A PKPD Model-Based Meta-Analysis of Subcutaneously Administered Insulins in Clinical Glucose Clamp Studies

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Introduction

Motivation
- Novel insulin analogs have modified PK/PD properties from regular human insulin (RHI) in order to achieve improvement in glucose lowering and/or hypoglycemia rate
- A comparative model of insulin analog PK/PD properties would enable
  - Designing and simulating new insulin analogs with existing analog backbones
  - Comparing novel insulin performance to standard of care through simulation
  - Understanding the relationship between PK/PD properties and long-term glucose control and hypoglycemia

Objectives
- A model-based meta-analysis (MBMA) of subcutaneously (SC) administered insulins in clinical glucose clamp studies was conducted to develop pharmacokinetic (PK) and glucose metabolism (PD) models to support systems pharmacology model development and clamp trial design for novel insulins.
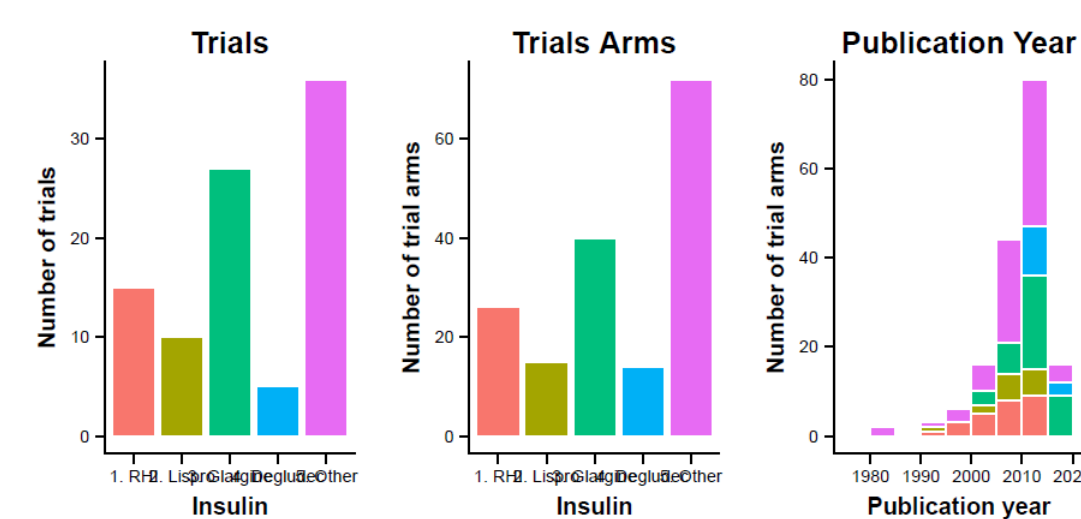
Euglycemic Clamp
- Gold standard for evaluating single insulin dose PK/PD response
- Procedure
  - Insulin is injected SC or IV infusions
  - Plasma glucose concentration is held constant at basal levels (clamp) by a variable glucose infusion rate (GIR)
  - Experiment ends when insulin effect can no longer be measured (GIR=0)
- Insulin PK: Insulin Plasma Concentration
  - Affected by intrinsic insulin properties such as structure, receptor affinity
  - Affected by extrinsic factors such as formulation, injection site, volume, renal function, diabetic state
- Insulin PD: Glucose Infusion Rate (GIR)
  - Reflects insulin effect on glucose disposal rate minus glucose production rate
  - Depends on insulin PK, PD (potency), and subject insulin sensitivity
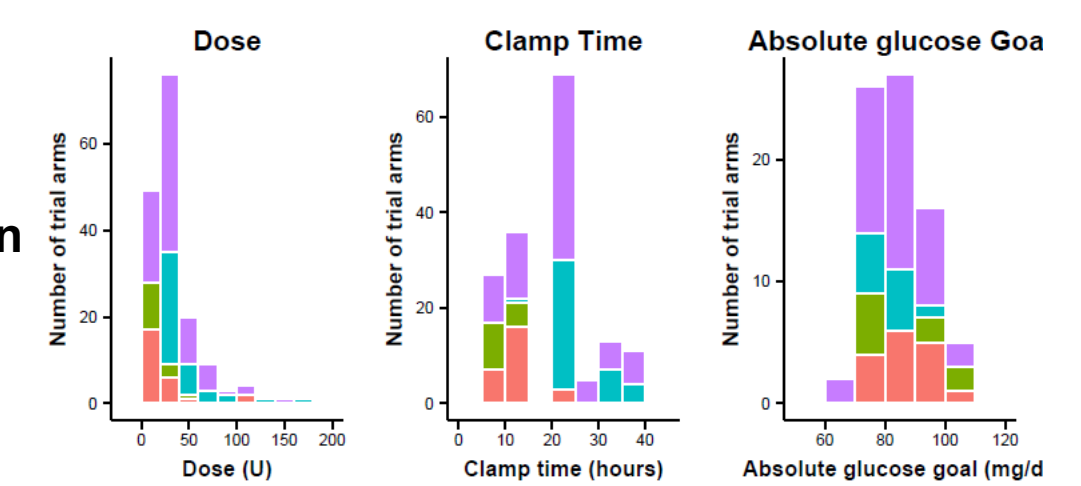
Database

- 53 trials/165 arms with published insulin concentration and glucose infusion rate (GIR) time-action profiles were digitized and converted to common units.
  - Prandial insulins: regular human insulin (RHI), Lispro
  - Basal insulins: Glargine, Degludec
- Demographics:
  - Similar distributions for each insulin class
- Trial Design
  - Doses higher and clamp duration longer for basal insulins

Subset	Trials	Arms
All	53	166
Insulins		
RHI	17	29
lispro	14	30
glargine	27	50
degludec	5	14
Indication		
HV	22	75
T1DM	17	43
T2DM	15	43

Trials — **Trials Arms** — **Publication Year**

Insulin
1. RHI
2. Lispro
3. Glargine
4. Degludec
5. Other

Database

Dose — **Clamp Time** — **Absolute glucose Goal**

Study Design

Population

Percentage of males — Weight — Disease duration — BMI — Baseline hbA1c — Baseline hbA1c

indication
HV
T1DM
T2DM
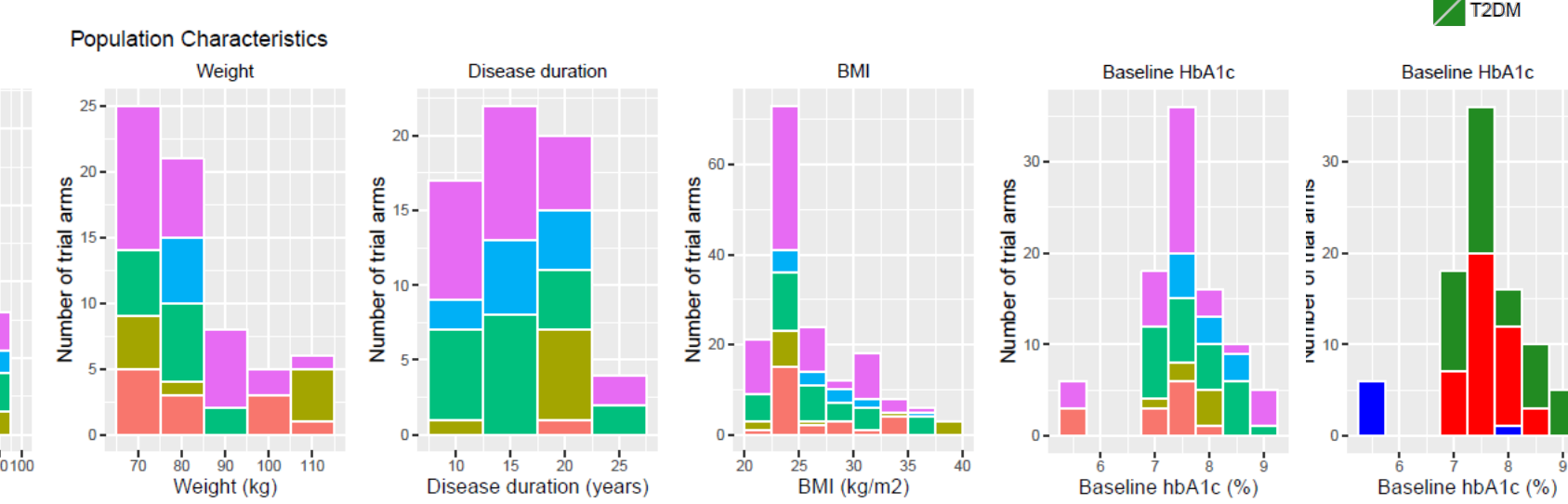
Prior and Exploratory Modeling

Insulin PK
- Insulin exhibits Michaelis-Menten plus linear clearance during RHI IV clamp (Fancourt, 2015)
- ND and T1DM exhibit similar PK during RHI IV clamp (Burroughs, 2015)
- RHI, Lispro, and Glargine have similar IV PK (unpublished survey of insulin IV studies)
  - Examples:

Lispro vs. RHI IV PK (Humalog Label)

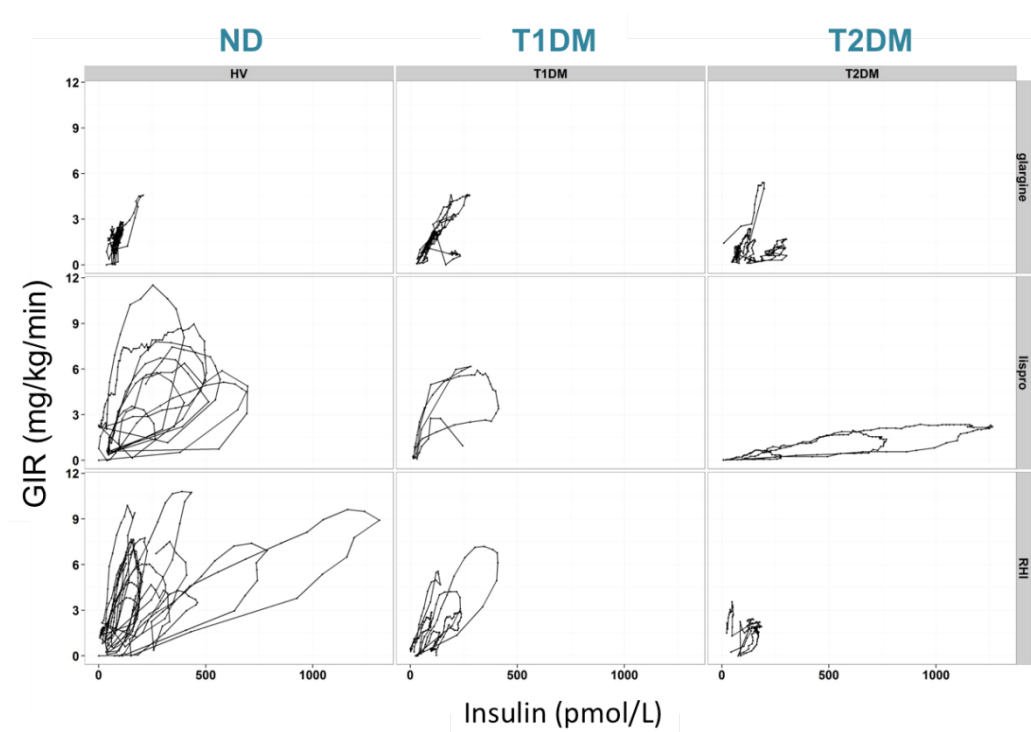| Disease	Insulin	Dose (U/kg)	CL (mL/kg/min)	V (L/kg)	T1/2 (min)
Healthy	Lispro	0.1	21.0	1.55	51
		0.2	9.6	0.72	55
	RHI	0.1	21.4	1.37	47
		0.2	9.4	1.12	77

Glargine vs. RHI IV PK (Mudaliar, 2002)
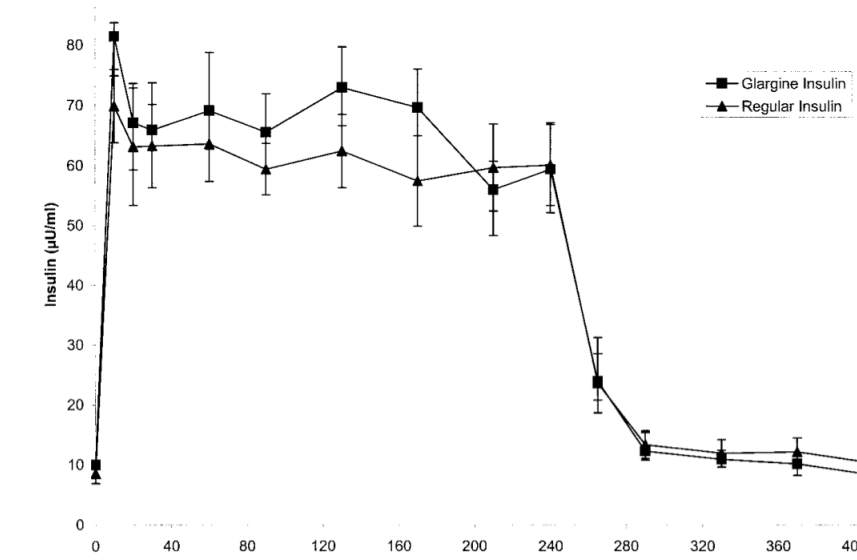
Insulin PK – PD Effect Delay
- A hysteresis (delay) between PK and PD was observed
- Non-parametric analysis: typical delay half-life of ~30 min across disease/insulin
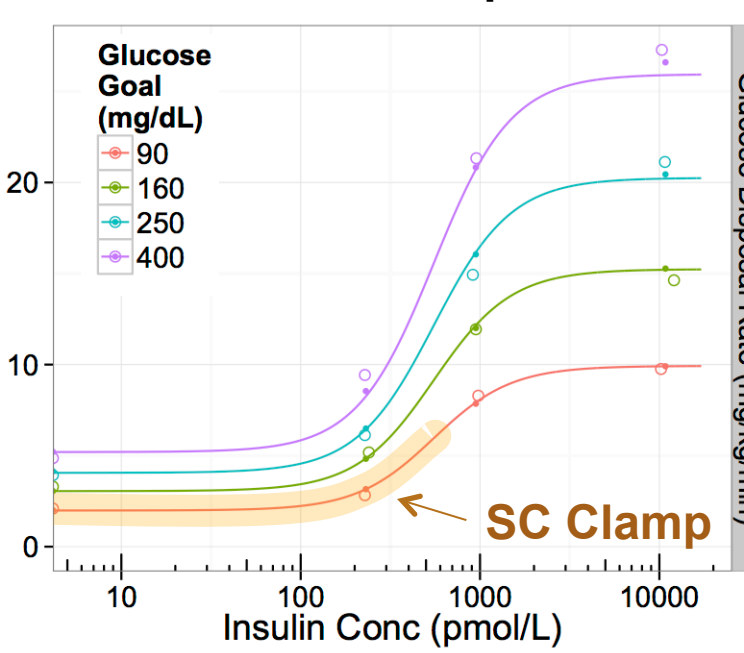
SC Database PK-PD Hysteresis

SC Database PK-PD Delay

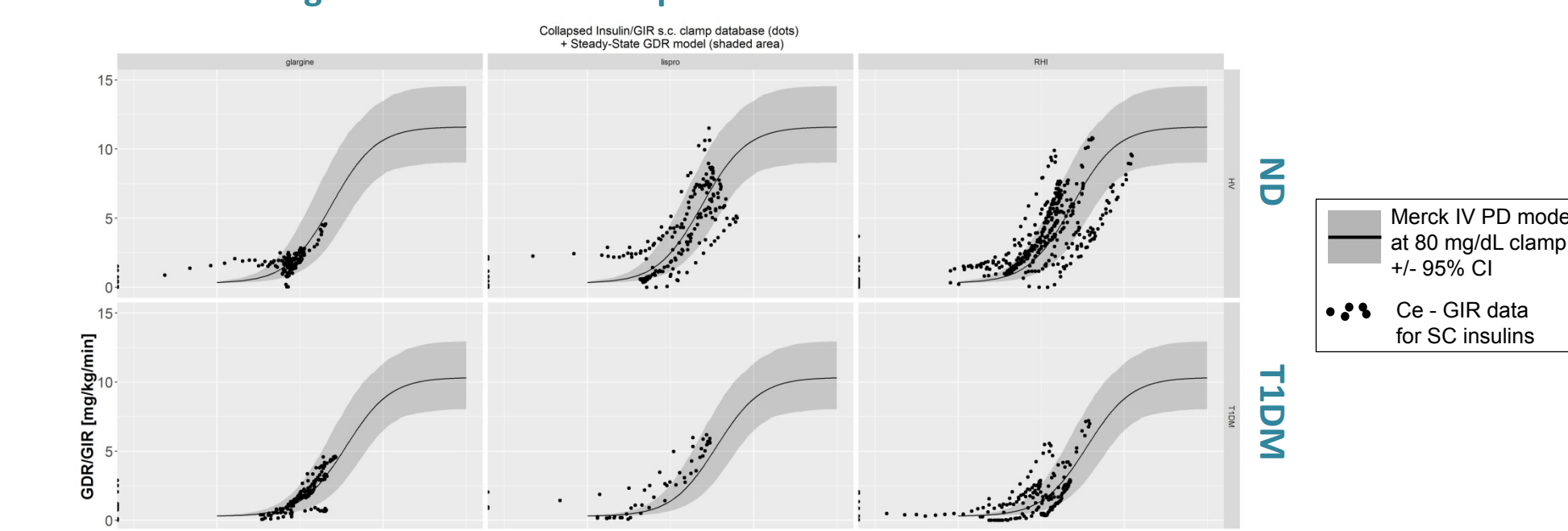| Disease	Drug	N trial arms	Keo (1/min) mean	s.d.
HV	degludec	3	0.002	
	glargine	10	0.077	0.086
	lispro	9	0.021	0.006
	RHI	15	0.022	0.009
T1DM	degludec	3	0.025	0.032
	glargine	12	0.085	0.088
	lispro	3	0.144	0.105
	RHI	6	0.048	0.026
T2DM	degludec	3	0.008	0.009
	glargine	10	0.036	0.062
	lispro	3	0.019	0.005
	RHI	4	0.011	0.007

Insulin PD
- Insulins have similar IV clamp PK-PD structural relationship (Fancourt, 2015)
  - Supported by similar in-vitro properties
  - Insulin conc. drives GIR as Hill function
  - Emax and EC50 varies with disease/population

Merck IV RHI Clamp PD Model

Glucose Goal (mg/dL)
- 90
- 160
- 250
- 400

SC Clamp

- SC clamp studies conducted at basal conditions
  - euglycemic glucose goals (70-100 mg/dL)
  - low insulin concentrations (< 1000 pM)
  - Low GIR (< 10 mg/kg/min)
  - (orange shaded area in figure)
- PD response to SC insulin is similar to IV RHI clamp
  - After non-parametric hysteresis collapse, PK-GIR relationship after SC dosing is superimposable on Merck IV RHI clamp steady-state PD model

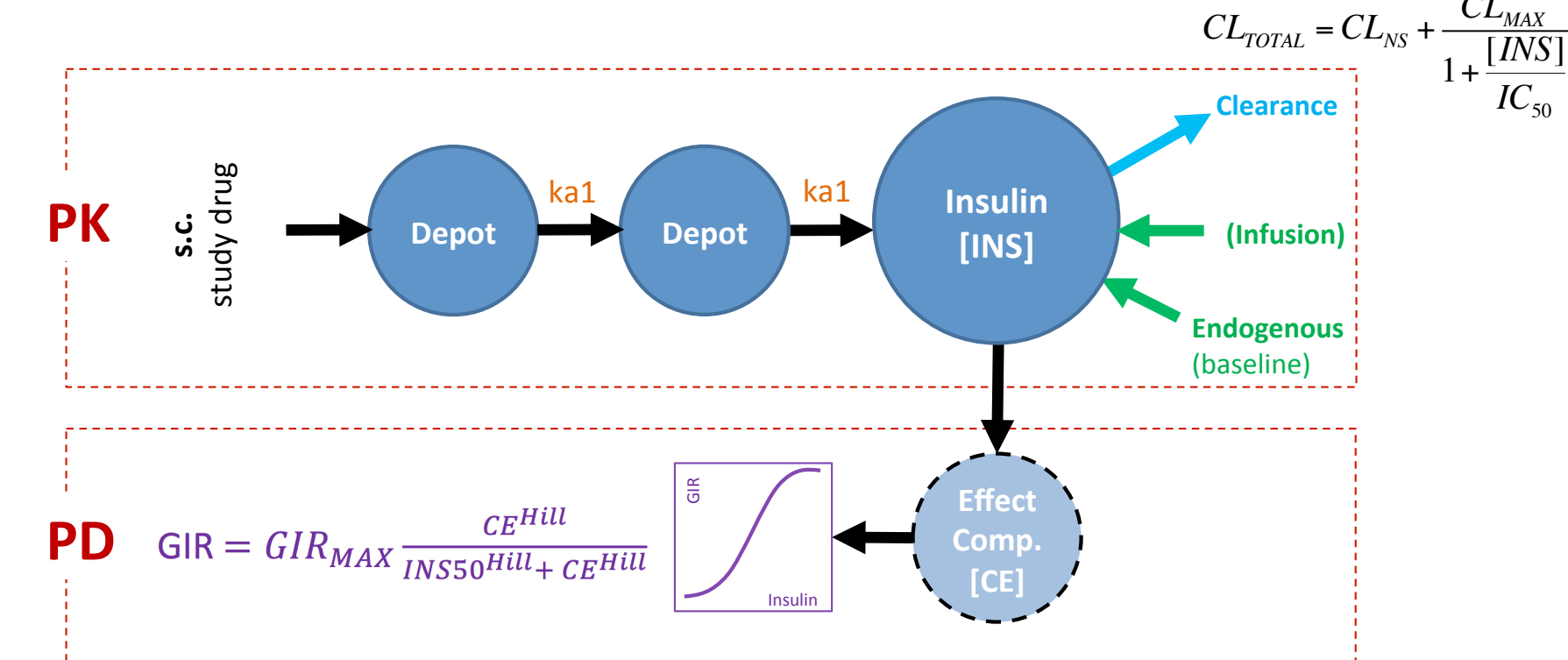**Comparison of SC Database PK-PD data after hysteresis collapse, with Merck IV RHI Clamp PD Model**

Glargine — Lispro — RHI

Merck IV PD model at 80 mg/dL clamp
Ce - GIR data for SC insulins

ND / T1DM

Modeling

Final SC PK/PD Model

$$CL_{TOTAL} = CL_{INS} + \frac{CL_{MAX}}{1 + \frac{[INS]}{IC_{50}}}$$

PK: s.c. study drug → Depot → ka1 → Depot → ka1 → Insulin [INS]
- Clearance
- (Infusion)
- Endogenous (baseline)

PD: $GIR = GIR_{MAX} \frac{CE^{Hill}}{INS50^{Hill} + CE^{Hill}}$ → Effect Comp. [CE]

PK Model Structure
- One-compartment with two sequential absorption compartments
  - RHI, Lispro, and Glargine: Michaelis-Menten (MM) + linear clearance
  - Degludec: linear clearance
- Constant endogenous infusion represents baseline background basal insulin therapy and/or endogenous insulin production

PK Parameters
- KA1: insulin absorption rate (through two sequential absorption compartments)
- $CL_{(INS)}$: 1st order linear insulin clearance
- CL_{MAX}: maximum MM insulin clearance
- IC_{50}: insulin conc at ½ maximum MM insulin clearance
- V: Volume of distribution
- BSLN: baseline insulin, represented as constant endogenous insulin infusion
- F: SC bioavailability

PK Variability
- Trial level: baseline, absorption rate and bioavailability
- Trial arm level: absorption rate and bioavailability
  - Baseline assumed to be the same for each population within a trial
- Residual variability: additive and proportional

PK Training
- Priors: intrinsic clearance parameterization using IV clearance and volume
  - Allows estimation of true bioavailability and absorption rate
- RHI, Lispro, and Glargine
  - Fixed Michaelis-Menten and linear clearance (Burroughs, 2015) and volume (Kandala, 2015) from IV RHI clamp studies
- Degludec
  - Fixed linear clearance and volume from degludec IV/SC cross-over study (Novo Nordisk CSR NN1250-4000)

PD Model Structure
- Insulin effect compartment (Ce) for time-delay
- Sigmoidal (Hill) function predicts GIR from insulin conc

PD Parameters
- Keo: delay rate between measured plasma insulin conc. and GIR response
- GIR_{MAX}: Maximum GIR = 900 mg/min (ND) or 750 mg/min in T1/2DM (Fancourt, 2016).
  - Cannot be estimated from SC studies due to low insulin conc.
- IN_{50}: depends on patient population and insulin
  - degludec has higher value due to high plasma protein binding
- Hill coefficient: steepness of the Ce-GIR relationship

PD Variability
- No differences between insulins once in the systemic circulation: ke0 and Hill are independent of insulin and population
- No between-trial or arm variability (assumed represented by PK variability)
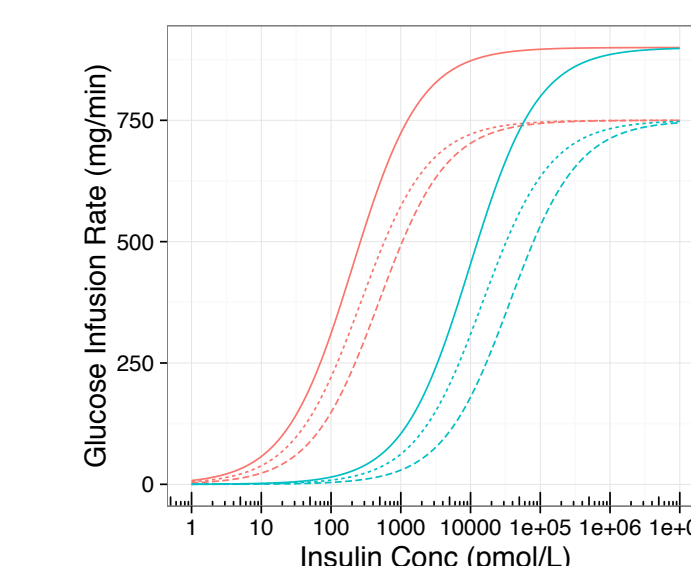- Additive residual variability on GIR

Results

PK Parameters

Insulin	Disease	F IIV	F IOV	KA1 (1/min) IIV	KA1 (1/min) IOV	BSLN (pM) IIV	BSLN (pM) IOV	CL_INS (L/min) All	CL_MAX (L/min) All	V (L) All
RHI	ND	0.93	0.21	0.0095	0.24	43	0.62	0.41	1.05	12.4
lispro	ND	1.03		0.0165		46		0.41	1.05	12.4
glargine	ND	0.47	0.11	0.0019	0.12	73	-	0.41	1.05	12.4
degludec	ND	0.74		0.0032		0		0.042	-	18.7
RHI	T1DM	0.78		0.0194		16		0.41	1.05	12.4
lispro	T1DM	0.65	0.18	0.0204	0.13	19	0.91	0.41	1.05	12.4
glargine	T1DM	0.46		0.0025	0.13	51	-	0.41	1.05	12.4
degludec	T1DM	1.31		0.0021		0		0.042	-	18.7
RHI	T2DM	0.60		0.0070		99		0.41	1.05	12.4
lispro	T2DM	1.06	0.27	0.0113	0.15	20	0.38	0.41	1.05	12.4
glargine	T2DM	0.25		0.0023		84	-	0.41	1.05	12.4
degludec	T2DM	1.08		0.0012		0		0.042	-	18.7

PD Parameters

Disease	Keo (1/min)	Keo half-life (min)	GIR_MAX (mg/min)	INS50 RHI, lispro, glargine (pM)	INS50 degludec (pM)	HILL (-)
ND	0.0209	33	900*	205	9 800	0.89
T1DM	0.0209	33	750*	267	14 900	0.89
T2DM	0.0209	33	750*	483	36 600	0.89

Typical Steady-State PK-PD Relationship

Insulin: RHI, lispro, glargine; degludec
Disease: ND, T1DM, T2DM

Typical PK Time-Action Profile — **Typical PD Time-Action Profile**
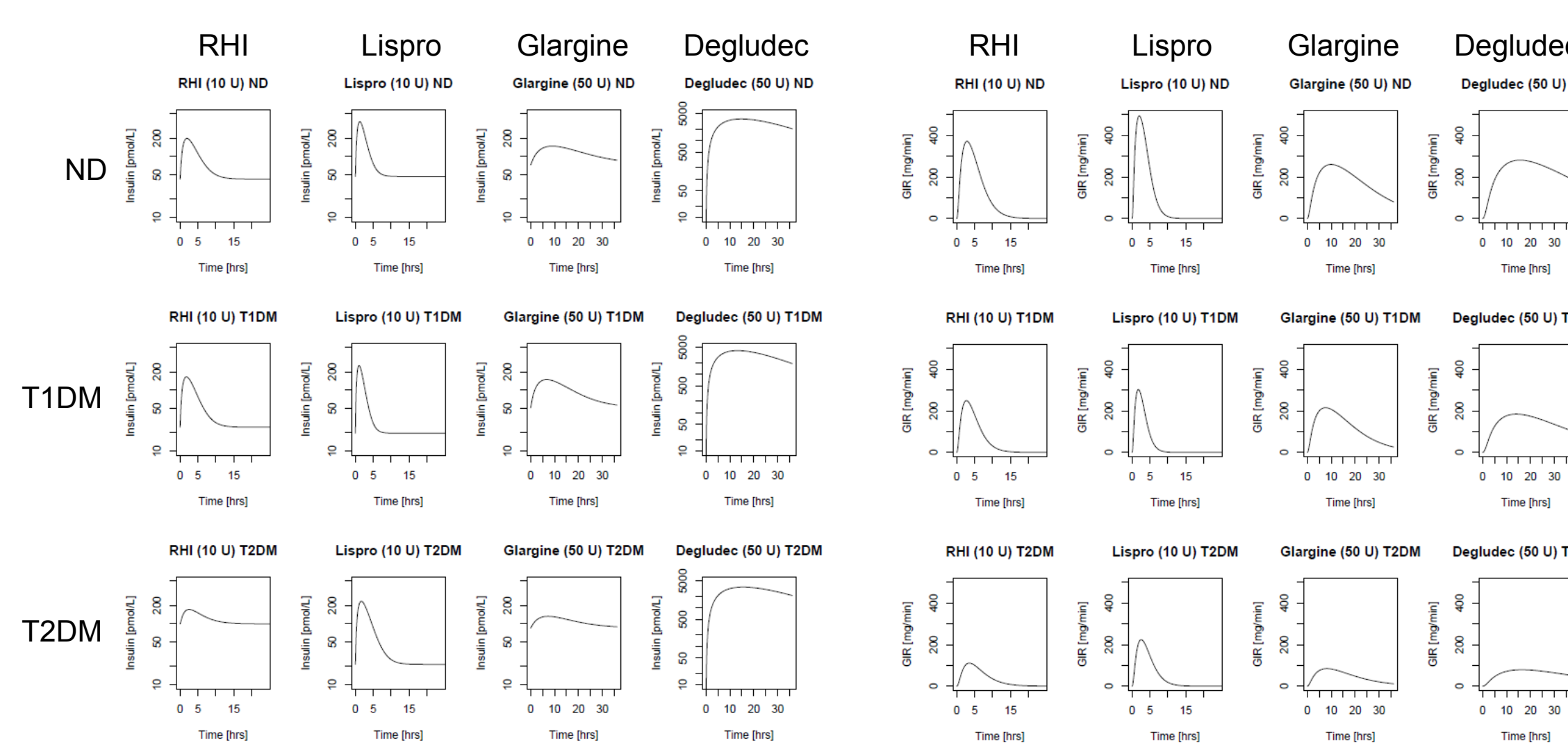
RHI — Lispro — Glargine — Degludec (ND, T1DM, T2DM)
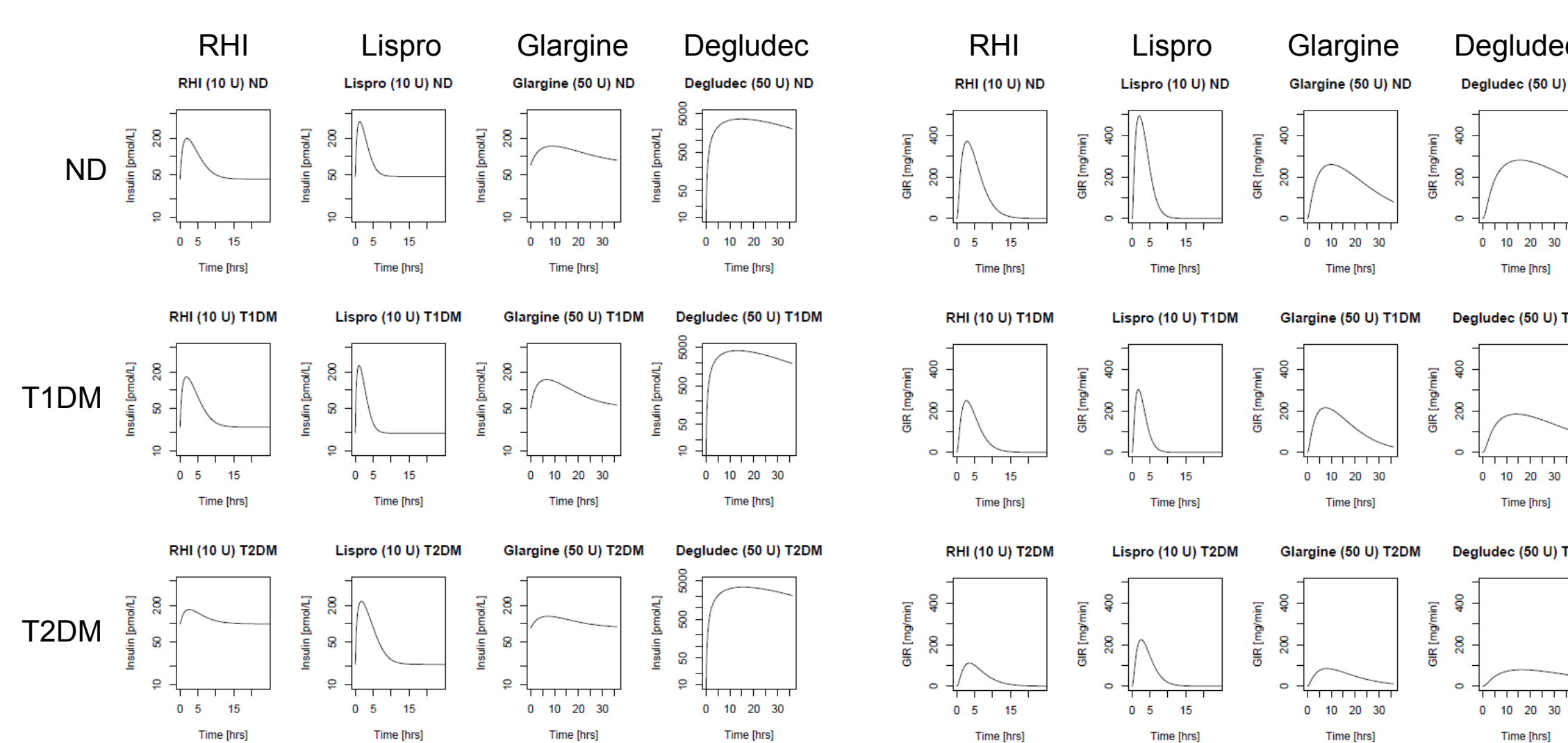
Conclusions

- A curated database of SC insulins in clinical glucose clamp studies was modeled, affirming that lispro, RHI, and glargine time-action profiles can be explained by the same structural PKPD model with differences in bioavailability and absorption.
- The models are useful both as comparators and hypothetical backbones for novel insulins.

References
- Fancourt C, Valiathan C, Tatosian D, Cho C, Visser SA. Development of a Joint PKPD Model of the Hyperinsulinemic Glucose Clamp. ACOP 2016.
- Burroughs EG, Fancourt C, Dykstra K, Visser SA. A Model-Based Meta-Analysis of Insulin PK-PD in Glucose Clamp Studies of Diabetes Mellitus Type 1 and Non-Diabetic Human Subjects. ACOP 2016
- Kandala B, Fancourt C, Tsai K, Iwamoto M, Canales C, Cheng A, Crutchlow M, Kelley DE, Visser SA. A Dynamic Model-Based Analysis of a Multi-Level Glycemic Clamp Study of Regular Human Insulin in T1DM Subjects. ACOP 2016.