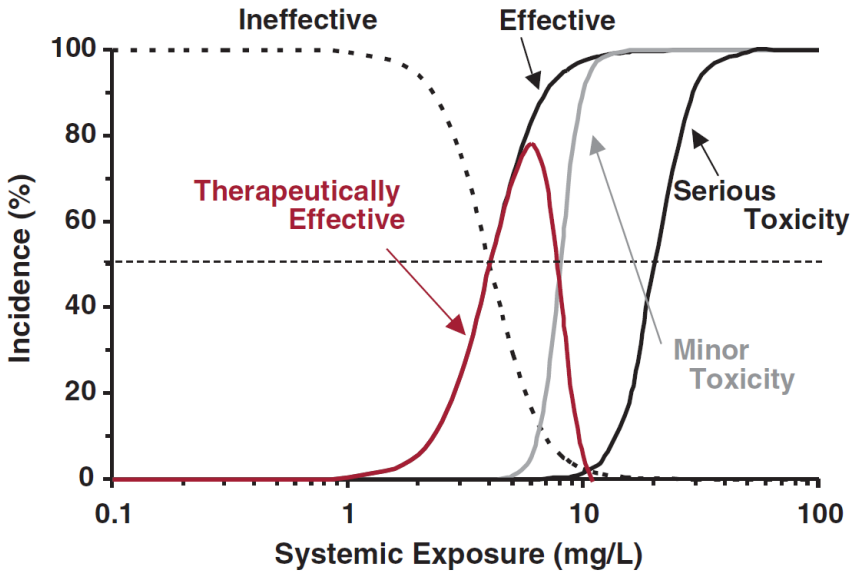

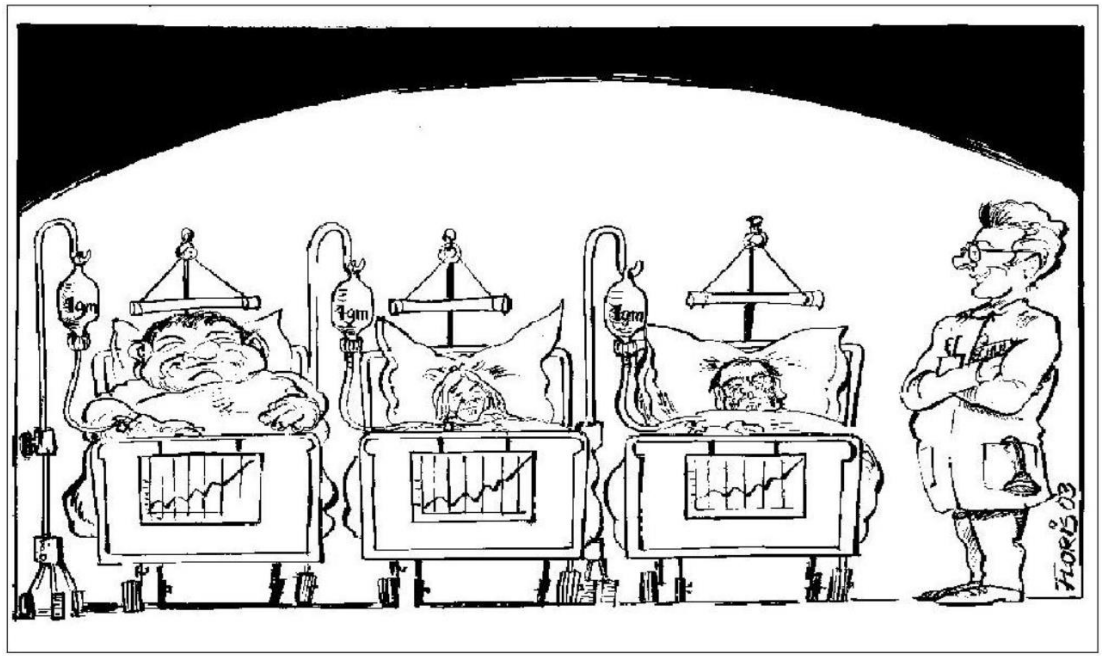

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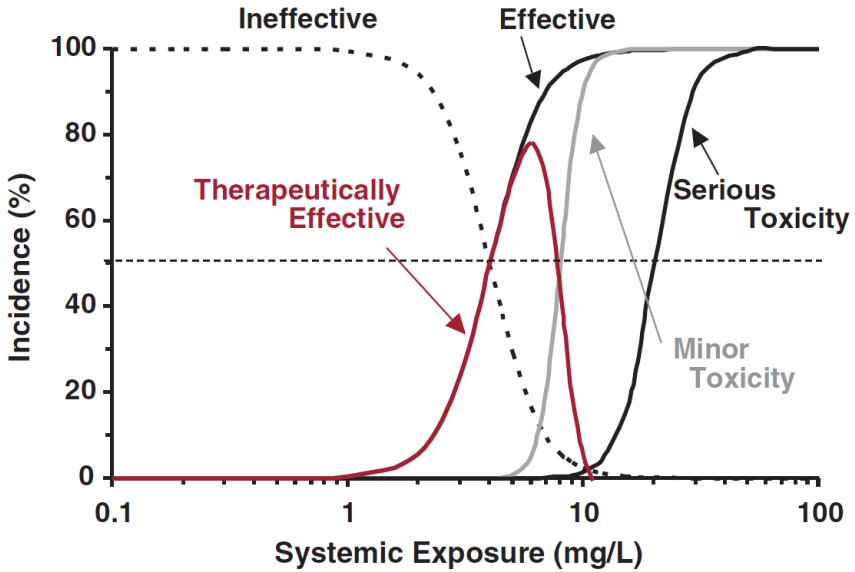
- Gender, Race
- Drug-drug interactions
- Environmental factors
- Concomitant diseases
- Placebo effect
- Drug receptor or enzyme polymorphisms
- Tolerance, tachyphylaxis



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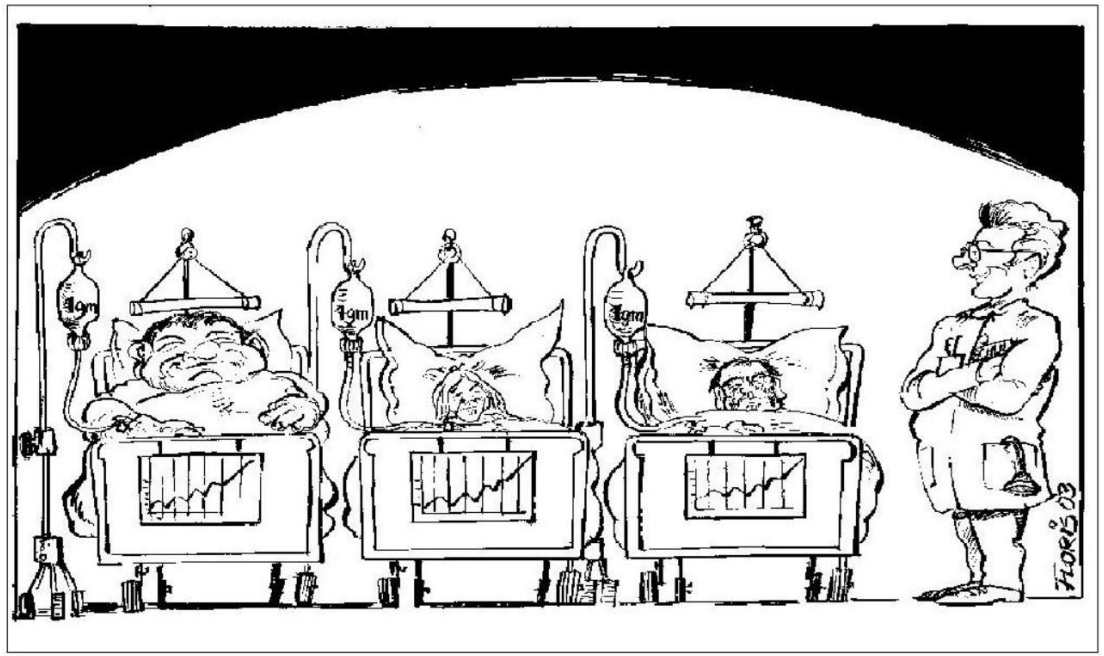

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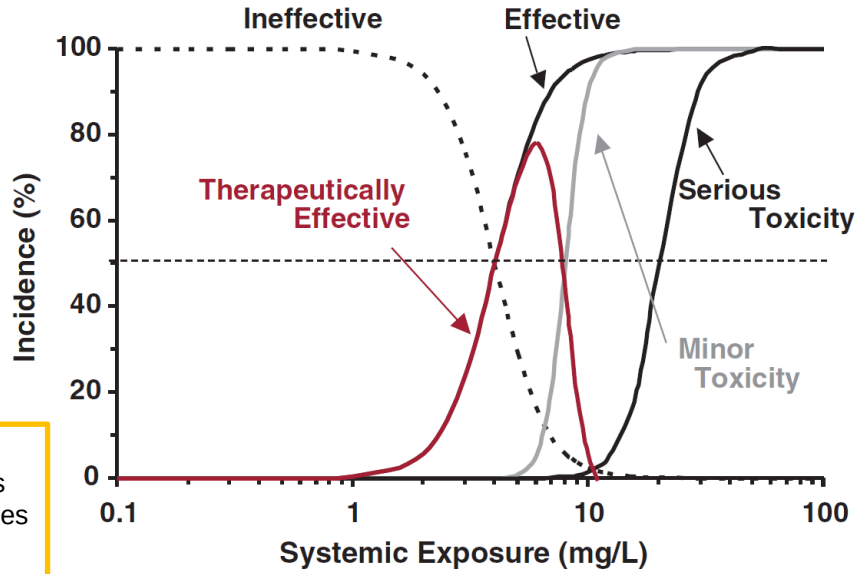
- Uncertainty in disease pathways
- Monogenic vs. polygenic diseases
- Endogenous (e.g., receptor, protein) vs. exogenous (e.g., pathogens) targets



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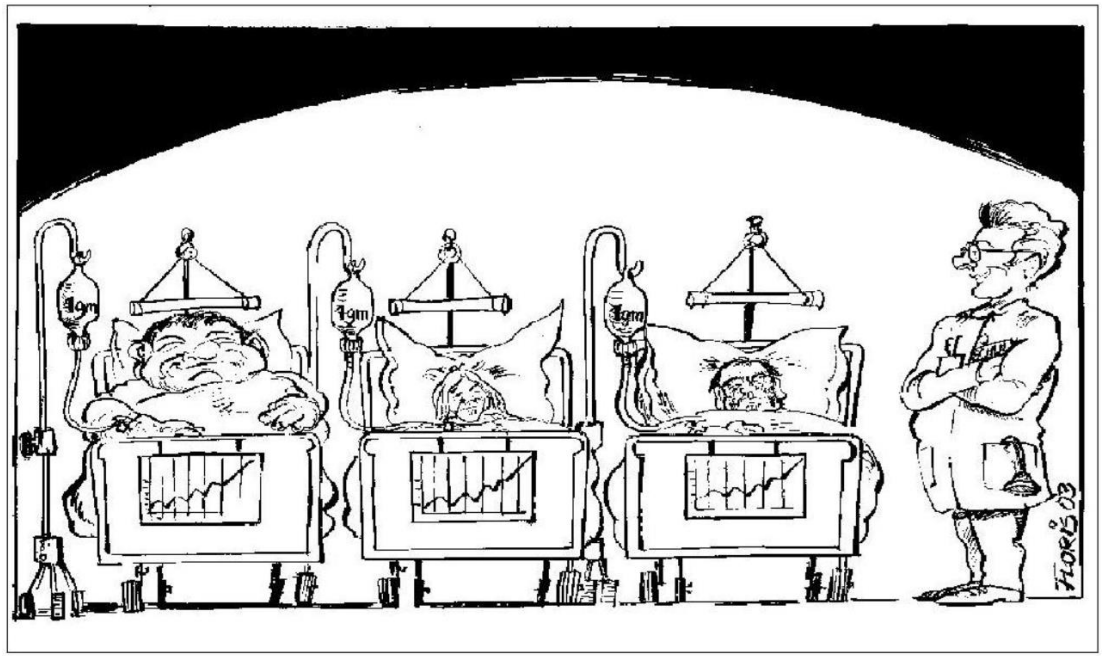

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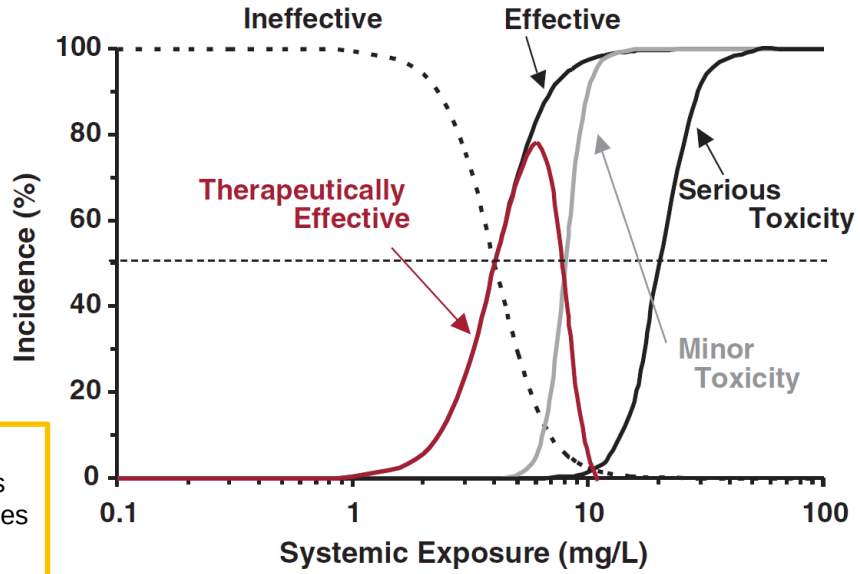

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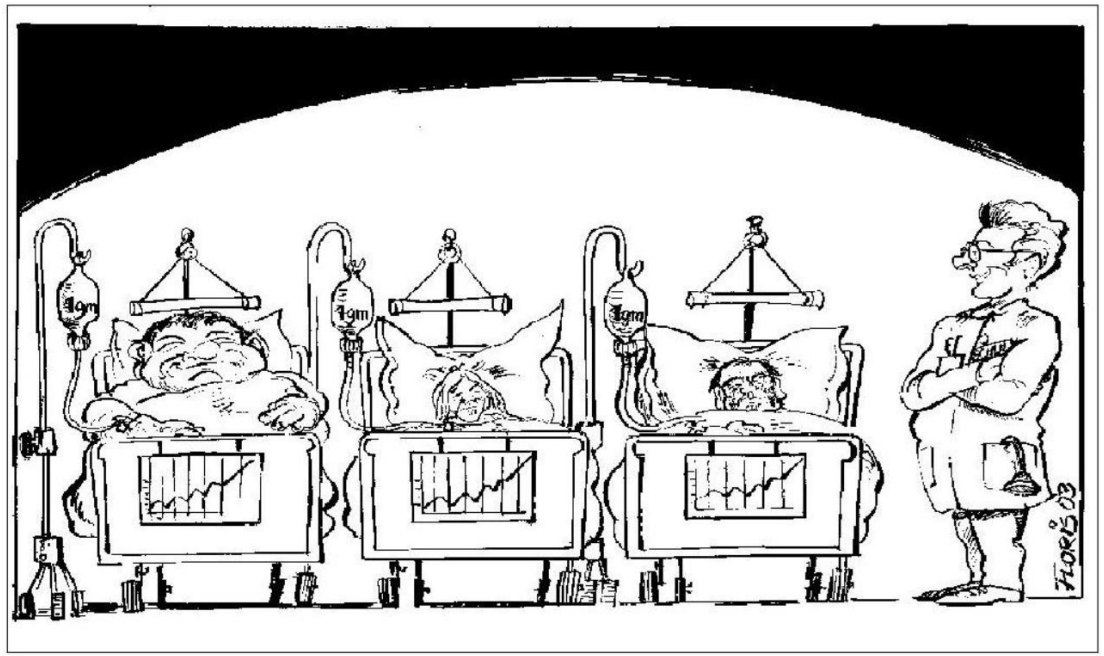

→ Opportunity for QSP models:
- Preclinical-clinical translation (e.g., mapping complex physiological pathways, identifying targets for drug prioritization)
- Identification of optimal combination (chemo)therapy
- Establish virtual twins for rare diseases
- Understand biomarker dynamics → inform clinical trial design

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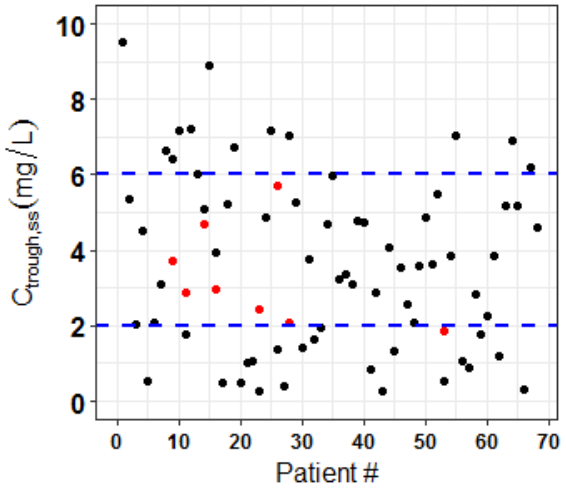
The Importance of Integrating PK & PD: A Voriconazole Case Example

Variability in PK



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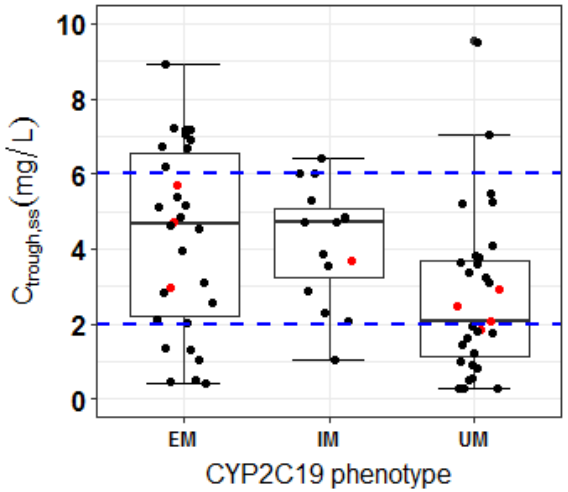

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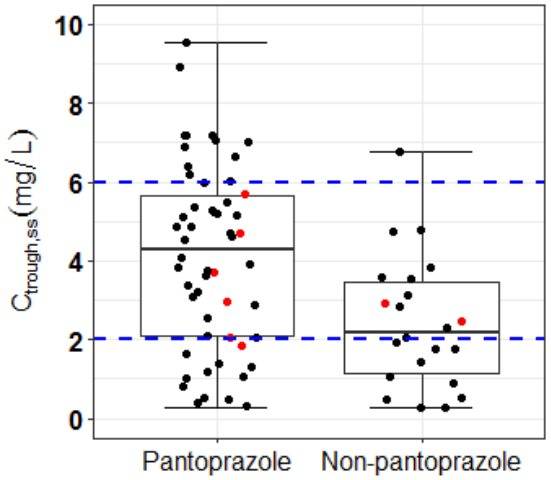

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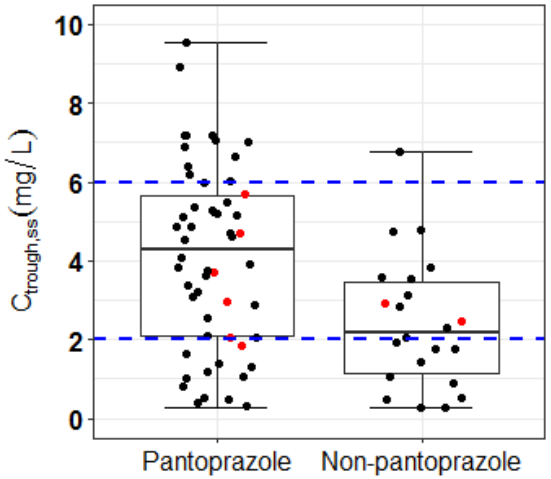
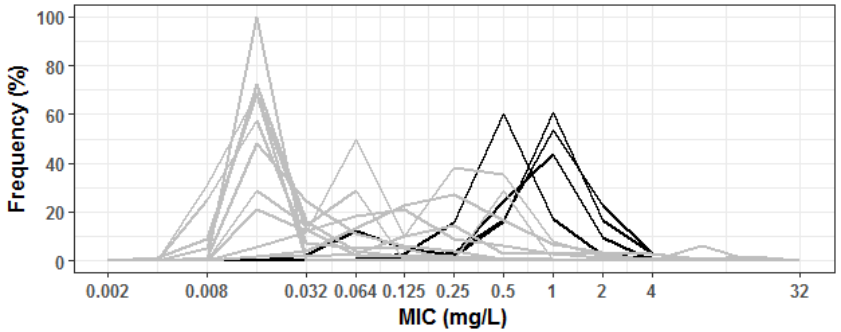


Variability in PD (exogenous target)



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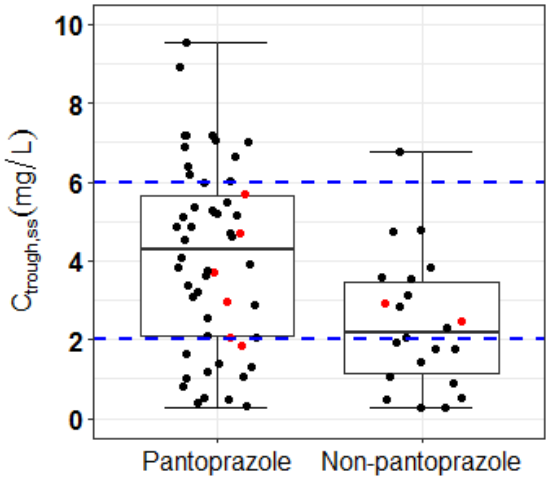
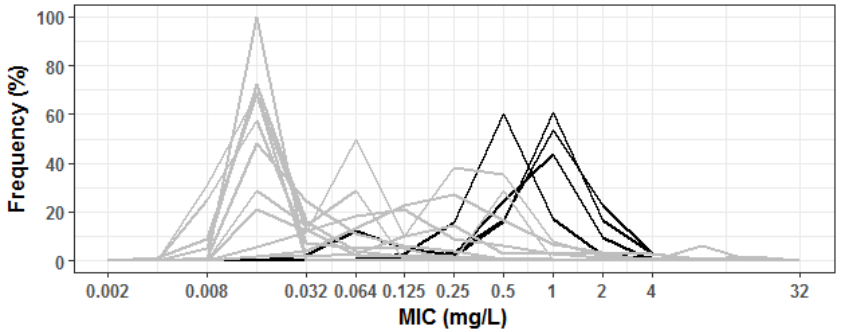
The Importance of Integrating PK & PD: A Voriconazole Case Example

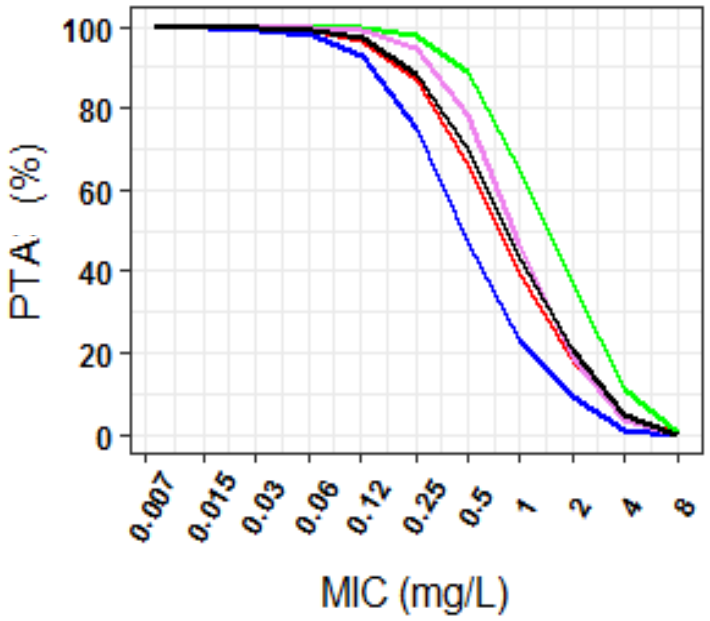
Variability in PK



Variability in PD (exogenous target)



Probability of Achieving C_{trough}/MIC>2



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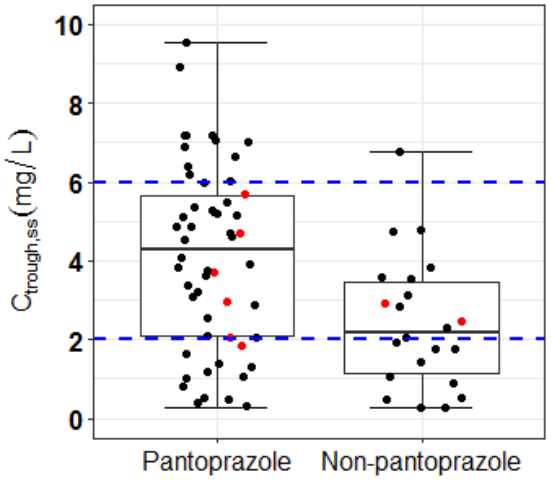

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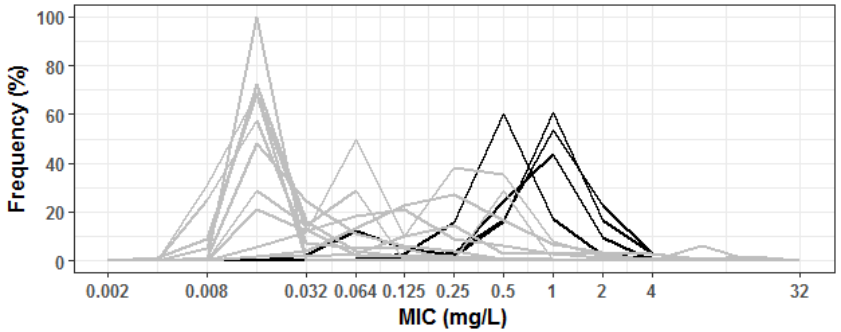

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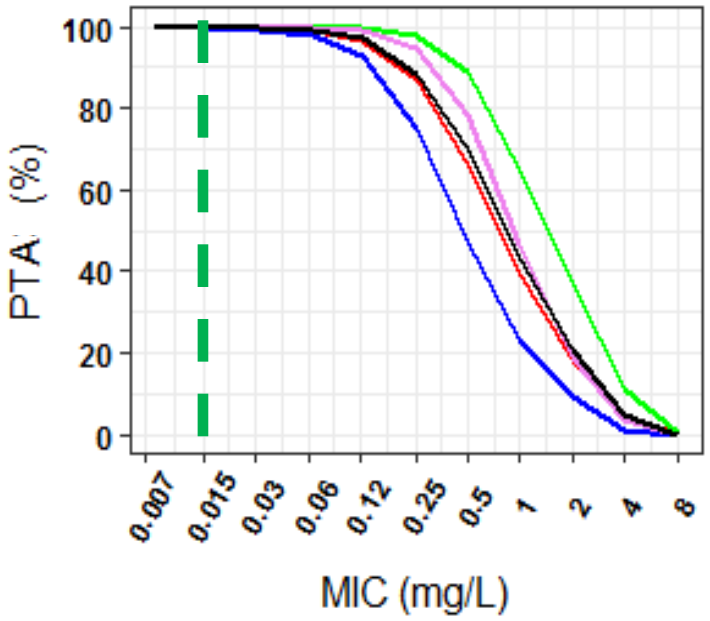

High susceptibility, MIC = 0.015 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	~ 100
EM/IM non-pantoprazole	~ 100
UM pantoprazole	~ 100
EM/IM pantoprazole	~ 100
Overall	~ 100

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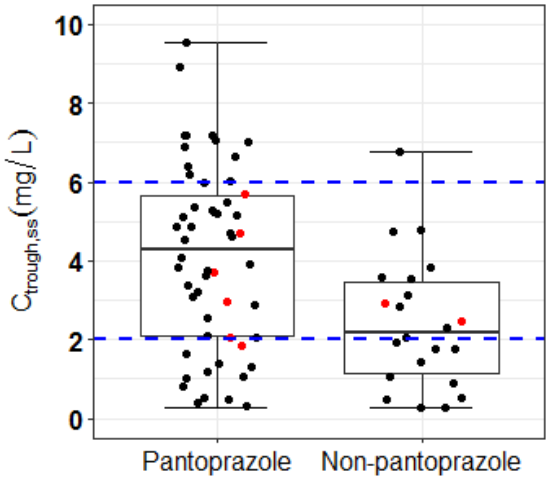

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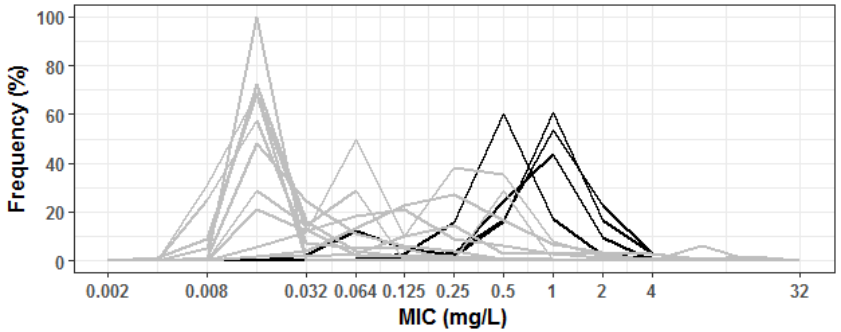

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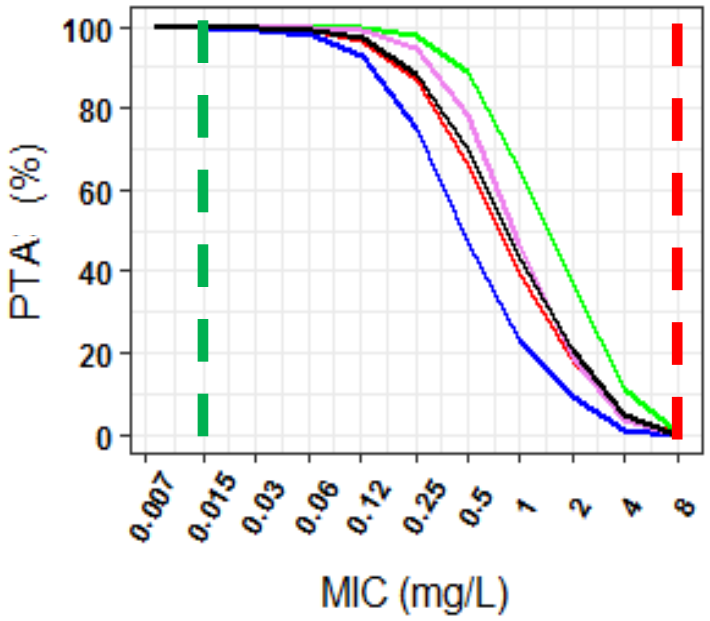

Low susceptibility, MIC = 8 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	<5
EM/IM non-pantoprazole	<5
UM pantoprazole	<5
EM/IM pantoprazole	<5
Overall	<5

High susceptibility, MIC = 0.015 mg/L

Phenotype	PTA (%)
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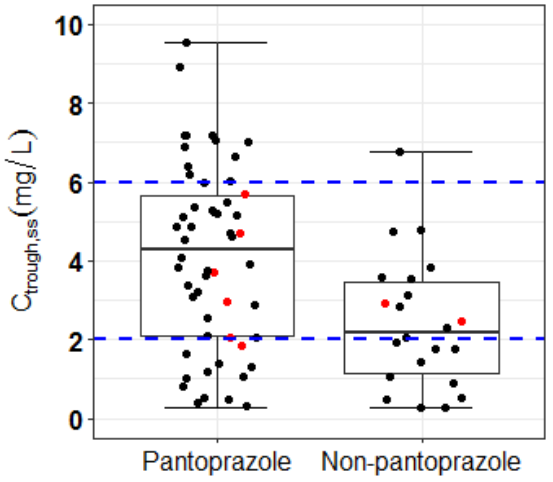

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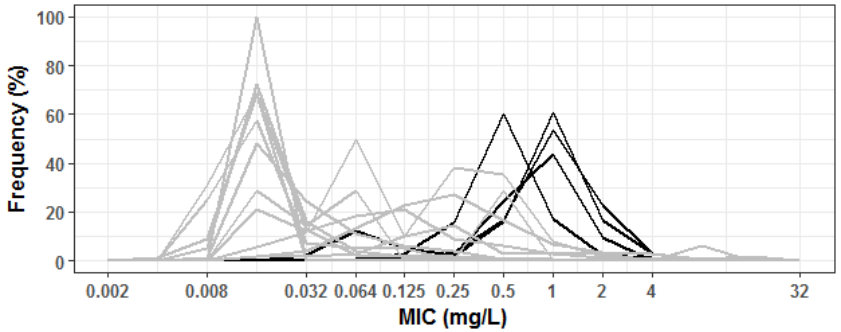

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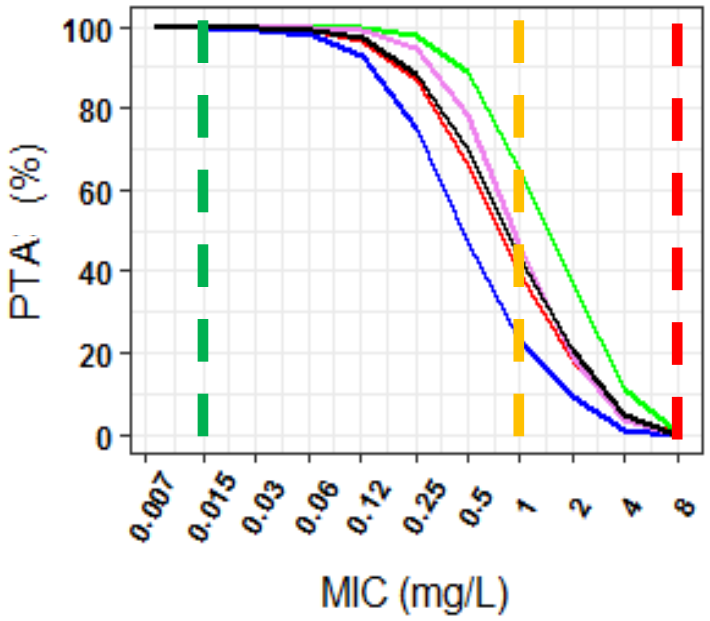

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Phenotype	PTA (%)
UM non-pantoprazole	<5
EM/IM non-pantoprazole	<5
UM pantoprazole	<5
EM/IM pantoprazole	<5
Overall	<5

Intermediate susceptibility, MIC = 1 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	23.2
EM/IM non-pantoprazole	39.9
UM pantoprazole	46.5
EM/IM pantoprazole	64.9
Overall	43.6

High susceptibility, MIC = 0.015 mg/L

Phenotype	PTA (%)
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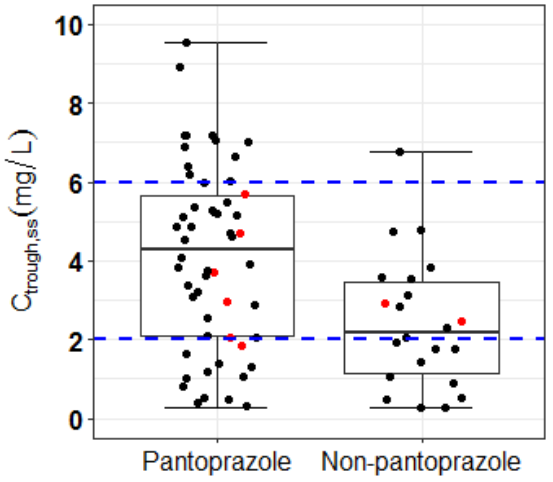

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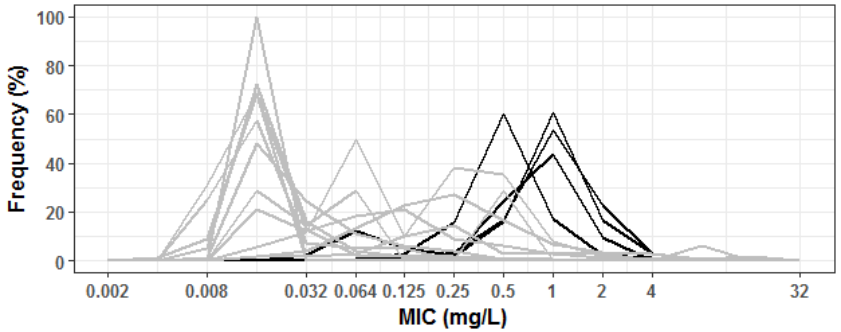

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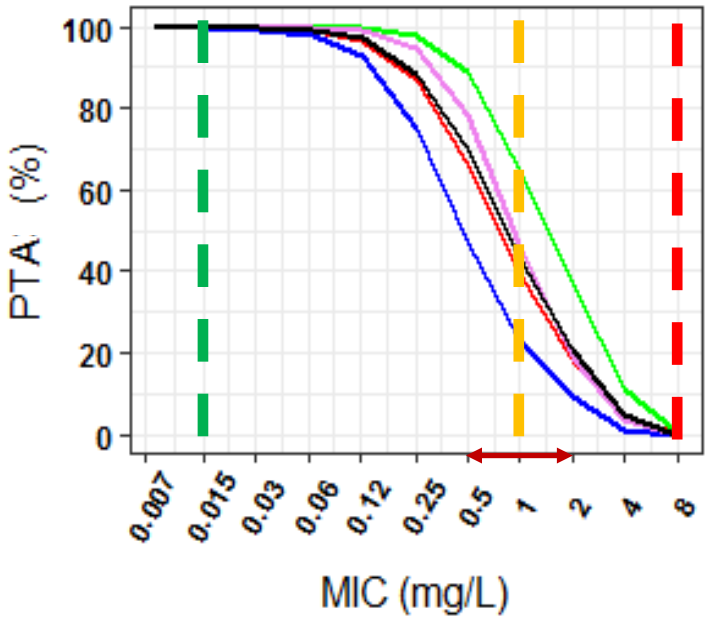

Measurement error (2-fold increments in MIC determination)

Low susceptibility, MIC = 8 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	<5
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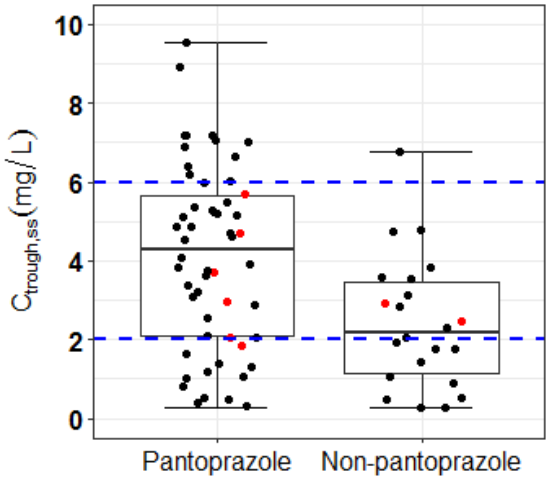

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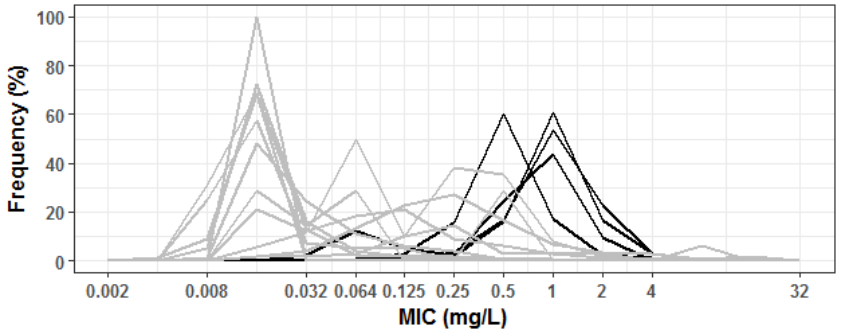

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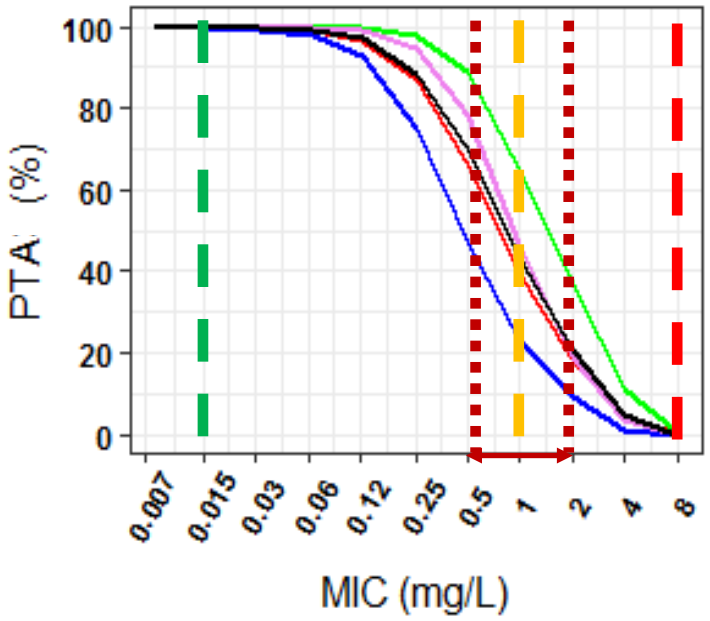

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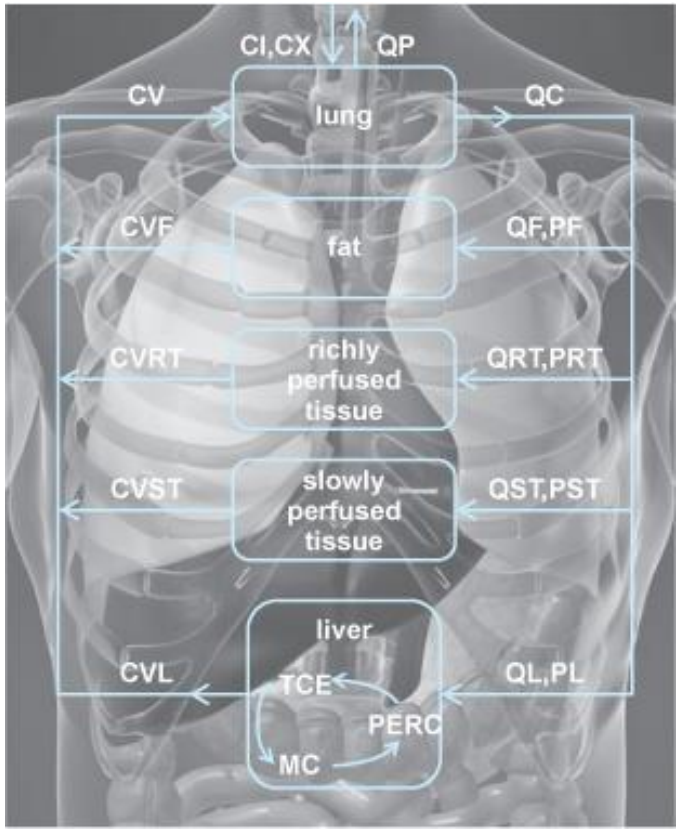
What Are We Willing to Assume?

Impact of Research Question on Model Complexity



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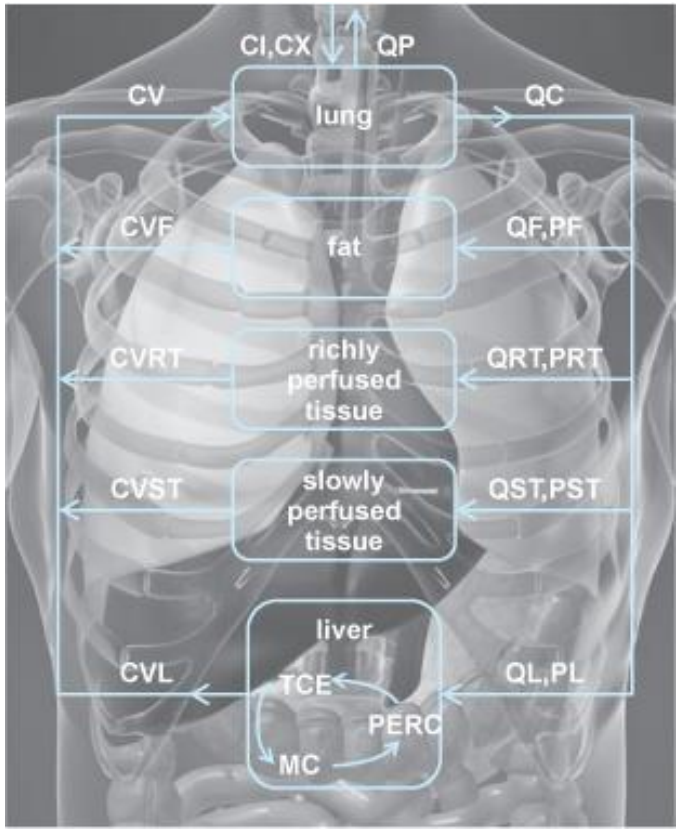

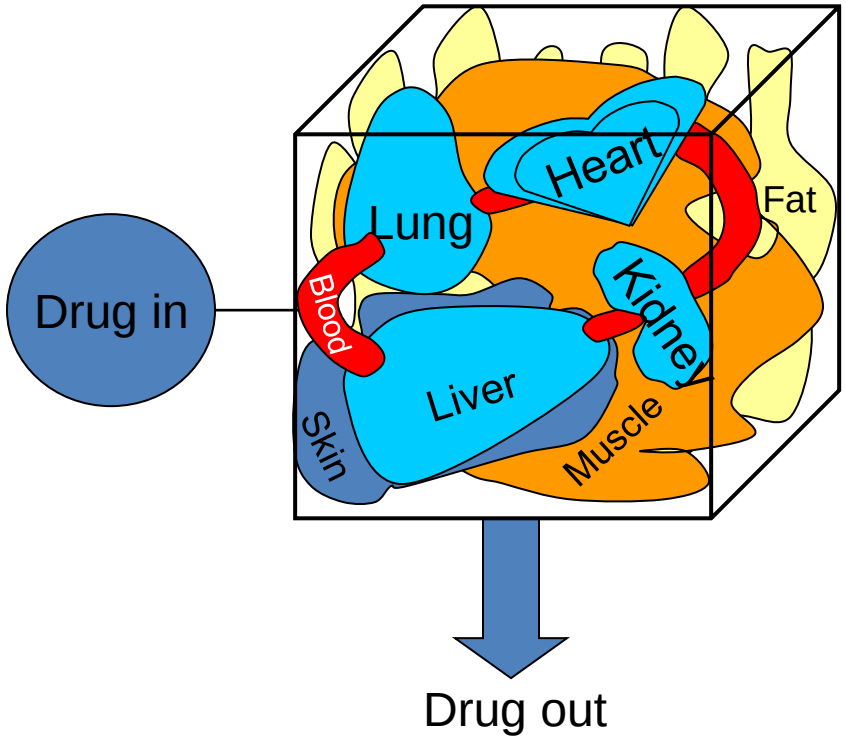

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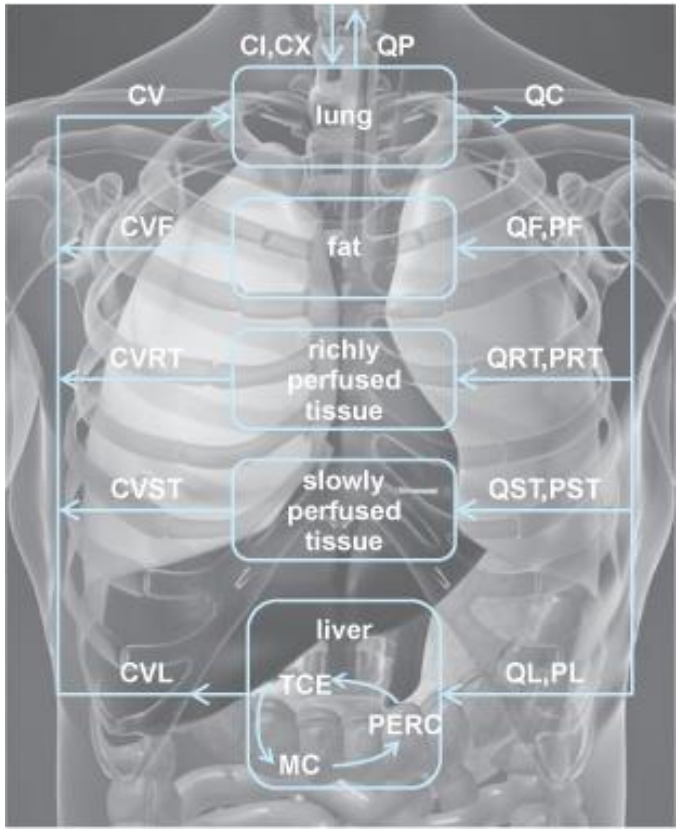
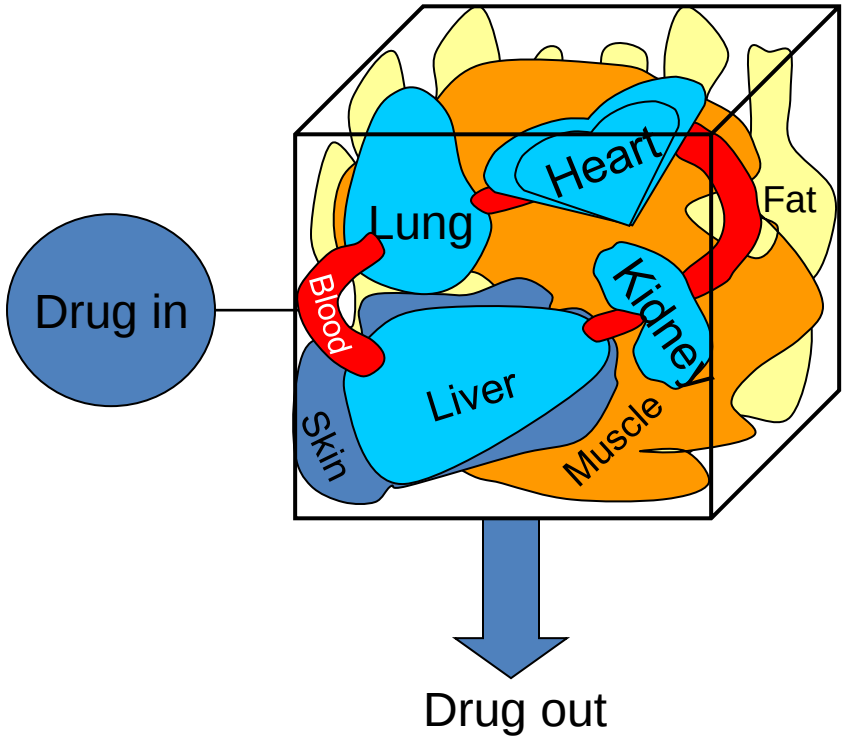
Impact of Research Question on Model Complexity

PBPK: Focus on process characterization





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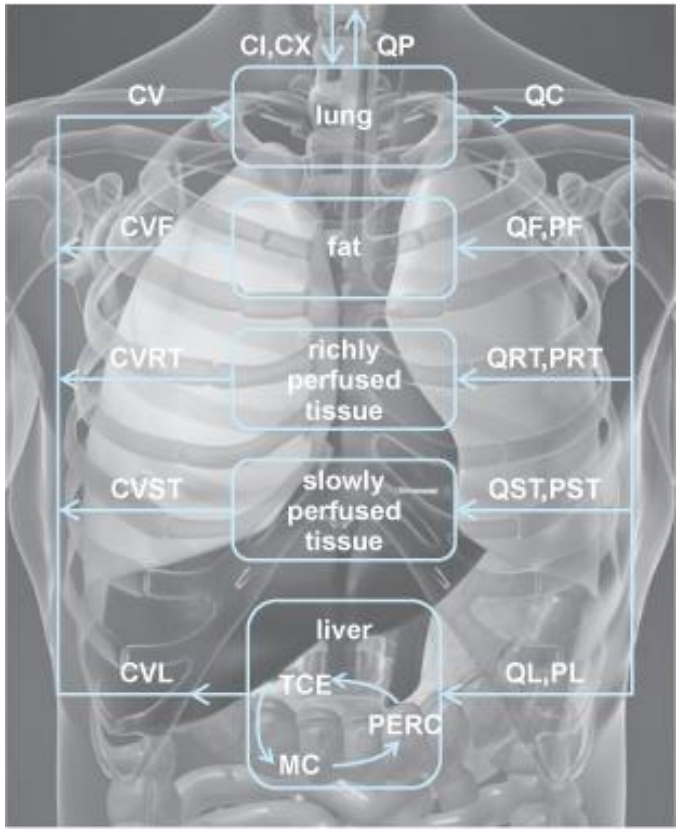
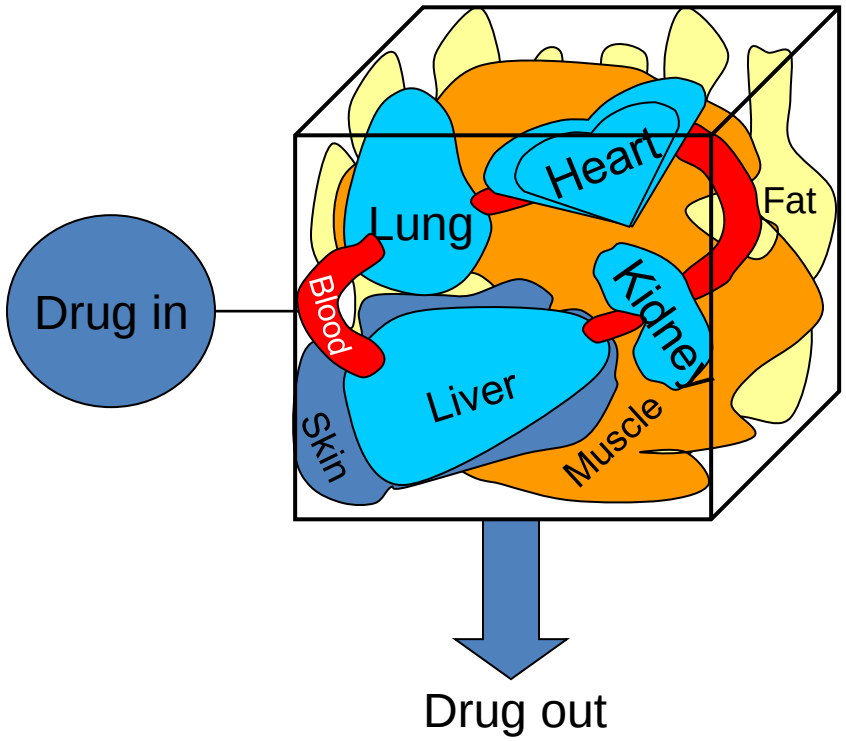


Pop-PK: Focus on parameter identifiability & estimation



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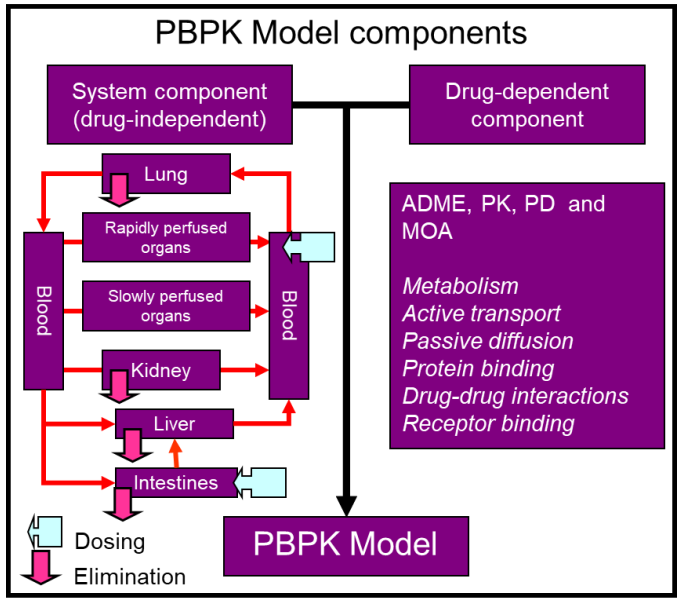
What Are We Willing to Assume?
Impact of Knowledge Base on Model Complexity

Physiologically-based models

Pharmacokinetics



Focus on characterization of ADME (PK) processes (typically well-known)

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Impact of Knowledge Base on Model Complexity

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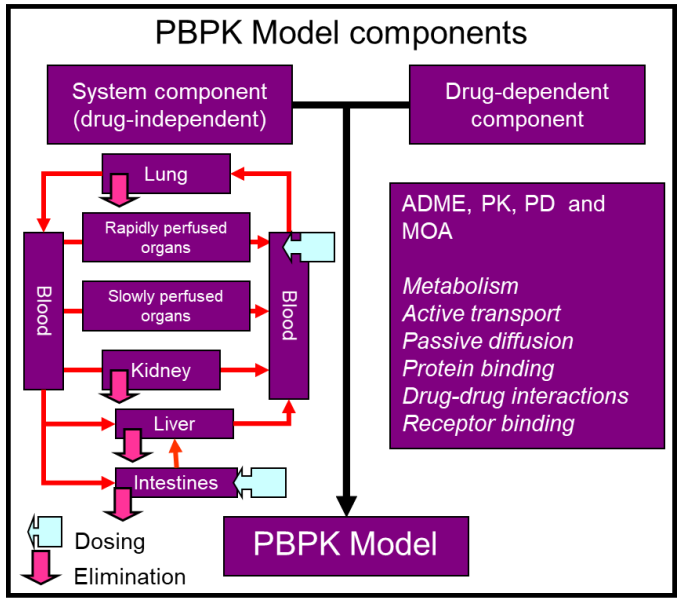

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QSP models

Pharmacodynamics

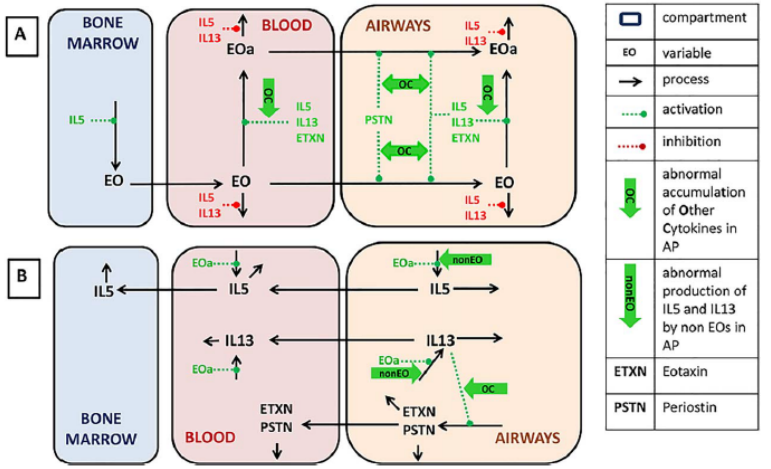

Figure 1 Schematic representation of key processes considered in the model. (**a**) Eosinophil (EOS) dynamics and regulations. (**b**) Cytokine dynamics and regulations. Black arrows denote model reactions. Positive and negative influences are marked by dashed green and red arrows, correspondingly. Abnormal processes switched on in asthmatics (sensitization of model processes and regulations by other cytokines and interleukin (IL)-5/IL-13 production by non-EOS) are marked by thick green arrows.

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Impact of Knowledge Base on Model Complexity

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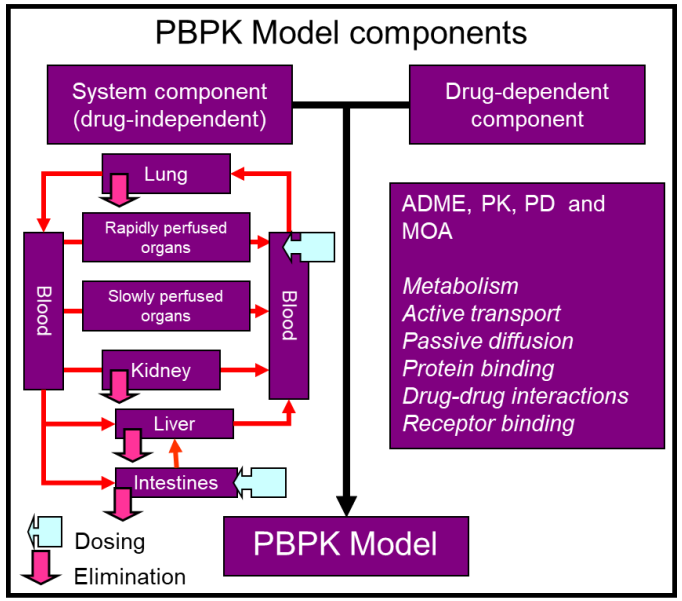

Pharmacodynamics

$$E = m \cdot C$$

$$E = m \cdot log\ C + b$$

$$E = \frac{E_{max} \cdot C}{EC_{50} + C}$$

$$E = \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}$$

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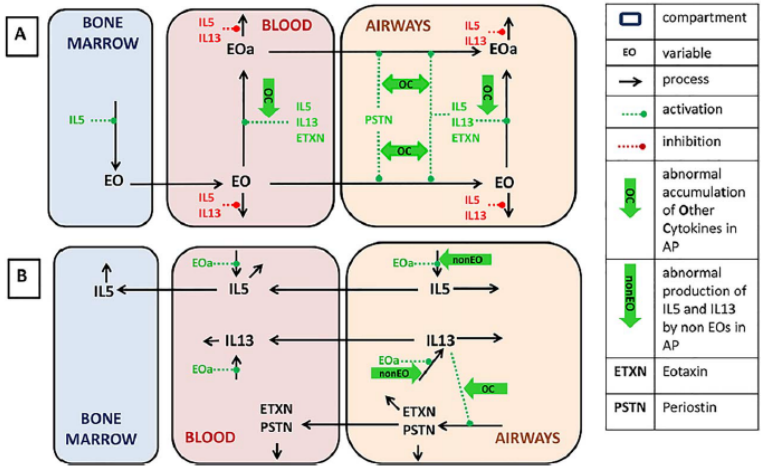
Pharmacodynamics



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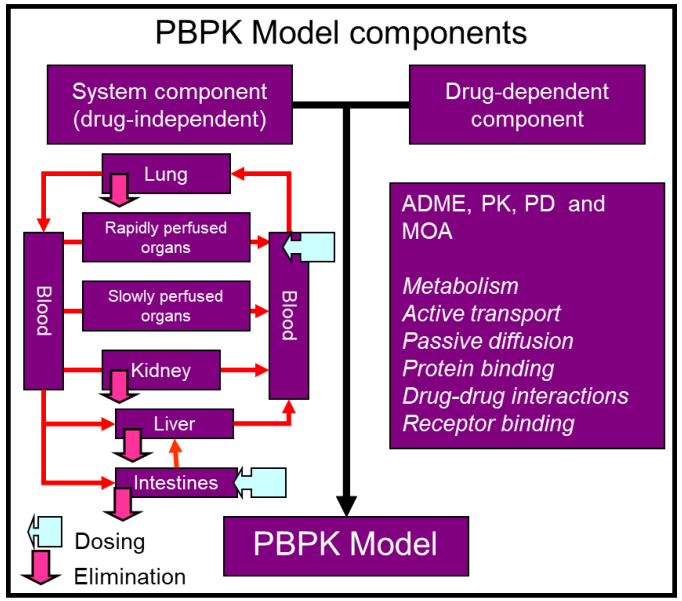

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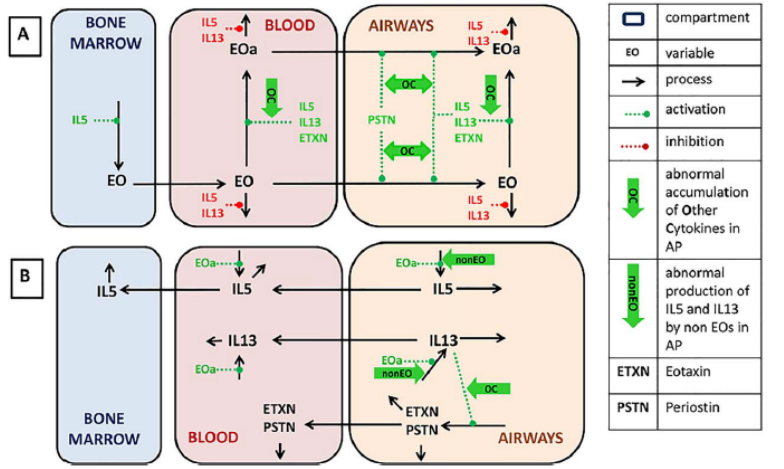
QSP models

Pharmacokinetics

1-comp

2-comp

Pharmacodynamics



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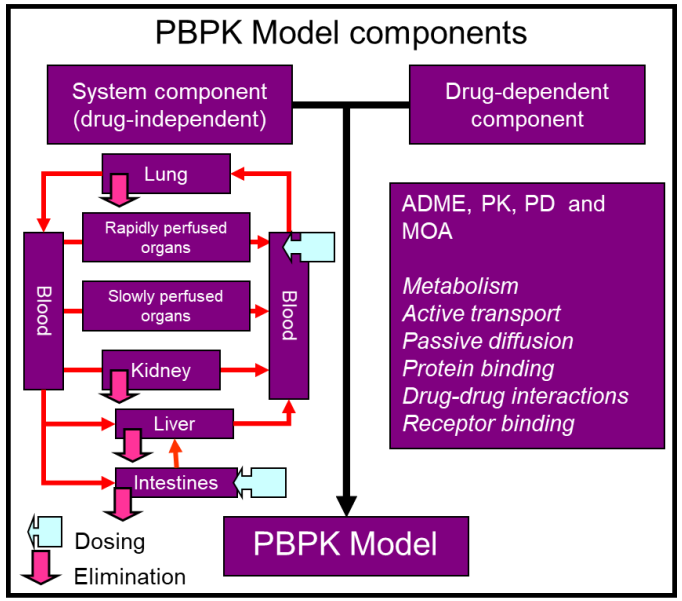

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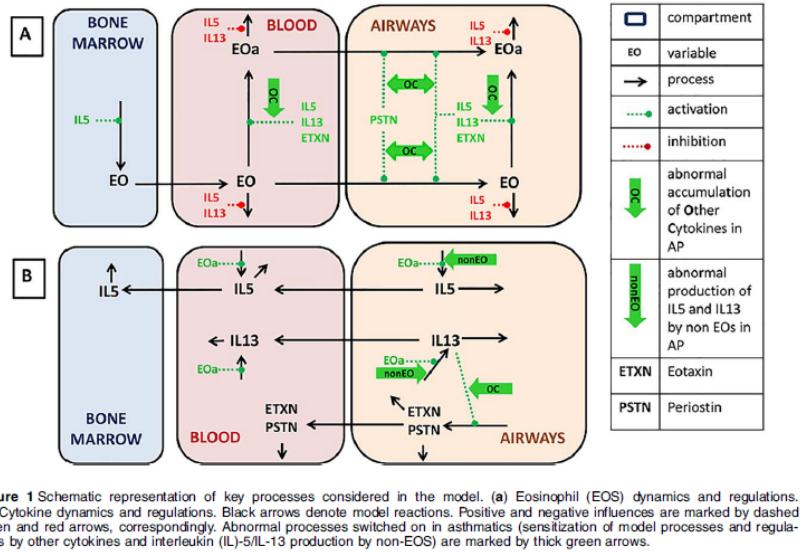

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Key question: How confident are we in our assumptions?

Integrating What We Know to Narrow Down What To Do Next: The Importance of (Global) Sensitivity Analysis

A clopidogrel case example:

- Clopidogrel is an irreversible P2Y12 inhibitor → inhibition of platelet aggregation
- Approved in 1997 by U.S. FDA
- Reduces the risk of major adverse cardiovascular events (MACE):
  - Myocardial infarction
  - Stroke
  - Cardiovascular death
  - Stent thrombosis
- Large between-patient variability in response to clopidogrel treatment (Boxed warning from FDA)

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Research Question: Can we use our knowledge on the underlying metabolic pathways to identify clinically-relevant sources of between-patient variability?

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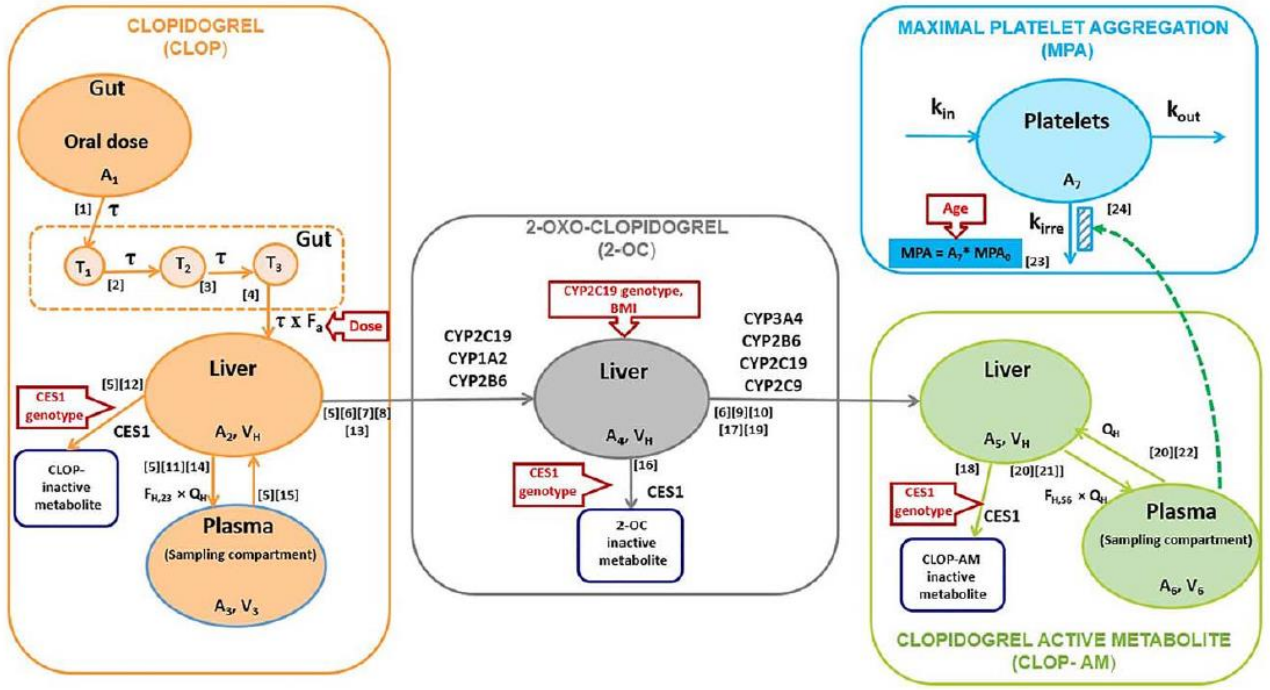
- Large between-patient variability in response to clopidogrel treatment (Boxed warning from FDA)

Research Question: Can we use our knowledge on the underlying metabolic pathways to identify clinically-relevant sources of between-patient variability?



Samant S et al. Clin Pharmacol Ther. 2017 Feb;101(2):264-273. doi: 10.1002/cpt.459. Epub 2016 Oct 11.

Integrating What We Know to Narrow Down What To Do Next: The Importance of (Global) Sensitivity Analysis

A clopidogrel case example:

- Clopidogrel is an irreversible P2Y12 inhibitor → inhibition of platelet aggregation
- Approved in 1997 by U.S. FDA
- Reduces the risk of major adverse cardiovascular events (MACE):
  - Myocardial infarction
  - Stroke
  - Cardiovascular death
  - Stent thrombosis
- Large between-patient variability in response to clopidogrel treatment (Boxed warning from FDA)

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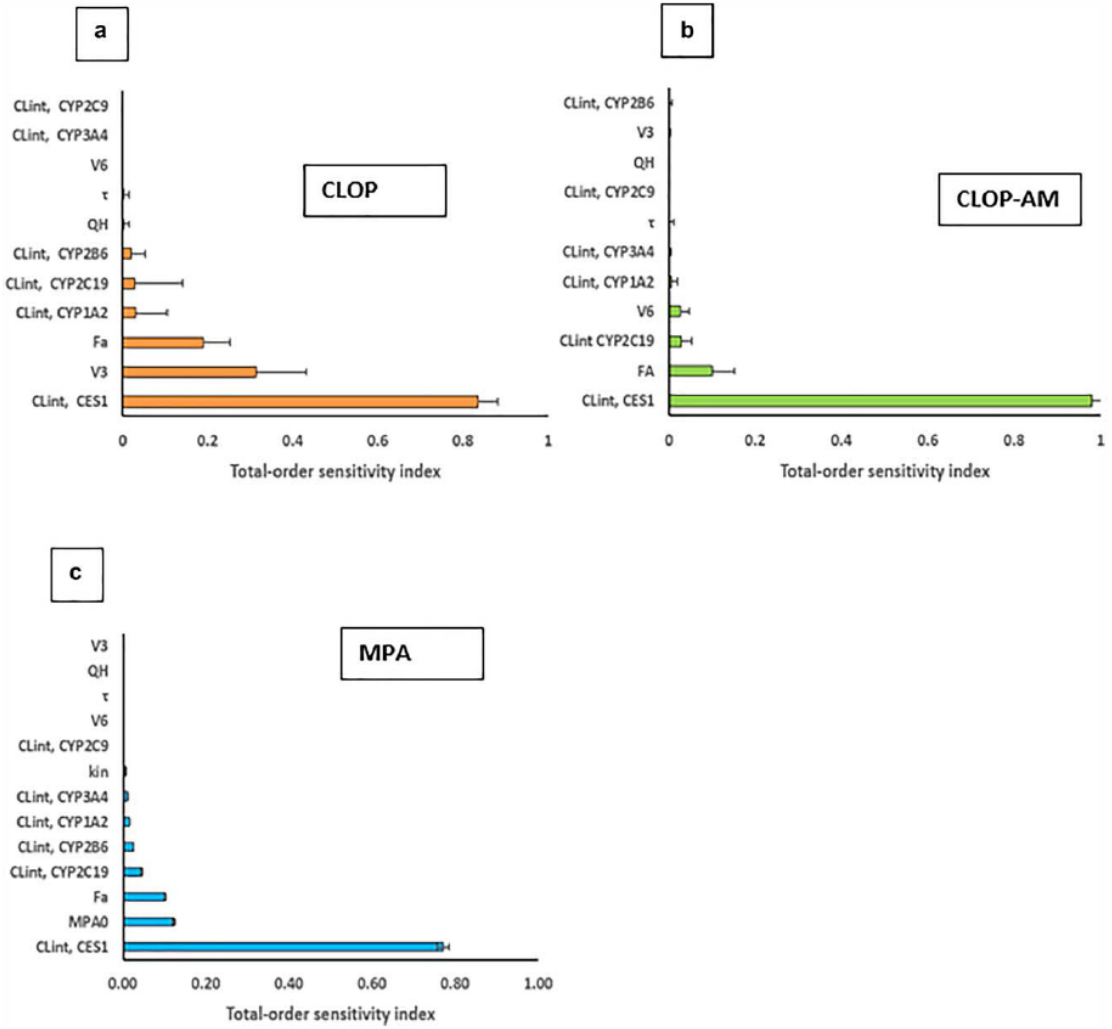

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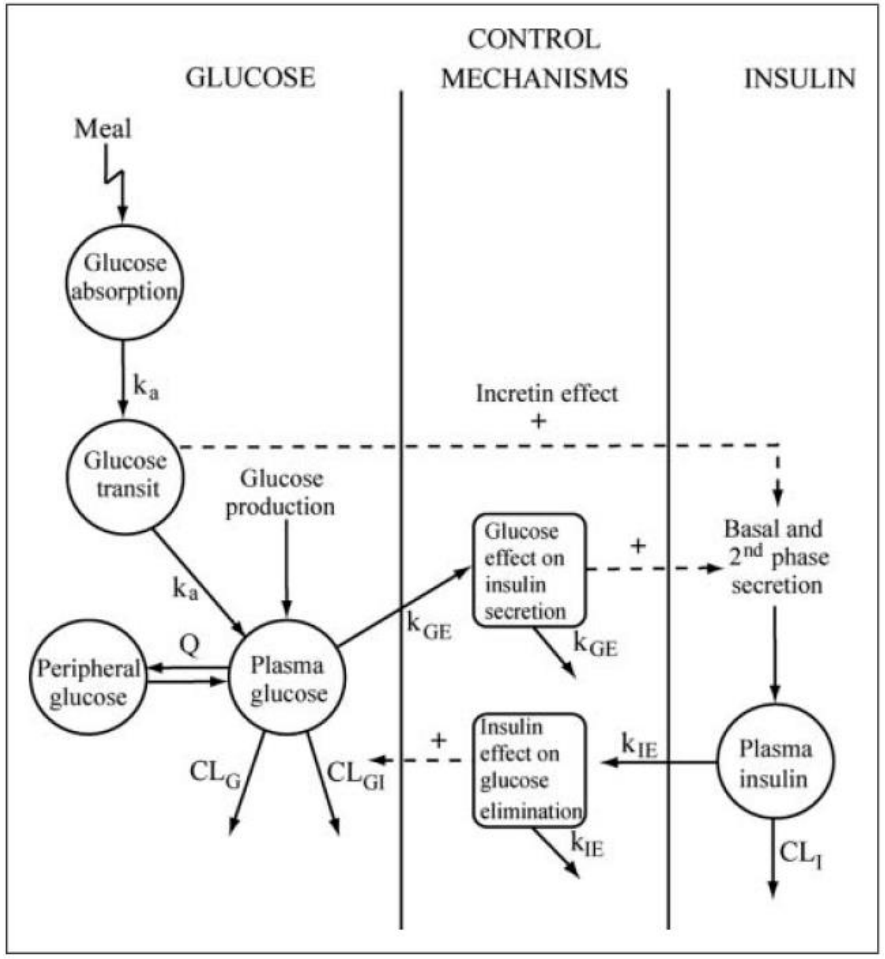
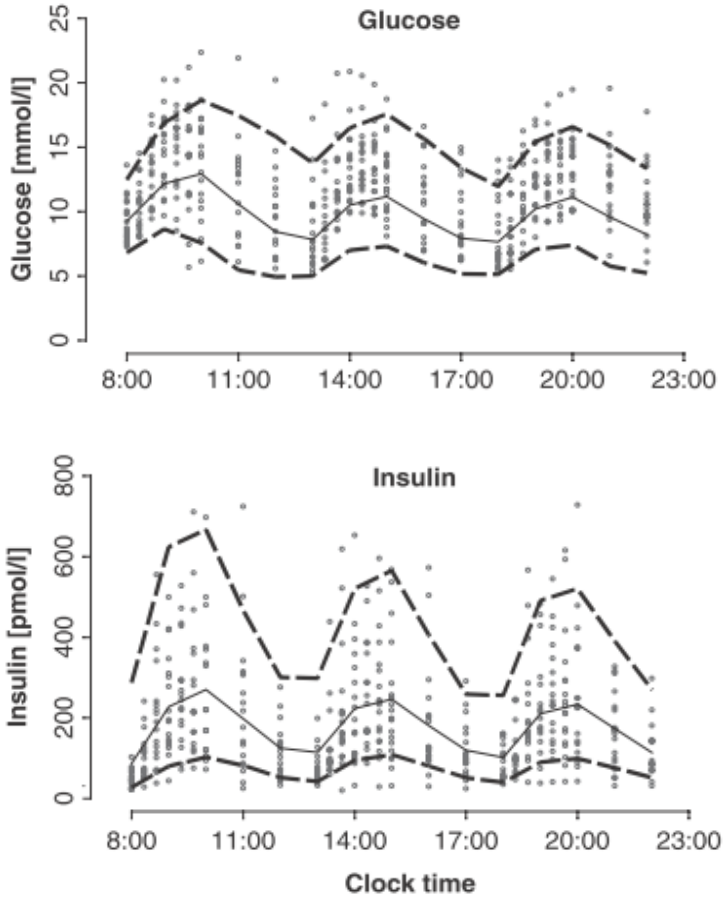
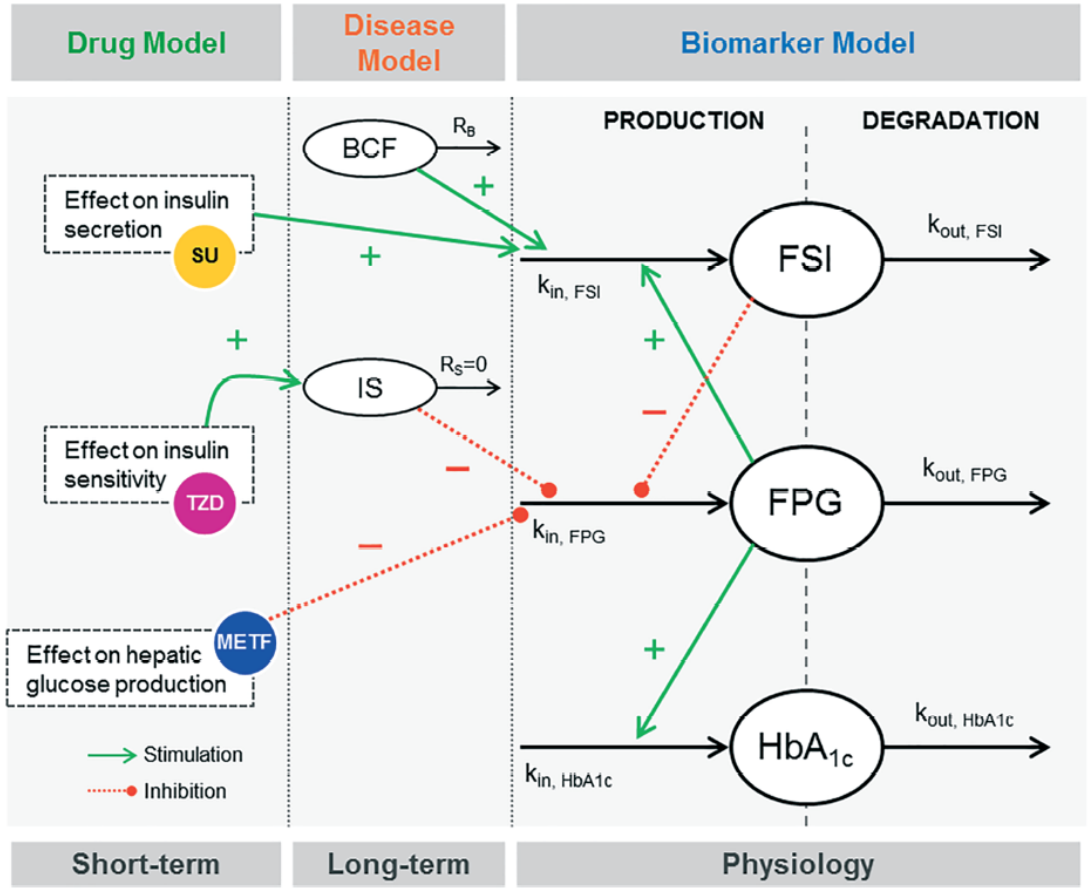
Impact of Time Scale on Model Granularity: Translating Short-Term Behaviour Into Long-Term Outcome



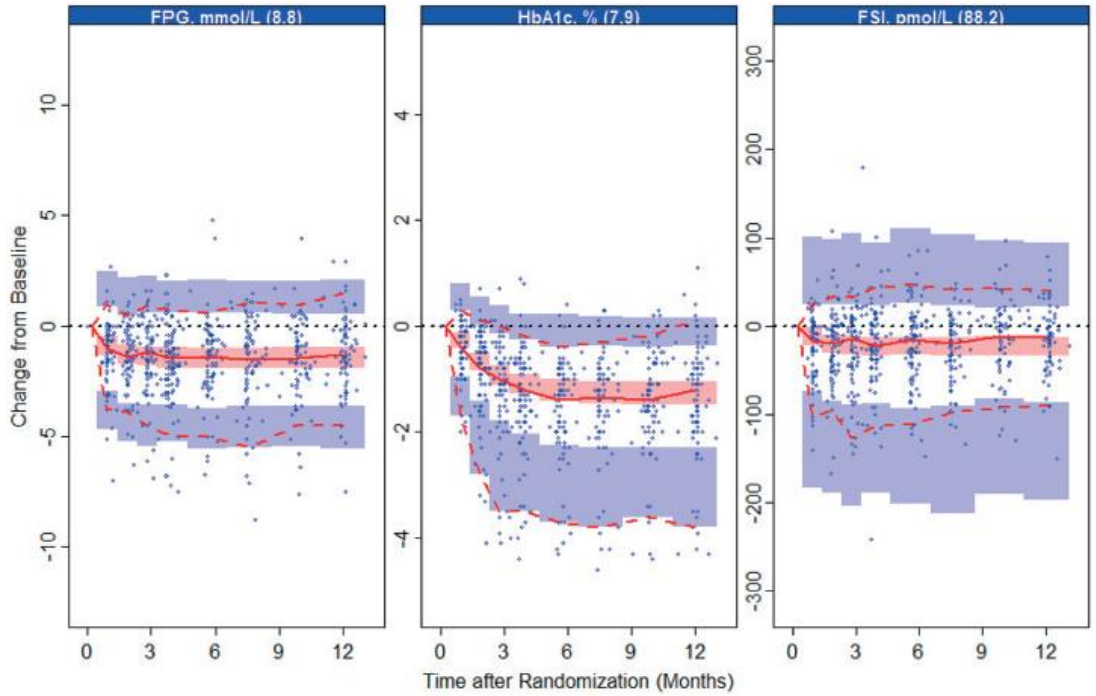


Jauslin-Stetina et al., J Clin Pharmacol (2011) 51:153-164

Time Varying Exposure-Response: Impact of Disease on Model Granularity



Treatment with thiazolidinedione (insulin sensitizer)



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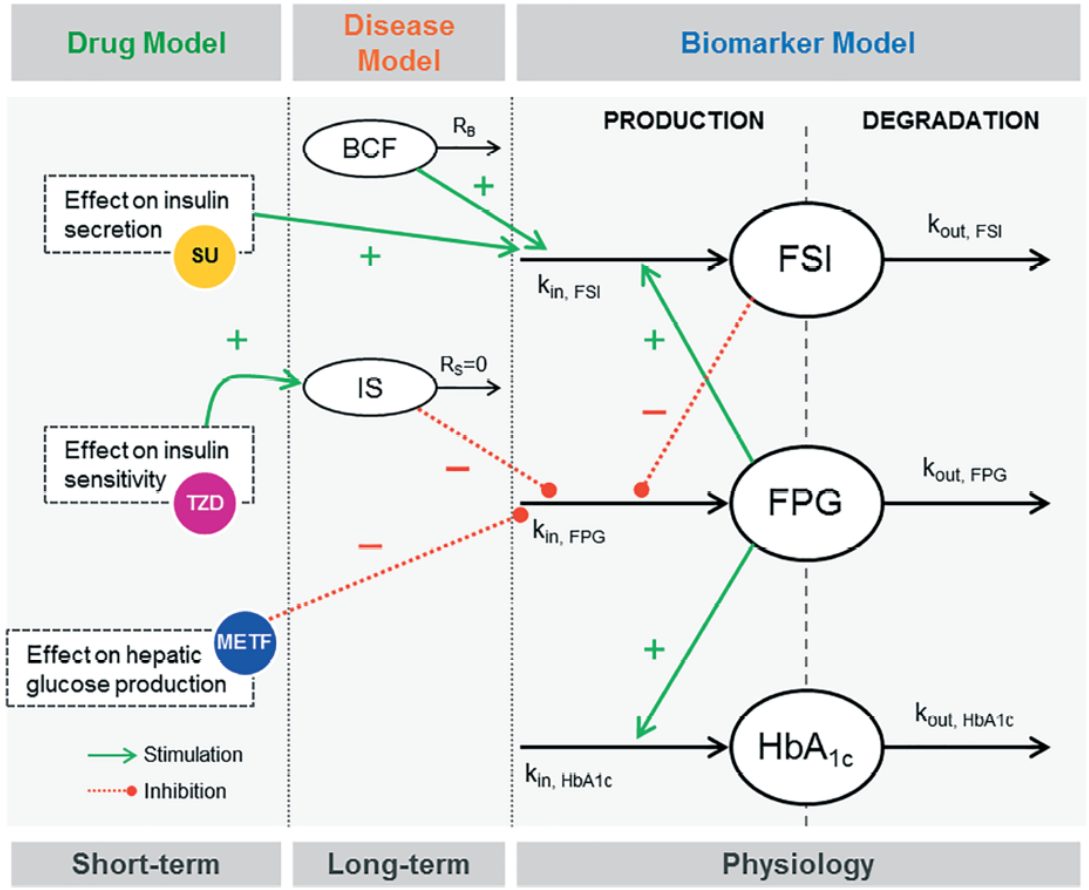

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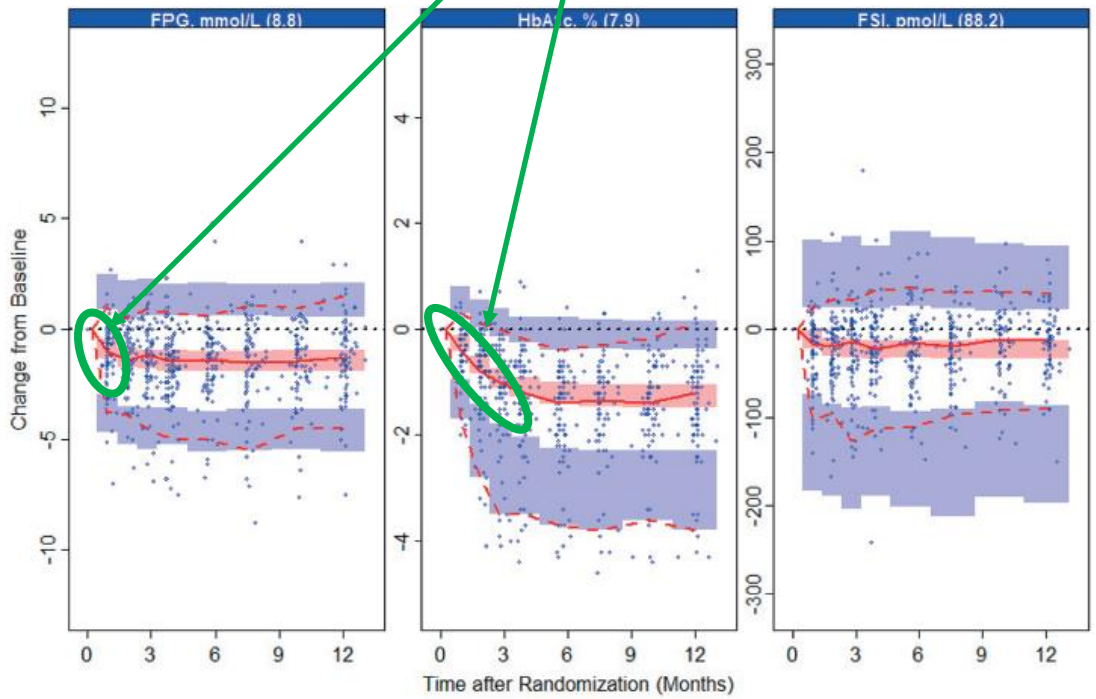

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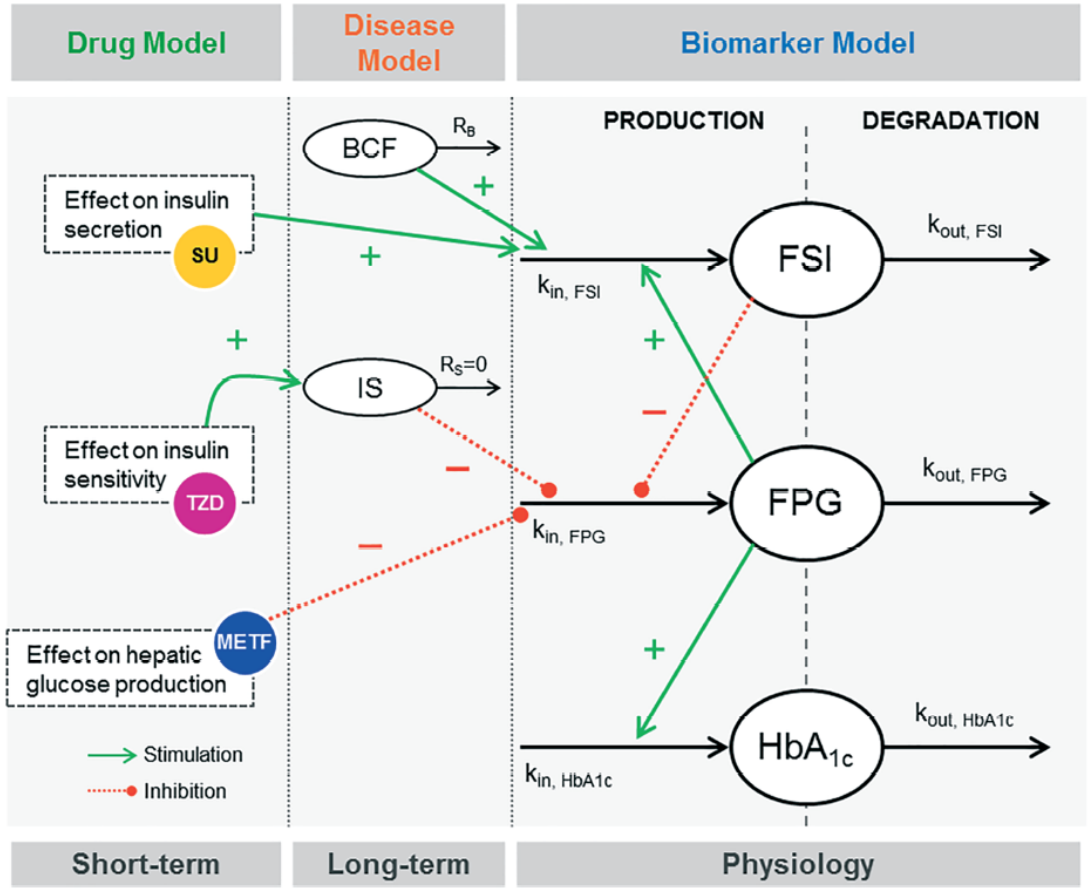

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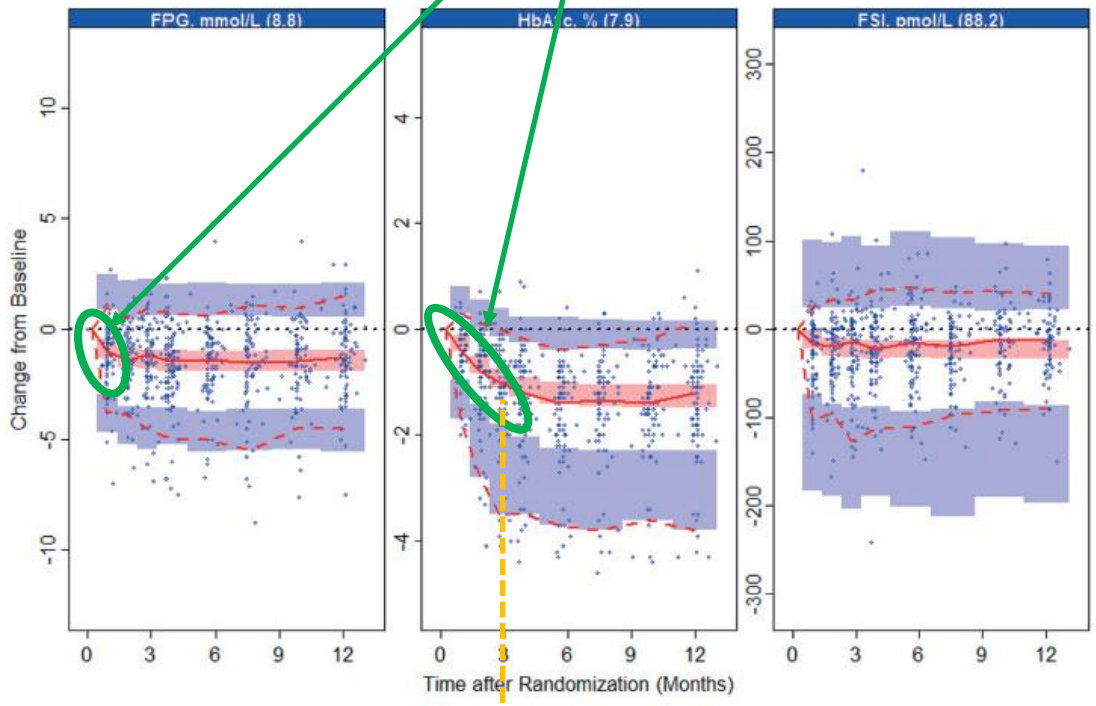

Pivotal endpoint determination

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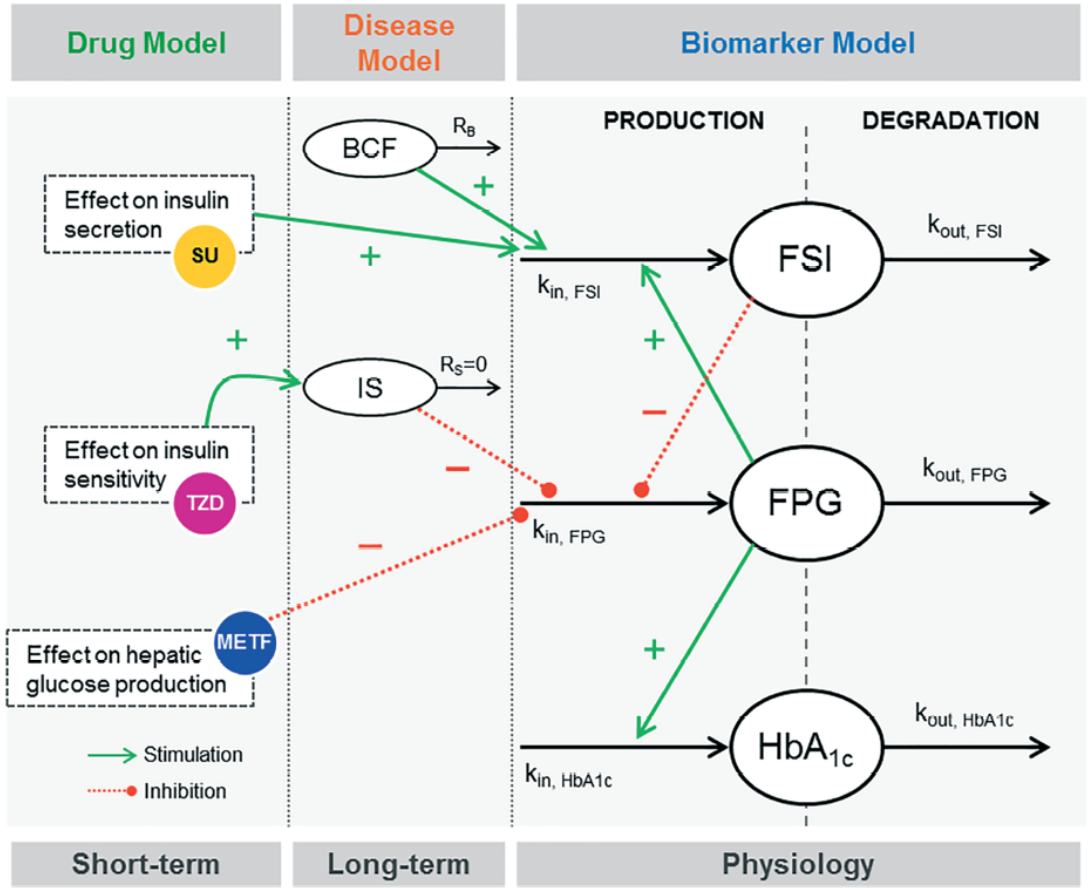

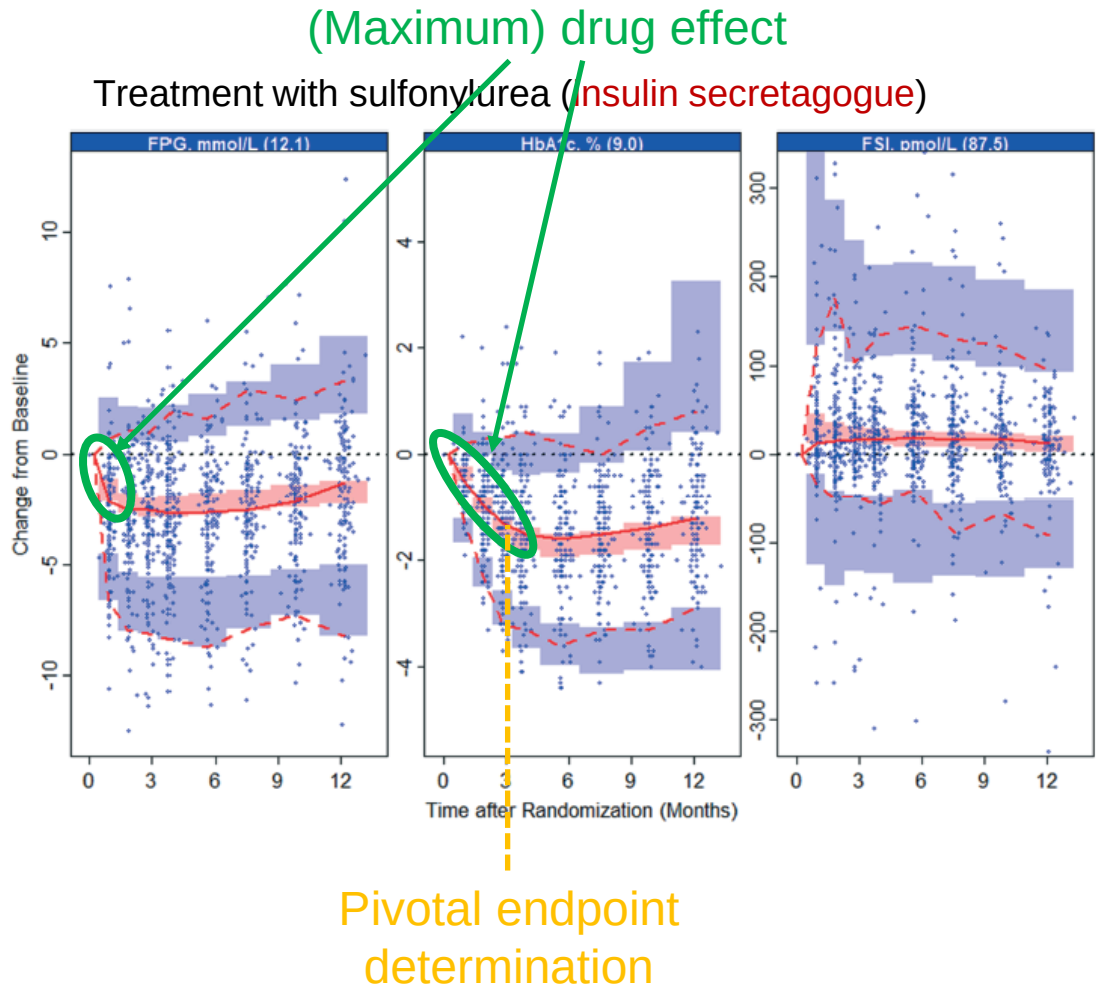

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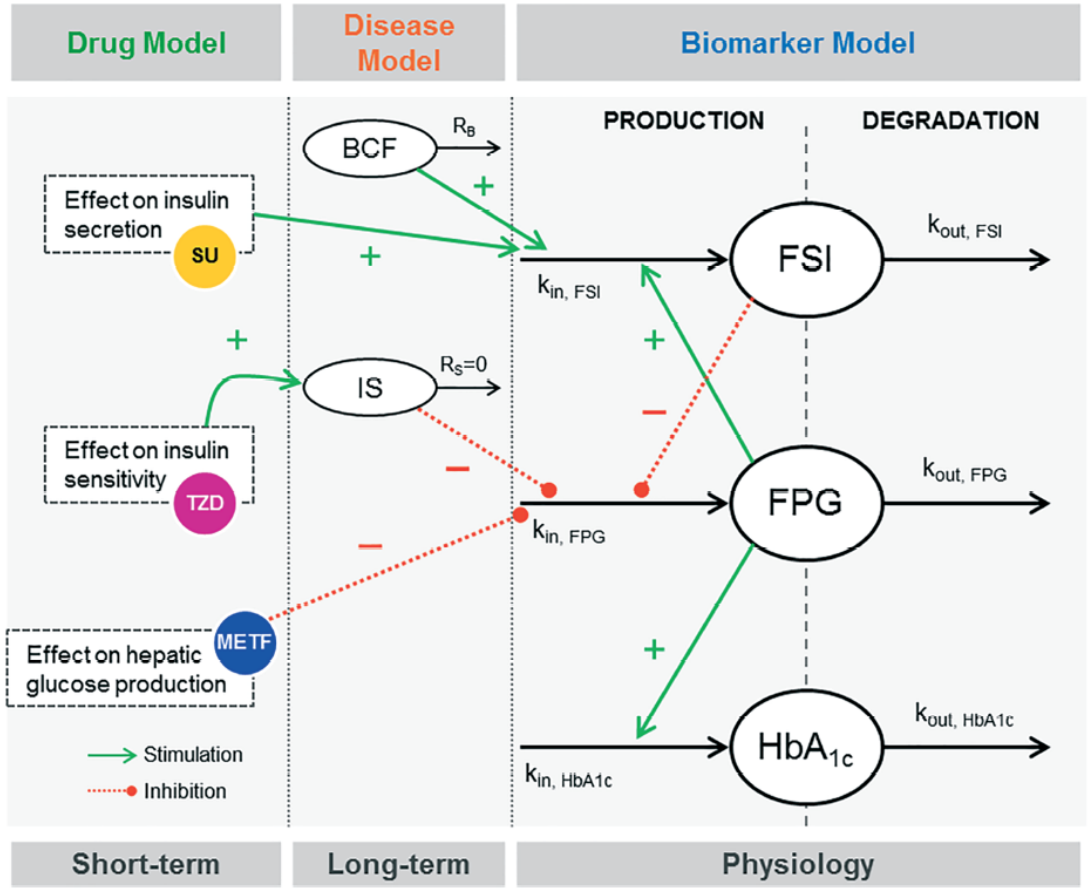

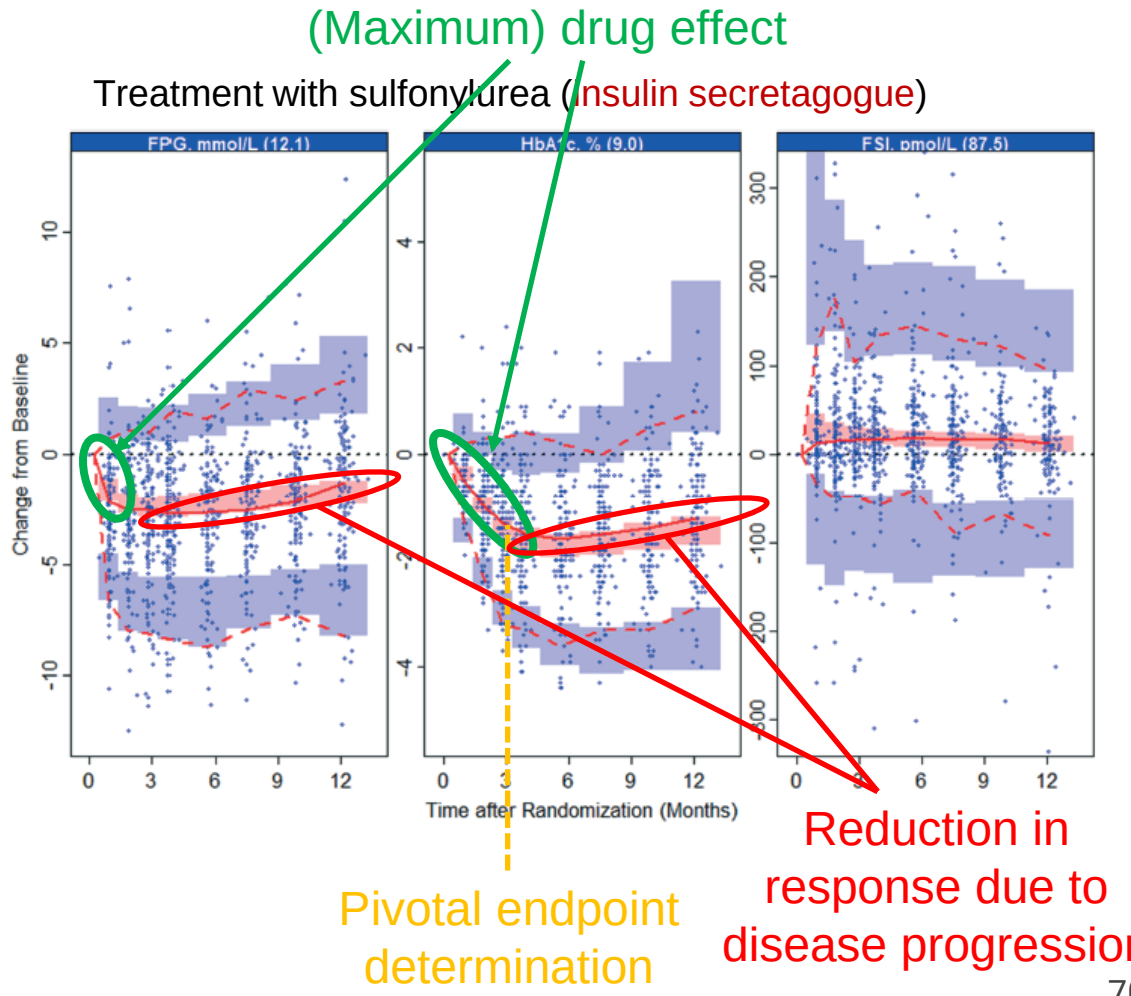

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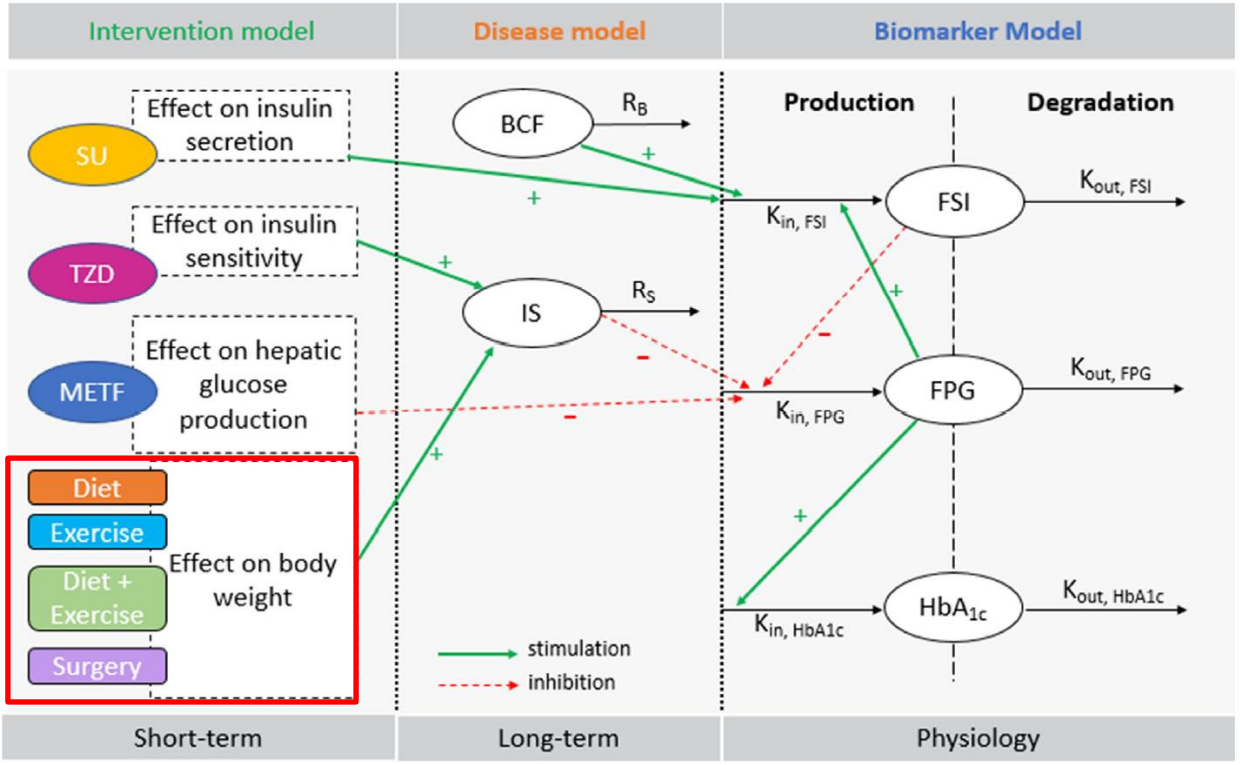

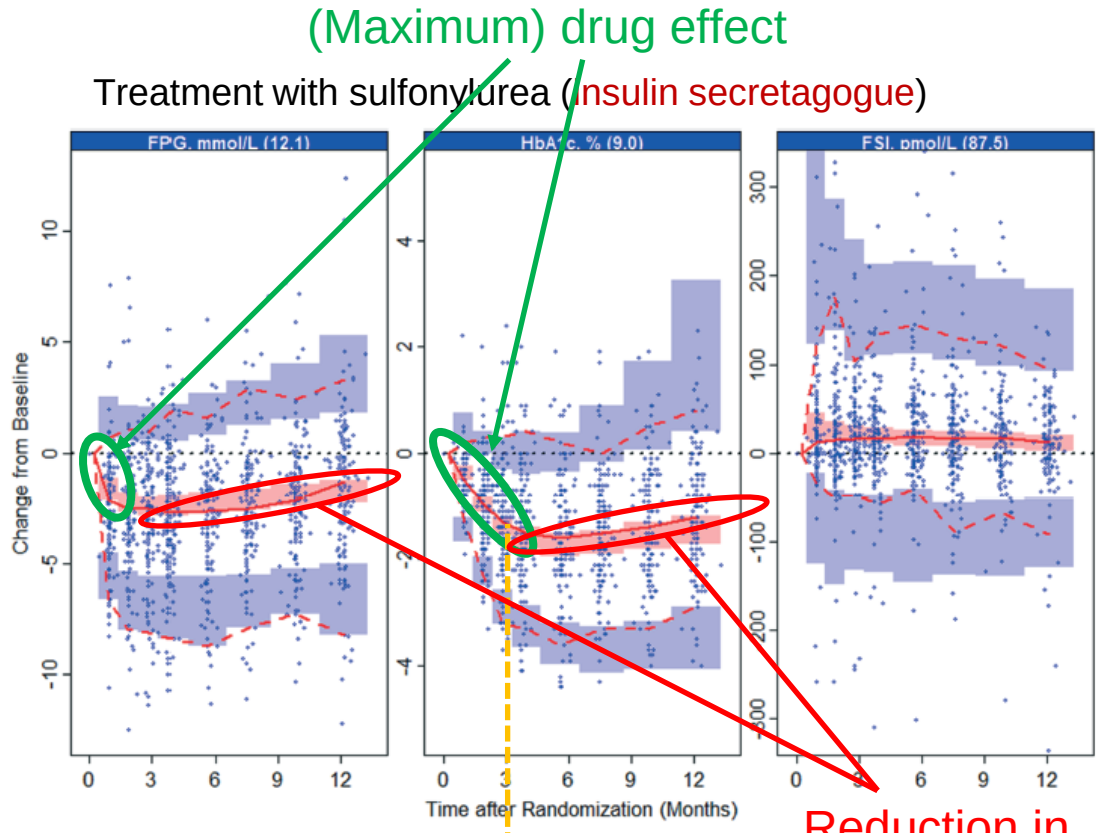

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Farhan et al. J Clin Pharmacol. 2021 Feb;61(2):234-243. doi: 10.1002/jcph.1728. Epub 2020 Sep 7.

Here Is What I Think We Should Do Next

- Focus on building consensus rather than silos. It’s a modeling continuum, not a modeling competition.
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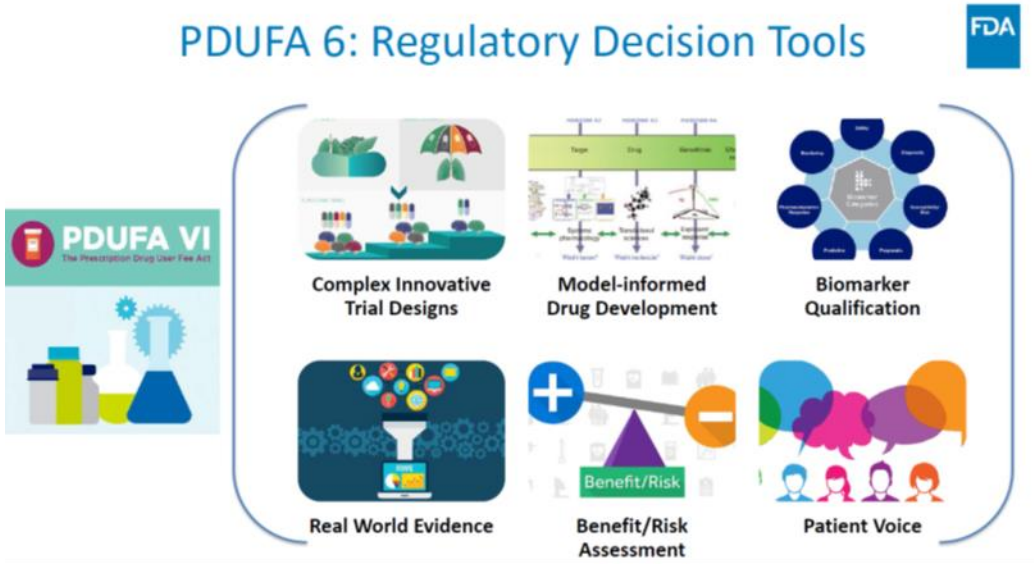

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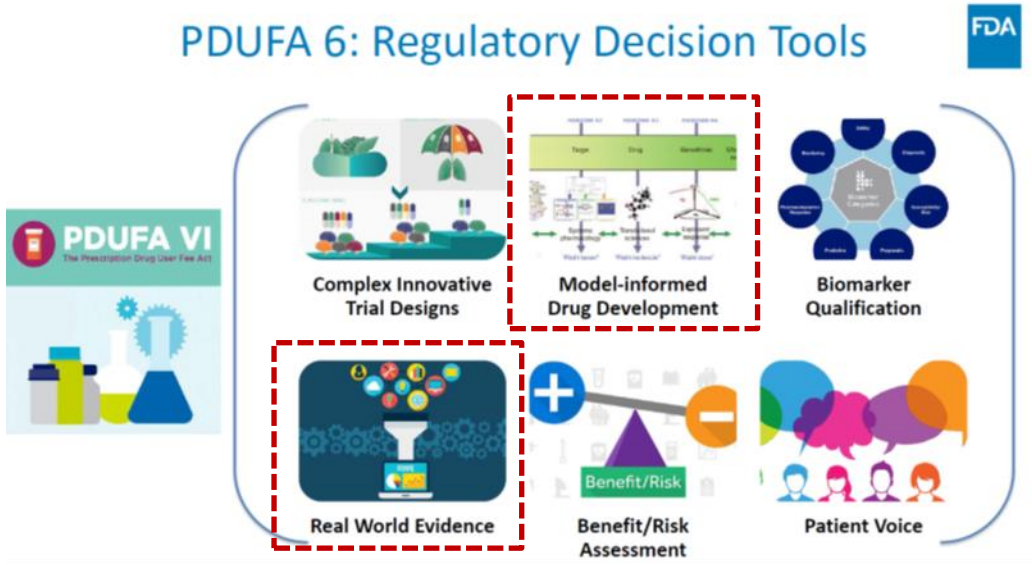
Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 352–355; doi:10.1002/psp4.12425

PERSPECTIVE

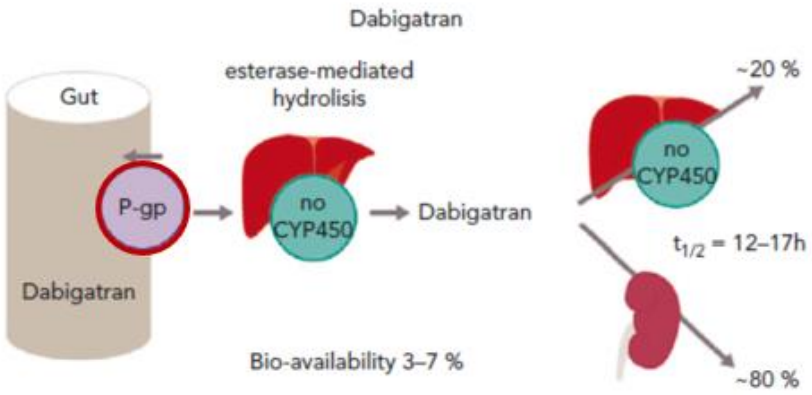
Pharmacometrics, Physiologically Based Pharmacokinetics, Quantitative Systems Pharmacology—What's Next?—Joining Mechanistic and Epidemiological Approaches

Stephan Schmidt[1,*], Sarah Kim[1], Valvanera Vozmediano[1], Rodrigo Cristofoletti[1], Almut G. Winterstein[2] and Joshua D. Brown[2]



Dabigatran Case Example

- Dabigatran:
  - ✓ Factor IIa inhibitor
  - ✓ G-pg substrate
  - ✓ Low oral bioavailability
  - ✓ Primarily cleared via the kidneys
- Dose reduction is recommended only in subjects with impaired renal function



https://www.pradaxapro.com/dosing-administration

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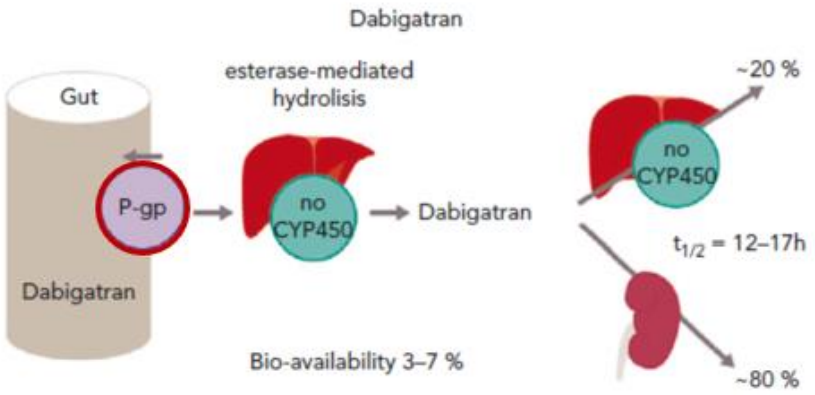


RWE Results: Impact of P-gp Inhibitors in Subjects With Normal Renal Function

	HR (95% CI)		
Bleeding categories	Dabigatran	Rivaroxaban	Apixaban
Verapamil or diltiazem vs amlodipine			
Overall bleeding	1.52 (1.05-2.20)[a]	0.99 (0.71-1.38)	0.89 (0.49-1.63)
Overall GI bleeding	2.16 (1.30-3.60)[a]	0.64 (0.37-1.09)	0.70 (0.25-1.99)
Major/moderate bleeding	2.27 (0.97-5.29)	1.23 (0.65-2.35)	1.57 (0.35-7.16)
Major/moderate GI bleeding	2.27 (0.72-7.11)	0.51 (0.17-1.53)	2.17 (0.11-43.08)
Minor bleeding	1.56 (1.07-2.27)[a]	0.95 (0.68-1.35)	0.87 (0.47-1.63)
GI minor bleeding	2.16 (1.29-3.63)[a]	0.62 (0.35-1.09)	0.70 (0.25-1.99)
Verapamil or diltiazem vs metoprolol			
Overall bleeding	1.43 (1.02-2.00)[a]	0.76 (0.55-1.06)	0.78 (0.45-1.36)
Overall GI bleeding	2.32 (1.42-3.79)[a]	0.72 (0.42-1.22)	0.86 (0.40-1.86)
Major/moderate bleeding	3.32 (1.54-7.16)[a]	0.99 (0.50-1.98)	1.46 (0.33-6.41)
Major/moderate GI bleeding	5.49 (1.67-18.03)[a]	0.73 (0.23-2.25)	0.42 (0.02-8.71)
Minor bleeding	1.38 (0.98-1.95)	0.75 (0.54-1.06)	0.67 (0.37-1.21)
GI minor bleeding	2.33 (1.42-3.82)[a]	0.72 (0.42-1.24)	0.86 (0.40-1.86)

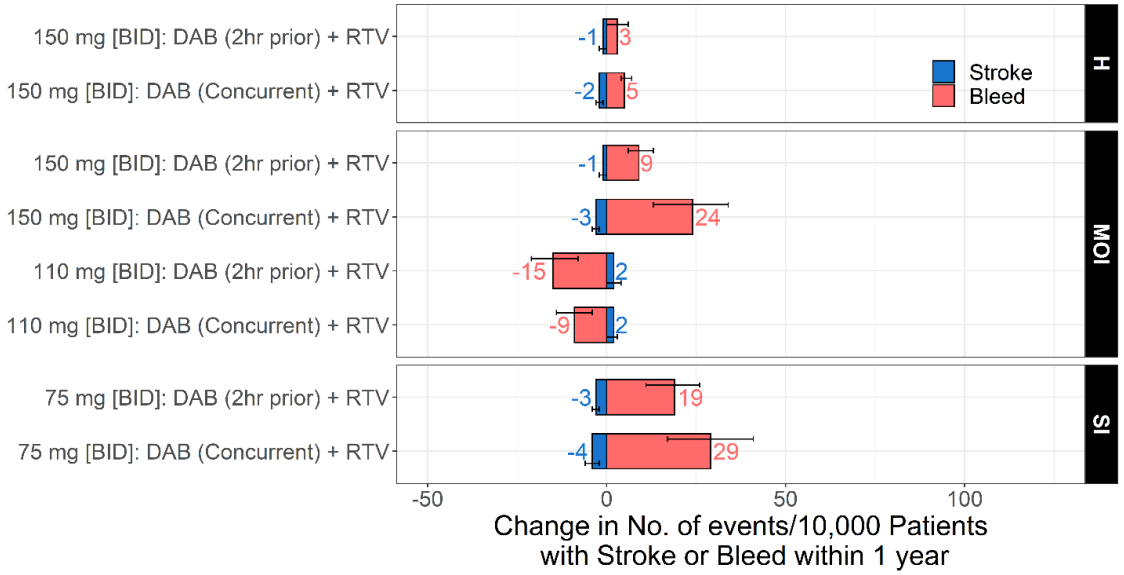
Dabigatran dose reduction may have to be considered in subjects with normal renal function receiving P-gp inhibitors

https://www.pradaxapro.com/dosing-administration

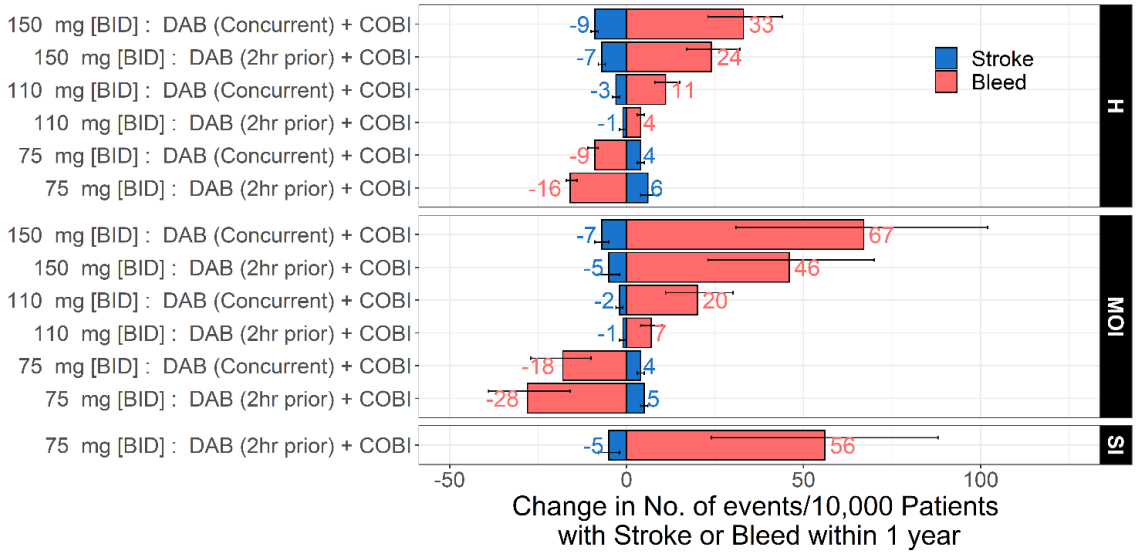
*Pham et al. JAMA Netw Open. 2020 Apr 1;**3(4)**:e203593. doi: 10.1001/jamanetworkopen.2020.3593.*

What About Subjects With Renal Impairment Receiving P-gp Inhibitors?

Dabigatran + Ritonavir



Dabigatran + Cobicistat



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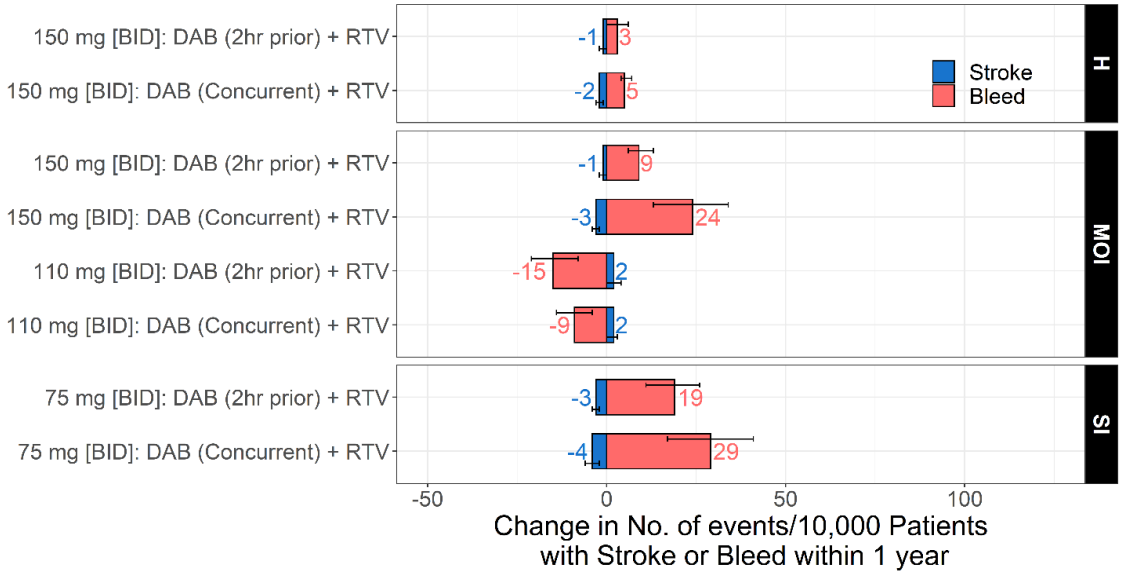

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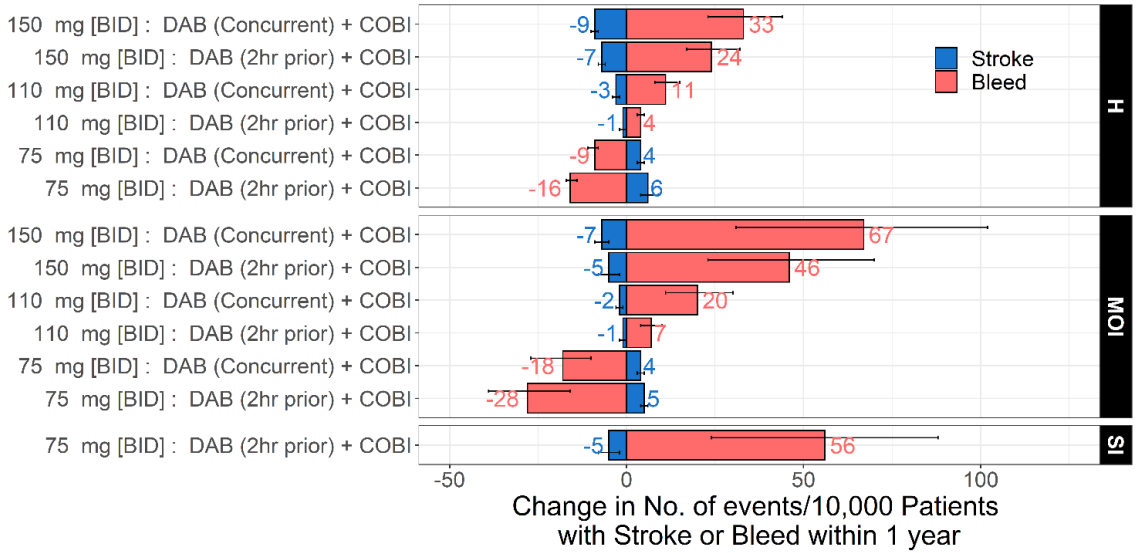

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- ✓ In subjects with moderate renal impairment and receiving RTV, dose separation or dabigatran dose reduction to 110 mg b.i.d. may be necessary.
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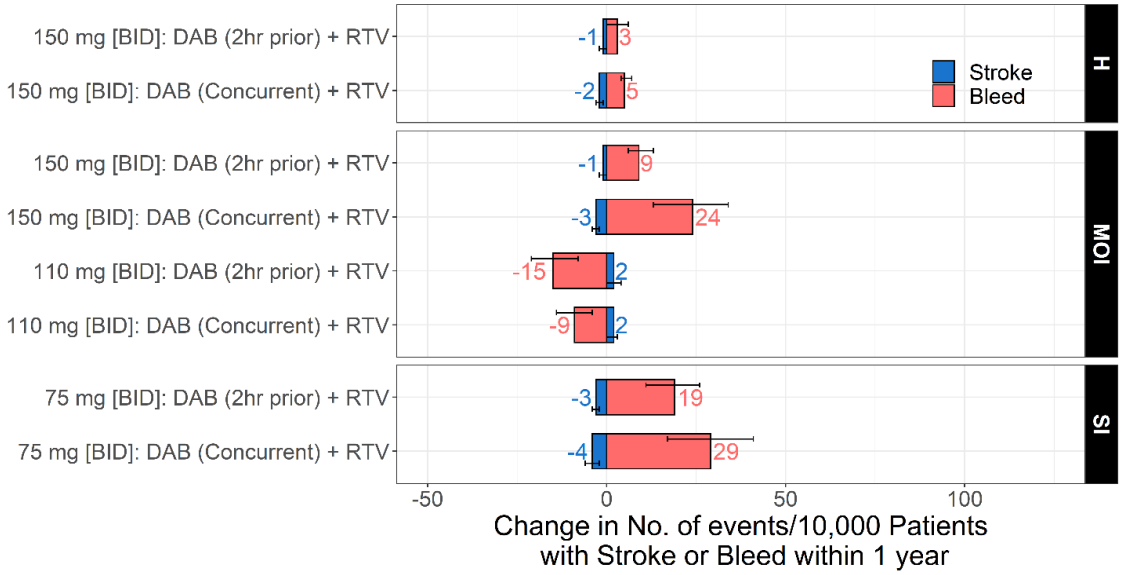

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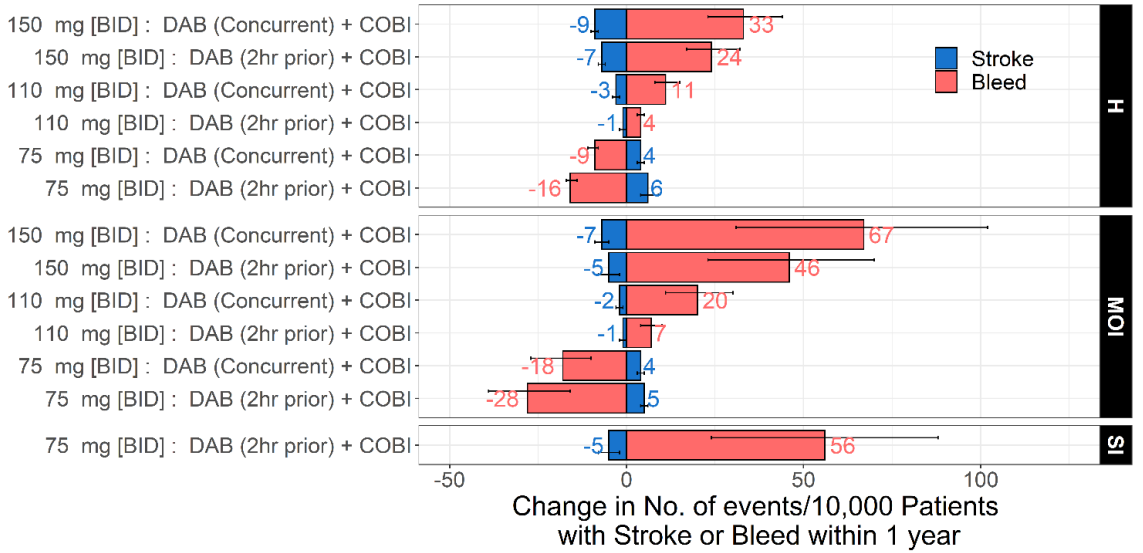

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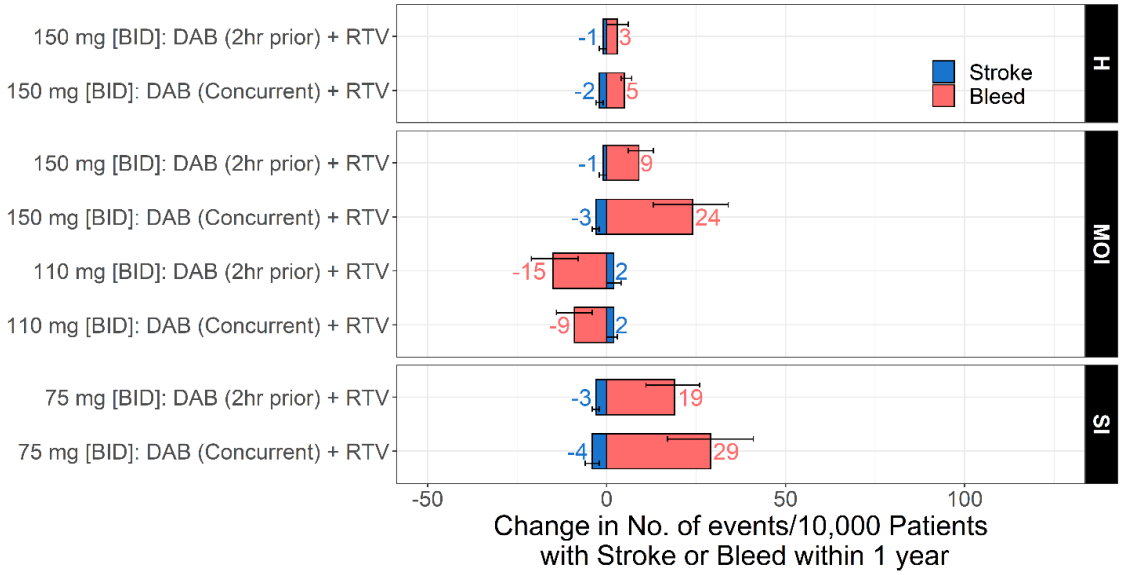

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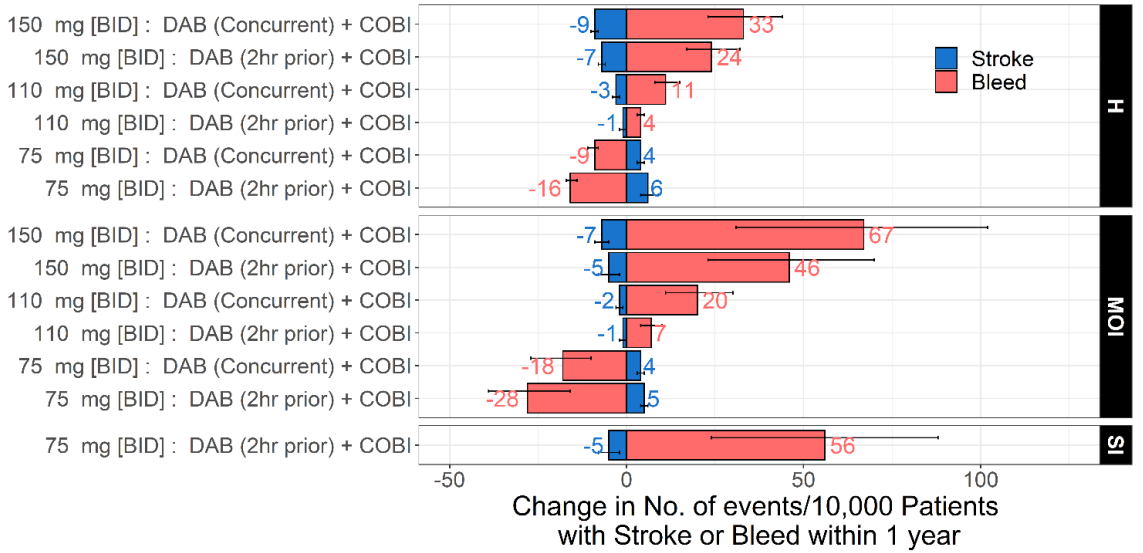

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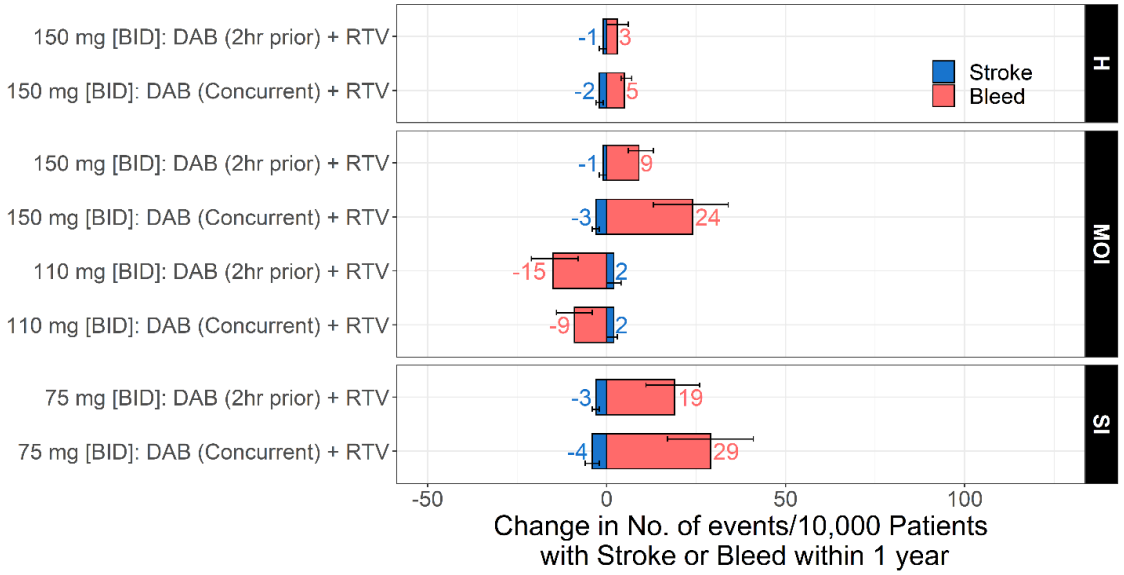

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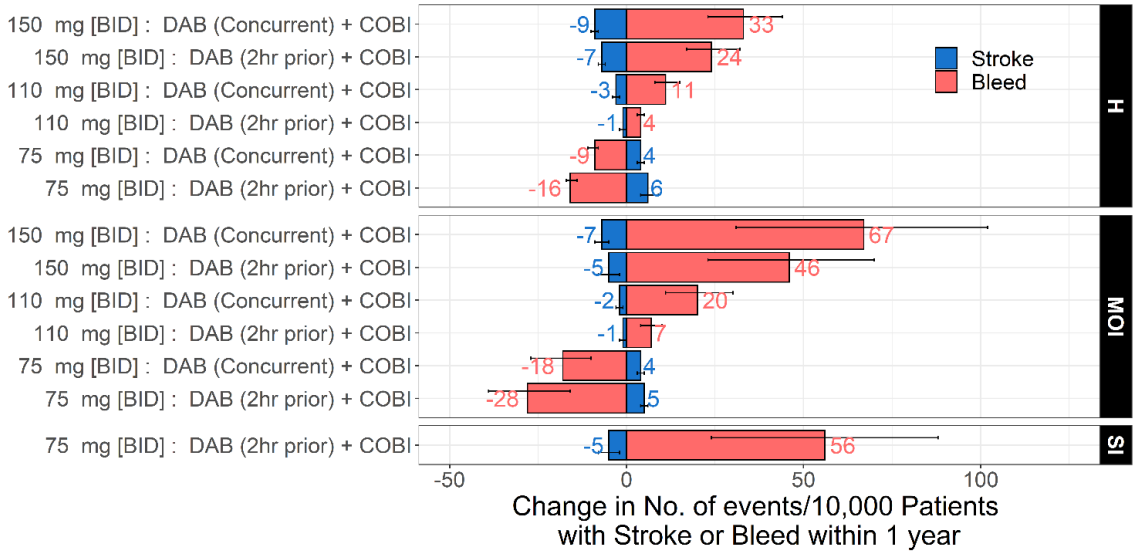

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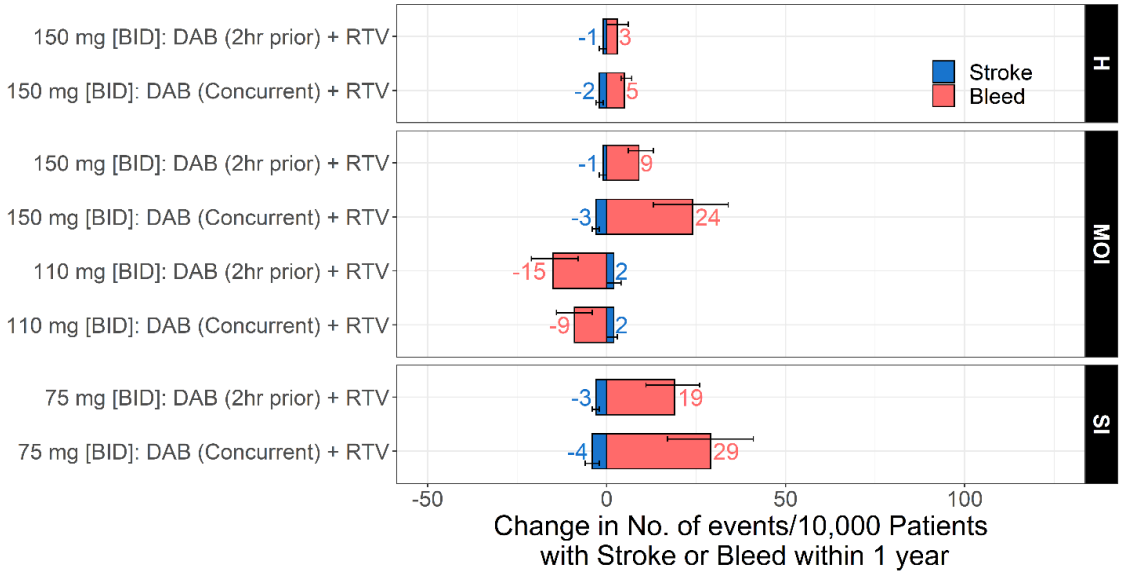

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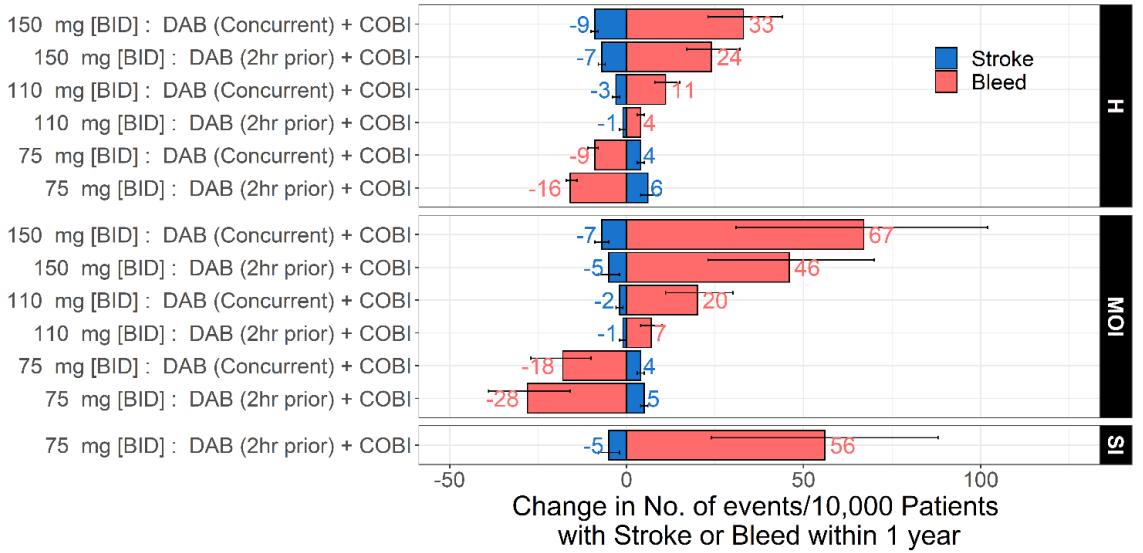

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