Physiologically Based Pharmacokinetic (PBPK) Modeling of Clopidogrel and Its Four Relevant Metabolites for CYP2B6, CYP2C8, CYP2C19, and CYP3A4 Drug–Drug–Gene Interaction Predictions

Supplementary Materials

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S1 PBPK Model Building

S1.1 System-Dependent Parameters

Table S1: System-dependent parameters

Enzyme/ Transporter	Mean reference conc.[a] [µmol/l]	Relative organ expression[b]	Localization/ Direction	Half-life liver [h]	Half-life intestine [h]
11β-HSD	1.0[c]	Array [1]	intracellular	36	23
AADAC	1.0[c]	RT-PCR [2]	intracellular	36	23
CES1	42[d] [3]	RT-PCR [2]	intracellular	36	23
CES2	1.02[d,e] [3]	RT-PCR[f] [2]	intracellular	32	23
CYP2B6	1.56 [4]	RT-PCR [5]	intracellular	32	23
CYP2C8	2.56 [4]	RT-PCR [5]	intracellular	23	23
CYP2C9	3.84 [4]	RT-PCR [5]	intracellular	104	23
CYP2C19	0.76 [4]	RT-PCR [5]	intracellular	26	23
CYP3A4	4.32 [4]	RT-PCR [5]	intracellular	36	23
CYP3A5	0.04 [4]	RT-PCR [5]	intracellular	36	23
NRT[g]	1.0[c]	EST [6]	extracellular membrane	36	23
OATP1B1	0.07[h][7]	RT-PCR [8]	influx	36	23
OATP1B3	1.0[c]	Array [1]	influx	36	23
P-gp	1.41 [9]	RT-PCR[i] [8]	efflux	36	23
UGT2B7	0.09[j] [10]	EST [6]	intracellular	36	23

AADAC: arylacetamide deacetylase, Array: microarray expression profile, CES: carboxylesterase, conc.: concentration, CYP: cytochrome P450, EST: expressed sequence tags, HSD: hydroxysteroid dehydrogenase , NRT: noradrenaline reuptake transporter, OATP: organic-anion-transporting, polypeptide, P-gp: P-glycoprotein, RT-PCR: reverse transcription polymerase chain reaction, UGT: uridine 5'-diphospho-glucuronosyltransferase.
[a]: µmol protein/l in the tissue of highest expression
[b]: according to PK-Sim® expression database
[c]: if no information was available, the mean reference concentration was set to 1.0 µmol/l and the catalytic catalytic rate constant was optimized according to [11]
[d]: calculated from protein per mg microsomal protein x 40.0 mg microsomal protein per g liver [12],
[e]: intestinal expression extrapolated from liver expression
[f]: expression reduced to intestinal mucosa duodenum, upper/ lower jejunum, upper/ lower ileum, colon ascendens/ transversum/ descendens/ sigmoid,
non-mucosal tissue small/ large intestine
[g]: expression profile used for general binding partner bupropion
[h]: calculated from transporter per mg membrane protein x 37.0 mg membrane protein per g liver [7]
[i]: with the relative expression in the intestinal mucosa increased by factor 3.57
[j]: calculated from transporter per mg membrane protein x 26.2 mg human kidney microsomal protein per g kidney [12]

S1.2 Clinical Study Data

Table S2: Clinical studies of clopidogrel used for PBPK model development

Compound measured	Clopidogrel dosing regimen		n	Females [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Dataset	Reference
	Route	Dose [mg]								
Clo	iv (bolus, s.d.)	0.1	24	46	White American	46.0±13.0	76.3±15.8	169±9	test	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	1	24	50	White American	41.3±14.7	68.4±11.5	165±9	training	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	10	24	46	White American	44.5±14.9	72.2±13.4	166±8	test	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	30	24	46	White American	43.0±15.9	74.9±12.4	170±7	test	Cushing 2012 [13]
Clo	iv (inf, 4 min, s.d.)	100	24	33	White American	44.4±14.1	77.2±12.4	169±9	training	Cushing 2012 [13]
Clo	iv (inf, 8 min, s.d.)	300	24	50	White American	43.3±15.3	75.6±15.8	167±11	training	Cushing 2012 [13]
Clo	po (tab, s.d.)	75	6	50	European	32.2±14.5	-	-	training	Savu 2016 [14]
Clo	po (-, s.d.)	75	10	-	European	-	-	-	training	Silvestro 2013 [15]
Clo	po (-, s.d.)	75	6	-	Asian	-	-	-	test	Nirogi 2006 [16]
Clo	po (tab, s.d.)	75	20	0	Asian	24.3 (22–29)	64.1 (55–71)	171 (163–185)	test	Zou 2012 [17]
Clo	po (tab, s.d.)	75	24	46	White American	33.7±5.2 (21–42)	72.4±6.83 (59–82)	171±7 (160–181)	test	Di Girolamo 2010 [18]
Clo	po (tab, s.d.)	75	92	0	White American	36±8 (18–52)	75.6±7.0 (60.3–89.7)	174±6 (161–191)	test	Brvar 2014 [19]
Clo	po (tab, s.d.)	75	46	0	European	27.3±6.3	58.2±5.0	166.7±5.7	test	McGregor 2016 [20]
Clo	po (tab, s.d.)	150	8	0	Asian	(20–28)	63.9±7.3	-	training	Shin 2007 [21]
Clo	po (tab, s.d.)	150	36	-	European	-	-	-	test	Robinson 2007 [22]
Clo	po (tab, s.d.)	300	27	0	Asian	24.9±2.4	68.0±7.2	174.5±5.0	training	Kim 2016 [23]
Clo	po (tab, s.d.)	300	20	0	Asian	(25–30)	-	-	test	Zhou 2018 [24]
Clo	po (-, l.d./m.d., 5d)	300/75	24	0	European	31.5±5.5 (23–40)	80.4±7.4 (64–91)	-	training	Härtter 2013 [25]
Clo	po (-, l.d./m.d., 7d)	300/75	8 PM	0	Asian	24.1±2.8	67.3±5.6	-	training	Kim 2008 [26]
Clo	po (-, l.d./m.d., 5d)	300/75	40	0	Asian	26.5±4.0	69.4±6.2	-	test	Kim 2012 [27]
Clo	po (-, l.d./m.d., 6d)	300/75	44	0	Asian	24.3±2.7 (19–33)	70.0±8.2 (56.7–88.9)	175.5±5.5 (163–187)	test	Kim 2009 [28]
Clo	po (-, s.d.)	600	12	0	European	32.8±5.6 (22–40)	81.6±9.4 (68–100)	-	training	Härtter 2013 [25]
Clo	po (tab, s.d.)	600	14	43	European	22.0±1.5 (21–26)	69±10 (54–88)	174±6 (164–183)	training	Holmberg 2014 [29]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, d: dosage period in days, inf: infusion, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet; values for age, weight and height are shown as mean ± standard deviation (range).

Table S2: Clinical studies of clopidogrel used for PBPK model development *(continued)*

Compound measured	Clopidogrel dosing regimen		n	Females [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Dataset	Reference
	Route	Dose [mg]								
Clo-COOH	iv (bolus, s.d.)	0.1	24	46	White American	46.0±13.0	76.3±15.8	169±9	test	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	1	24	50	White American	41.3±14.7	68.4±11.5	165±9	training	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	10	24	46	White American	44.5±14.9	72.2±13.4	166±8	training	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	30	24	46	White American	43.0±15.9	74.9±12.4	170±7	test	Cushing 2012 [13]
Clo-COOH	iv (inf, 4 min, s.d.)	100	24	33	White American	44.4±14.1	77.2±12.4	169±9	training	Cushing 2012 [13]
Clo-COOH	iv (inf, 8 min, s.d.)	300	24	50	White American	43.3±15.3	75.6±15.8	167±11	training	Cushing 2012 [13]
Clo-COOH	po (tab, s.d.)	75	6	50	European	32.2±14.5	-	-	training	Savu 2016 [14]
Clo-COOH	po (-, s.d.)	75	10	-	European	-	-	-	training	Silvestro 2013 [15]
Clo-COOH	po (tab, s.d.)	75	20	0	Asian	24.3 (22–29)	64.1 (55–71)	171 (163–185)	test	Zou 2012 [17]
Clo-COOH	po (-, s.d.)	75	10	-	European	-	-	-	test	Silvestro 2011 [30]
Clo-COOH	po (tab, s.d.)	75	42	50	White American	28.7±7.6 (18–43)	66.7±8.1 (48.8–81.2)	170±1.1 (150–190)	test	Junior 2010 [31]
Clo-COOH	po (tab, s.d.)	75	76	0	Asian	29.1±6.9 (18–45)	77.7±8.8	-	test	Yousef 2013 [32]
Clo-COOH	po (tab, s.d.)	75	12	0	Asian	27.9±3.1	76.5±4.0	174.6±5.4	test	Souri 2006 [33]
Clo-COOH	po (tab, s.d.)	75	32	-	European	-	-	-	test	Ksycinska 2006 [34]
Clo-COOH	po (tab, s.d.)	75	92	0	White American	36±8 (18–52)	75.6±7.0 (60.3–89.7)	174±6 (161–191)	test	Brvar 2014 [19]
Clo-COOH	po (tab, s.d.)	150	24	0	Asian	24.8±6.5	75.3±4.2	-	training	Bahrami 2008 [35]
Clo-COOH	po (tab, s.d.)	300	24	23	White American	42±13 (19–59)	82.8±14.3 (57.5–107)	176±8 (158–190)	training	Small 2008 [36]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	24	0	European	31.5±5.5	80.4±7.4	-	training	Härtter 2013 [25]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	40	0	Asian	26.5±4.0	69.4±6.2	-	test	Kim 2012 [27]
Clo-COOH	po (-, l.d./m.d., 6d)	300/75	44	0	Asian	24.3±2.7 (19–33)	70.0±8.2 (56.7–88.9)	175.5±5.5 (163–187)	test	Kim 2009 [28]
Clo-COOH	po (-, s.d.)	600	12	0	European	32.8±5.6	81.6±9.4	-	training	Härtter 2013 [25]
Clo-AG	po (tab, s.d.)	75	6	50	European	32.2±14.5	-	-	training	Savu 2016 [14]
Clo-AG	po (-, s.d.)	75	10	-	European	-	-	-	training	Silvestro 2013 [15]
Clo-AG	po (-, s.d.)	75	10	-	European	-	-	-	test	Silvestro 2011 [30]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, d: dosage period in days, inf: infusion, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet; values for age, weight and height are shown as mean ± standard deviation (range).

Table S2: Clinical studies of clopidogrel used for PBPK model development *(continued)*

Compound measured	Clopidogrel dosing regimen		n	Females [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Dataset	Reference
	Route	Dose [mg]								
2-Oxo-Clo	po (-, s.d.)	75	5	-	European	-	-	-	training	Silvestro 2013 [15]
Clo-AM	po (-, s.d.)	75	5	-	European	-	-	-	test	Silvestro 2013 [15]
Clo-AM	po (-, m.d., 10d)	75	9	33	Asian	30.3±7.5	63.8±8.5	165.4±7.2	test	Li 2018 [37]
Clo-AM	po (tab, s.d.)	300	27	0	Asian	24.9±2.4	68.0±7.2	174.5±5.0	training	Kim 2016 [23]
Clo-AM	po (tab, s.d.)	300	20	0	Asian	(25–30)	-	-	test	Zhou 2018 [24]
Clo-AM	po (tab, s.d.)	300	36	39	Japanese	-	-	-	test	Umemura 2016 [38]
Clo-AM	po (tab, s.d.)	300	66	29	White American	42±17	76.3±11.6	-	test	Takahashi 2008 [39]
Clo-AM	po (tab, s.d.)	300	16	19	Asian	31±10	65.2±8.9	-	test	Small 2010 [40]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	0	Japanese	(20–35)	(50.4–87.4)	-	training	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	0	Japanese	(20–35)	(50.4–87.4)	-	training	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	17	White American	33.8±10 (29–44)	75.9±10.8 (49.6–76.8)	171.7±9.3	training	Angiolillo 2011 [42]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	66	0	European	31±10	78.5±8.9	175.3±6.3	test	Hurbin 2012 [43]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	-	White American	-	-	-	test	Furlong 2013 [44]
Clo-AM	po (tab, s.d.)	600	14	43	European	22.0±1.5 (21–26)	69±10 (54–88)	174±6 (164–183)	training	Holmberg 2014 [29]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, d: dosage period in days, inf: infusion, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet; values for age, weight and height are shown as mean ± standard deviation (range).

S1.3 Drug-Dependent Parameters

Table S3: Drug-dependent parameters of the final clopidogrel parent-metabolite PBPK model

Parameter	Unit	Value	Source	Literature	Reference	Description
			Clopidogrel			
Molecular weight	g/mol	321.82	Lit.	321.82	[46]	Molecular weight
TPSA*	$Å^2$		Lit.	29.54	[46]	Topological polar surface area
pKa, base		4.66[a]	Lit.	4.6–4.77	[46–48]	Acid dissociation constant
Solubility (pH)	mg/ml	0.06 (7.4)	Lit.	0.06 (7.4)	[46]	Solubility
Lipophilicity	log units	3.23	Opt.	logP: 2.50–4.03; $logD_{7.4}$: 4.03[b]	[46–48]	Lipophilicity
f_u	%	2	Lit.	2	[49]	Fraction unbound
CES1 K_M → Clo-COOH	µmol/l	46.40	Lit.	46.40[c]	[50]	Michaelis-Menten constant
CES1 k_{cat} → Clo-COOH	1/min	2.51	Opt.	3558.00	[50]	Catalytic rate constant
CES2 K_M → Clo-COOH	µmol/l	14.08	Lit.	14.08[c]	[51]	Michaelis-Menten constant
CES2 k_{cat} → Clo-COOH	1/min	4960.15	Opt.	357.00	[51]	Catalytic rate constant
CYP2C19 K_M → 2-Oxo-Clo	µmol/l	0.05	Lit.	0.05[c]	[52]	Michaelis-Menten constant
CYP2C19 NM k_{cat} → 2-Oxo-Clo	1/min	28.51	Opt.	7.52	[52]	Catalytic rate constant
CYP2C19 IM k_{cat} → 2-Oxo-Clo	1/min	14.26	Calc.	-	-	Catalytic rate constant
CYP2C19 PM k_{cat} → 2-Oxo-Clo	1/min	0	Calc.	-	-	Catalytic rate constant
CYP3A4 K_M → 2-Oxo-Clo	µmol/l	2.07	Lit.	2.07[c]	[51]	Michaelis-Menten constant
CYP3A4 k_{cat} → 2-Oxo-Clo	1/min	55.36	Opt.	266.00	[51]	Catalytic rate constant
GFR fraction		1	Asm.	-	-	Filtered drug in the urine
EHC continuous fraction		1	Asm.	-	-	Bile fraction continously released
Intestinal permeability	cm/min	$1.50 \cdot 10^{-4}$	Opt.	$7.98 \cdot 10^{-6}$	[53]	Transcellular intestinal permeability
Cellular permeability	cm/min	0.07	Calc.	Charge dependent Schmitt	[54]	Permeability into the cellular space
Partition coefficients			Calc.	PK-Sim Standard	[55]	Organ-plasma partition coefficients
Dissolution time (Weibull)	min	15.16	Lit.	15.16[d]	[56]	Dissolution time (50%)
Dissolution shape (Weibull)		1.16	Opt.	3.17	[56]	Dissolution shape

-: not available, *: no model parameter, listed for additional information, [a]: mean, [b]: calculated by Chemicalize, [c]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$) calculated according to [45], [d]: obtained from literature dissolution profile, 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, IM: intermediate metabolizer, lit.: literature, MBI: mechanism-based inactivation, NM: normal metabolizer, OATP: organic-anion-transporting polypeptide, opt.: optimized, PM: poor metabolizer, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S3: Drug-dependent parameters of the final clopidogrel parent-metabolite PBPK model *(continued)*

Parameter	Unit	Value	Source	Literature	Reference	Description
CYP1A2 K_i	µmol/l	12.15	Lit.	12.15	[57]	Conc. for half-maximal inhibition (CI)
CYP2B6 K_i	µmol/l	$7.3 \cdot 10^{-3}$	Lit.	$7.3 \cdot 10^{-3}$–$1.7 \cdot 10^{-2}$[c]	[57–59]	Conc. for half-maximal inhibition (CI)
CYP2B6 K_I	µmol/l	$5.7 \cdot 10^{-3}$	Lit.	$5.7 \cdot 10^{-3}$–2.4[c]	[59–63]	Conc. for half-maximal inactivation (MBI)
CYP2B6 k_{inact}	1/min	1.3	Lit.	$3.7 \cdot 10^{-2}$–1.9	[59–63]	Maximum inactivation rate constant (MBI)
CYP2C8 K_i	µmol/l	8.10[a]	Lit.	1.4–16.6[c]	[48, 57, 64, 65]	Conc. for half-maximal inhibition (CI)
CYP2C9 K_i	µmol/l	6.70	Lit.	6.70	[57]	Conc. for half-maximal inhibition (CI)
CYP2C19 K_i	µmol/l	5.00[a]	Lit.	0.262, 9.74[c]	[57, 66]	Conc. for half-maximal inhibition (CI)
CYP2C19 K_I	µmol/l	4.86	Lit.	4.86[c]	[66]	Conc. for half-maximal inactivation (MBI)
CYP2C19 k_{inact}	1/min	$5.57 \cdot 10^{-2}$	Lit.	$5.57 \cdot 10^{-2}$	[66]	Maximum inactivation rate constant (MBI)
CYP3A4 K_i	µmol/l	17.41[a]	Lit.	3.7, 31.13[c]	[48, 64]	Conc. for half-maximal inhibition (CI)
CYP3A4 K_I	µmol/l	19.36	Lit.	19.36[c]	[48]	Conc. for half-maximal inactivation (MBI)
CYP3A4 k_{inact}	1/min	$5.3 \cdot 10^{-2}$	Lit.	$5.3 \cdot 10^{-2}$	[48]	Maximum inactivation rate constant (MBI)
OATP1B1 K_i	µmol/l	1.975	Lit.	1.975	[67]	Conc. for half-maximal inhibition (CI)
Clopidogrel carboxylic acid						
Molecular weight	g/mol	307.79	Lit.	307.79	[68]	Molecular weight
TPSA*	$Å^2$		Lit.	40.54	[68]	Topological polar surface area
pKa, base		5.75	Lit.	5.75	[68]	Acid dissociation constant
pKa, acid		1.79	Lit.	1.79	[68]	Acid dissociation constant
Solubility (pH)	mg/ml	3.98 (7.4)	Lit.	3.98 (7.4)	[68]	Solubility
Lipophilicity	log units	3.01	Opt.	logP: 2.57; $logD_{7.4}$: 1.03[b]	[68]	Lipophilicity
f_u	%	0.10	Opt.	≤ 1	[69]	Fraction unbound
UGT2B7 $K_M \rightarrow$ Clo-AG	µmol/l	20.30	Lit.	20.30[c]	[70]	Michaelis-Menten constant
UGT2B7 $k_{cat} \rightarrow$ Clo-AG	1/min	14637.76	Opt.	50.50	[70]	Catalytic rate constant
GFR fraction		1	Asm.	-	-	Filtered drug in the urine
EHC continuous fraction		1	Asm.	-	-	Bile fraction continously released
Intestinal permeability	cm/min	$1.45 \cdot 10^{-4}$	Calc.	$1.45 \cdot 10^{-4}$	-	Transcellular intestinal permeability
Cellular permeability	cm/min	0.05	Calc.	PK-Sim Standard	[55]	Permeability into the cellular space
Partition coefficients			Calc.	PK-Sim Standard	[55]	Organ-plasma partition coefficients
CYP2C8 K_i	µmol/l	61.00[a]	Lit.	54, 68	[64]	Conc. for half-maximal inhibition (CI)
CYP3A4 K_i	µmol/l	280.00	Lit.	280	[64]	Conc. for half-maximal inhibition (CI)

-: not available, *: no model parameter, listed for additional information, [a]: mean, [b]: calculated by Chemicalize, [c]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$) calculated according to [45], [d]: obtained from literature dissolution profile, 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, IM: intermediate metabolizer, lit.: literature, MBI: mechanism-based inactivation, NM: normal metabolizer, OATP: organic-anion-transporting polypeptide, opt.: optimized, PM: poor metabolizer, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S3: Drug-dependent parameters of the final clopidogrel parent-metabolite PBPK model *(continued)*

Parameter	Unit	Value	Source	Literature	Reference	Description
			Clopidogrel acyl glucuronide			
Molecular weight	g/mol	483.92	Lit.	483.92	[71]	Molecular weight
TPSA*	$Å^2$		Lit.	136.76	[71]	Topological polar surface area
pKa, base		4.42[a]	Lit.	4.23, 4.60	[48, 71]	Acid dissociation constant
pKa, acid		2.83[a]	Lit.	2.65, 3.01	[48, 71]	Acid dissociation constant
Solubility (pH)	mg/ml	74.17 (7.4)	Lit.	74.17 (7.4)	[71]	Solubility
Lipophilicity	log units	0.02	Opt.	logP: 0.264, 1.345; $logD_{7.4}$: -1.53[b]	[48, 71]	Lipophilicity
f_u	%	1	Lit.	1	[48]	Fraction unbound
$CL_{ren} \rightarrow$ sink	1/min	1076.46	Opt.	-	-	Unspecific renal clearance
EHC continuous fraction		1	Asm.	-	-	Bile fraction continously released
Intestinal permeability	cm/min	$1.71 \cdot 10^{-8}$	Calc.	$1.71 \cdot 10^{-8}$	-	Transcellular intestinal permeability
Cellular permeability	cm/min	$3.10 \cdot 10^{-6}$	Calc.	PK-Sim Standard	[55]	Permeability into the cellular space
Partition coefficients			Calc.	PK-Sim Standard	[55]	Organ-plasma partition coefficients
CYP2C8 K_i	µmol/l	10.80	Lit.	1.9–28.19[c]	[48, 64]	Conc. for half-maximal inhibition (CI)
CYP2C8 K_I	µmol/l	9.87	Lit.	9.87[c]	[48]	Conc. for half-maximal inactivation (MBI)
CYP2C8 k_{inact}	1/min	$4.7 \cdot 10^{-2}$	Lit.	$4.7 \cdot 10^{-2}$	[48]	Maximum inactivation rate constant (MBI)
CYP3A4 K_i	µmol/l	95.46[a]	Lit.	21, 169.92[c]	[48, 64]	Conc. for half-maximal inhibition (CI)
OATP1B1 K_i	µmol/l	5.45	Lit.	5.45	[67]	Conc. for half-maximal inhibition (CI)

-: not available, *: no model parameter, listed for additional information, [a]: mean, [b]: calculated by Chemicalize, [c]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$) calculated according to [45], [d]: obtained from literature dissolution profile, 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, IM: intermediate metabolizer, lit.: literature, MBI: mechanism-based inactivation, NM: normal metabolizer, OATP: organic-anion-transporting polypeptide, opt.: optimized, PM: poor metabolizer, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S3: Drug-dependent parameters of the final clopidogrel parent-metabolite PBPK model *(continued)*

Parameter	Unit	Value	Source	Literature	Reference	Description
			2-Oxo-clopidogrel			
Molecular weight	g/mol	337.82	Lit.	337.82	[72]	Molecular weight
TPSA*	$Å^2$		Lit.	46.61	[72]	Topological polar surface area
pKa, base		4.18[a]	Lit.	3.945, 4.42	[72, 73]	Acid dissociation constant
pKa, acid		8.46	Lit.	8.46	[72]	Acid dissociation constant
Solubility (pH)	mg/ml	0.02 (7.4)	Lit.	0.02 (7.4)	[72]	Solubility
Lipophilicity	log units	3.06	Opt.	logP: 2.868; $logD_{7.4}$: 2.83[b]	[72]	Lipophilicity
f_u	%	7.42	Lit.	7.42	[74]	Fraction unbound
CYP2C19 $K_M \rightarrow$ Clo-AM	µmol/l	3.03	Lit.	3.03[c]	[52]	Michaelis-Menten constant
CYP2C19 NM $k_{cat} \rightarrow$ Clo-AM	1/min	0.15	Opt.	9.06	[52]	Catalytic rate constant
CYP2C19 IM $k_{cat} \rightarrow$ Clo-AM	1/min	0.07	Calc.	-	-	Catalytic rate constant
CYP2C19 PM $k_{cat} \rightarrow$ Clo-AM	1/min	0	Calc.	-	-	Catalytic rate constant
CYP3A4 $K_M \rightarrow$ Clo-AM	µmol/l	6.97	Lit.	6.97[c]	[52]	Michaelis-Menten constant
CYP3A4 $k_{cat} \rightarrow$ Clo-AM	1/min	33.64	Opt.	3.63	[52]	Catalytic rate constant
$CL_{hep} \rightarrow$ sink	1/min	$3.33 \cdot 10^{-3}$	Opt.	-	-	Unspecific hepatic clearance
GFR fraction		1	Asm.	-	-	Filtered drug in the urine
EHC continuous fraction		1	Asm.	-	-	Bile fraction continously released
Intestinal permeability	cm/min	$1.03 \cdot 10^{-4}$	Calc.	$1.03 \cdot 10^{-4}$	-	Transcellular intestinal permeability
Cellular permeability	cm/min	0.03	Calc.	PK-Sim Standard	[55]	Permeability into the cellular space
Partition coefficients			Calc.	Schmitt	[75]	Organ-plasma partition coefficients
CYP2B6 K_i	µmol/l	0.65	Lit.	0.65	[57]	Conc. for half-maximal inhibition (CI)
CYP2B6 K_I	µmol/l	0.71	Lit.	0.71[c]	[60]	Conc. for half-maximal inactivation (MBI)
CYP2B6 k_{inact}	1/min	$1.63 \cdot 10^{-1}$	Lit.	$1.63 \cdot 10^{-1}$	[60]	Maximum inactivation rate constant (MBI)
CYP2C8 K_i	µmol/l	8.77[a]	Lit.	2.1–16.95[c]	[48, 57, 64]	Conc. for half-maximal inhibition (CI)
CYP2C19 K_i	µmol/l	7.49[a]	Lit.	0.50–14.49[c]	[57, 66]	Conc. for half-maximal inhibition (CI)
CYP3A4 K_i	µmol/l	4.05[a]	Lit.	2.4, 5.70[c]	[48, 64]	Conc. for half-maximal inhibition (CI)
OATP1B1 K_i	µmol/l	4.09	Lit.	4.09	[67]	Conc. for half-maximal inhibition (CI)

-: not available, *: no model parameter, listed for additional information, [a]: mean, [b]: calculated by Chemicalize, [c]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$) calculated according to [45], [d]: obtained from literature dissolution profile, 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, IM: intermediate metabolizer, lit.: literature, MBI: mechanism-based inactivation, NM: normal metabolizer, OATP: organic-anion-transporting polypeptide, opt.: optimized, PM: poor metabolizer, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S3: Drug-dependent parameters of the final clopidogrel parent-metabolite PBPK model *(continued)*

Parameter	Unit	Value	Source	Literature	Reference	Description
			Clopidogrel thiol H4			
Molecular weight	g/mol	355.83	Lit.	355.83	[76]	Molecular weight
TPSA*	$Å^2$		Lit.	66.84	[76]	Topological polar surface area
pKa, base		4.93[a]	Lit.	4.43–5.45	[47, 73, 76]	Acid dissociation constant
pKa1, acid		3.15[a]	Lit.	2.47–3.98	[47, 73, 76]	Acid dissociation constant
pKa2, acid		9.49[a]	Lit.	9.15, 9.82	[47, 76]	Acid dissociation constant
Solubility (pH)	mg/ml	9.83 (7.4)	Lit.	9.83 (7.4)	[76]	Solubility
Lipophilicity	log units	3.00	Opt.	logP: 1.137–1.96; $logD_{7.4}$: -0.48[b]	[47, 73, 76]	Lipophilicity
f_u	%	0.97	Opt.	≤ 1	[69]	Fraction unbound
$CL_{hep} \rightarrow$ sink	1/min	452.55	Opt.	-	-	Unspecific hepatic clearance
GFR fraction		1	Asm.	-	-	Filtered drug in the urine
EHC continuous fraction		1	Asm.	-	-	Bile fraction continously released
Intestinal permeability	cm/min	$7.03 \cdot 10^{-5}$	Calc.	$7.03 \cdot 10^{-5}$	-	Transcellular intestinal permeability
Cellular permeability	cm/min	0.02	Calc.	PK-Sim Standard	[55]	Permeability into the cellular space
Partition coefficients			Calc.	Rodgers + Rowland	[77, 78]	Organ-plasma partition coefficients

-: not available, *: no model parameter, listed for additional information, [a]: mean, [b]: calculated by Chemicalize, [c]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$) calculated according to [45], [d]: obtained from literature dissolution profile, 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, IM: intermediate metabolizer, lit.: literature, MBI: mechanism-based inactivation, NM: normal metabolizer, OATP: organic-anion-transporting polypeptide, opt.: optimized, PM: poor metabolizer, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S4: Partition coefficients between intracellular space and plasma of the final clopidogrel parent-metabolite PBPK model

Tissue	Clopidogrel[a]	Clo-COOH[a]	Clo-AG[a]	2-Oxo-Clo[b]	Clo-AM[c]
Bone	9.31	0.28	$7.95 \cdot 10^{-3}$	2.06	0.10
Brain	3.81	0.12	$9.38 \cdot 10^{-3}$	9.36	0.05
Fat	27.21	0.82	$9.97 \cdot 10^{-3}$	75.02	0.05
Gonads	1.16	0.04	$8.55 \cdot 10^{-3}$	2.87	0.05
Heart	3.54	0.11	$8.67 \cdot 10^{-3}$	9.53	0.16
Kidney	1.91	0.06	$8.60 \cdot 10^{-3}$	5.44	0.13
Stomach	2.22	0.07	$8.82 \cdot 10^{-3}$	5.93	0.16
Small intestine	2.22	0.07	$8.82 \cdot 10^{-3}$	5.93	0.16
Large intestine	2.22	0.07	$8.82 \cdot 10^{-3}$	5.93	0.16
Liver periportal	2.50	0.08	$8.53 \cdot 10^{-3}$	7.03	0.09
Liver pericentral	2.50	0.08	$8.53 \cdot 10^{-3}$	7.03	0.09
Lung	0.49	0.02	$8.51 \cdot 10^{-3}$	3.65	0.21
Muscle	0.59	0.02	$8.57 \cdot 10^{-3}$	1.25	0.07
Pancreas	2.83	0.09	$8.18 \cdot 10^{-3}$	4.34	0.06
Skin	3.63	0.11	$7.70 \cdot 10^{-3}$	12.31	0.28
Spleen	0.71	0.02	$8.31 \cdot 10^{-3}$	2.15	0.10
Saliva	0.02	$1.00 \cdot 10^{-3}$	0.01	0.07	$9.66 \cdot 10^{-3}$

[a]: estimated via PK-Sim Standard [55], [b]: estimated via Schmitt [75], [c]: estimated via Rodgers + Rowland [77, 78], 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid.

S2 PBPK Model Evaluation

S2.1 Plasma Concentration-Time Profiles (Semilogarithmic)

S2.1.1 Clopidogrel

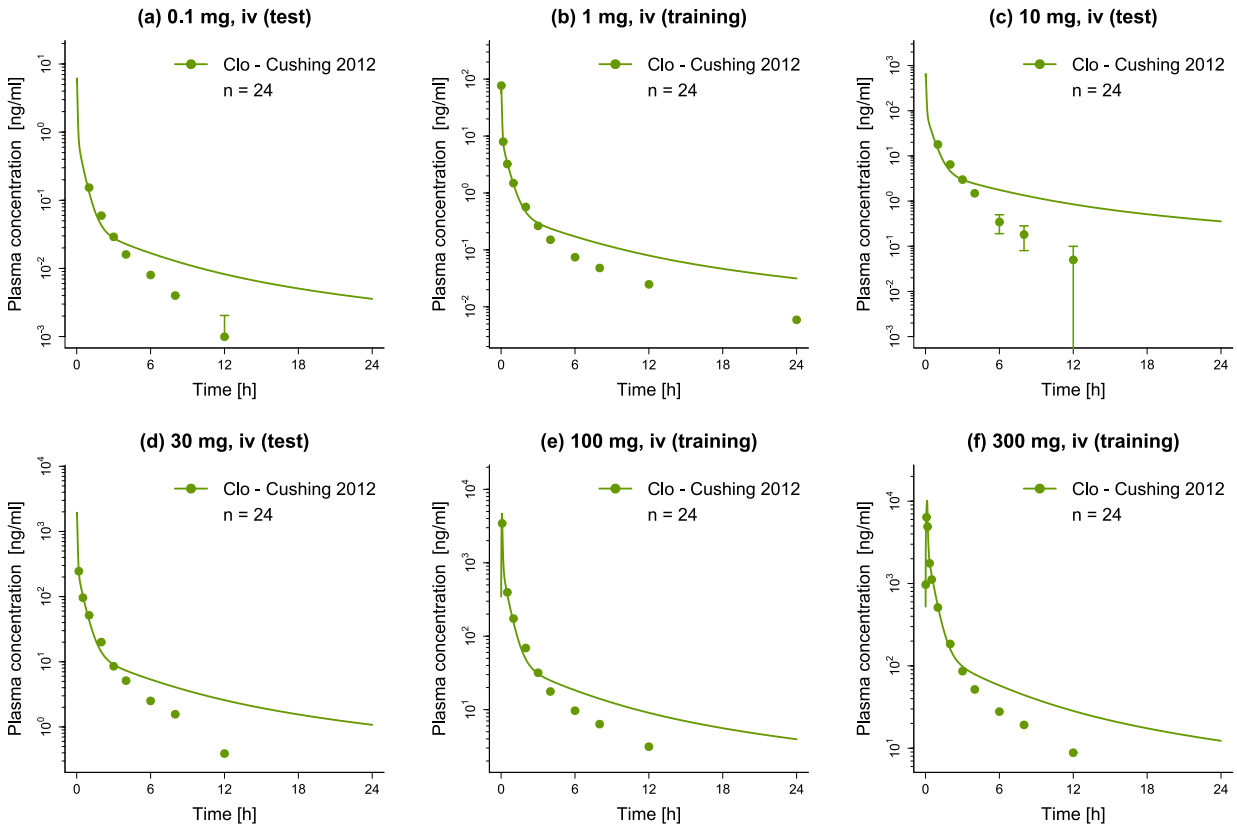


Figure S1: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [13]. Clo: clopidogrel, iv: intravenous, n: number of participants.

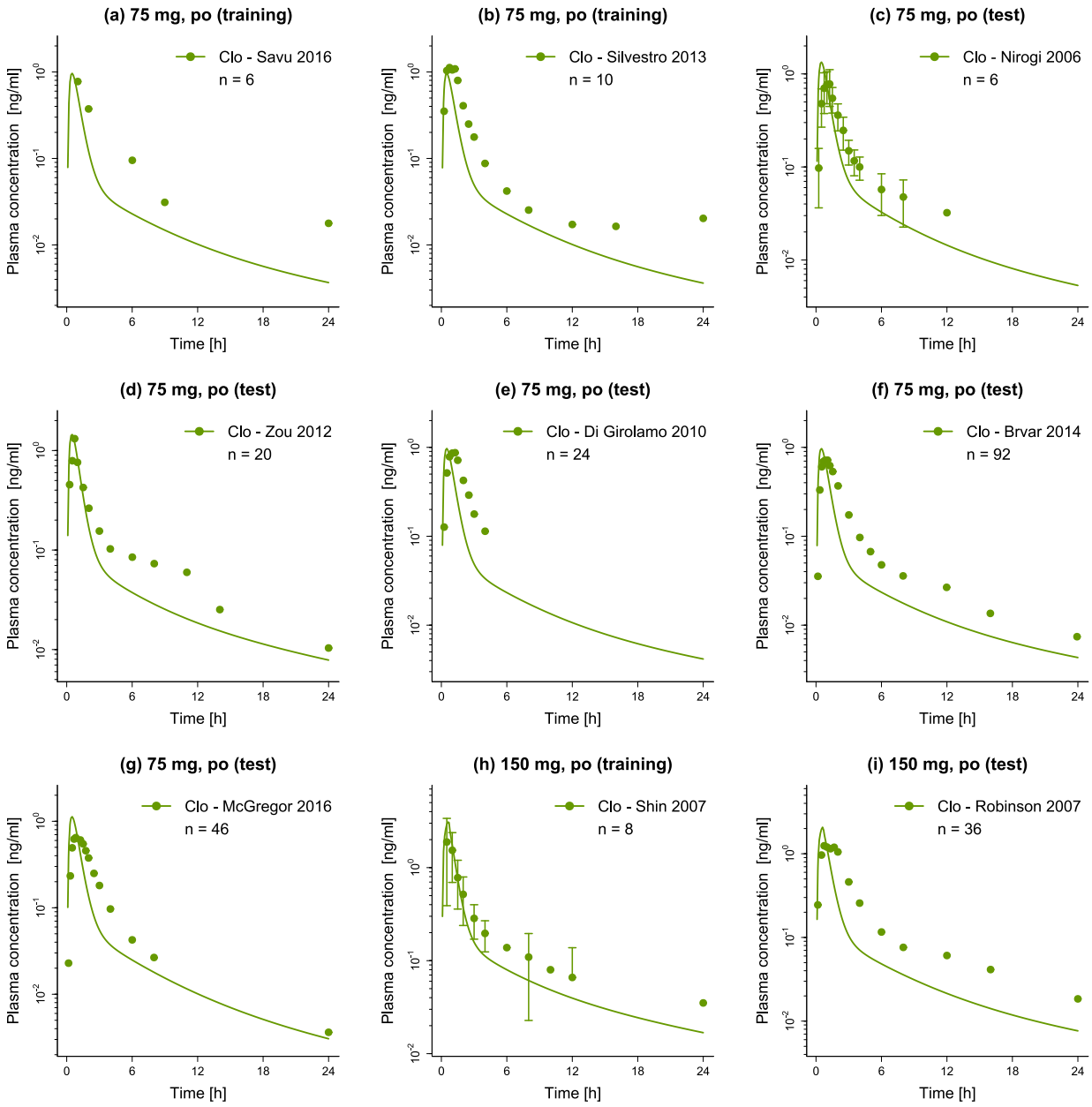


Figure S2: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14–22]. Clo: clopidogrel, n: number of participants, po: peroral.

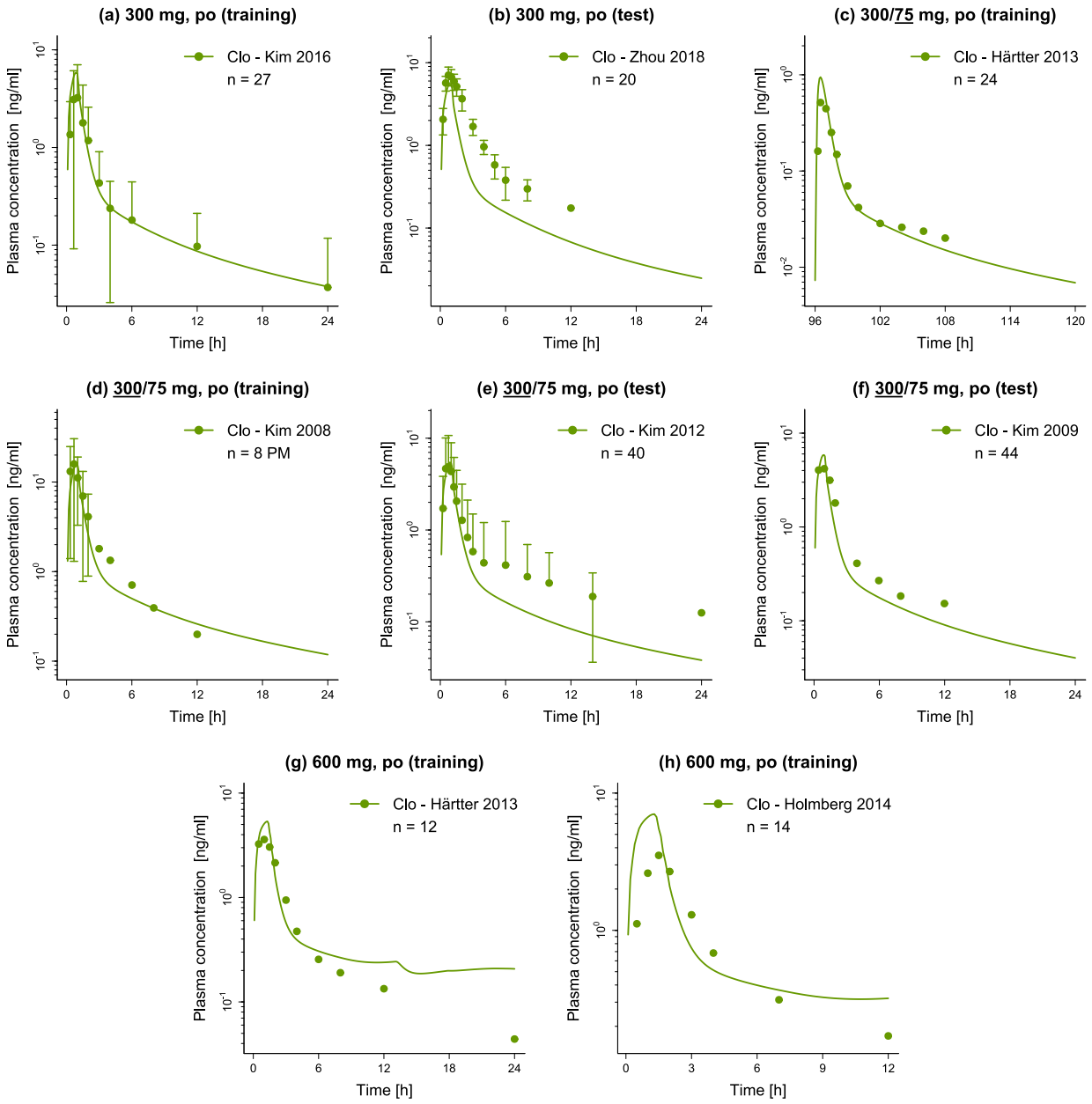


Figure S3: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [23–29]. Clo: clopidogrel, n: number of participants, PM: cytochrome P450 2C19 poor metabolizer, po: peroral.

S2.1.2 Clopidogrel Carboxylic Acid

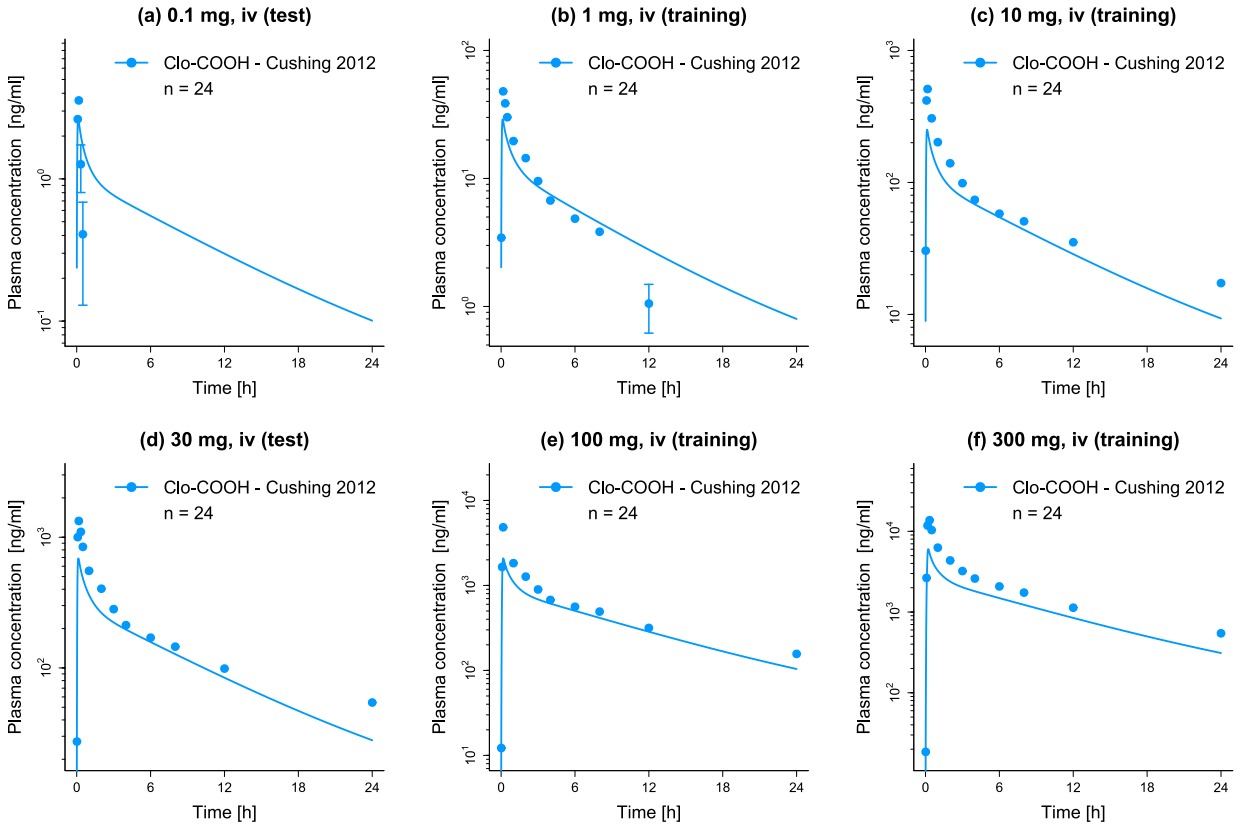


Figure S4: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [13]. Clo-COOH: clopidogrel carboxylic acid, iv: intravenous, n: number of participants.

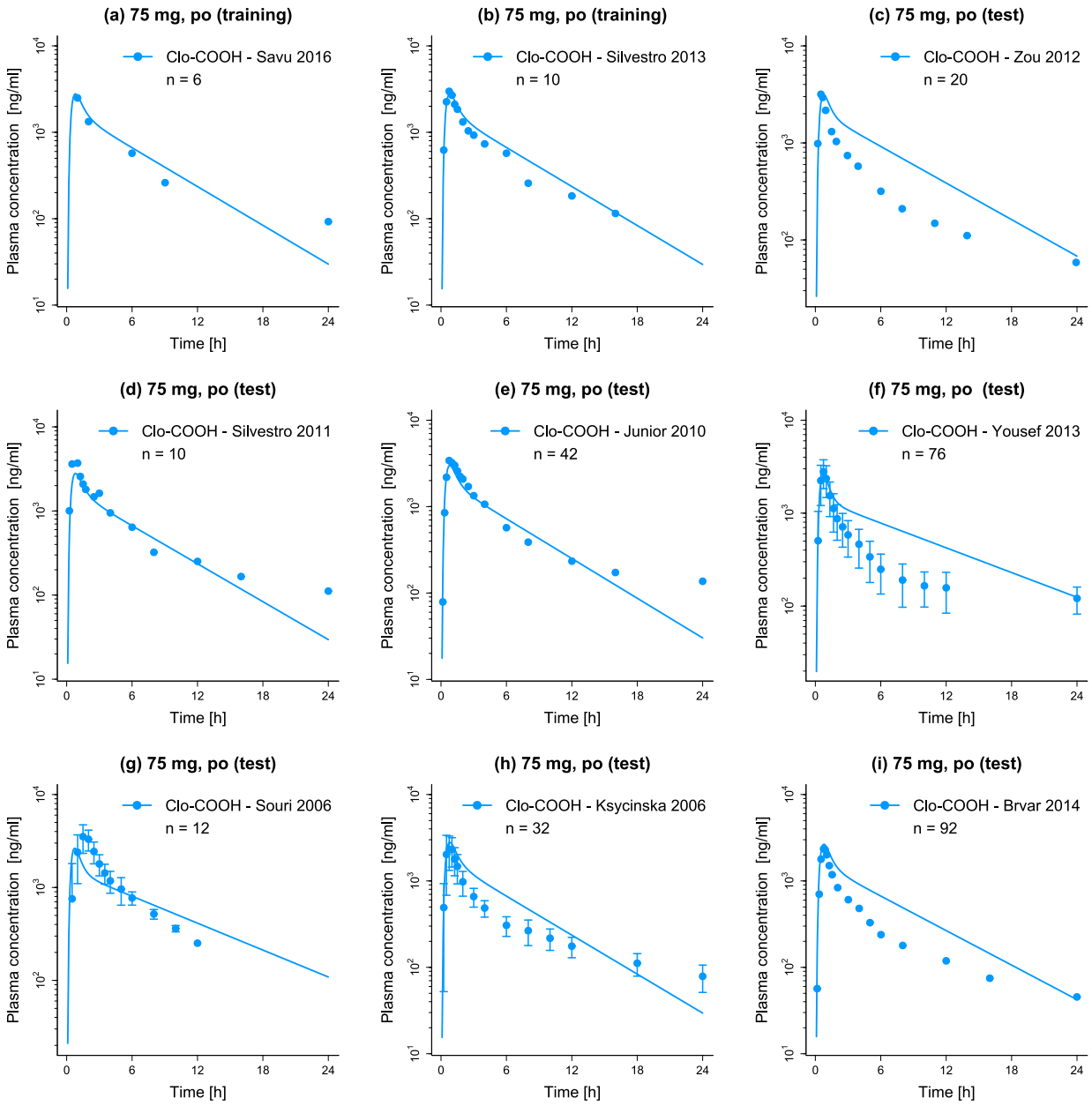


Figure S5: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14, 15, 17, 19, 30–34]. Clo-COOH: clopidogrel carboxylic acid, n: number of participants, po: peroral.

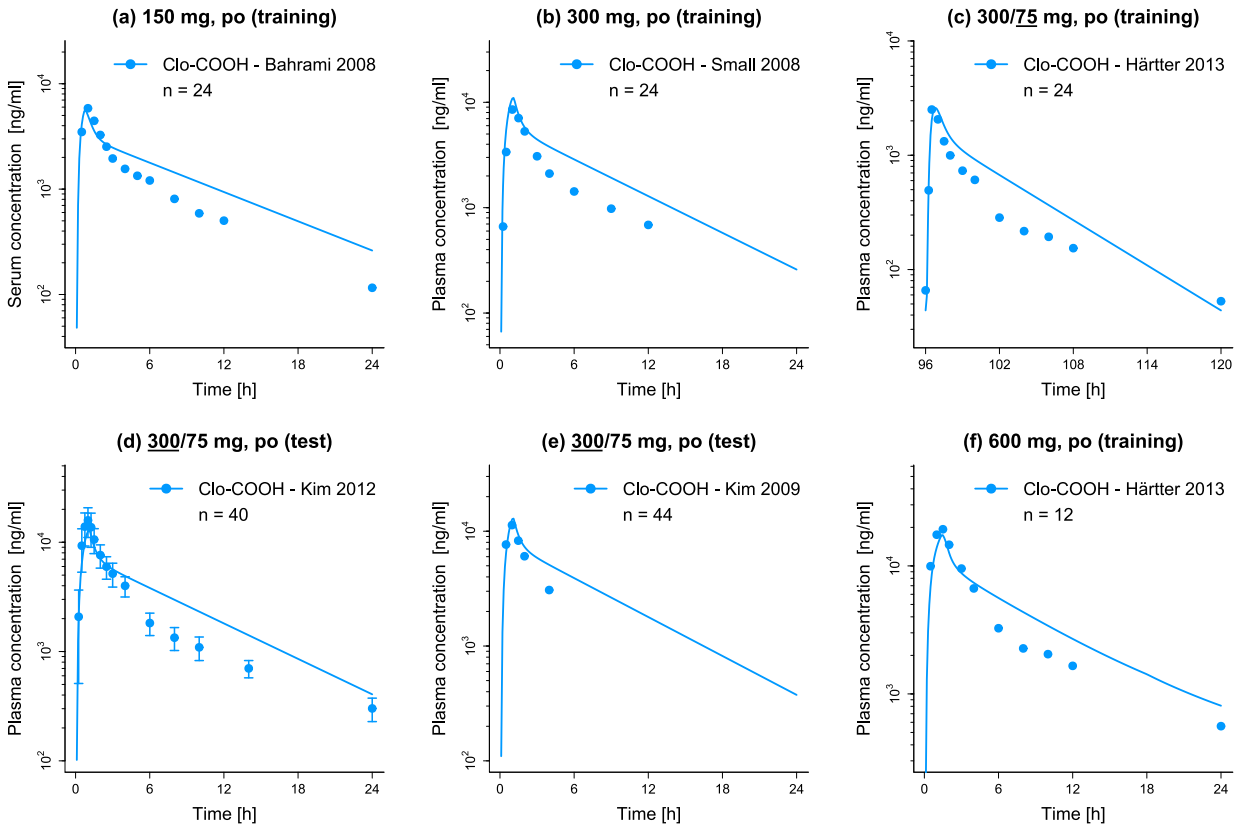


Figure S6: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [25, 27, 28, 35, 36]. Clo-COOH: clopidogrel carboxylic acid, n: number of participants, po: peroral.

S2.1.3 Clopidogrel Acyl Glucuronide

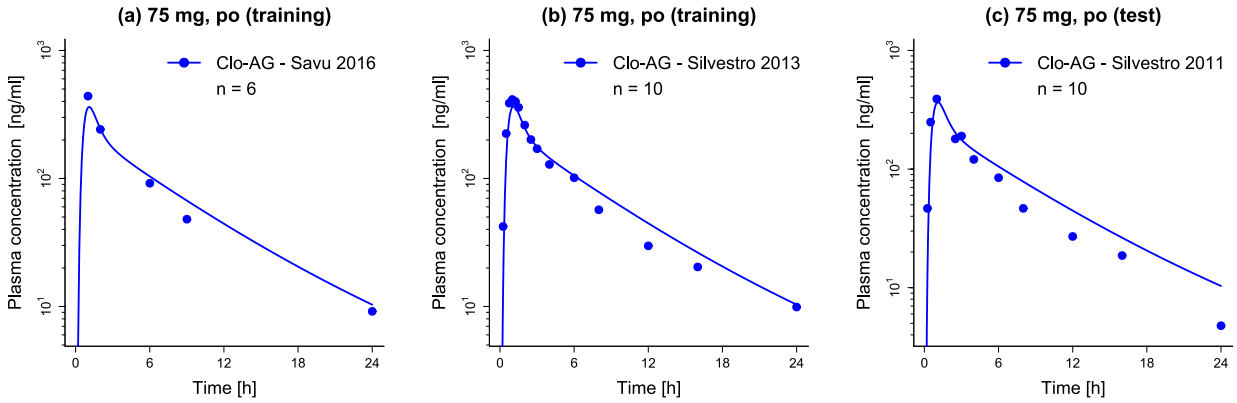


Figure S7: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14, 15, 30]. Clo-AG: clopidogrel acyl glucuronide, n: number of participants, po: peroral.

S2.1.4 2-Oxo-Clopidogrel

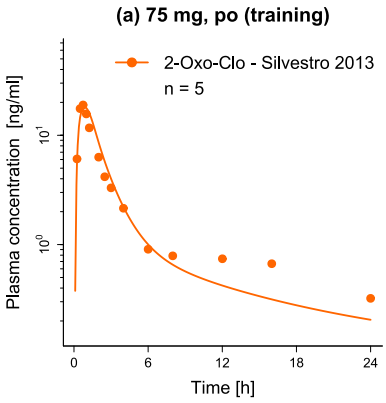


Figure S8: Semilogarithmic plots of predicted plasma concentration-time profiles of 2-oxo-clopidogrel following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [15]. 2-Oxo-Clo: 2-Oxo-clopidogrel, n: number of participants, po: peroral.

S2.1.5 Clopidogrel Thiol H4

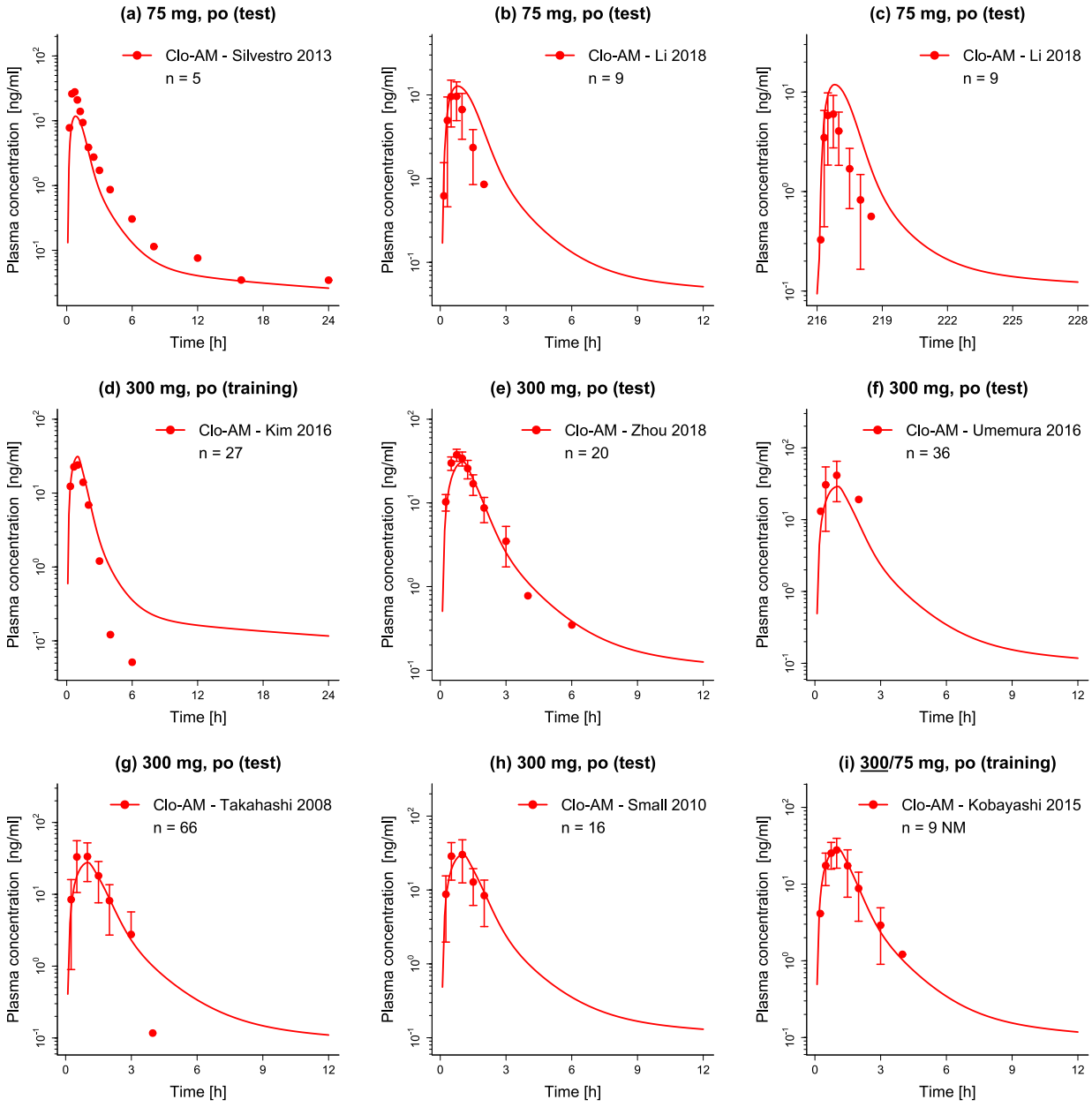


Figure S9: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel thiol H4 following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [15, 23, 24, 37–41]. Clo-AM: clopidogrel thiol H4, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, po: peroral.

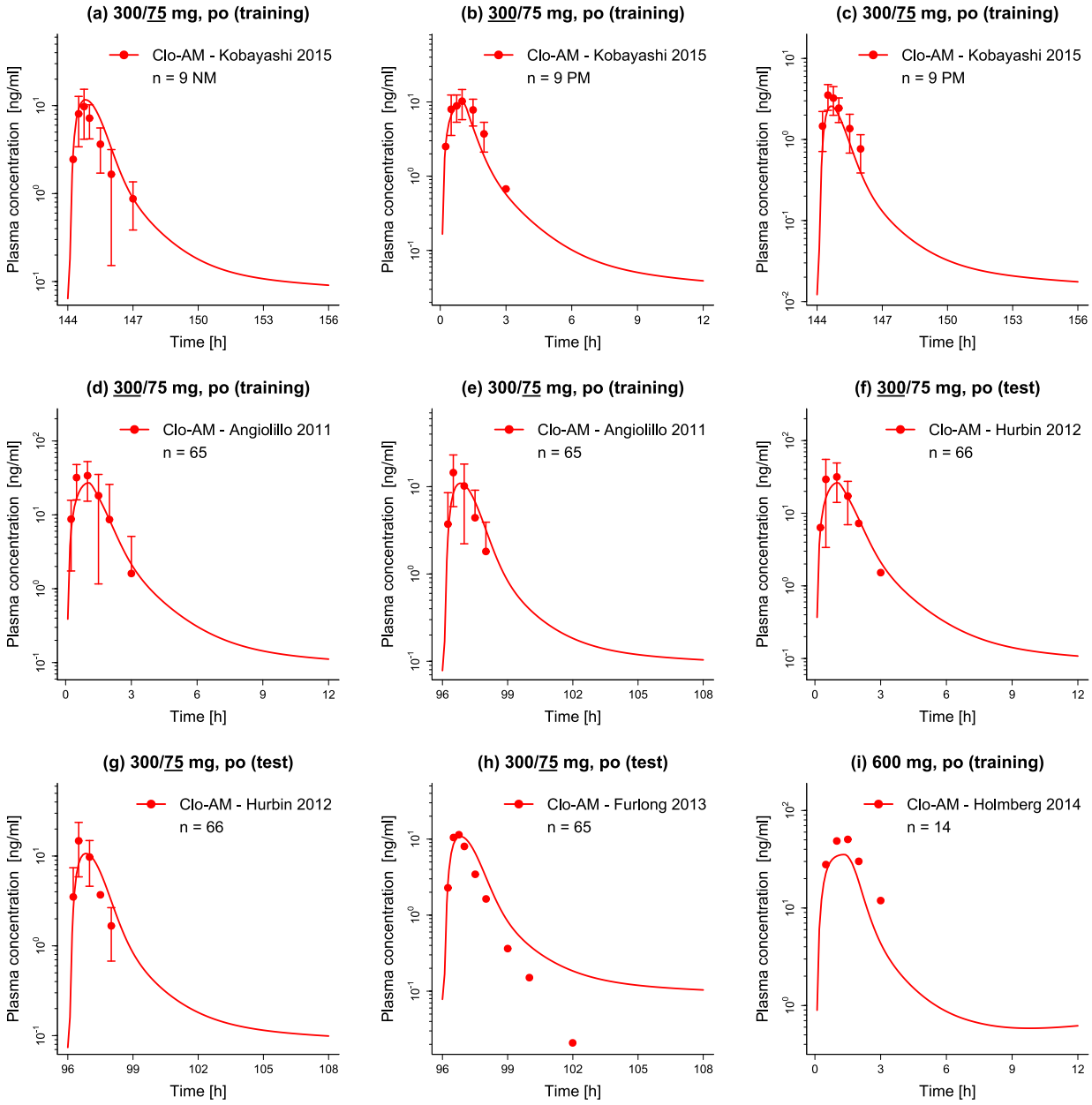


Figure S10: Semilogarithmic plots of predicted plasma concentration-time profiles of clopidogrel thiol H4 following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [29, 41–44]. Clo-AM: clopidogrel thiol H4, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral.

S2.2 Plasma Concentration-Time Profiles (Linear)

S2.2.1 Clopidogrel

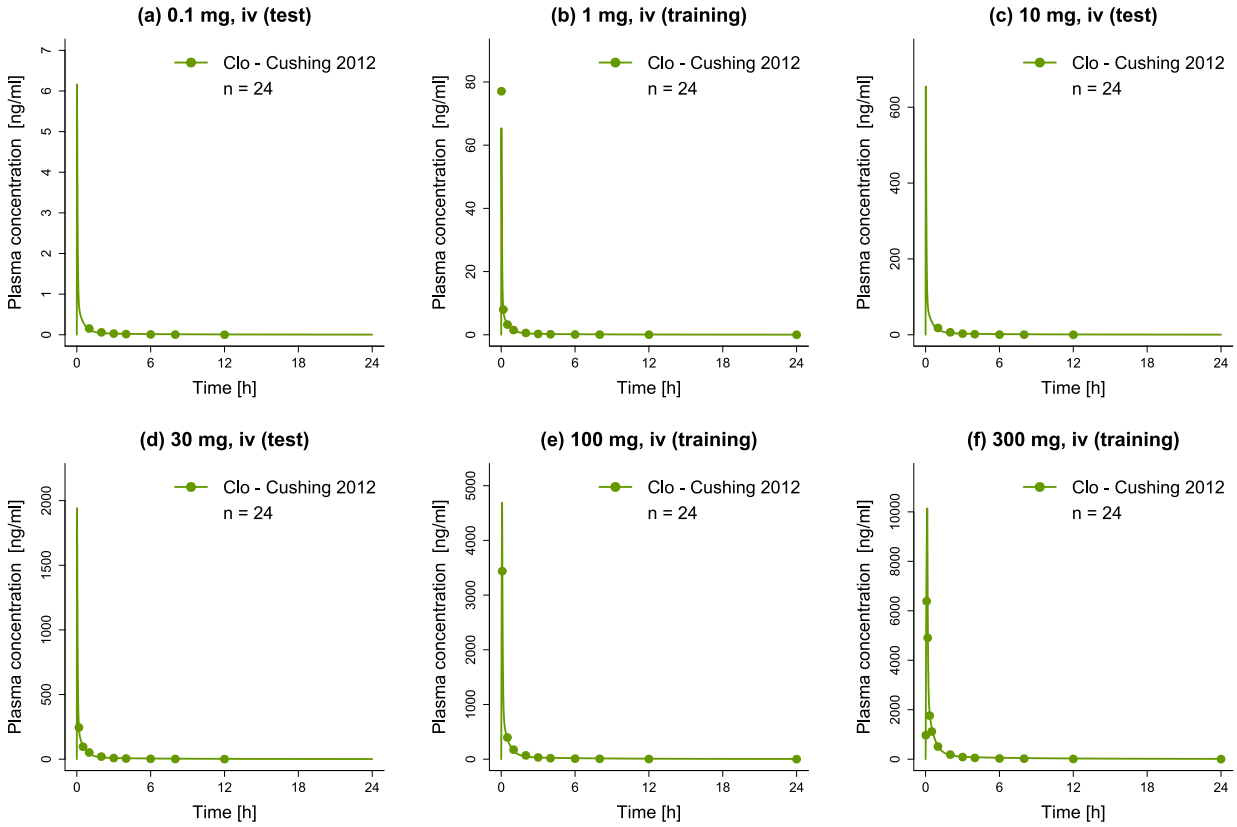


Figure S11: Linear plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [13]. Clo: clopidogrel, iv: intravenous, n: number of participants.

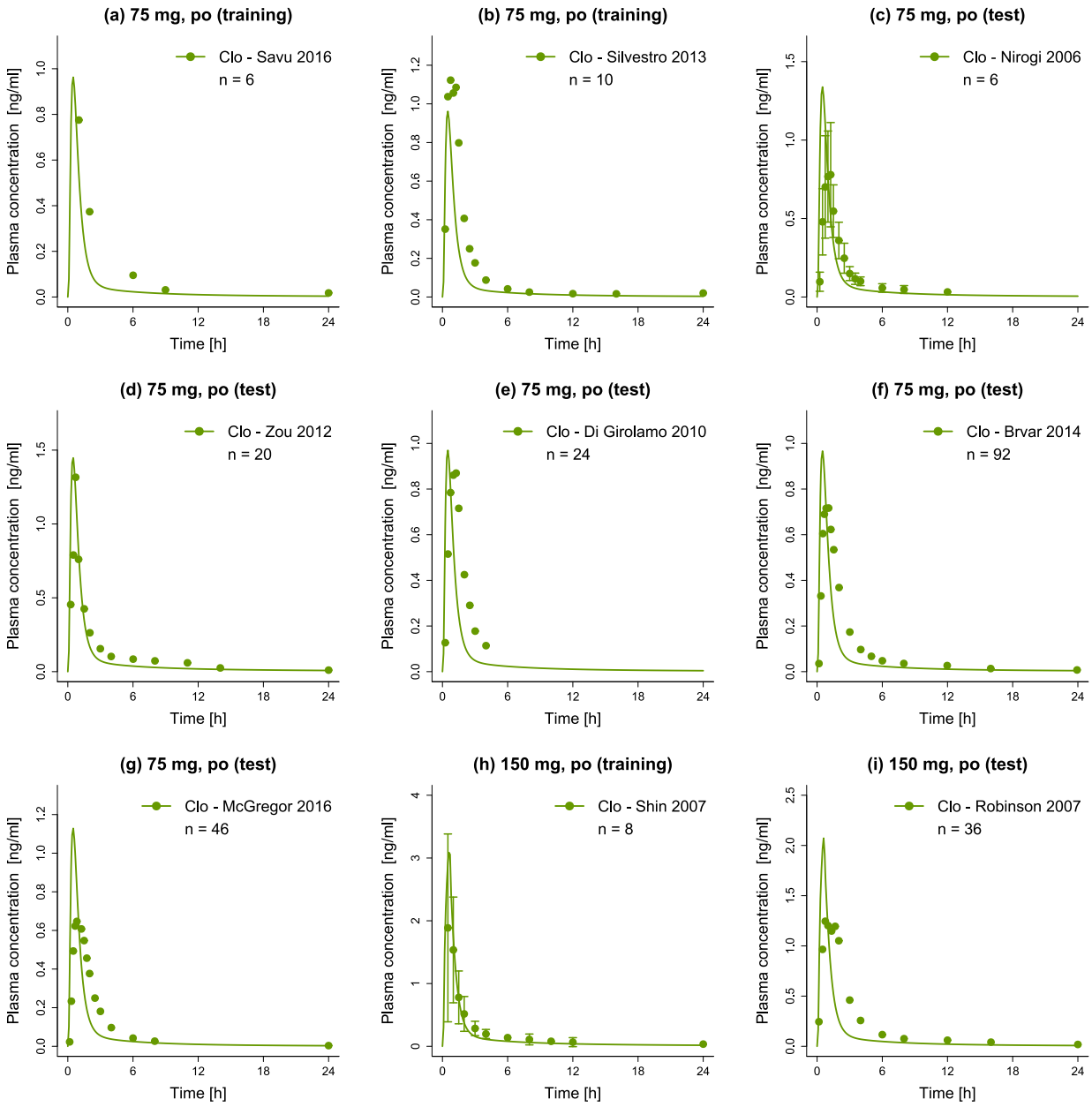


Figure S12: Linear plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14–22]. Clo: clopidogrel, n: number of participants, po: peroral.

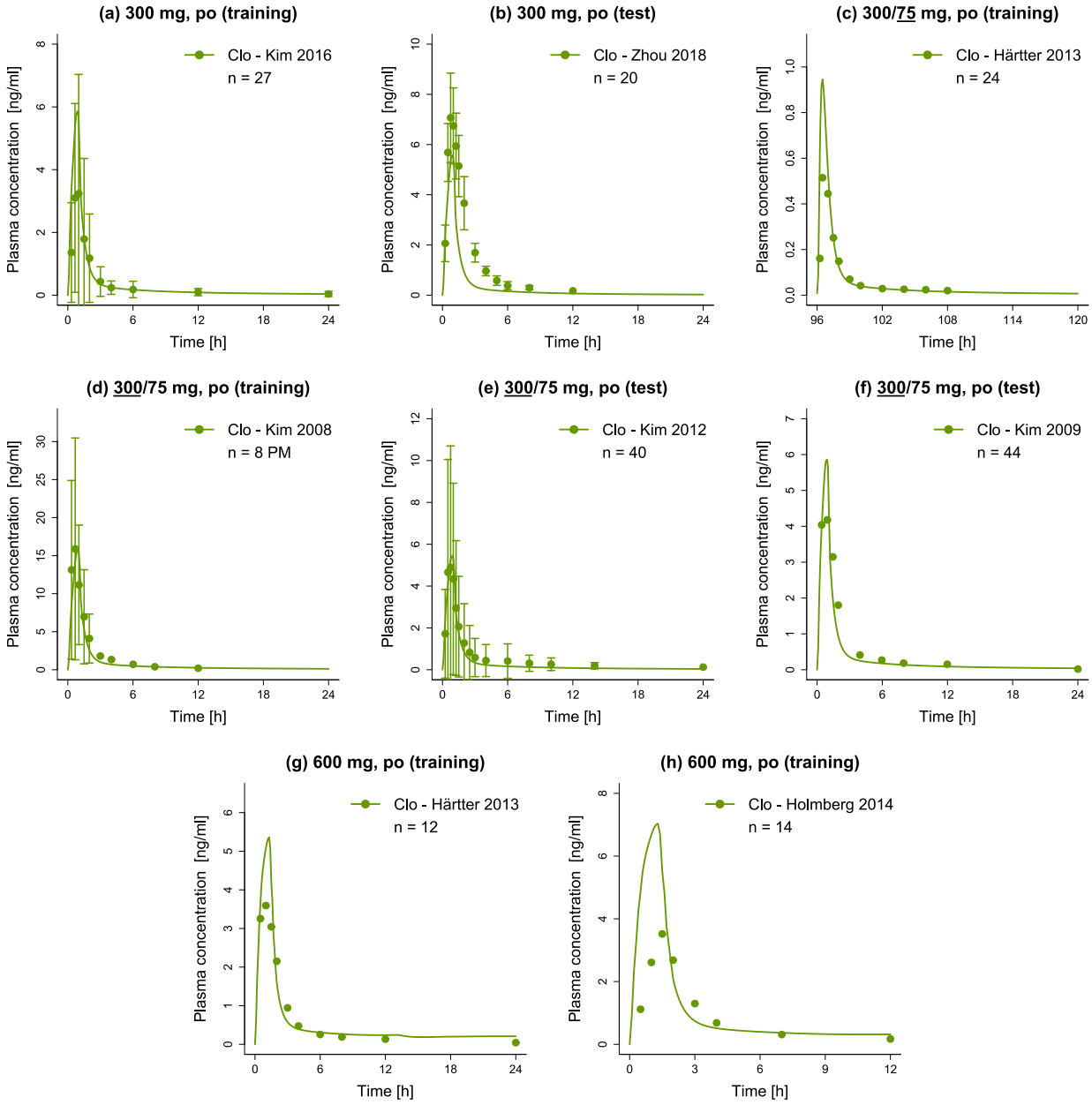


Figure S13: Linear plots of predicted plasma concentration-time profiles of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [23–29]. Clo: clopidogrel, n: number of participants, PM: cytochrome P450 2C19 poor metabolizer, po: peroral.

S2.2.2 Clopidogrel Carboxylic Acid

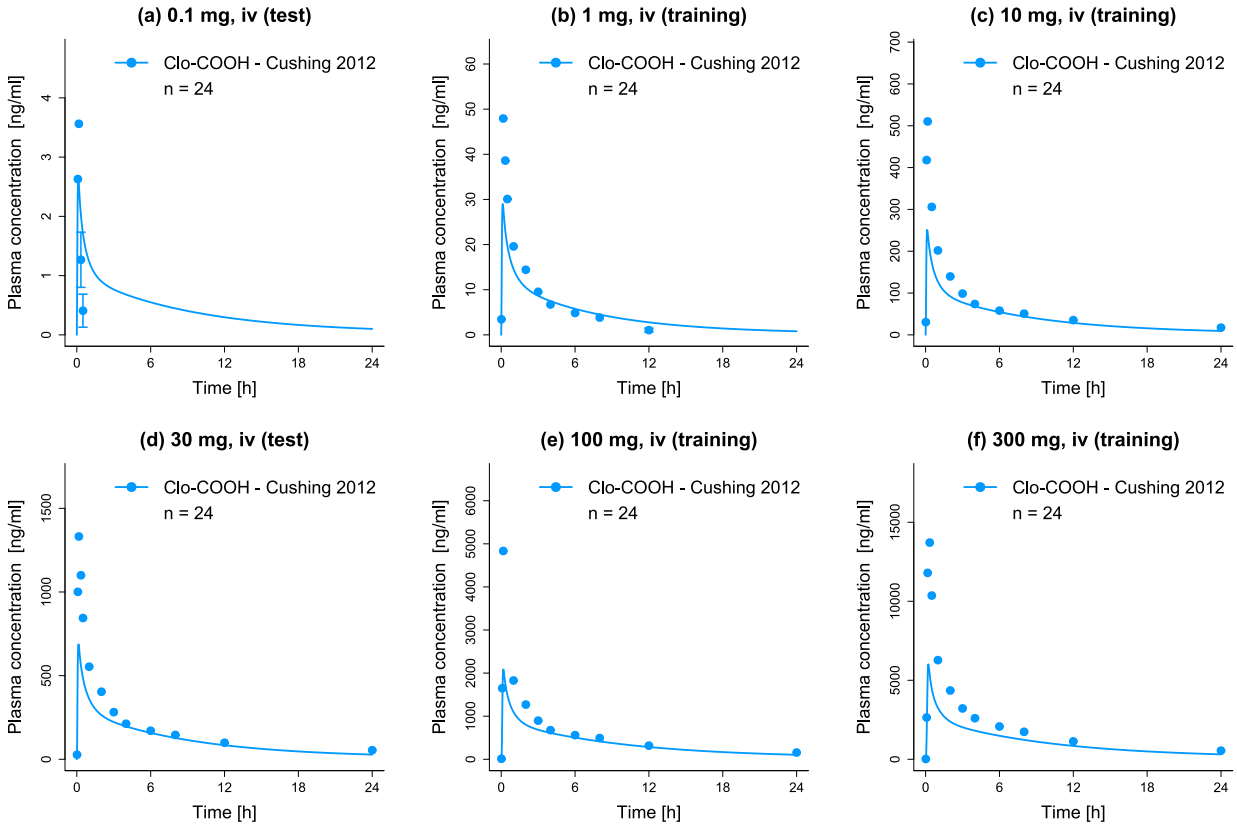


Figure S14: Linear plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [13]. Clo-COOH: clopidogrel carboxylic acid, iv: intravenous, n: number of participants.

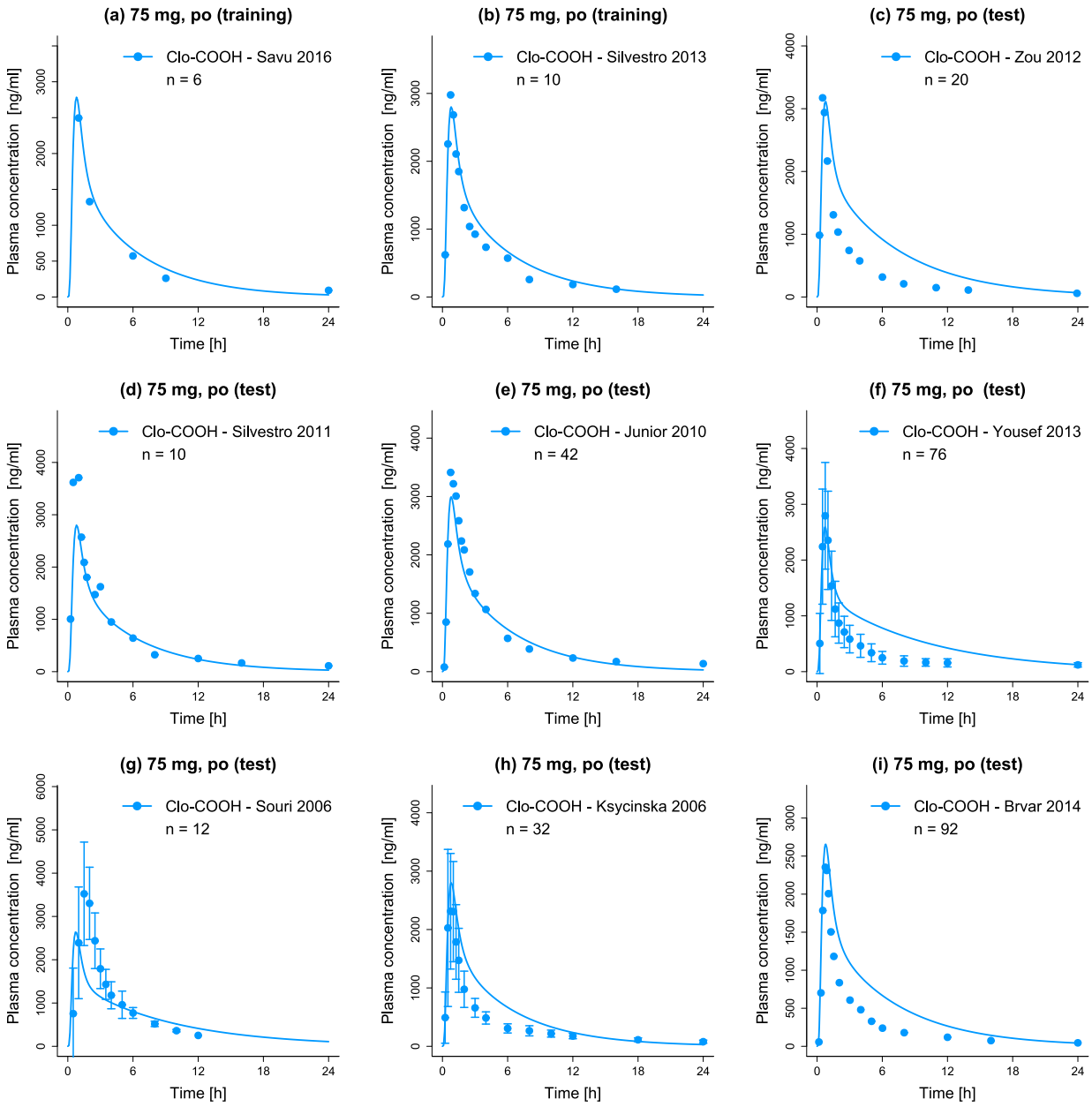


Figure S15: Linear plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14, 15, 17, 19, 30–34]. Clo-COOH: clopidogrel carboxylic acid, n: number of participants, po: peroral.

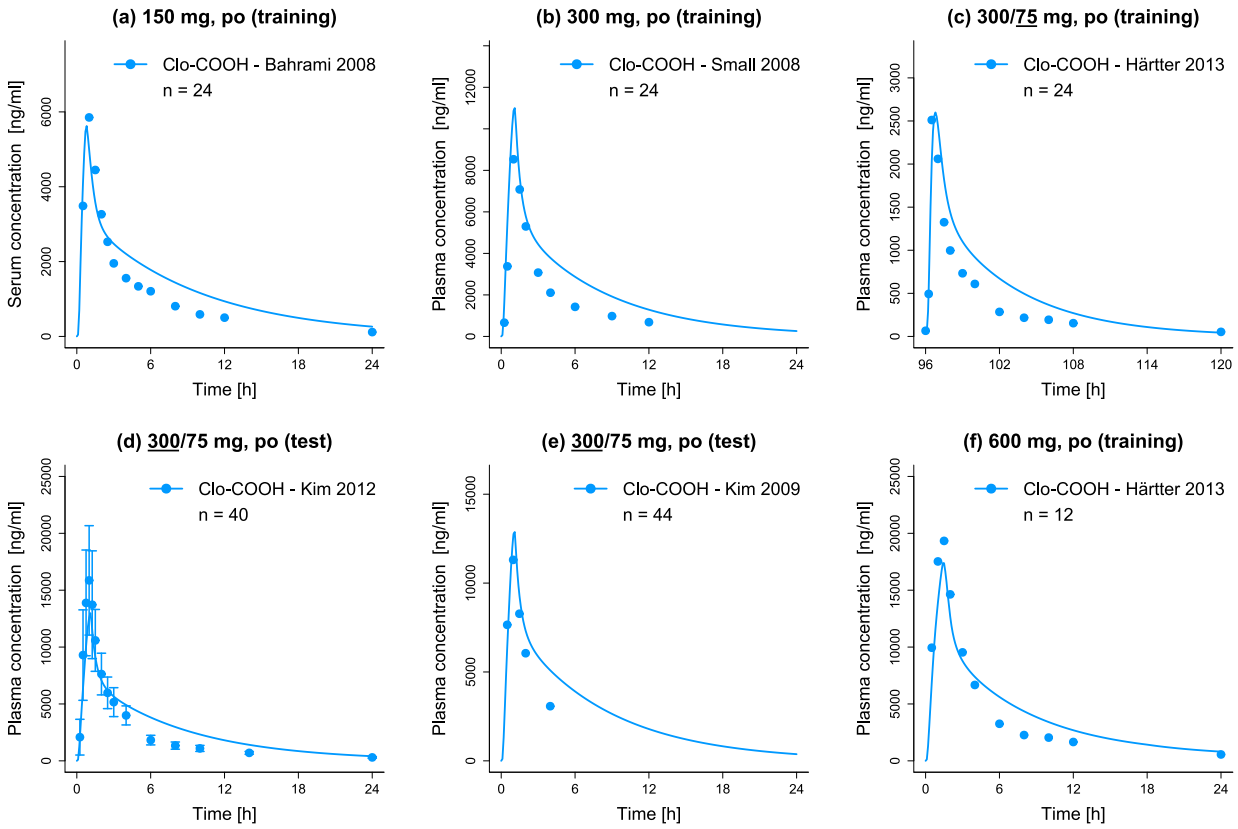


Figure S16: Linear plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [25, 27, 28, 35, 36]. Clo-COOH: clopidogrel carboxylic acid, n: number of participants, po: peroral.

S2.2.3 Clopidogrel Acyl Glucuronide

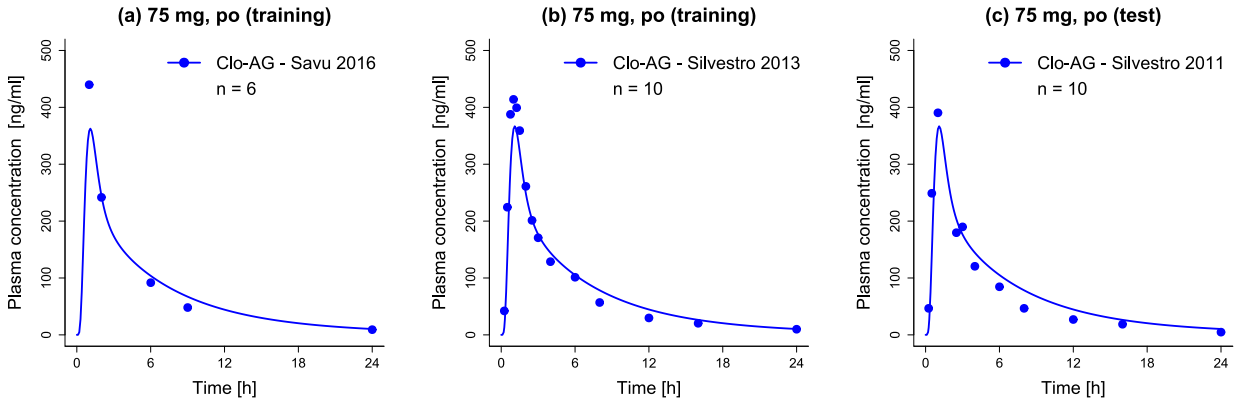


Figure S17: Linear plots of predicted plasma concentration-time profiles of clopidogrel carboxylic acid following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [14, 15, 30]. Clo-AG: clopidogrel acyl glucuronide, n: number of participants, po: peroral.

S2.2.4 2-Oxo-Clopidogrel

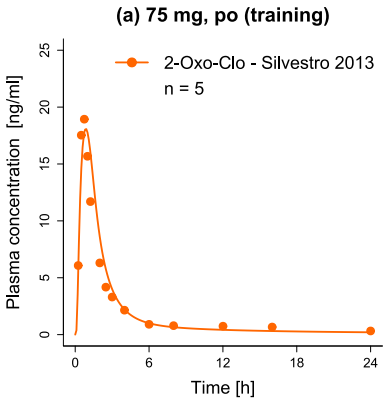


Figure S18: Linear plots of predicted plasma concentration-time profiles of 2-oxo-clopidogrel following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [15]. 2-Oxo-Clo: 2-Oxo-clopidogrel, n: number of participants, po: peroral.

S2.2.5 Clopidogrel Thiol H4

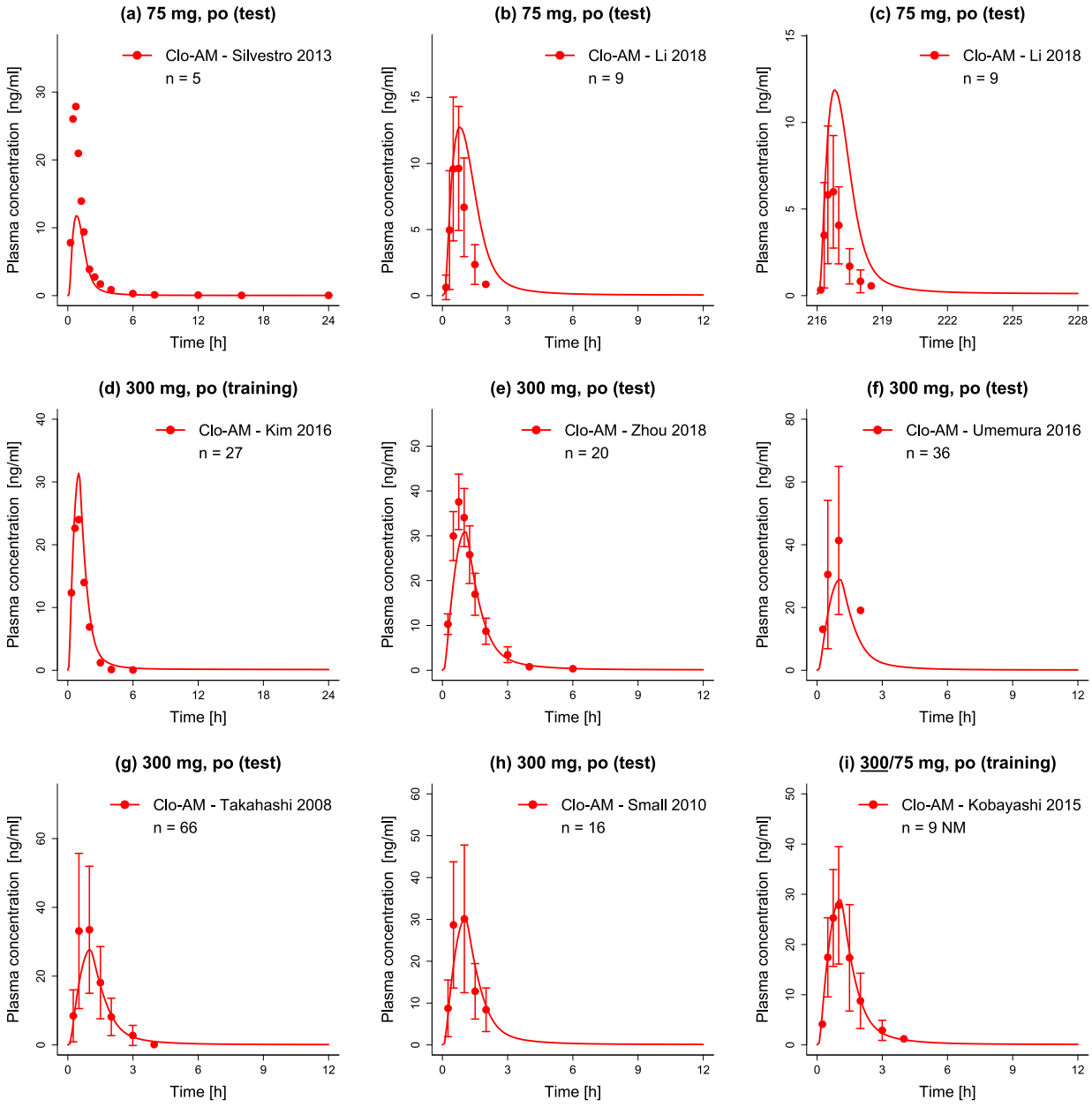


Figure S19: Linear plots of predicted plasma concentration-time profiles of clopidogrel thiol H4 following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [15, 23, 24, 37–41]. Clo-AM: clopidogrel thiol H4, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, po: peroral.

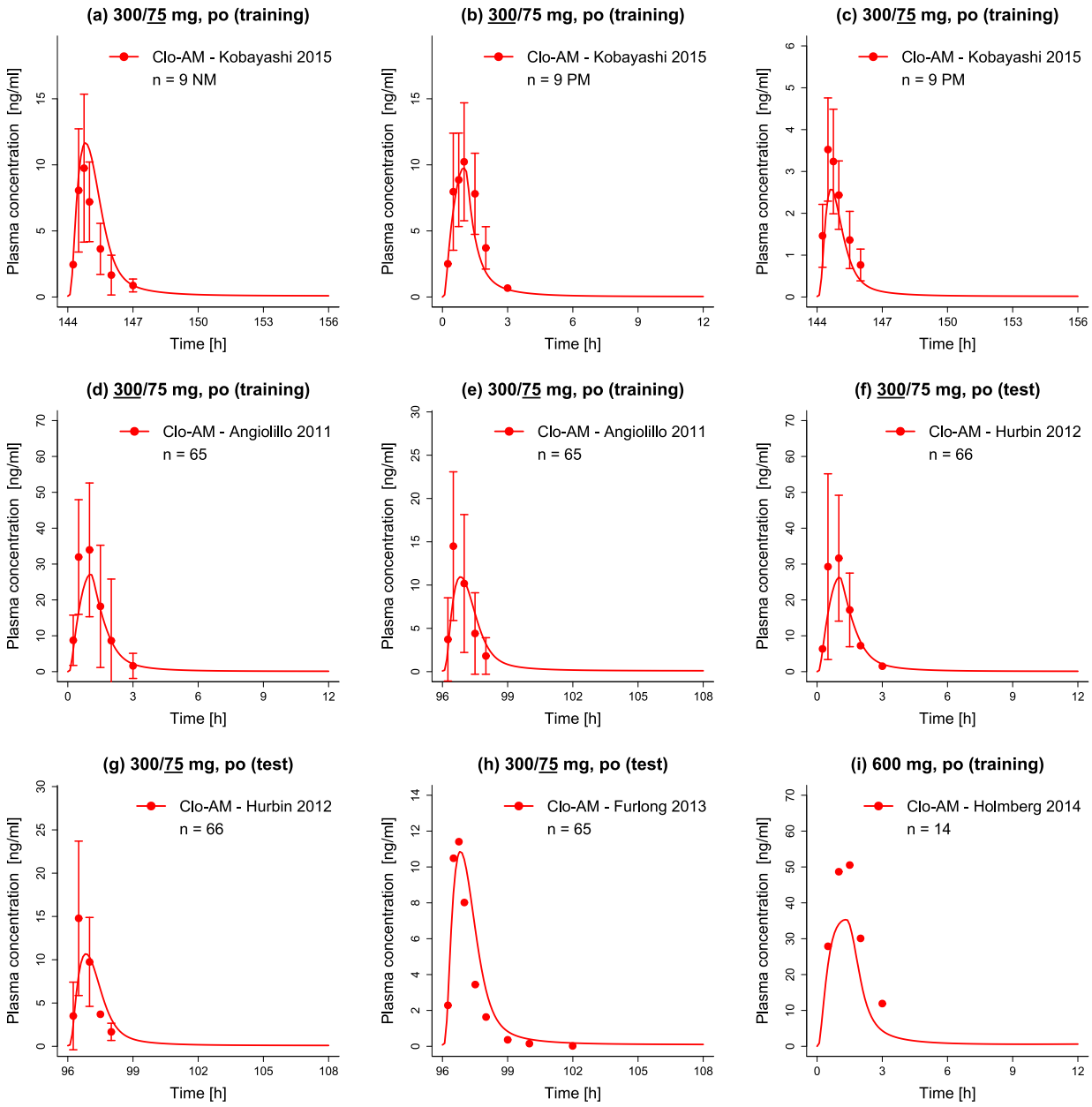


Figure S20: Linear plots of predicted plasma concentration-time profiles of clopidogrel thiol H4 following administration of clopidogrel. Solid lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available) [29, 41–44]. Clo-AM: clopidogrel thiol H4, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral.

S2.3 Plasma Concentration Goodness-of-Fit Plots

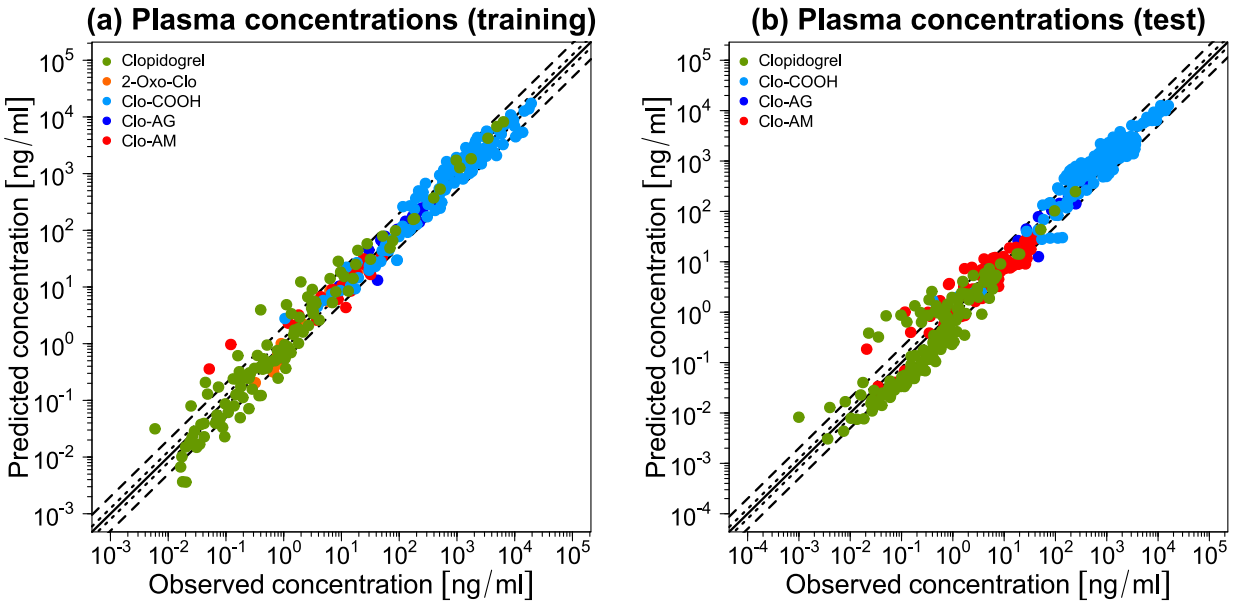


Figure S21: Plasma goodness-of-fit plots of the final clopidogrel parent-metabolite model. Divided by training and test dataset, each predicted plasma concentration measurement point is plotted against the corresponding observed value. The solid line represents the line of identity, while dotted lines indicate 1.25-fold and dashed lines 2-fold deviation from the respective observed value. 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo-AM: clopidogrel thiol H4, Clo-AG: clopidogrel acyl glucuronide, Clo-COOH: clopidogrel carboxylic acid.

S2.4 AUC_{last} and C_{max} Goodness-of-Fit Plots

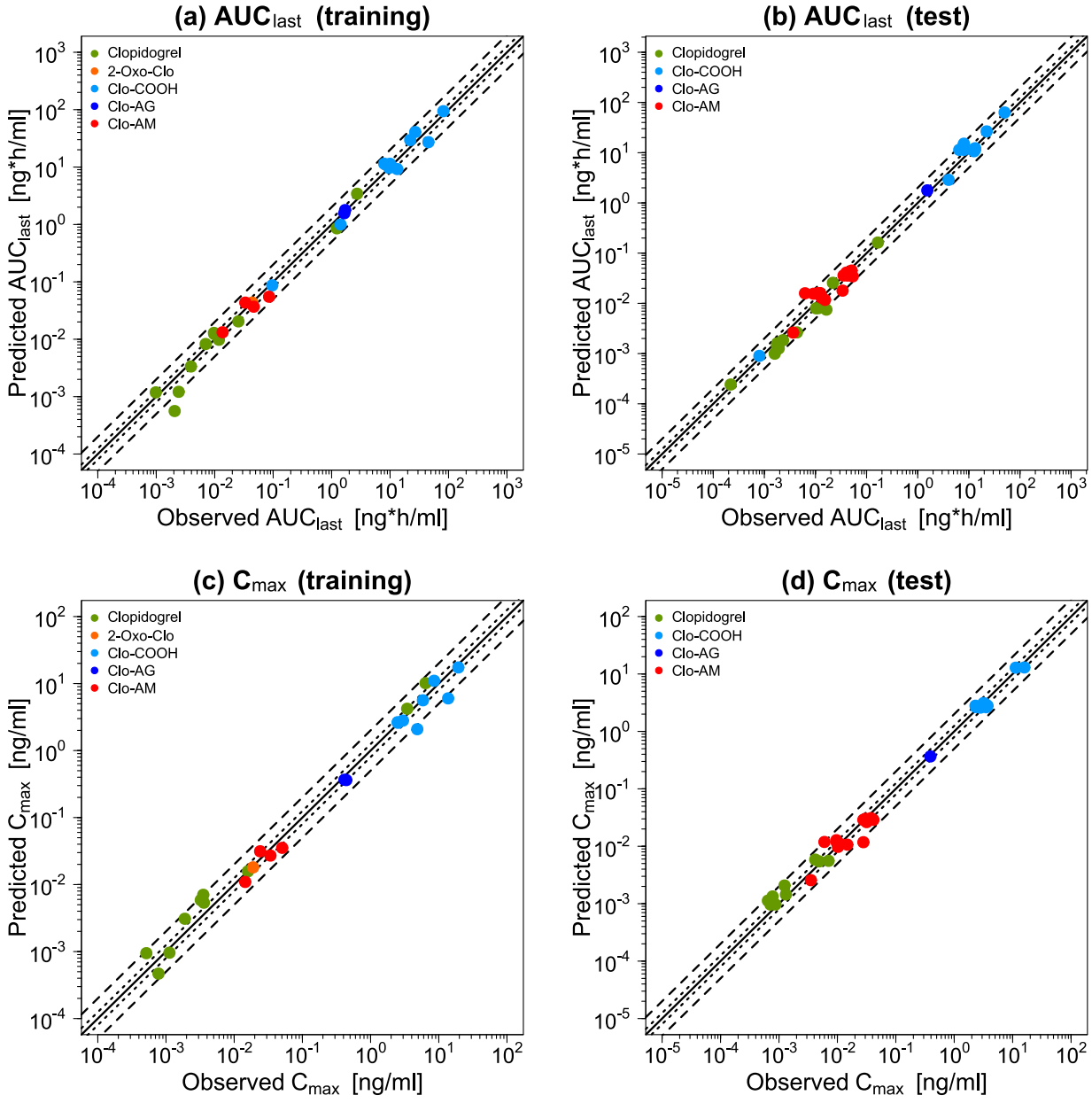


Figure S22: AUC_{last} and C_{max} goodness-of-fit plots of the final clopidogrel parent-metabolite model. Divided by training and test dataset, predicted (a–b) AUC_{last} and (c–d) C_{max} values are plotted against their corresponding observed counterparts. The solid line represents the line of identity, while dotted lines indicate 1.25-fold and dashed lines 2-fold deviation from the respective observed value. 2-Oxo-Clo: 2-Oxo-clopidogrel, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo-AM: clopidogrel thiol H4, Clo-AG: clopidogrel acyl glucuronide, Clo-COOH: clopidogrel carboxylic acid, C_{max}: maximum plasma concentration.

S2.5 MRD of Plasma Concentration Predictions

Table S5: MRD values of plasma concentration predictions

Compound	Clopidogrel dosing regimen		n	Dataset	MRD	Reference
	Route	Dose [mg]				
Clo	iv (bolus, s.d.)	0.1	24	test	2.65	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	1	24	training	2.11	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	10	24	test	4.34	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	30	24	test	2.16	Cushing 2012 [13]
Clo	iv (inf, 4 min, s.d.)	100	24	training	2.41	Cushing 2012 [13]
Clo	iv (inf, 8 min, s.d.)	300	24	training	2.05	Cushing 2012 [13]
Clo	po (tab, s.d.)	75	6	training	3.12	Savu 2016 [14]
Clo	po (-, s.d.)	75	10	training	2.59	Silvestro 2013 [15]
Clo	po (-, s.d.)	75	6	test	2.42	Nirogi 2006 [16]
Clo	po (tab, s.d.)	75	20	test	1.90	Zou 2012 [17]
Clo	po (tab, s.d.)	75	24	test	3.00	Di Girolamo 2010 [18]
Clo	po (tab, s.d.)	75	92	test	2.52	Brvar 2014 [19]
Clo	po (tab, s.d.)	75	46	test	2.94	McGregor 2016 [20]
Clo	po (tab, s.d.)	150	8	training	1.64	Shin 2007 [21]
Clo	po (tab, s.d.)	150	36	test	2.63	Robinson 2007 [22]
Clo	po (tab, s.d.)	300	27	training	1.49	Kim 2016 [23]
Clo	po (tab, s.d.)	300	20	test	2.64	Zhou 2018 [24]
Clo	po (-, l.d./m.d., 5d)	300/75	24	training	1.61 (D5)	Härtter 2013 [25]
Clo	po (-, l.d./m.d., 7d)	300/75	8 PM	training	1.48 (D1)	Kim 2008 [26]
Clo	po (-, l.d./m.d., 5d)	300/75	40	test	1.91 (D1)	Kim 2012 [27]
Clo	po (-, l.d./m.d., 6d)	300/75	44	test	1.64 (D1)	Kim 2009 [28]
Clo	po (-, s.d.)	600	12	training	1.80	Härtter 2013 [25]
Clo	po (tab, s.d.)	600	14	training	2.05	Holmberg 2014 [29]
Clo-COOH	iv (bolus, s.d.)	0.1	24	test	2.17	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	1	24	training	1.54	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	10	24	training	1.54	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	30	24	test	1.56	Cushing 2012 [13]
Clo-COOH	iv (inf, 4 min, s.d.)	100	24	training	1.55	Cushing 2012 [13]
Clo-COOH	iv (inf, 8 min, s.d.)	300	24	training	1.80	Cushing 2012 [13]
Clo-COOH	po (tab, s.d.)	75	6	training	1.73	Savu 2016 [14]
Clo-COOH	po (-, s.d.)	75	10	training	1.44	Silvestro 2013 [15]
Clo-COOH	po (tab, s.d.)	75	20	test	2.09	Zou 2012 [17]
Clo-COOH	po (-, s.d.)	75	10	test	1.59	Silvestro 2011 [30]
Clo-COOH	po (tab, s.d.)	75	42	test	1.55	Junior 2010 [31]
Clo-COOH	po (tab, s.d.)	75	76	test	1.98	Yousef 2013 [32]
Clo-COOH	po (tab, s.d.)	75	12	test	1.69	Souri 2006 [33]
Clo-COOH	po (tab, s.d.)	75	32	test	1.62	Ksycinska 2006 [34]
Clo-COOH	po (tab, s.d.)	75	92	test	1.84	Brvar 2014 [19]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, d: dosage period in days, D: day of pharmacokinetic sampling, inf: infusion, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), MRD: mean relative deviation, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet.

Table S5: MRD values of plasma concentration predictions *(continued)*

Compound	Clopidogrel dosing regimen		n	Dataset	MRD	Reference
	Route	Dose [mg]				
Clo-COOH	po (tab, s.d.)	150	24	training	1.54	Bahrami 2008 [35]
Clo-COOH	po (tab, s.d.)	300	24	training	1.72	Small 2008 [36]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	24	training	1.62 (D5)	Härtter 2013 [25]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	40	test	1.53 (D1)	Kim 2012 [27]
Clo-COOH	po (-, l.d./m.d., 6d)	300/75	44	test	1.30 (D1)	Kim 2009 [28]
Clo-COOH	po (-, s.d.)	600	12	training	1.46	Härtter 2013 [25]
Clo-AG	po (tab, s.d.)	75	6	training	1.21	Savu 2016 [14]
Clo-AG	po (-, s.d.)	75	10	training	1.45	Silvestro 2013 [15]
Clo-AG	po (-, s.d.)	75	10	test	1.74	Silvestro 2011 [30]
2-Oxo-Clo	po (-, s.d.)	75	5	training	1.39	Silvestro 2013 [15]
Clo-AM	po (-, s.d.)	75	5	test	1.89	Silvestro 2013 [15]
Clo-AM	po (-, m.d., 10d)	75	9	test	2.23 (D1)	Li 2018 [37]
Clo-AM	po (-, m.d., 10d)	75	9	test	2.83 (D10)	Li 2018 [37]
Clo-AM	po (tab, s.d.)	300	27	training	2.85	Kim 2016 [23]
Clo-AM	po (tab, s.d.)	300	20	test	1.30	Zhou 2018 [24]
Clo-AM	po (tab, s.d.)	300	36	test	1.76	Umemura 2016 [38]
Clo-AM	po (tab, s.d.)	300	66	test	2.36	Takahashi 2008 [39]
Clo-AM	po (tab, s.d.)	300	16	test	1.31	Small 2010 [40]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	training	1.21 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	training	1.50 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	training	1.41 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	training	1.57 (D5)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	training	1.41 (D1)	Angiolillo 2011 [42]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	training	1.54 (D5)	Angiolillo 2011 [42]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	66	test	1.34 (D1)	Hurbin 2012 [43]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	66	test	1.63 (D5)	Hurbin 2012 [43]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	test	2.47 (D5)	Furlong 2013 [44]
Clo-AM	po (tab, s.d.)	600	14	training	1.75	Holmberg 2014 [29]
		Overall mean MRD (range)			1.91 (1.21–4.34)	
		MRD ≤ 2			44/66	

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, d: dosage period in days, D: day of pharmacokinetic sampling, inf: infusion, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), MRD: mean relative deviation, n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet.

S2.6 Predicted and Observed AUC_{last} and C_{max} Values with Mean GMFEs

Table S6: Predicted versus observed AUC_{last} and C_{max} values, along with GMFE values

Compound	Clopidogrel dosing regimen		n	Dataset	AUC_{last}			C_{max}			Reference
	Route	Dose [mg]			Pred $[\frac{ng*h}{ml}]$	Obs $[\frac{ng*h}{ml}]$	Pred/Obs	Pred $[\frac{ng}{ml}]$	Obs $[\frac{ng}{ml}]$	Pred/Obs	
Clo	iv (bolus, s.d.)	0.1	24	test	0.24	0.22	1.10	-	-	-	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	1	24	training	9.80	11.78	0.83	-	-	-	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	10	24	test	25.68	21.96	1.17	-	-	-	Cushing 2012 [13]
Clo	iv (bolus, s.d.)	30	24	test	162.68	166.20	0.98	-	-	-	Cushing 2012 [13]
Clo	iv (inf, 4 min, s.d.)	100	24	training	855.37	1226.90	0.70	4210.44	3437.8	1.22	Cushing 2012 [13]
Clo	iv (inf, 8 min, s.d.)	300	24	training	3429.21	2726.75	1.26	10143.06	6385	1.59	Cushing 2012 [13]
Clo	po (tab, s.d.)	75	6	training	0.56	2.06	0.27	0.47	0.78	0.60	Savu 2016 [14]
Clo	po (-, s.d.)	75	10	training	1.21	2.42	0.50	0.96	1.12	0.86	Silvestro 2013 [15]
Clo	po (-, s.d.)	75	6	test	1.60	1.78	0.90	1.34	0.78	1.72	Nirogi 2006 [16]
Clo	po (tab, s.d.)	75	20	test	1.85	2.32	0.80	1.45	1.32	1.10	Zou 2012 [17]
Clo	po (tab, s.d.)	75	24	test	0.99	1.59	0.62	0.97	0.87	1.11	Di Girolamo 2010 [18]
Clo	po (tab, s.d.)	75	92	test	1.27	1.91	0.66	0.97	0.72	1.35	Brvar 2014 [19]
Clo	po (tab, s.d.)	75	46	test	1.42	1.77	0.80	1.13	0.65	1.74	McGregor 2016 [20]
Clo	po (tab, s.d.)	150	8	training	3.35	3.92	0.85	3.09	1.89	1.64	Shin 2007 [21]
Clo	po (tab, s.d.)	150	36	test	2.64	4.34	0.61	2.07	1.25	1.66	Robinson 2007 [22]
Clo	po (tab, s.d.)	300	27	training	8.26	7.00	1.18	5.87	3.23	1.81	Kim 2016 [23]
Clo	po (tab, s.d.)	300	20	test	7.50	16.34	0.46	5.58	7.07	0.79	Zhou 2018 [24]
Clo	po (-, l.d./m.d., 5d)	300/75	24	training	1.19	0.98	1.21 (D5)	0.95	0.51	1.84 (D5)	Härtter 2013 [25]
Clo	po (-, l.d./m.d., 7d)	300/75	8 PM	training	20.46	25.42	0.80 (D1)	15.75	15.88	0.99 (D1)	Kim 2008 [26]
Clo	po (-, l.d./m.d., 5d)	300/75	40	test	8.04	11.53	0.70 (D1)	5.45	4.89	1.12 (D1)	Kim 2012 [27]
Clo	po (-, l.d./m.d., 6d)	300/75	44	test	7.98	10.26	0.78 (D1)	5.86	4.18	1.40 (D1)	Kim 2009 [28]
Clo	po (-, s.d.)	600	12	training	12.31	9.82	1.25	5.36	3.59	1.49	Härtter 2013 [25]
Clo	po (tab, s.d.)	600	14	training	12.90	9.70	1.33	7.03	3.52	2.00	Holmberg 2014 [29]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, C_{max}: maximum plasma concentration, d: dosage period in days, D: day of pharmacokinetic sampling, inf: infusion, GMFE: geometric mean fold error, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, obs: observed, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, pred: predicted, s.d.: single dose, tab: tablet.

Table S6: Predicted versus observed AUC_{last} and C_{max} values, along with GMFE values *(continued)*

Compound	Clopidogrel dosing regimen		n	Dataset	AUC_{last}			C_{max}			Reference
	Route	Dose [mg]			Pred $[\frac{ng*h}{ml}]$	Obs $[\frac{ng*h}{ml}]$	Pred/Obs	Pred $[\frac{ng}{ml}]$	Obs $[\frac{ng}{ml}]$	Pred/Obs	
Clo-COOH	iv (bolus, s.d.)	0.1	24	test	0.90	0.80	1.13	-	-	-	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	1	24	training	86.99	96.40	0.90	-	-	-	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	10	24	training	998.68	1419.97	0.70	-	-	-	Cushing 2012 [13]
Clo-COOH	iv (bolus, s.d.)	30	24	test	2882.92	4021.05	0.72	-	-	-	Cushing 2012 [13]
Clo-COOH	iv (inf, 4 min, s.d.)	100	24	training	9227.09	13261.50	0.70	2084.94	4833.6	0.43	Cushing 2012 [13]
Clo-COOH	iv (inf, 8 min, s.d.)	300	24	training	27186.60	45293.51	0.60	6010.82	13714	0.44	Cushing 2012 [13]
Clo-COOH	po (tab, s.d.)	75	6	training	9676.82	9628.72	1.00	2649.93	2495.5	1.06	Savu 2016 [14]
Clo-COOH	po (-, s.d.)	75	10	training	11401.62	9955.33	1.15	2800.56	2978	0.94	Silvestro 2013 [15]
Clo-COOH	po (tab, s.d.)	75	20	test	15133.77	8022.51	1.89	3113.45	3172.96	0.98	Zou 2012 [17]
Clo-COOH	po (-, s.d.)	75	10	test	11401.80	13204.02	0.86	2800.48	3708	0.76	Silvestro 2011 [30]
Clo-COOH	po (tab, s.d.)	75	42	test	12285.91	13277.68	0.93	2992.86	3411.88	0.88	Junior 2010 [31]
Clo-COOH	po (tab, s.d.)	75	76	test	13654.84	7761.20	1.76	2592.13	2793.2	0.93	Yousef 2013 [32]
Clo-COOH	po (tab, s.d.)	75	12	test	10695.22	12636.01	0.85	2637.74	3522.86	0.75	Souri 2006 [33]
Clo-COOH	po (tab, s.d.)	75	32	test	11401.88	8027.59	1.42	2800.54	2313.16	1.21	Ksycinska 2006 [34]
Clo-COOH	po (tab, s.d.)	75	92	test	11394.77	6490.65	1.76	2655.54	2353.38	1.13	Brvar 2014 [19]
Clo-COOH	po (tab, s.d.)	150	24	training	29536.93	22093.33	1.34	5622.88	5852.1	0.96	Bahrami 2008 [35]
Clo-COOH	po (tab, s.d.)	300	24	training	40760.28	26893.08	1.52	10998.85	8534	1.29	Small 2008 [36]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	24	training	11441.36	7943.94	1.44 (D5)	2598.70	2511.04	1.03 (D5)	Härtter 2013 [25]
Clo-COOH	po (-, l.d./m.d., 5d)	300/75	40	test	63226.49	50100.02	1.26 (D1)	12982.35	15863	0.82 (D1)	Kim 2012 [27]
Clo-COOH	po (-, l.d./m.d., 6d)	300/75	44	test	26601.46	22289.85	1.19 (D1)	12872.45	11306.5	1.14 (D1)	Kim 2009 [28]
Clo-COOH	po (-, s.d.)	600	12	training	94049.45	81518.43	1.15	17387.22	19333.5	0.90	Härtter 2013 [25]
Clo-AG	po (tab, s.d.)	75	6	training	1569.80	1646.22	0.95	362.58	439.8	0.82	Savu 2016 [14]
Clo-AG	po (-, s.d.)	75	10	training	1780.04	1702.59	1.05	366.71	414	0.89	Silvestro 2013 [15]
Clo-AG	po (-, s.d.)	75	10	test	1780.40	1540.48	1.16	366.74	390.4	0.94	Silvestro 2011 [30]

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, C_{max}: maximum plasma concentration, d: dosage period in days, D: day of pharmacokinetic sampling, inf: infusion, GMFE: geometric mean fold error, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, obs: observed, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, pred: predicted, s.d.: single dose, tab: tablet.

Table S6: Predicted versus observed AUC_{last} and C_{max} values, along with GMFE values *(continued)*

Compound	Clopidogrel dosing regimen		n	Dataset	AUC_{last}			C_{max}			Reference
	Route	Dose [mg]			Pred $[\frac{ng*h}{ml}]$	Obs $[\frac{ng*h}{ml}]$	Pred/Obs	Pred $[\frac{ng}{ml}]$	Obs $[\frac{ng}{ml}]$	Pred/Obs	
2-Oxo-Clo	po (-, s.d.)	75	5	training	43.55	43.83	0.99	18.07	18.94	0.95	Silvestro 2013 [15]
Clo-AM	po (-, s.d.)	75	5	test	17.94	33.91	0.53	11.77	27.86	0.42	Silvestro 2013 [15]
Clo-AM	po (-, m.d., 10d)	75	9	test	15.56	9.17	1.70 (D1)	12.75	9.62	1.33 (D1)	Li 2018 [37]
Clo-AM	po (-, m.d., 10d)	75	9	test	15.88	6.24	2.54 (D10)	11.88	5.99	1.98 (D10)	Li 2018 [37]
Clo-AM	po (tab, s.d.)	300	27	training	43.51	33.31	1.31	31.37	24.00	1.31	Kim 2016 [23]
Clo-AM	po (tab, s.d.)	300	20	test	45.02	50.99	0.88	30.87	37.57	0.82	Zhou 2018 [24]
Clo-AM	po (tab, s.d.)	300	36	test	34.53	53.40	0.65	28.87	41.35	0.70	Umemura 2016 [38]
Clo-AM	po (tab, s.d.)	300	66	test	38.94	47.93	0.81	27.77	33.49	0.83	Takahashi 2008 [39]
Clo-AM	po (tab, s.d.)	300	16	test	35.87	35.41	1.01	30.08	30.13	1.00	Small 2010 [40]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	training	40.99	40.41	1.01 (D1)	28.88	27.80	1.04 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	training	15.95	10.97	1.45 (D7)	11.66	9.75	1.20 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	training	11.75	15.37	0.76 (D1)	9.76	10.23	0.95 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	training	2.62	3.66	0.72 (D7)	2.57	3.52	0.73 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	training	36.92	46.44	0.79 (D1)	27.07	33.95	0.80 (D1)	Angiolillo 2011 [42]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	training	13.24	13.64	0.97 (D5)	10.94	14.49	0.75 (D5)	Angiolillo 2011 [42]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	66	test	35.77	42.40	0.84 (D1)	26.33	31.63	0.83 (D1)	Hurbin 2012 [43]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	66	test	12.93	13.12	0.99 (D5)	10.67	14.78	0.72 (D5)	Hurbin 2012 [43]
Clo-AM	po (-, l.d./m.d., 5d)	300/75	65	test	16.02	12.35	1.30 (D5)	10.85	11.41	0.95 (D5)	Furlong 2013 [44]
Clo-AM	po (tab, s.d.)	600	14	training	55.01	85.13	0.65	35.30	50.54	0.70	Holmberg 2014 [29]
		Overall mean GMFE (range)				1.38 (1.00–3.68)			1.35 (1.00–2.37)		
		GMFE ≤ 2				63/66			55/58		

-: not given, 2-Oxo-Clo: 2-Oxo-clopidogrel, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, C_{max}: maximum plasma concentration, d: dosage period in days, D: day of pharmacokinetic sampling, inf: infusion, GMFE: geometric mean fold error, iv: intravenous, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, obs: observed, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, pred: predicted, s.d.: single dose, tab: tablet.

S2.7 Local Sensitivity Analysis

S2.7.1 Method

Local sensitivity of the final model to single parameter changes was calculated according to Equation S1 as ratio between the relative change of simulated area under the plasma concentration-time curve determined between first and last concentration measurements (AUC_{last}) and the relative variation of the respective parameter value used in the model. A relative perturbation of 1000% was applied (variation range 10.0, maximum number of 9 steps) and parameters included were either optimized or assumed to affect AUC_{last}.

$$S = \frac{\Delta AUC_{last}}{\Delta p} \cdot \frac{p}{AUC_{last}} \tag{S1}$$

where S = sensitivity of AUC_{last} to the examined model parameter, ΔAUC_{last} = change of AUC_{last}, Δp = change of the examined parameter value, p = original parameter value, and AUC_{last} = simulated AUC_{last} with the original parameter value.

The threshold for sensitivity was set at 0.5, which corresponds to a 50% change in simulated AUC_{last} given a 100% change in the parameter value examined.

S2.7.2 Results

Local sensitivity analysis of a multiple dose simulation over ten days involving administration of 75 mg clopidogrel daily was conducted. Table S7 lists all parameters evaluated for their influence on AUC_{last} of clopidogrel or its metabolites. Separate results are shown in Figures S23, S24, S25, S26, and S27 for clopidogrel and each metabolite, respectively.

Table S7: Parameters evaluated during the local sensitivity analysis of clopidogrel and its metabolites

Compound	Parameter	Source	Compound	Parameter	Source
Clo	CES1 k_{cat}	Optimized	Clo-AG	CL_{ren}	Optimized
Clo	CES1 K_M	Literature	Clo-AG	CYP3A4 K_i CI	Literature
Clo	CES2 k_{cat}	Optimized	Clo-AG	f_u	Literature
Clo	CES2 K_M	Literature	Clo-AG	lipophilicity	Optimized
Clo	CYP2C19 NM k_{cat}	Optimized	Clo-AG	pKa, acid	Literature
Clo	CYP2C19 K_i CI	Literature	Clo-AG	pKa, base	Literature
Clo	CYP2C19 K_i MBI	Literature	Clo-AG	Solubility	Literature
Clo	CYP2C19 K_I MBI	Literature	Clo-AG	Intestinal permeability	Calculated
Clo	CYP2C19 k_{inact} MBI	Literature	2-Oxo-Clo	CL_{hep}	Optimized
Clo	CYP2C19 K_M	Literature	2-Oxo-Clo	CYP2C19 NM k_{cat}	Optimized
Clo	CYP3A4 k_{cat}	Optimized	2-Oxo-Clo	CYP2C19 K_i CI	Literature
Clo	CYP3A4 K_i CI	Literature	2-Oxo-Clo	CYP2C19 K_M	Literature
Clo	CYP3A4 K_i MBI	Literature	2-Oxo-Clo	CYP3A4 k_{cat}	Optimized
Clo	CYP3A4 K_I MBI	Literature	2-Oxo-Clo	CYP3A4 K_i CI	Literature
Clo	CYP3A4 k_{inact} MBI	Literature	2-Oxo-Clo	CYP3A4 K_M	Literature
Clo	CYP3A4 K_M	Literature	2-Oxo-Clo	f_u	Literature
Clo	Dissolution shape	Optimized	2-Oxo-Clo	GFR fraction	Assumed
Clo	Dissolution time	Optimized	2-Oxo-Clo	lipophilicity	Optimized
Clo	f_u	Literature	2-Oxo-Clo	pKa, acid	Literature
Clo	GFR fraction	Assumed	2-Oxo-Clo	pKa, base	Literature
Clo	lipophilicity	Optimized	2-Oxo-Clo	Solubility	Literature
Clo	pKa, base	Literature	2-Oxo-Clo	Intestinal permeability	Calculated
Clo	Solubility	Literature	Clo-AM	CL_{hep}	Optimized
Clo	Intestinal permeability	Optimized	Clo-AM	f_u	Optimized
Clo-COOH	CYP3A4 K_i CI	Literature	Clo-AM	GFR fraction	Assumed
Clo-COOH	f_u	Optimized	Clo-AM	lipophilicity	Optimized
Clo-COOH	GFR fraction	Assumed	Clo-AM	pKa1, acid	Literature
Clo-COOH	lipophilicity	Optimized	Clo-AM	pKa2, acid	Literature
Clo-COOH	pKa, acid	Literature	Clo-AM	pKa, base	Literature
Clo-COOH	pKa, base	Literature	Clo-AM	Solubility	Literature
Clo-COOH	Solubility	Literature	Clo-AM	Intestinal permeability	Calculated
Clo-COOH	Intestinal permeability	Calculated			
Clo-COOH	UGT2B7 k_{cat}	Optimized			
Clo-COOH	UGT2B7 K_M	Literature			

2-Oxo-Clo: 2-Oxo-clopidogrel, CES: carboxylesterase, CI: competitive inhibition, Clo: clopidogrel, CL_{hep}: unspecific hepatic clearance, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, CL_{ren}: unspecific renal clearance, CYP: cytochrome P450, f_u: fraction unbound, GFR: glomerular filtration rate, k_{cat}: catalytic rate constant, K_i: concentration for half-maximal inhibition, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, MBI: mechanism-based inactivation, NM: normal metabolizer, pKa: acid dissociation constant, UGT: uridine 5'-diphospho-glucuronosyltransferase.

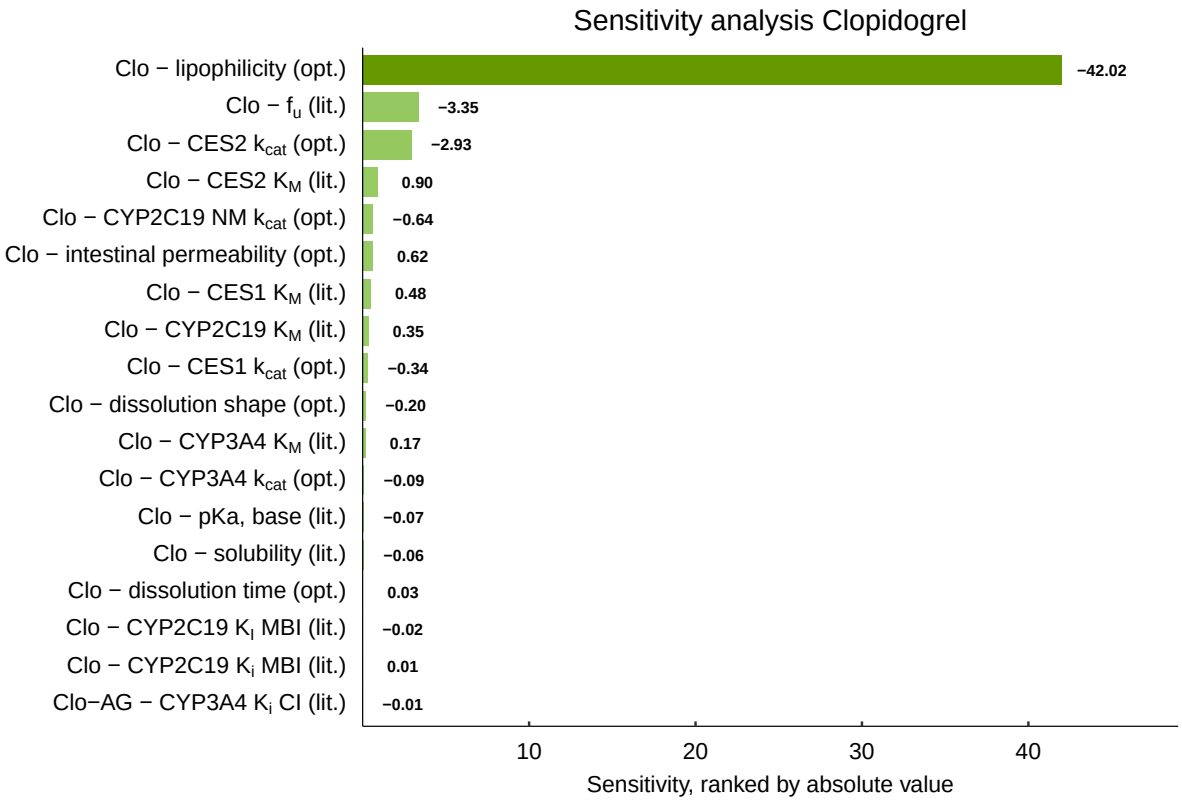


Figure S23: Clopidogrel model sensitivity analysis - clopidogrel. CES: carboxylesterase, CI: competitive inhibition, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, CYP: cytochrome P450, f_u: fraction unbound, k_{cat}: catalytic rate constant, K_i: concentration for half-maximal inhibition, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, lit.: literature, MBI: mechanism-based inactivation, NM: cytochrome P450 2C19 normal metabolizer, opt.: optimized, pKa: acid dissociation constant.

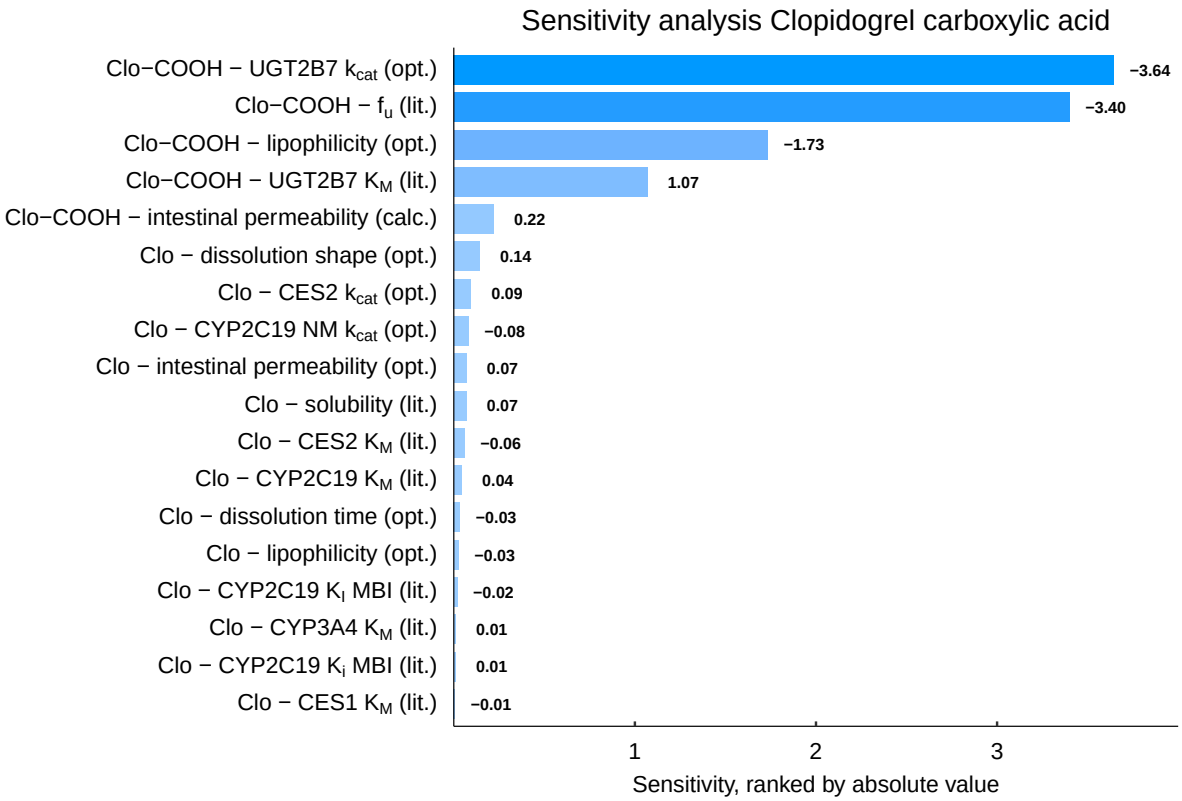


Figure S24: Clopidogrel model sensitivity analysis - clopidogrel carboxylic acid. Calc.: calculated, CES: carboxylesterase, Clo: clopidogrel, Clo-COOH: clopidogrel carboxylic acid, CYP: cytochrome P450, f_u: fraction unbound, k_{cat}: catalytic rate constant, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, lit.: literature, MBI: mechanism-based inactivation, NM: cytochrome P450 2C19 normal metabolizer, opt.: optimized, UGT: uridine 5'-diphospho-glucuronosyltransferase.

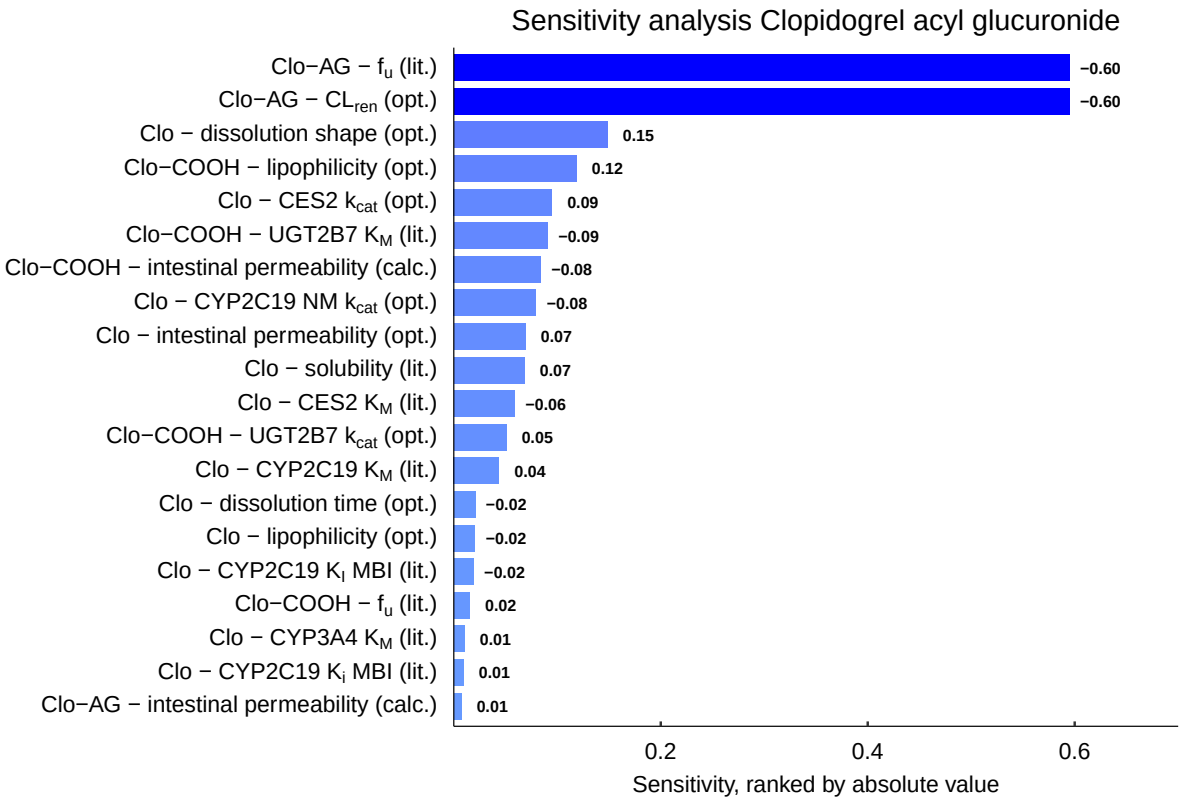


Figure S25: Clopidogrel model sensitivity analysis - clopidogrel acyl glucuronide. Calc.: calculated, CES: carboxylesterase, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-COOH: clopidogrel carboxylic acid, CL_{ren}: unspecific renal clearance, CYP: cytochrome P450, f_u: fraction unbound, k_{cat}: catalytic rate constant, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, lit.: literature, MBI: mechanism-based inactivation, NM: cytochrome P450 2C19 normal metabolizer, opt.: optimized, UGT: uridine 5'-diphospho-glucuronosyltransferase.

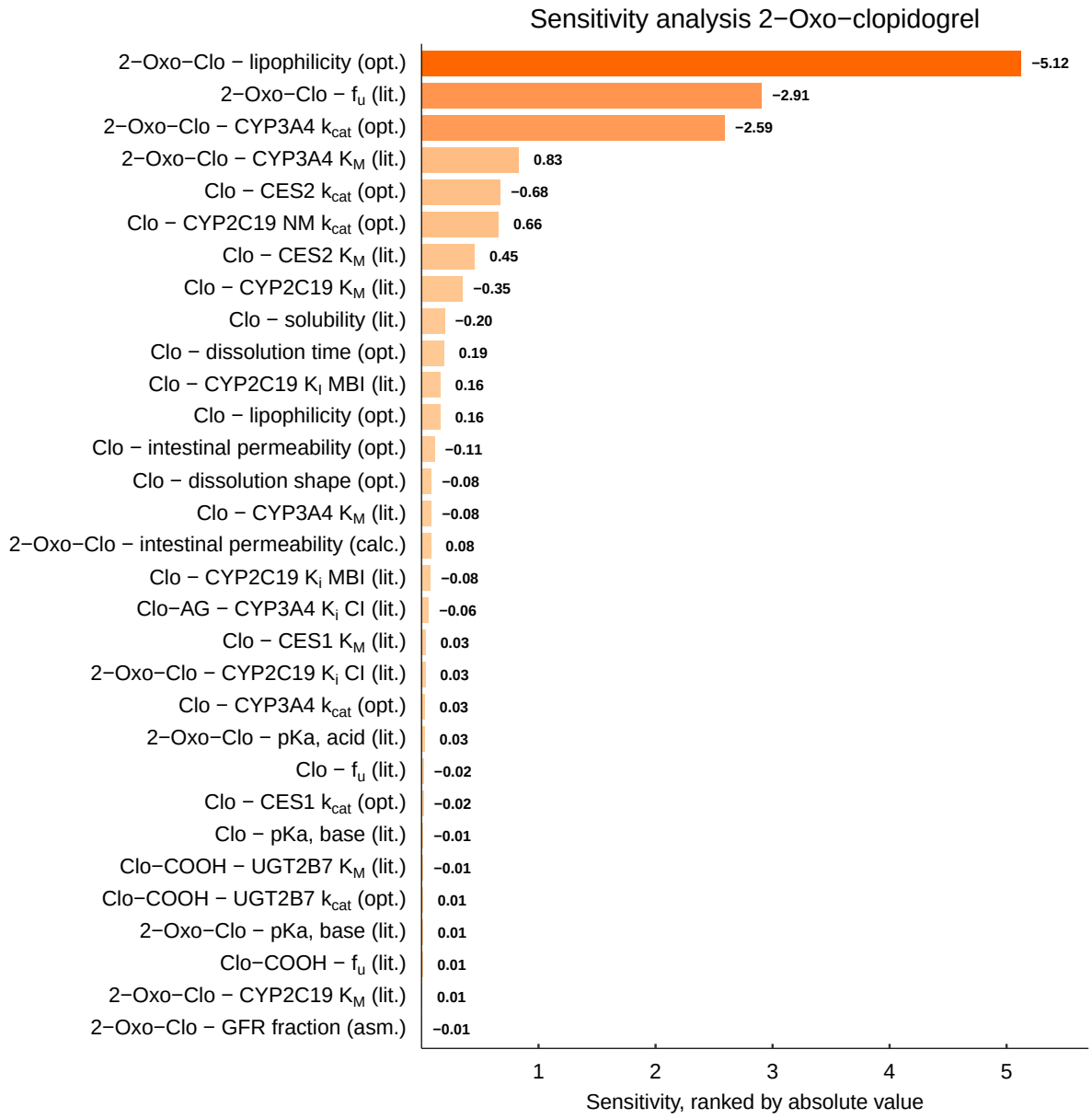


Figure S26: Clopidogrel model sensitivity analysis - 2-oxo-clopidogrel. 2-Oxo-Clo: 2-Oxo-clopidogrel, asm.: assumed, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-COOH: clopidogrel carboxylic acid, CYP: cytochrome P450, f_u: fraction unbound, GFR: glomerular filtration rate, k_{cat}: catalytic rate constant, K_i: concentration for half-maximal inhibition, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, lit.: literature, MBI: mechanism-based inactivation, NM: cytochrome P450 2C19 normal metabolizer, pKa: acid dissociation constant, opt.: optimized, UGT: uridine 5'-diphospho-glucuronosyltransferase.

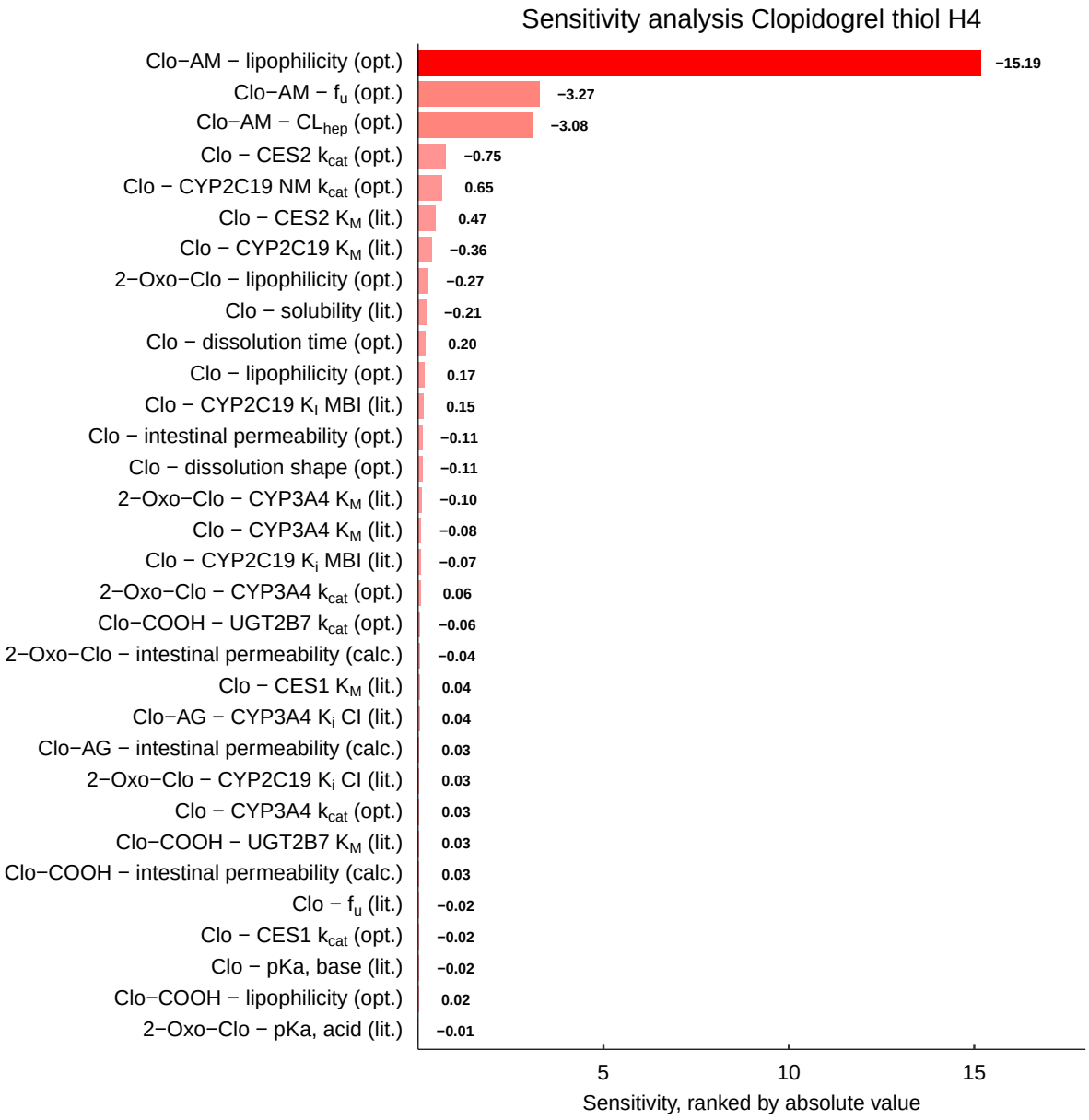


Figure S27: Clopidogrel model sensitivity analysis - clopidogrel thiol H4. 2-Oxo-Clo: 2-Oxo-clopidogrel, calc.: calculated, CES: carboxylesterase, CI: competitive inhibition, Clo: clopidogrel, CL_{hep}: unspecific hepatic clearance, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, CYP: cytochrome P450, f_u: fraction unbound, k_{cat}: catalytic rate constant, K_i: concentration for half-maximal inhibition, K_I: concentration for half-maximal inactivation, k_{inact}: maximum inactivation rate constant, K_M: Michaelis-Menten constant, lit.: literature, MBI: mechanism-based inactivation, NM: cytochrome P450 2C19 normal metabolizer, pKa: acid dissociation constant, opt.: optimized, UGT: uridine 5'-diphospho-glucuronosyltransferase.

S3 DGI Modeling

S3.1 Clinical Study Data

Table S8: Clopidogrel DGI model study table

Compound measured	Clopidogrel dosing regimen		n	Females [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Reference
	Route	Dose [mg]							
Clo	po (tab, s.d.)	300	8 NM	-	Asian	22.3±1.6	64.8±4.7	172.9±3.3	Song 2018 [79]
Clo	po (tab, s.d.)	300	10 IM	-	Asian	21.6±1.1	65.0±5.1	173.6±3.4	Song 2018 [79]
Clo	po (tab, s.d.)	300	2 PM	-	Asian	20.0±0.0	58.5±0.7	169.0±1.4	Song 2018 [79]
Clo	po (-, l.d./m.d., 7d)	300/75	8 NM	0	Asian	23.5±2.9	66.6±5.6	-	Kim 2008 [26]
Clo	po (-, l.d./m.d., 7d)	300/75	8 IM	0	Asian	24.3±1.7	73.0±6.3	-	Kim 2008 [26]
Clo	po (-, l.d./m.d., 7d)	300/75	8 PM	0	Asian	24.1±2.8	67.3±5.6	-	Kim 2008 [26]
Clo-AM	po (-, m.d., 10d)	75	5 NM	33	Asian	30.3±7.5	63.8±8.5	165.4±7.2	Li 2018 [37]
Clo-AM	po (-, m.d., 10d)	75	4 IM	33	Asian	30.3±7.5	63.8±8.5	165.4±7.2	Li 2018 [37]
Clo-AM	po (tab, s.d.)	300	8 NM	-	Asian	22.3±1.6	64.8±4.7	172.9±3.3	Song 2018 [79]
Clo-AM	po (tab, s.d.)	300	10 IM	-	Asian	21.6±1.1	65.0±5.1	173.6±3.4	Song 2018 [79]
Clo-AM	po (tab, s.d.)	300	2 PM	-	Asian	20.0±0.0	58.5±0.7	169.0±1.4	Song 2018 [79]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 NM	56	Asian	36.7±5.6 (24–43)	64.8±8.4 (51.3–79.8)	-	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 IM	50	Asian	33.7±6.8 (19–42)	62.8±6.5 (51.4–78.6)	-	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 PM	44	Asian	35.0±4.8 (29–44)	63.7±6.6 (49.6–76.8)	-	Zhang 2020 [80]

-: not given, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, d: dosage period in days, IM: cytochrome P450 2C19 intermediate metabolizer, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet; values for age, weight and height are presented as mean ± standard deviation (range).

Table S8: Clopidogrel DGI model study table *(continued)*

Compound measured	Clopidogrel dosing regimen		n	Females [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Reference
	Route	Dose [mg]							
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 NM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 IM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 NM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 IM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 PM	0	Japanese	(20–35)	(50.4–87.4)	-	Kobayashi 2015 [41]

-: not given, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, d: dosage period in days, IM: cytochrome P450 2C19 intermediate metabolizer, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, s.d.: single dose, tab: tablet; values for age, weight and height are presented as mean ± standard deviation (range).

S3.2 Plasma Concentration-Time Profiles (Semilogarithmic)

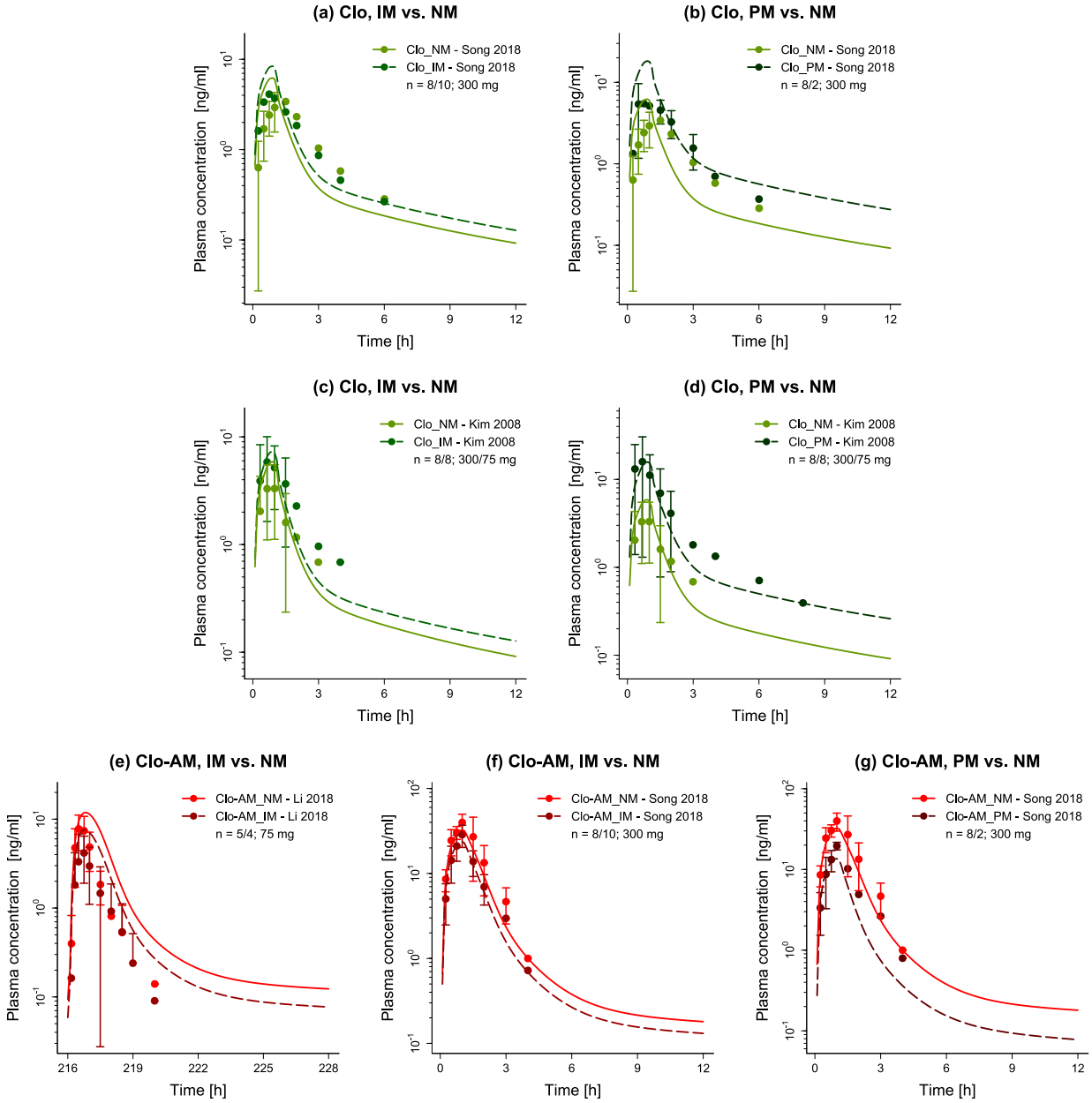


Figure S28: Drug–gene interaction model evaluation. Presented are predicted plasma concentration-time profiles (semilogarithmic plots) of (a–d) clopidogrel and (e–g) Clo-AM for IM and PM compared separately to NM phenotypes, alongside corresponding observed data [26, 37, 79]. Dashed (IM or PM) and solid (NM) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, IM: cytochrome P450 (CYP) 2C19 intermediate metabolizer, n: number of participants, NM: CYP2C19 normal metabolizer, PM: CYP2C19 poor metabolizer.

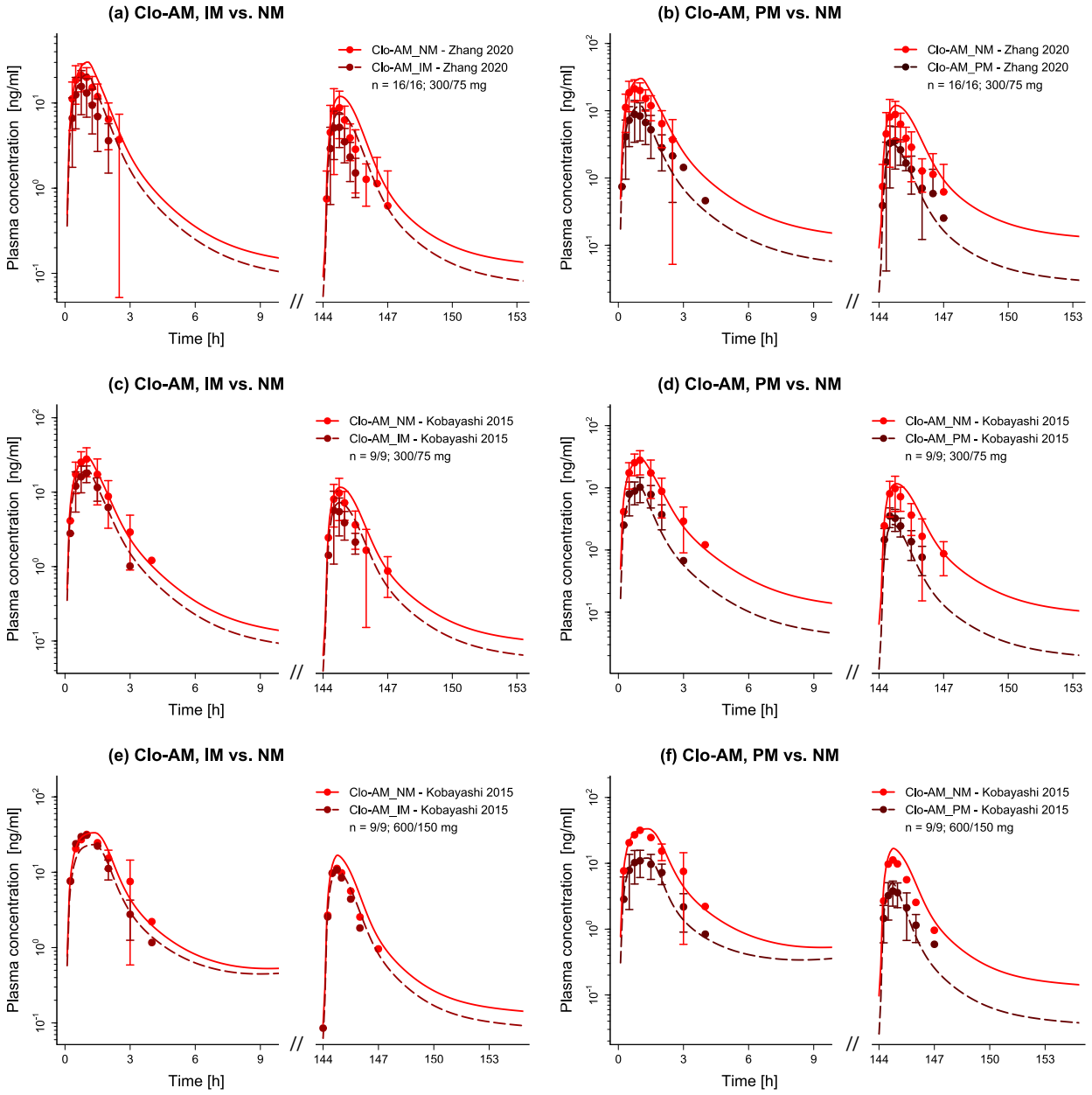


Figure S29: Drug–gene interaction model evaluation. Presented are predicted plasma concentration-time profiles (semilogarithmic plots) of Clo-AM for IM and PM compared separately to NM phenotypes, alongside corresponding observed data [41, 80]. Dashed (IM or PM) and solid (NM) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo-AM: clopidogrel thiol H4, IM: cytochrome P450 (CYP) 2C19 intermediate metabolizer, n: number of participants, NM: CYP2C19 normal metabolizer, PM: CYP2C19 poor metabolizer.

S3.3 Plasma Concentration-Time Profiles (Linear)

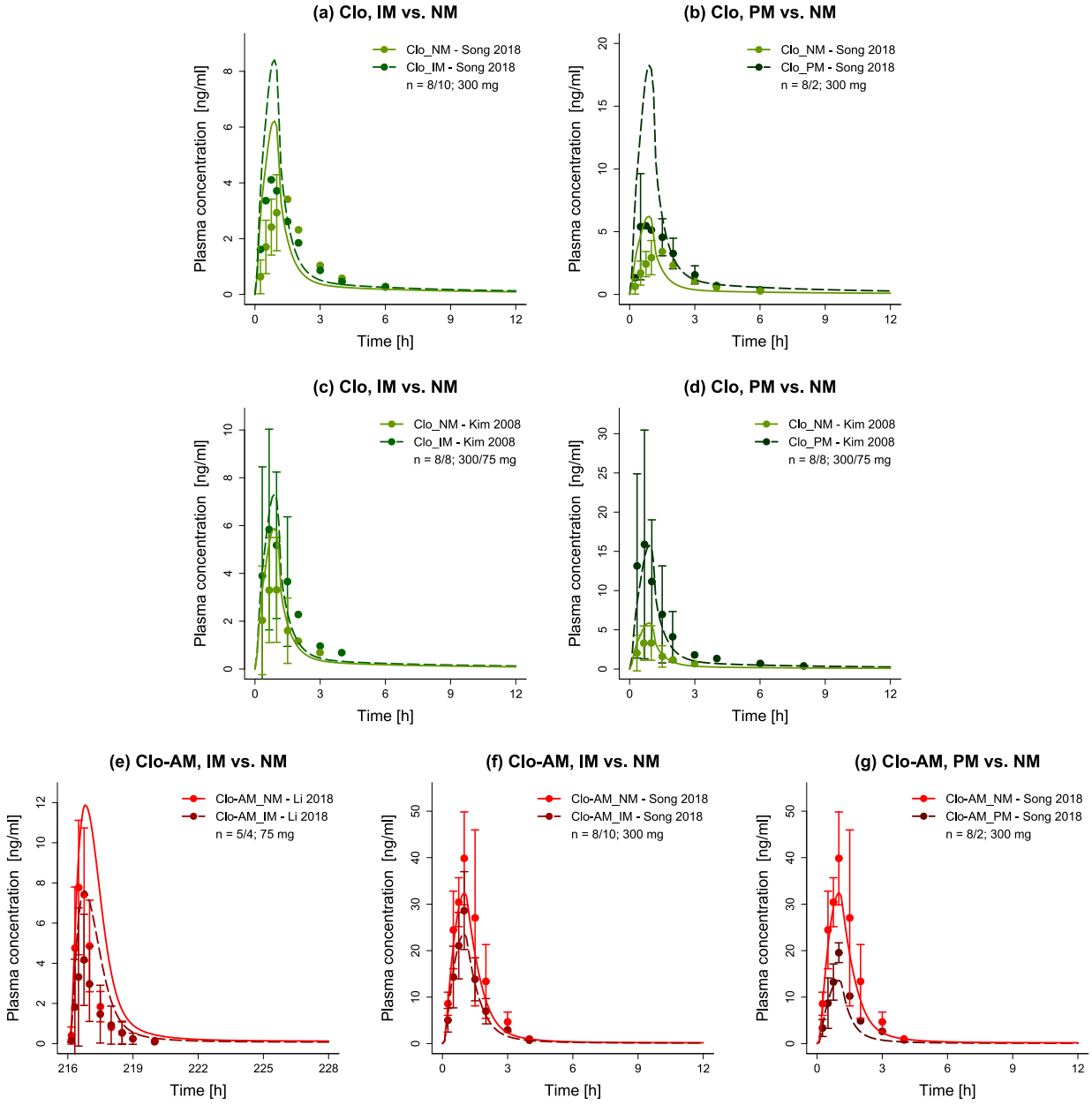


Figure S30: Drug–gene interaction model evaluation. Presented are predicted plasma concentration-time profiles (linear plots) of (a–d) clopidogrel and (e–g) Clo-AM for IM and PM compared separately to NM phenotypes, alongside corresponding observed data [26, 37, 79]. Dashed (IM or PM) and solid (NM) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, IM: cytochrome P450 (CYP) 2C19 intermediate metabolizer, n: number of participants, NM: CYP2C19 normal metabolizer, PM: CYP2C19 poor metabolizer.

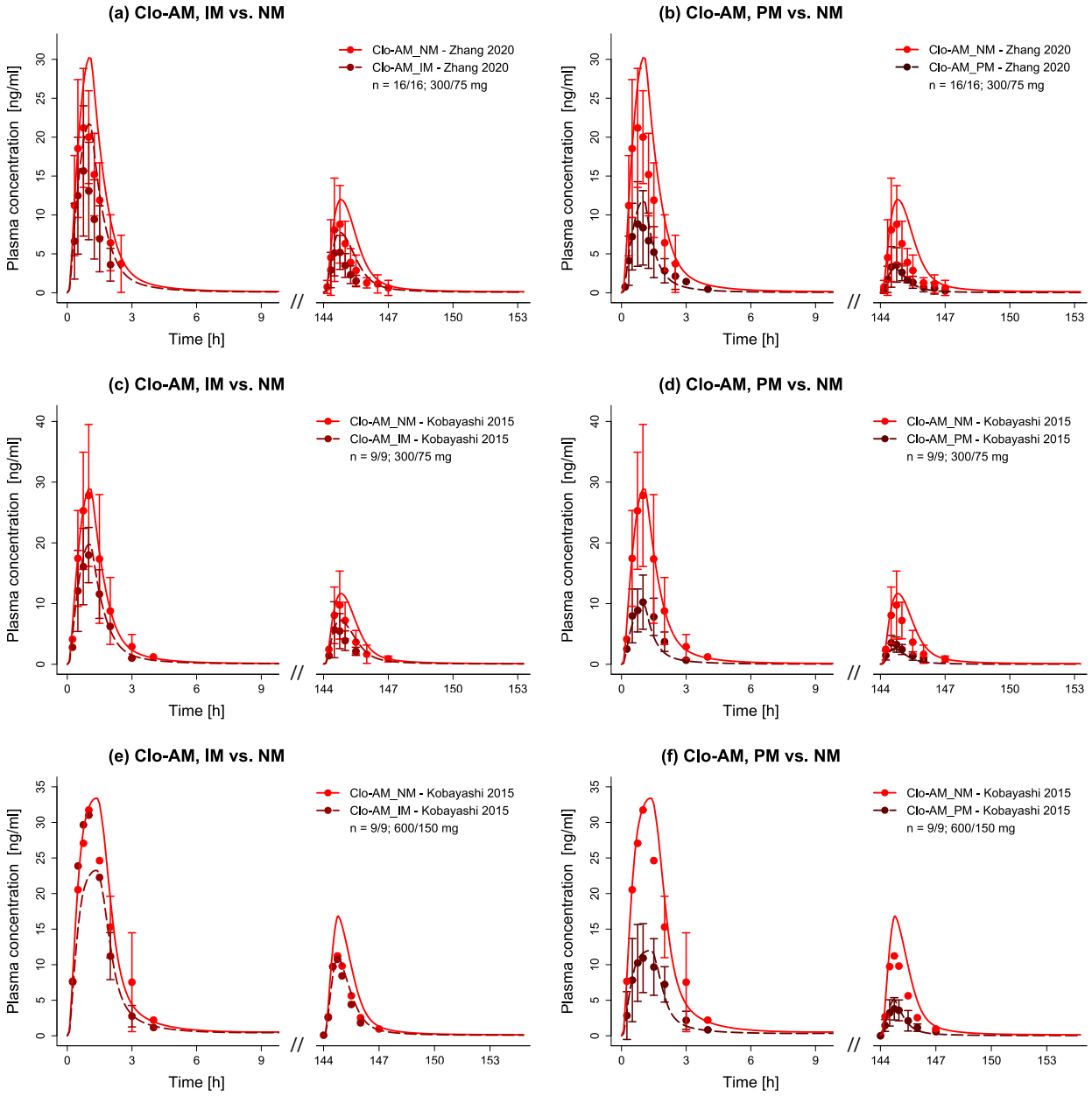


Figure S31: Drug–gene interaction model evaluation. Presented are predicted plasma concentration-time profiles (linear plots) of Clo-AM for IM and PM compared separately to NM phenotypes, alongside corresponding observed data [41, 80]. Dashed (IM or PM) and solid (NM) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo-AM: clopidogrel thiol H4, IM: cytochrome P450 (CYP) 2C19 intermediate metabolizer, n: number of participants, NM: CYP2C19 normal metabolizer, PM: CYP2C19 poor metabolizer.

S3.4 DGI AUC_{last} and DGI C_{max} Ratio Goodness-of-Fit Plots

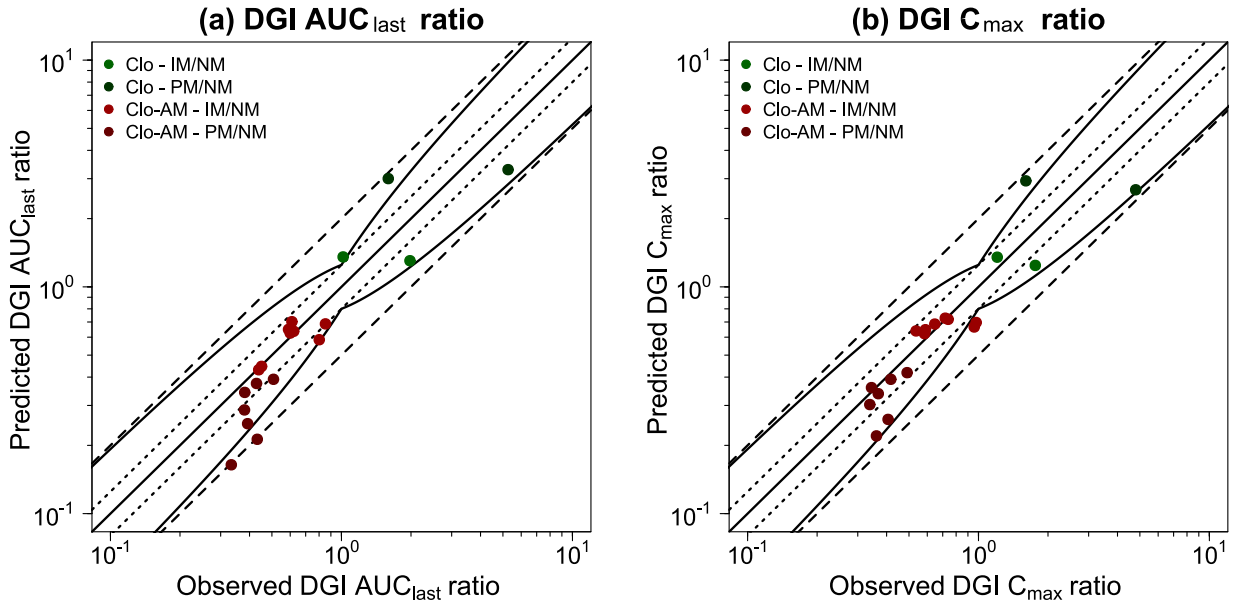


Figure S32: Drug–gene interaction model evaluation. Predicted versus observed (a) DGI AUC_{last} and (b) DGI C_{max} ratios are shown with the solid line representing the line of identity, dotted lines indicating 1.25-fold and dashed lines 2-fold deviation from the respective observed value [26, 37, 41, 79, 80], along with the curved lines marking the prediction success limits proposed by Guest et al. [81] (including 20% variability to account for uncertainties in observed ratios). AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, C_{max}: maximum plasma concentration, DGI: drug–gene interaction, IM: cytochrome P450 (CYP) 2C19 intermediate metabolizer, n: number of participants, NM: CYP2C19 normal metabolizer, PM: CYP2C19 poor metabolizer.

S3.5 Predicted and Observed DGI AUC_{last} and DGI C_{max} Ratios with Mean GMFEs

Table S9: Predicted versus observed DGI AUC_{last} and DGI C_{max} ratios, along with GMFE values

Compound	Clopidogrel dosing regimen		n	DGI AUC_{last} ratio			DGI C_{max} ratio			Reference
	Route	Dose [mg]		Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	
Clo	po (tab, s.d.)	300	10 IM/8 NM	1.36	1.02	1.33	1.35	1.21	1.12	Song 2018 [79]
Clo	po (tab, s.d.)	300	2 PM/8 NM	3.00	1.59	1.88	2.93	1.60	1.83	Song 2018 [79]
Clo	po (-, l.d./m.d., 7d)	300/75	8 IM/8 NM	1.30	1.98	0.66 (D1)	1.24	1.76	0.71 (D1)	Kim 2008 [26]
Clo	po (-, l.d./m.d., 7d)	300/75	8 PM/8 NM	3.29	5.26	0.62 (D1)	2.68	4.80	0.56 (D1)	Kim 2008 [26]
Clo-AM	po (-, m.d., 10d)	75	4 IM/5 NM	0.63	0.60	1.04 (D10)	0.64	0.54	1.19 (D10)	Li 2018 [37]
Clo-AM	po (tab, s.d.)	300	10 IM/8 NM	0.70	0.61	1.15	0.73	0.72	1.01	Song 2018 [79]
Clo-AM	po (tab, s.d.)	300	2 PM/8 NM	0.38	0.43	0.87	0.42	0.49	0.85	Song 2018 [79]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 IM/16 NM	0.65	0.59	1.10 (D1)	0.72	0.74	0.97 (D1)	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 IM/16 NM	0.43	0.44	0.98 (D7)	0.65	0.59	1.10 (D7)	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 PM/16 NM	0.39	0.51	0.77 (D1)	0.39	0.42	0.94 (D1)	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	16 PM/16 NM	0.21	0.43	0.49 (D7)	0.26	0.41	0.64 (D7)	Zhang 2020 [80]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 IM/9 NM	0.64	0.62	1.03 (D1)	0.69	0.65	1.06 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 IM/9 NM	0.45	0.45	0.99 (D7)	0.62	0.58	1.07 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM/9 NM	0.29	0.38	0.75 (D1)	0.34	0.37	0.92 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	300/75	9 PM/9 NM	0.16	0.33	0.49 (D7)	0.22	0.36	0.61 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 IM/9 NM	0.69	0.85	0.81 (D1)	0.70	0.98	0.71 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 IM/9 NM	0.58	0.80	0.73 (D7)	0.67	0.96	0.69 (D7)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 PM/9 NM	0.34	0.38	0.90 (D1)	0.36	0.34	1.05 (D1)	Kobayashi 2015 [41]
Clo-AM	po (-, l.d./m.d., 7d)	600/150	9 PM/9 NM	0.25	0.39	0.64 (D7)	0.30	0.34	0.89 (D7)	Kobayashi 2015 [41]
			Overall mean GMFE (range)			1.36 (1.01–2.03)			1.27 (1.01–1.83)	
			GMFE ≤ 2			17/19			19/19	

-: not given, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, d: dosage period in days, C_{max}: maximum plasma concentration, D: day of pharmacokinetic sampling, IM: cytochrome P450 2C19 intermediate metabolizer, l.d.: loading dose, m.d.: maintenance dose (once daily), n: number of participants, NM: cytochrome P450 2C19 normal metabolizer, obs: observed, PM: cytochrome P450 2C19 poor metabolizer, po: peroral, pred: predicted, s.d.: single dose, tab: tablet.

S4 DDI Network Modeling

S4.1 Types of Interaction Implemented

S4.1.1 Competitive Inhibition

Competitive inhibition (CI) involves reversible binding of an inhibitor to the respective enzyme or transporter, thus competing with substrates for the binding site, increasing the apparent Michaelis-Menten constant ($K_{M,app}$) while leaving the maximum reaction velocity (v_{max}) unaltered (Equations S2 and S3) [55]. Due to its reversibility, the inhibition can be overcome through an increase in substrate concentration (concentration-dependent).

$$v = \frac{v_{max} \cdot [S]}{K_{M,app} + [S]} \tag{S2}$$

$$K_{M,app} = K_M \cdot (1 + \frac{[I]}{K_i}) \tag{S3}$$

where v = reaction velocity, v_{max} = maximum reaction velocity, $[S]$ = free substrate concentration, $K_{M,app}$ = apparent Michaelis-Menten constant (inhibitor present), K_M = Michaelis-Menten constant (inhibitor absent), $[I]$ = free inhibitor concentration, and K_i = dissociation constant of the inhibitor-enzyme/ -transporter complex.

S4.1.2 Mechanism-Based Inactivation

In the case of mechanism-based inactivation (MBI), the inactivator, in addition to reversibly binding to the enzyme or transporter in question, is irreversibly converted into a reactive species that forms a covalent complex with the respective target (time-dependent inhibition). Due to the irreversibility, MBI can only be reversed by *de novo* synthesis of the relevant enzyme or transporter. In PK-Sim®, MBI and its resulting impact on enzyme turnover is implemented according to Equation S4 [55].

$$\frac{d[T]}{dt} = k_{deg} \cdot [T]_0 - (k_{deg} + \frac{k_{inact} \cdot [I]}{K_I + [I]}) \cdot [T] \tag{S4}$$

where $d[T]/dt$ = enzyme or transporter turnover, k_{deg} = degradation rate constant, $[T]_0$ = initial enzyme or transporter concentration at time 0, k_{inact} = maximum inactivation rate constant, K_I = concentration for half-maximal inactivation, $[I]$ = free inactivator concentration, and $[T]$ = enzyme or transporter concentration.

S4.1.3 Induction

Induction of enzymes or transporters is usually caused by activation of specific nuclear receptors through binding of an inducer, resulting in increased *de novo* synthesis of the enzyme or transporter of interest. Equation S5 describes the correlation between maximum induction effect (E_{max}), concentration for half-maximal induction (EC_{50}) and the magnitude of induction, with the first two parameters used for implementation of an induction process in PK-Sim® [55, 82].

$$E = \frac{E_{max} \cdot [Ind]}{EC_{50} + [Ind]} \tag{S5}$$

where E = magnitude of induction, E_{max} = maximum induction effect, $[Ind]$ = free inducer concentration (steady-state), and EC_{50} = concentration for half-maximal induction.

S4.2 Clinical Study Data

Table S10: Clopidogrel DDI network study table

Perpetrator	Perpetrator application [mg]	Victim	Victim application [mg]	Compound measured	n	F [%]	Ethnicity implemented	Age [years]	Weight [kg]	Height [cm]	Dataset	Reference
Omep	d1–29: 80 po (cap, m.d.)	Clo	d1: 300 d2–29: 75 po (tab, l.d./m.d.)	Clo-AM	81	42	White American	30±9	73.9±11.8	171.5±9.8	test	Andersson 2014 [83]
Omep	d1–7: 20 po (-, m.d.)	Clo	d1–7: 75 po (-, m.d.)	Clo-AM	36	0	European	33.6±7.9	74.1±8.7	-	test	Funck-Brentano 2013 [84]
Rifa	d1–15: 300 po (-, b.i.d.)	Clo	d8: 600 d9–15: 75 po (-, l.d./m.d.)	Clo-AM	12	0	European	24 (19–42)	-	-	test	Judge 2010 [85]
Clo	d1–4: 75 po (tab, m.d.)	Bupro	d4+1h: 150 po (tab SR, s.d.)	(OH-)Bupro	12	0	European	(22–27)	(67–95)	-	test	Turpeinen 2005 [86]
Clo	d1: 300 d2: 75 po (tab, l.d./m.d.)	Monte	d1+1h: 10 po (tab, s.d.)	Monte	12	58	European	(19–31)	-	-	test	Itkonen 2018 [87]
Clo	d1: 300 d2–4: 75 po (tab, l.d./m.d.)	Omep	d4+1h: 40 po (-, s.d.)	Omep	6	0	Asian	(20–24)	-	-	test	Chen 2009 [88]
Clo	d1: 300 d2–3: 75 po (tab, l.d./m.d.)	Pio	d1+1h: 15 po (tab, s.d.)	Pio	10	40	European	(20–35)	-	-	test	Itkonen 2016 [89]
Clo	d1: 300 d2–3: 75 po (tab, l.d./m.d.)	Repa	d1+1h: 0.25 d3+1h: 0.25 po (tab, s.d.)	Repa	9	44	European	24±4 (19–30)	68±14 (49–100)	175±10 (156–192)	training	Tornio 2014 [48]

-: not given, b.i.d.: maintenance dose (twice daily), Bupro: bupropion, cap: capsule, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, d: day, F: females, l.d.: loading dose, m.d.: maintenance dose (once daily), Monte: montelukast, n: number of participants, OH-Bupro: hydroxybupropion, Omep: omeprazole, Pio: pioglitazone, po: peroral, Repa: repaglinide, Rifa: rifampicin, s.d.: single dose, SR: sustained release formualtion, tab: tablet; values for age, weight and height are presented as mean ± standard deviation (range).

S4.3 Implemented Interaction Processes

Sections S4.3.1 to S4.3.6 provide an overview per drug–drug interaction (DDI) partner of the respective metabolic and transport pathways described in the literature as well as of enzymes/transporters inhibited/induced by said DDI partner. Table S11 summarizes the interaction processes implemented in the final DDI network. The precise values of the incorporated interaction parameters can be found for the DDI partners in Section S4.4 and for clopidogrel and its metabolites in Table S3.

S4.3.1 Bupropion

The antidepressant and smoking cessation agent bupropion is primarily hydroxylated to hydroxybupropion (OH-Bupro) via cytochrome P450 (CYP) 2B6, with additional metabolization to threo-/erythrohydrobupropion via 11β-hydroxysteroid dehydrogenase [90–92]. Bupropion is listed by the United States Food and Drug Administration (FDA) as sensitive clinical substrate of CYP2B6 and strong clinical inhibitor of CYP2D6 [93]. Table S12 lists the drug-dependent parameters used in the bupropion parent-metabolite physiologically based pharmacokinetic (PBPK) model.

S4.3.2 Montelukast

Regarding the metabolism of the antiasthmatic agent montelukast, CYP2C8 showed by far the greatest influence *in vitro*, followed by CYP3A4, CYP2C9, and CYP3A5 [94]. The FDA lists montelukast as moderate sensitive clinical substrate of CYP2C8 [93]. Table S13 lists the drug-dependent parameters used in the montelukast PBPK model.

S4.3.3 Omeprazole

CYP2C19 and CYP3A4 are mainly associated with the conversion of the proton pump inhibitor omeprazole [95, 96]. The FDA lists omeprazole (R-/S-omeprazole) as sensitive clinical substrate of CYP2C19 as well as weak clinical inhibitor of CYP2C19 [93]. Table S14 lists the drug-dependent parameters for R-omeprazole and S-omeprazole used in the omeprazole PBPK model.

S4.3.4 Pioglitazone

The antidiabetic agent pioglitazone is metabolized primarily via CYP2C8, being listed by the FDA as moderate sensitive clinical substrate of CYP2C8 [93, 97]. Table S15 lists the drug-dependent parameters used in the pioglitazone PBPK model.

S4.3.5 Repaglinide

The antidiabetic agent repaglinide is listed by the FDA as sensitive clinical substrate of CYP2C8 and clinical substrate of organic-anion-transporting polypeptide (OATP) 1B1/OATP1B3 [93], while also being metabolized via CYP3A4 in addition to CYP2C8 [98]. Table S16 lists the drug-dependent parameters used in the repaglinide PBPK model.

S4.3.6 Rifampicin

The antibiotic agent rifampicin demonstrates a high DDI potential being listed by the FDA as strong clinical index inducer of CYP2C19 and CYP3A4, moderate clinical index inducer of CYP2B6, CYP2C8, and CYP2C9, moderate clinical inducer of CYP1A2, and clinical inhibitor of OATP1B1/ OATP1B3 [93]. In addition, it affects unlisted enzymes/transporters like arylacetamide deacetylase (AADAC), an enzyme responsible for rifampicin deacetylation [99]. Table S17 lists the drug-dependent parameters used in the rifampicin PBPK model.

Table S11: Implemented interaction processes

		PERPETRATOR						
		Enzyme/ Transporter	Clo	Clo-COOH	Clo-AG	2-Oxo-Clo	R-/S-Omep	Rifa
VICTIM	Bupro	**CYP2B6**	**MBI**			MBI		
	Monte	**CYP2C8**	CI	CI	**MBI**	CI		
		CYP2C9	CI					
		CYP3A4	MBI	CI	CI	CI		
	Omep	**CYP2C19**	**MBI**			CI		
		CYP3A4	MBI	CI	CI	CI		
	Pio	**CYP2C8**	CI	CI	**MBI**	CI		
	Repa	**CYP2C8**	CI	CI	**MBI**	CI		
		CYP3A4	MBI	CI	CI	CI		
		OATP1B1	CI		CI	CI		
	Clo	**CYP2C19**					**MBI**	
	Clo	**CYP2C19**						**IND**
		CYP3A4						**CI, IND**
		UGT2B7						CI, IND

2-Oxo-Clo: 2-Oxo-clopidogrel, Bupro: bupropion, CI: competitive inhibition, Clo: clopidogrel, Clo-AG: clopidogrel acyl glucuronide, Clo-AM: clopidogrel thiol H4, Clo-COOH: clopidogrel carboxylic acid, CYP: cytochrome P450, IND: induction, MBI: mechanism-based inactivation, Monte: montelukast, OATP: organic-anion-transporting polypeptide, Omep: omeprazole, Pio: pioglitazone, Repa: repaglinide, Rifa: rifampicin, R-Omep: R-omeprazole, S-Omep: S-omeprazole, UGT: uridine 5'-diphospho-glucuronosyltransferase; the respective main interaction processes are highlighted in bold print.

S4.4 Drug-Dependent Parameters DDI Partner

S4.4.1 Bupropion

Table S12: Drug-dependent parameters of the bupropion PBPK model [100]

Parameter	Unit	Value	Source	Description
		Bupropion		
Molecular weight	g/mol	239.74	Lit.	Molecular weight
TPSA*	$Å^2$	29.1	Lit.	Topological polar surface area
pKa, base		8.75	Lit.	Acid dissociation constant
Solubility (pH)	mg/ml	364.56 (7.4)	Lit.	Solubility
Lipophilicity		2.70	Opt.	Lipophilicity
f_u	%	16	Lit.	Fraction unbound
11β-HSD K_M → E-BU/T-BU	µmol/l	39.10	Lit.	Michaelis-Menten constant
11β-HSD k_{cat} → E-BU	1/min	2.15	Opt.	Catalytic rate constant
11β-HSD k_{cat} → T-BU	1/min	8.18	Opt.	Catalytic rate constant
CYP2B6 K_M → OH-Bupro	µmol/l	25.80[a]	Lit.	Michaelis-Menten constant
CYP2B6 k_{cat} → OH-Bupro	1/min	21.74	Opt.	Catalytic rate constant
CYP2C19 K_M → sink	µmol/l	8.30	Lit.	Michaelis-Menten constant
CYP2C19 k_{cat} → sink	1/min	2.59	Opt.	Catalytic rate constant
Binding partner K_D	µmol/l	0.44	Opt.	Dissociation constant for binding
Binding partner k_{off}	1/min	0.05	Opt.	Dissociation rate constant for binding
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$3.30 \cdot 10^{-5}$	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	Charge dependent Schmitt, 0.14	Calc. [54]	permeability into the cellular space
Partition coefficients		PK-Sim Standard	Calc. [55]	Organ-plasma partition coefficients
Dissolution time (Weibull)	min	100.00 (SR)	Opt.	Dissolution time (Weibull)
Dissolution shape (Weibull)		1.00 (SR)	Opt.	Dissolution shape

-: not available, *: no model parameter, listed for additional information, [a]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$), [b]: adjusted due to different reference concentrations in the original model and clopidogrel model, asm.: assumed, calc.: calculated, CYP: cytochrome P450, E-BU: erythrohydrobupropion, EHC: enterohepatic circulation, GFR: glomerular filtration rate, HSD: hydroxysteroid dehydrogenase, lit.: literature, OH-Bupro: hydroxybupropion, opt.: optimized, SR: sustained release formulation, T-BU: threohydrobupropion, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S12: Drug-dependent parameters of the bupropion PBPK model [100] *(continued)*

Parameter	Unit	Value	Source	Description
		Hydroxybupropion		
Molecular weight	g/mol	255.74	Lit.	Molecular weight
TPSA*	Å^2	49.33	Lit.	Topological polar surface area
pKa, base		7.65	Lit.	Acid dissociation constant
Solubility (pH)	mg/ml	0.91 (7.4)	Lit.	Solubility
Lipophilicity		1.90	Opt.	Lipophilicity
f_u	%	23	Lit.	Fraction unbound
UGT2B7 $K_M \rightarrow$ sink	µmol/l	14.64[a]	Lit.	Michaelis-Menten constant
UGT2B7 $k_{cat} \rightarrow$ sink	1/min	40.40[b]	Opt.	Catalytic rate constant
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$2.78 \cdot 10^{-5}$	Calc.	Transcellular intestinal permeability
Cellular permeability	cm/min	Charge dependent Schmitt, 0.01	Calc. [54]	permeability into the cellular space
Partition coefficients		Berezhkovskiy	Calc. [101]	Organ-plasma partition coefficients

-: not available, *: no model parameter, listed for additional information, [a]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$), [b]: adjusted due to different reference concentrations in the original model and clopidogrel model, asm.: assumed, calc.: calculated, CYP: cytochrome P450, E-BU: erythrohydrobupropion, EHC: enterohepatic circulation, GFR: glomerular filtration rate, HSD: hydroxysteroid dehydrogenase, lit.: literature, OH-Bupro: hydroxybupropion, opt.: optimized, SR: sustained release formulation, T-BU: threohydrobupropion, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S12: Drug-dependent parameters of the bupropion PBPK model [100] *(continued)*

Parameter	Unit	Value	Source	Description
		Erythro-/Threohydrobupropion		
Molecular weight	g/mol	241.76	Lit.	Molecular weight
TPSA*	Å^2	32.26	Lit.	Topological polar surface area
pKa, base		9.71	Lit.	Acid dissociation constant
Solubility (pH)	mg/ml	82.98 (7.4)	Lit.	Solubility
Lipophilicity		1.76	Opt.	Lipophilicity
f_u	%	58.00	Lit.	Fraction unbound
UGT2B7 $K_M \rightarrow$ sink	µmol/l	9.33[a] (E-BU), 6.22[a] (T-BU)	Lit.	Michaelis-Menten constant
UGT2B7 $k_{cat} \rightarrow$ sink	1/min	11.03[b] (E-BU), 2.94[b] (T-BU)	Opt.	Catalytic rate constant
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$2.64 \cdot 10^{-5}$	Calc.	Transcellular intestinal permeability
Cellular permeability	cm/min	Charge dependent Schmitt, 0.01	Calc. [54]	permeability into the cellular space
Partition coefficients		Berezhkovskiy	Calc. [101]	Organ-plasma partition coefficients

-: not available, *: no model parameter, listed for additional information, [a]: *in vitro* values corrected for binding in the assay ($f_{u,mic}$), [b]: adjusted due to different reference concentrations in the original model and clopidogrel model, asm.: assumed, calc.: calculated, CYP: cytochrome P450, E-BU: erythrohydrobupropion, EHC: enterohepatic circulation, GFR: glomerular filtration rate, HSD: hydroxysteroid dehydrogenase, lit.: literature, OH-Bupro: hydroxybupropion, opt.: optimized, SR: sustained release formulation, T-BU: threohydrobupropion, UGT: uridine 5'-diphospho-glucuronosyltransferase.

S4.4.2 Montelukast

Table S13: Drug-dependent parameters of the montelukast PBPK model [102]

Parameter	Unit	Value	Source	Description
		Montelukast		
Molecular weight	g/mol	586.20	Lit.	Molecular weight
TPSA*	$Å^2$	70.42	Lit.	Topological polar surface area
pKa, acid		4.40	Lit.	Acid dissociation constant
Solubility (pH)	mg/ml	$8.2 \cdot 10^{-6}$ (7.0)	Lit.	Solubility
Lipophilicity		3.32	Opt.	Lipophilicity
f_u	%	$1.8 \cdot 10^{-3}$	Lit.	Fraction unbound
CYP2C8 CL → sink	l/µmol/min	3.60	Lit.	Specific clearance
CYP2C9 CL → sink	l/µmol/min	0.48	Lit.	Specific clearance
CYP3A4 CL → sink	l/µmol/min	1.80	Lit.	Specific clearance
CYP3A5 CL → sink	l/µmol/min	0.16	Lit.	Specific clearance
GFR fraction		1	Lit.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	0.08	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	PK-Sim Standard, $1.84 \cdot 10^{-3}$	Calc. [55]	permeability into the cellular space
Partition coefficients		Rodgers + Rowland	Calc. [77, 78]	Organ-plasma partition coefficients
Dissolution time (Weibull)	min	130.79	Opt.	Dissolution time (50%)
Dissolution shape (Weibull)		1.31	Opt.	Dissolution shape

*: no model parameter, listed for additional information, asm.: assumed, calc.: calculated, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, lit.: literature, opt.: optimized.

S4.4.3 Omeprazole

Table S14: Drug-dependent parameters of the omeprazole PBPK model [103]

Parameter	Unit	Value	Value	Source	Description
		S-Omeprazole	**R-Omeprazole**		
Molecular weight	g/mol	345.42	345.42	Lit.	Molecular weight
TPSA*	Å^2	77.1	77.1	Lit.	Topological polar surface area
pKa, base		4.77	4.77	Lit.	Acid dissociation constant
pKa, acid		9.29	9.29	Lit.	Acid dissociation constant
Solubility (pH)	mg/ml	0.36 (7.0)	0.36 (7.0)	Lit.	Solubility
Lipophilicity		1.68	1.68	Opt.	Lipophilicity
f_u	%	3	4	Lit.	Fraction unbound
CYP3A4 CL $\rightarrow$ sink	1/min	0.37	0.16	Opt.	Specific clearance
CYP2C19 CL $\rightarrow$ sink	1/min	9.08^a	33.28^a	Opt.	Specific clearance
$CL_{hep} \rightarrow$ sink	1/min	0.03	0.03	Lit.	Unspecific hepatic clearance
EHC continuous fraction		1	1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$9.79 \cdot 10^{-5}$	$9.79 \cdot 10^{-5}$	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	PK-Sim Standard, $8.18 \cdot 10^{-4}$	PK-Sim Standard, $8.18 \cdot 10^{-4}$	Calc. [55]	permeability into the cellular space
Partition coefficients		Rodgers + Rowland	Rodgers + Rowland	Calc. [77, 78]	Organ-plasma partition coefficients
Dissolution time (Weibull)	min	41.65	41.65	Opt.	Dissolution time (50%)
Dissolution shape (Weibull)		1.02	1.02	Opt.	Dissolution shape
Lag time (Weibull)	min	30	30	Asm.	Dissolution lag time
CYP2C19 K_I	µmol/l	0.3	1.6	Lit.	Conc. for half-maximal inactivation (MBI)
CYP2C19 k_{inact}	1/h	5	4	Lit.	Maximum inactivation rate constant (MBI)

*: no model parameter, listed for additional information, ^{a}: subsequently adjusted due to modification of intestinal cytochrome P450 2C19 expression, asm.: assumed, calc.: calculated, conc.: concentration, CYP: cytochrome P450, lit.: literature, MBI: mechanism-based inactivation, opt.: optimized.

S4.4.4 Pioglitazone

Table S15: Drug-dependent parameters of the pioglitazone PBPK model [105]

Parameter	Unit	Value	Source	Description
		Pioglitazone		
Molecular weight	g/mol	356.40	Lit.	Molecular weight
TPSA*	$Å^2$	68.29	Lit.	Topological polar surface area
pKa, base		5.80	Lit.	Acid dissociation constant
pKa, acid		6.40	Lit.	Acid dissociation constant
Solubility (pH)	g/l	0.02 (6.5)	Lit.	Solubility
Lipophilicity		2.81	Opt.	Lipophilicity
f_u	%	0.21	Opt.	Fraction unbound
CYP2C8 $K_M \rightarrow$ sink	µmol/l	21.00	Lit.	Michaelis-Menten constant
CYP2C8 $k_{cat} \rightarrow$ sink	1/min	68.09	Opt.	Catalytic rate constant
$CL_{hep} \rightarrow$ sink	1/min	2.14	Opt.	Unspecific hepatic clearance
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$4.38 \cdot 10^{-5}$	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	PK-Sim Standard, $9.07 \cdot 10^{-3}$	Calc. [55]	Permeability into the cellular space
Partition coefficients		Berezhkovskiy	Calc. [101]	Organ-plasma partition coefficients
Formulation		Tablet[a]	Lit.	Formulation used in predictions

-: not available, *: no model parameter, listed for additional information, [a]: tablet dissolution profile from literature [104], asm.: assumed, calc.: calculated, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, opt.: optimized.

S4.4.5 Repaglinide

Table S16: Drug-dependent parameters of the repaglinide PBPK model [105]

Parameter	Unit	Value	Source	Description
		Repaglinide		
Molecular weight	g/mol	452.60	Lit.	Molecular weight
TPSA*	Å^2	78.87	Lit.	Topological polar surface area
pKa, base		6.01	Lit.	Acid dissociation constant
pKa, acid		4.16	Lit.	Acid dissociation constant
Solubility (pH)	g/l	0.14 (7.4)	Lit.	Solubility
Lipophilicity		2.72	Opt.	Lipophilicity
f_u	%	2.9	Opt.	Fraction unbound
CYP2C8 $K_M \rightarrow$ sink	µmol/l	2.8	Lit.	Michaelis-Menten constant
CYP2C8 $k_{cat} \rightarrow$ sink	1/min	4.56	Opt.	Catalytic rate constant
CYP3A4 $K_M \rightarrow$ sink	µmol/l	15.6	Lit.	Michaelis-Menten constant
CYP3A4 $k_{cat} \rightarrow$ sink	1/min	0.86	Opt.	Catalytic rate constant
OATP1B1 K_M	µmol/l	12.8	Lit.	Michaelis-Menten constant
OATP1B1 k_{cat}	1/min	22860.57[a]	Opt.	Transport rate constant
OATP1B3 K_M	µmol/l	12.8	Lit.	Michaelis-Menten constant
OATP1B3 k_{cat}	1/min	551.24	Opt.	Transport rate constant
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$2.02 \cdot 10^{-5}$	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	Charge dependent Schmitt, 0.04	Opt. [54]	Permeability into the cellular space
Partition coefficients		Schmitt	Calc. [75]	Organ-plasma partition coefficients
Formulation		Tablet[b]	Lit.	Formulation used in predictions

-: not available, *: no model parameter, listed for additional information, [a]: adjusted due to different reference concentrations in the original model and clopidogrel model, [b]: tablet dissolution profile from literature [106], asm.: assumed, calc.: calculated, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, lit.: literature, OATP: organic-anion-transporting polypeptide, opt.: optimized.

S4.4.6 Rifampicin

Table S17: Drug-dependent parameters of the rifampicin PBPK model [9]

Parameter	Unit	Value	Source	Description
		Rifampicin		
Molecular weight	g/mol	822.94	Lit.	Molecular weight
TPSA*	Å^2	220.15	Lit.	Topological polar surface area
pKa, base		7.90	Lit.	Acid dissociation constant
pKa, acid		1.70	Lit.	Acid dissociation constant
Solubility (pH)	g/l	2.80 (7.5)	Lit.	Solubility
Lipophilicity		2.50	Opt.	Lipophilicity
f_u	%	17.00	Lit.	Fraction unbound
Blood/plasma ratio		0.89	Calc.	Blood/plasma ratio
AADAC $K_M \rightarrow$ sink	µmol/l	195.10	Lit.	Michaelis-Menten constant
AADAC $k_{cat} \rightarrow$ sink	1/min	9.87	Opt.	Catalytic rate constant
OATP1B1 K_M	µmol/l	1.50	Lit.	Michaelis-Menten constant
OATP1B1 k_{cat}	1/min	111.37[a]	Opt.	Transport rate constant
P-gp K_M	µmol/l	55.00	Lit.	Michaelis-Menten constant
P-gp k_{cat}	1/min	0.61	Opt.	Transport rate constant
GFR fraction		1	Asm.	Filtered drug in the urine
EHC continuous fraction		1	Asm.	Bile fraction continously released
Intestinal permeability	cm/min	$1.24 \cdot 10^{-5}$	Opt.	Transcellular intestinal permeability
Cellular permeability	cm/min	PK-Sim Standard, $2.93 \cdot 10^{-5}$	Calc. [55]	Permeability into the cellular space
Partition coefficients		Rodgers + Rowland	Calc. [77, 78]	Organ-plasma partition coefficients
Formulation		Solution		Formulation used in predictions

-: not available, *: no model parameter, listed for additional information, [a]: adjusted due to different reference concentrations in the original model and clopidogrel model, AADAC: arylacetamide deacetylase, asm.: assumed, calc.: calculated, CI: competitive inhibition, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, lit.: literature, OATP: organic-anion-transporting polypeptide, opt.: optimized, P-gp: P-glycoprotein, UGT: uridine 5'-diphospho-glucuronosyltransferase.

Table S17: Drug-dependent parameters of the rifampicin PBPK model [9] *(continued)*

Parameter	Unit	Value	Source	Description
Induction EC_{50}	µmol/l	0.34	Lit.	Conc. for half-maximal induction
AADAC E_{max}		0.99	Opt.	Maximum in vivo induction effect
CYP2C19 E_{max}		2.10	Lit.	Maximum in vivo induction effect
CYP3A4 E_{max}		9.00	Lit.	Maximum in vivo induction effect
CYP3A4 K_i	µmol/l	18.50	Lit.	Conc. for half-maximal inhibition (CI)
OATP1B1 E_{max}		0.38	Opt.	Maximum in vivo induction effect
OATP1B1 K_i	µmol/l	0.48	Lit.	Conc. for half-maximal inhibition (CI)
P-gp E_{max}		2.50	Lit.	Maximum in vivo induction effect
P-gp K_i	µmol/l	169.00	Lit.	Conc. for half-maximal inhibition (CI)
UGT2B7 E_{max}		1.79	Lit.	Maximum in vivo induction effect
UGT2B7 K_i	µmol/l	554.87	Lit.	Conc. for half-maximal inhibition (CI)

-: not available, *: no model parameter, listed for additional information, [a]: adjusted due to different reference concentrations in the original model and clopidogrel model, AADAC: arylacetamide deacetylase, asm.: assumed, calc.: calculated, CI: competitive inhibition, conc.: concentration, CYP: cytochrome P450, EHC: enterohepatic circulation, GFR: glomerular filtration rate, lit.: literature, OATP: organic-anion-transporting polypeptide, opt.: optimized, P-gp: P-glycoprotein, UGT: uridine 5'-diphospho-glucuronosyltransferase.

S4.4.7 Partition Coefficients Intracellular : Plasma DDI Partner

Table S18: Partition coefficients between intracellular space and plasma of the DDI partners' PBPK models

Tissue	Bupro[a]	OH-Bupro[b]	E-BU/T-BU[b]	Monte[c]	R-Omep[c]	S-Omep[c]	Pio[b]	Repa[d]	Rifa[c]
Bone	22.15	1.59	2.59	0.10	0.15	0.13	0.34	0.14	0.53
Brain	9.14	1.69	2.66	0.05	0.15	0.13	0.50	0.93	0.36
Fat	64.58	0.45	0.12	0.05	0.17	0.14	0.08	1.09	0.32
Gonads	2.84	0.65	0.86	0.05	0.10	0.08	0.43	0.46	1.87
Heart	8.48	0.75	1.06	0.16	0.20	0.19	0.42	0.89	1.73
Kidney	4.62	0.93	1.36	0.13	0.19	0.17	0.45	0.68	3.79
Stomach	5.36	1.39	2.17	0.16	0.26	0.23	0.45	0.39	1.86
Small intestine	5.36	1.39	2.17	0.16	0.26	0.23	0.45	0.39	1.86
Large intestine	5.36	1.39	2.17	0.16	0.26	0.23	0.45	0.39	1.86
Liver periportal	6.01	1.21	1.85	0.09	0.15	0.13	0.46	0.84	3.43
Liver pericentral	6.01	1.21	1.85	0.09	0.15	0.13	0.46	0.84	3.43
Lung	1.27	0.59	0.77	0.21	0.27	0.26	0.44	0.37	2.96
Muscle	1.50	0.92	1.35	0.06	0.14	0.12	0.44	0.16	1.85
Pancreas	6.79	1.21	1.85	0.06	0.16	0.14	0.44	0.23	1.29
Skin	8.68	1.00	1.50	0.28	0.41	0.37	0.42	0.51	1.06
Spleen	1.76	0.94	1.38	0.10	0.13	0.13	0.45	0.28	2.41
Saliva	0.16	0.23	0.58	$1.80 \cdot 10^{-3}$	0.04	0.03	$2.07 \cdot 10^{-3}$	0.03	0.17

[a]: estimated via PK-Sim Standard [55], [b]: estimated via Berezhkovskiy [101], [c]: estimated via Rodgers + Rowland [77, 78], [d]: estimated via Schmitt [75], Bupro: bupropion, E-BU: erythrohydrobupropion, Monte: montelukast, OH-Bupro: hydroxybupropion, Pio: pioglitazone, Repa: repaglinide, Rifa: rifampicin, R-Omep: R-omeprazole, S-Omep: S-omeprazole, T-BU: threohydrobupropion.

S4.5 Plasma Concentration-Time Profiles (Semilogarithmic)

S4.5.1 Clopidogrel as Victim

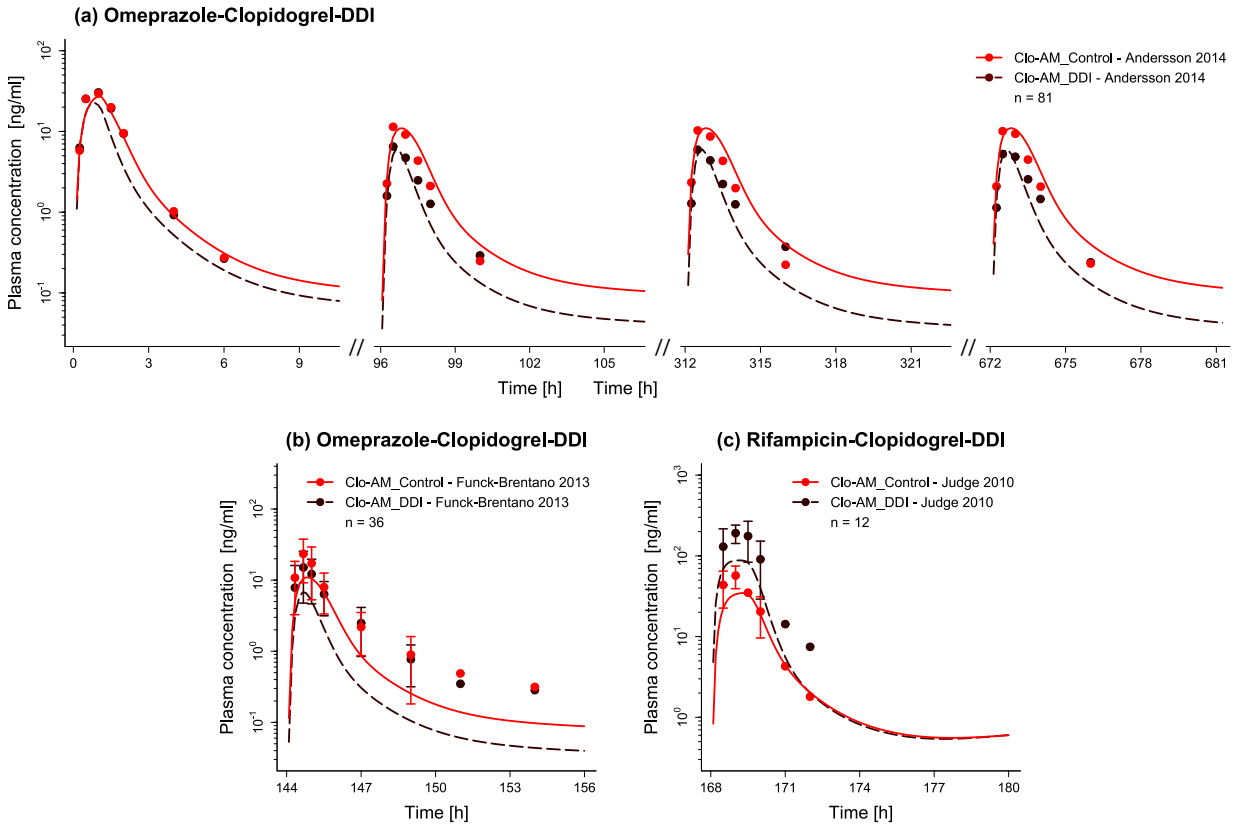


Figure S33: Drug–drug interaction network evaluation with clopidogrel as victim. Presented are predicted plasma concentration-time profiles (semilogarithmic plots) of Clo-AM with (DDI) and without (Control) intake of the respective perpetrator drug ((a–b) omeprazole, (c) rifampicin), alongside corresponding observed data [83–85]. Dashed (DDI) and solid (Control) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo-AM: clopidogrel thiol H4, DDI: drug–drug interaction, n: number of participants.

S4.5.2 Clopidogrel as Perpetrator

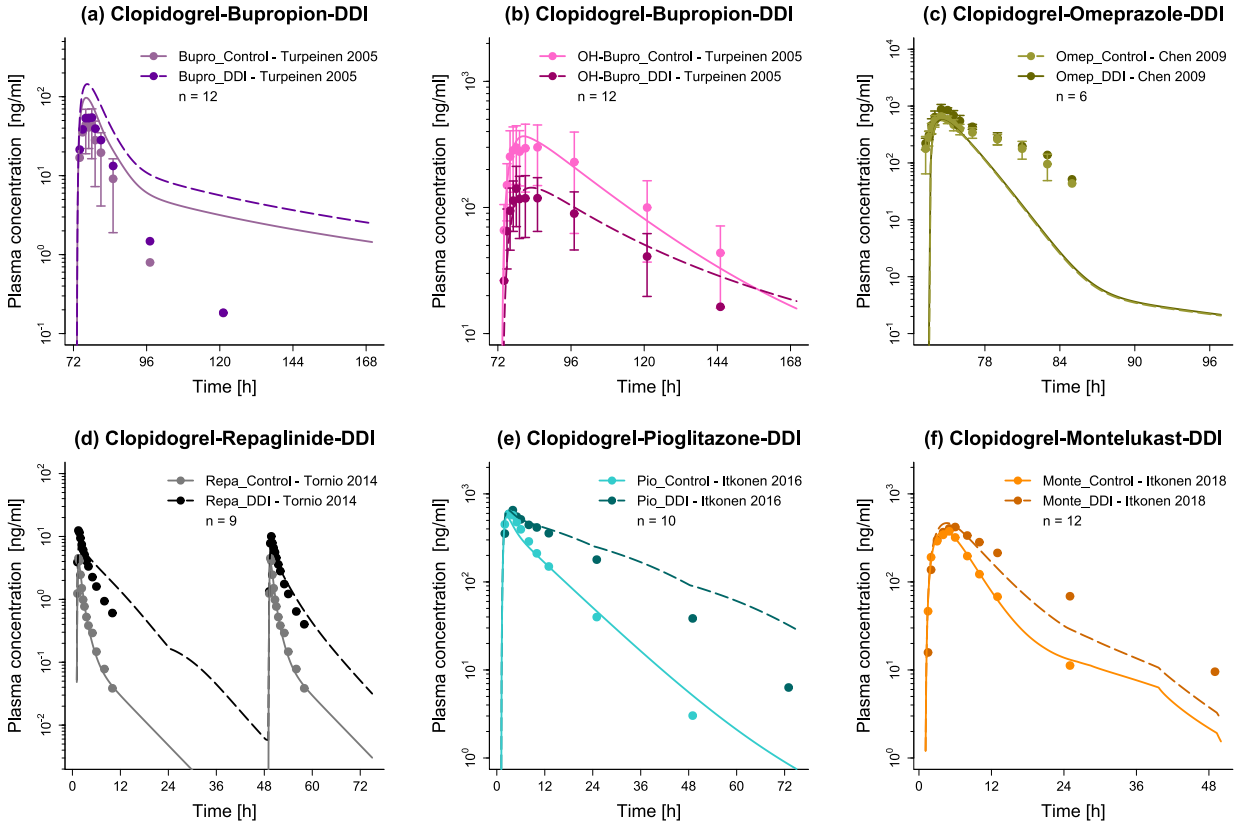


Figure S34: Drug–drug interaction network evaluation with clopidogrel as perpetrator. Presented are predicted plasma concentration-time profiles (semilogarithmic plots) of the respective victim with (DDI) and without (Control) intake of clopidogrel ((a) bupropion, (b) hydroxybupropion, (c) omeprazole, (d) repaglinide, (e) pioglitazone, (f) montelukast), alongside corresponding observed data [48, 86–89]. Dashed (DDI) and solid (Control) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Bupro: bupropion, DDI: drug–drug interaction, Monte: montelukast, n: number of participants, OH-Bupro: hydroxybupropion, Omep: omeprazole, Pio: pioglitazone, Repa: repaglinide.

S4.6 Plasma Concentration-Time Profiles (Linear)

S4.6.1 Clopidogrel as Victim

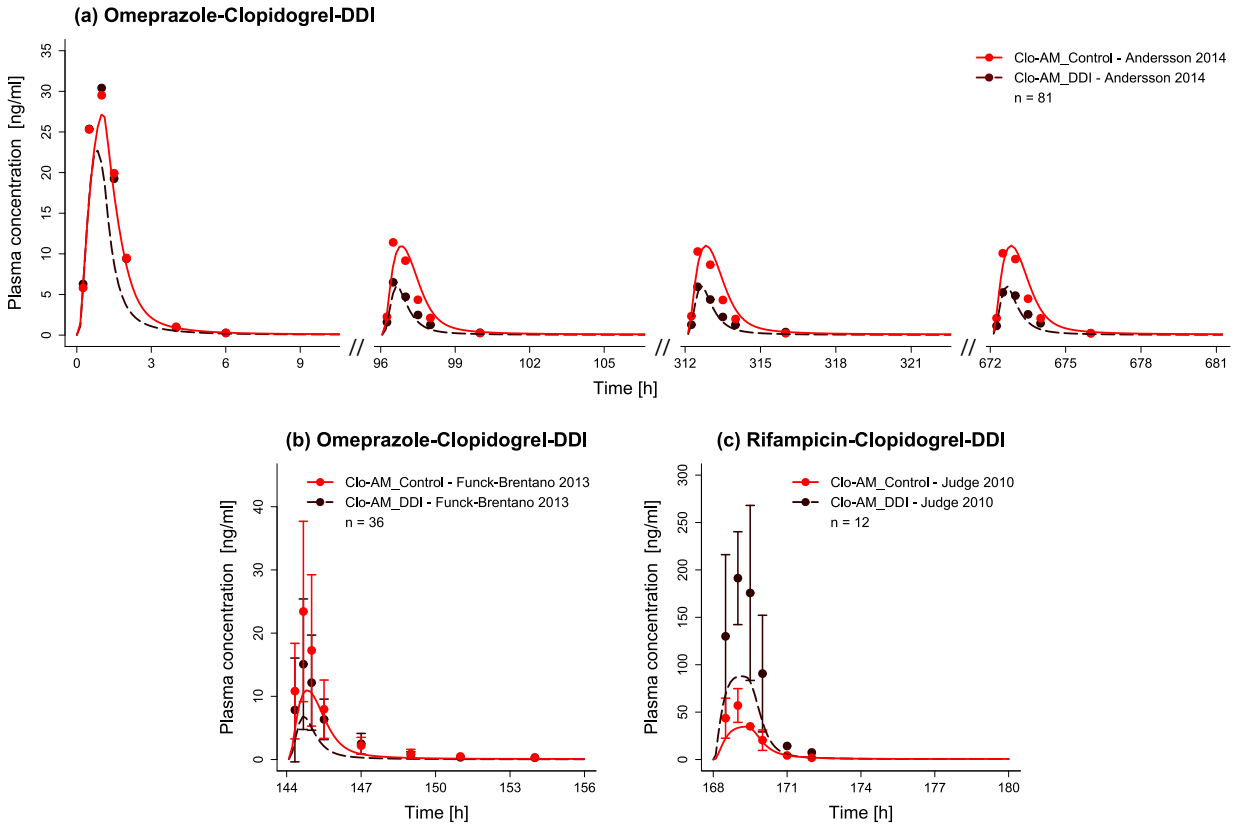


Figure S35: Drug–drug interaction network evaluation with clopidogrel as victim. Presented are predicted plasma concentration-time profiles (linear plots) of Clo-AM with (DDI) and without (Control) intake of the respective perpetrator drug ((a–b) omeprazole, (c) rifampicin), alongside corresponding observed data [83–85]. Dashed (DDI) and solid (Control) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Clo-AM: clopidogrel thiol H4, DDI: drug–drug interaction, n: number of participants.

S4.6.2 Clopidogrel as Perpetrator

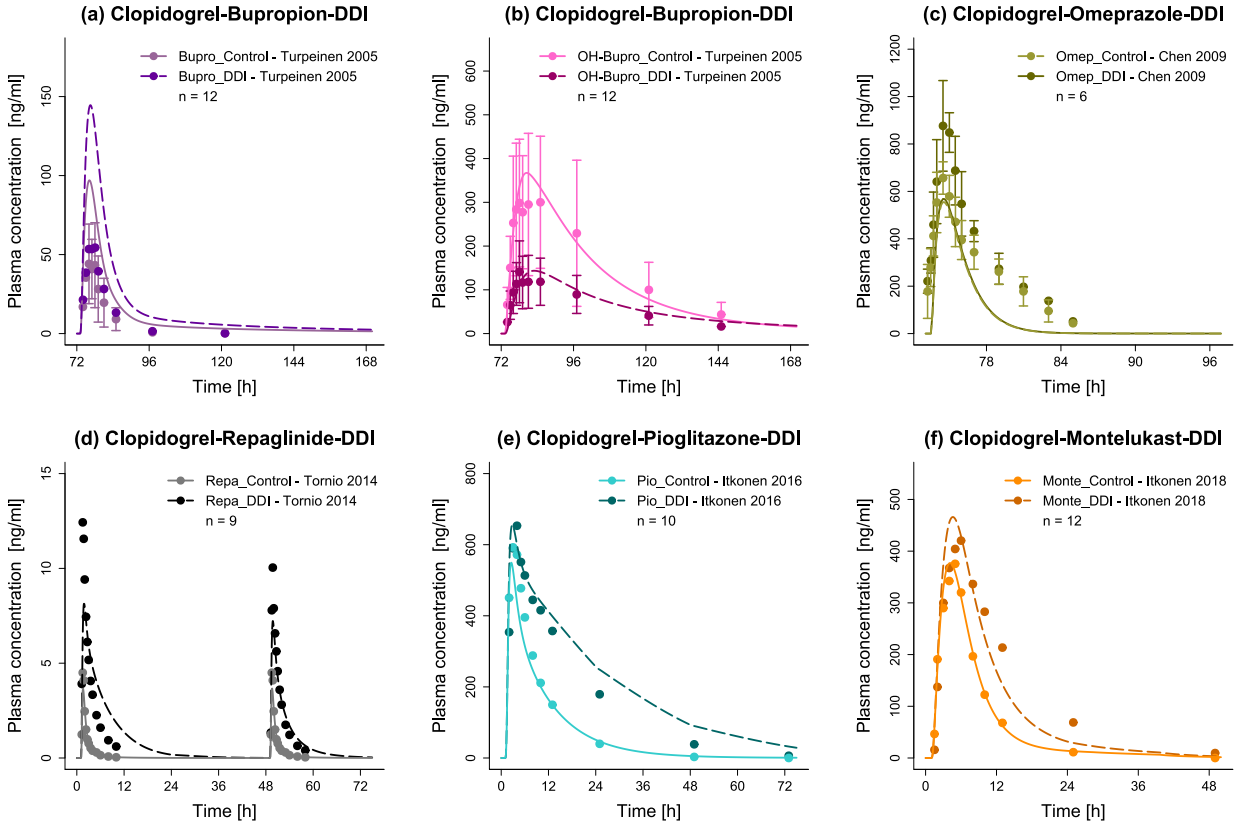


Figure S36: Drug–drug interaction network evaluation with clopidogrel as perpetrator. Presented are predicted plasma concentration-time profiles (linear plots) of the respective victim with (DDI) and without (Control) intake of clopidogrel ((a) bupropion, (b) hydroxybupropion, (c) omeprazole, (d) repaglinide, (e) pioglitazone, (f) montelukast), alongside corresponding observed data [48, 86–89]. Dashed (DDI) and solid (Control) lines represent the model predictions, while corresponding observed data are shown as symbols (± standard deviation, if available). Bupro: bupropion, DDI: drug–drug interaction, Monte: montelukast, n: number of participants, OH-Bupro: hydroxybupropion, Omep: omeprazole, Pio: pioglitazone, Repa: repaglinide.

S4.7 DDI AUC_{last} and DDI C_{max} Ratio Goodness-of-Fit Plots

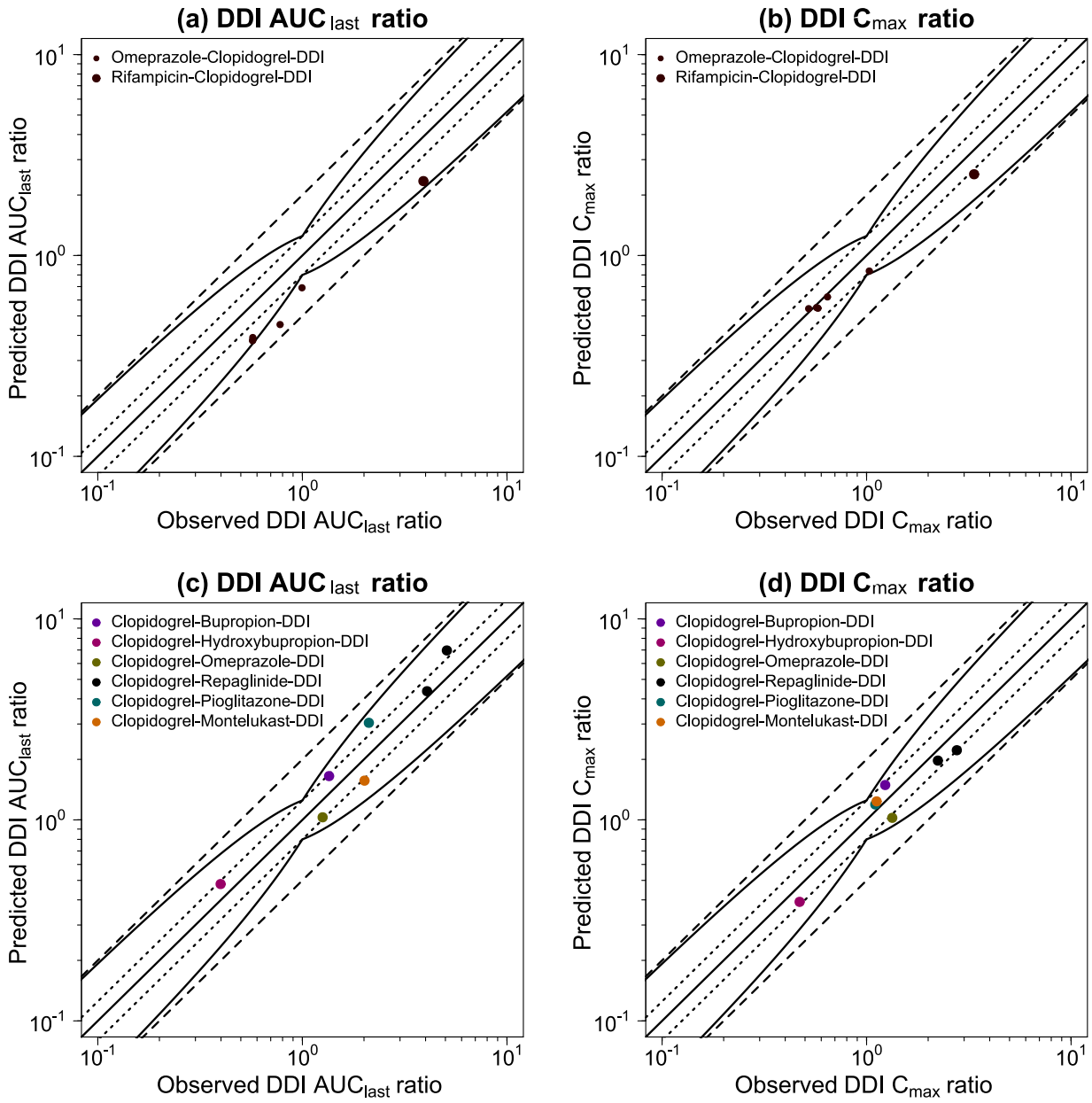


Figure S37: Drug–drug interaction network evaluation with clopidogrel as (a–b) victim and (c–d) perpetrator. Predicted versus observed (a,c) DDI AUC_{last} and (b,d) DDI C_{max} ratios of the respective victim are shown with the solid line representing the line of identity, dotted lines indicating 1.25-fold and dashed lines 2-fold deviation from the respective observed value [83–85], along with the curved lines marking the prediction success limits proposed by Guest et al. [81] (including 20% variability to account for uncertainties in observed ratios). AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, C_{max}: maximum plasma concentration, DDI: drug–drug interaction.

S4.8 Predicted and Observed DDI AUC_{last} and DDI C_{max} Ratios with Mean GMFEs

Table S19: Predicted versus observed DDI AUC_{last} and DDI C_{max} ratios, along with GMFE values

Perpetrator	Perpetrator application [mg]	Victim	Victim application [mg]	Compound measured	n	Dataset	DDI AUC_{last} ratio			DDI C_{max} ratio			Reference
							Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	
Omep	d1–29: 80 po (cap, m.d.)	Clo	d1: 300 d2–29: 75 po (tab, l.d./m.d.)	Clo-AM	81	test	0.69 0.39 0.38 0.38	1.00 0.57 0.57 0.57	0.69 (D1) 0.68 (D5) 0.66 (D14) 0.66 (D29)	0.84 0.55 0.55 0.54	1.03 0.57 0.58 0.52	0.81 (D1) 0.97 (D5) 0.94 (D14) 1.04 (D29)	Andersson 2014 [83]
Omep	d1–7: 20 po (-, m.d.)	Clo	d1–7: 75 po (-, m.d.)	Clo-AM	36	test	0.45	0.78	0.58 (D7)	0.62	0.64	0.97 (D7)	Funck-Brentano 2013 [84]
Rifa	d1–15: 300 po (-, b.i.d.)	Clo	d8: 600 d9–15: 75 po (-, l.d./m.d.)	Clo-AM	12	test	2.35	3.90	0.60 (D8)	2.54	3.36	0.76 (D8)	Judge 2010 [85]
				Mean GMFE (range) GMFE ≤ 2					1.55 (1.44–1.72) 6/6			1.12 (1.03–1.32) 6/6	

-: not given, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, b.i.d.: maintenance dose (twice daily), Bupro: bupropion, cap: capsule, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, C_{max}: maximum plasma concentration, d: day, D: day of pharmacokinetic sampling, l.d.: loading dose, m.d.: maintenance dose (once daily), Monte: montelukast, n: number of participants, obs: observed, OH-Bupro: hydroxybupropion, Omep: omeprazole, Pio: pioglitazone, po: peroral, pred: predicted, Repa: repaglinide, Rifa: rifampicin, s.d.: single dose, SR: sustained release formualtion, tab: tablet.

Table S19: Predicted versus observed DDI AUC_{last} and DDI C_{max} ratios, along with GMFE values *(continued)*

Perpetrator	Perpetrator application [mg]	Victim	Victim application [mg]	Compound measured	n	Dataset	DDI AUC_{last} ratio			DDI C_{max} ratio			Reference
							Pred	Obs	Pred/Obs	Pred	Obs	Pred/Obs	
Clo	d1–4: 75 po (tab, m.d.)	Bupro	d4+1h: 150 po (tab SR, s.d.)	Bupro OH-Bupro	12	test	1.65 0.48	1.35 0.40	1.22 (D4) 1.20 (D4)	1.49 0.39	1.23 0.47	1.21 (D4) 0.83 (D4)	Turpeinen 2005 [86]
Clo	d1: 300 d2: 75 po (tab, l.d./m.d.)	Monte	d1+1h: 10 po (tab, s.d.)	Monte	12	test	1.57	2.01	0.78 (D1)	1.24	1.12	1.10 (D1)	Itkonen 2018 [87]
Clo	d1: 300 d2–4: 75 po (tab, l.d./m.d.)	Omep	d4+1h: 40 po (-, s.d.)	Omep	6	test	1.03	1.26	0.82 (D4)	1.02	1.34	0.77 (D4)	Chen 2009 [88]
Clo	d1: 300 d2–3: 75 po (tab, l.d./m.d.)	Pio	d1+1h: 15 po (tab, s.d.)	Pio	10	test	3.04	2.11	1.44 (D1)	1.19	1.10	1.08 (D1)	Itkonen 2016 [89]
Clo	d1: 300 d2–3: 75 po (tab, l.d./m.d.)	Repa	d1+1h: 0.25 d3+1h: 0.25 po (tab, s.d.)	Repa	9	training	6.97 4.36	5.08 4.07	1.37 (D1) 1.07 (D3)	2.22 1.97	2.76 2.23	0.80 (D1) 0.88 (D3)	Tornio 2014 [48]
				Mean GMFE (range) GMFE ≤ 2					1.26 (1.07–1.44) 7/7			1.18 (1.08–1.30) 7/7	
				Overall mean GMFE (range) GMFE ≤ 2					1.39 (1.07–1.72) 13/13			1.15 (1.03–1.32) 13/13	

-: not given, AUC_{last}: area under the plasma concentration-time curve determined between first and last concentration measurements, b.i.d.: maintenance dose (twice daily), Bupro: bupropion, cap: capsule, Clo: clopidogrel, Clo-AM: clopidogrel thiol H4, C_{max}: maximum plasma concentration, d: day, D: day of pharmacokinetic sampling, l.d.: loading dose, m.d.: maintenance dose (once daily), Monte: montelukast, n: number of participants, obs: observed, OH-Bupro: hydroxybupropion, Omep: omeprazole, Pio: pioglitazone, po: peroral, pred: predicted, Repa: repaglinide, Rifa: rifampicin, s.d.: single dose, SR: sustained release formualtion, tab: tablet.

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