Klinische Signifikanz von Arzneimitteltransportern bei DDIs

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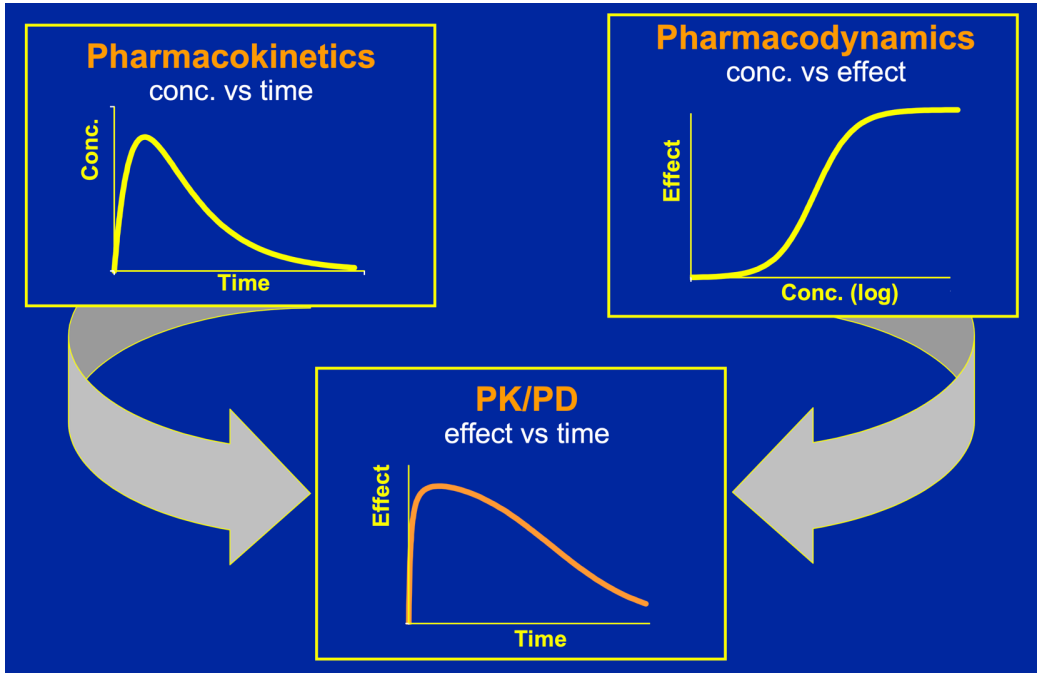
Was Sie heute nicht bekommen

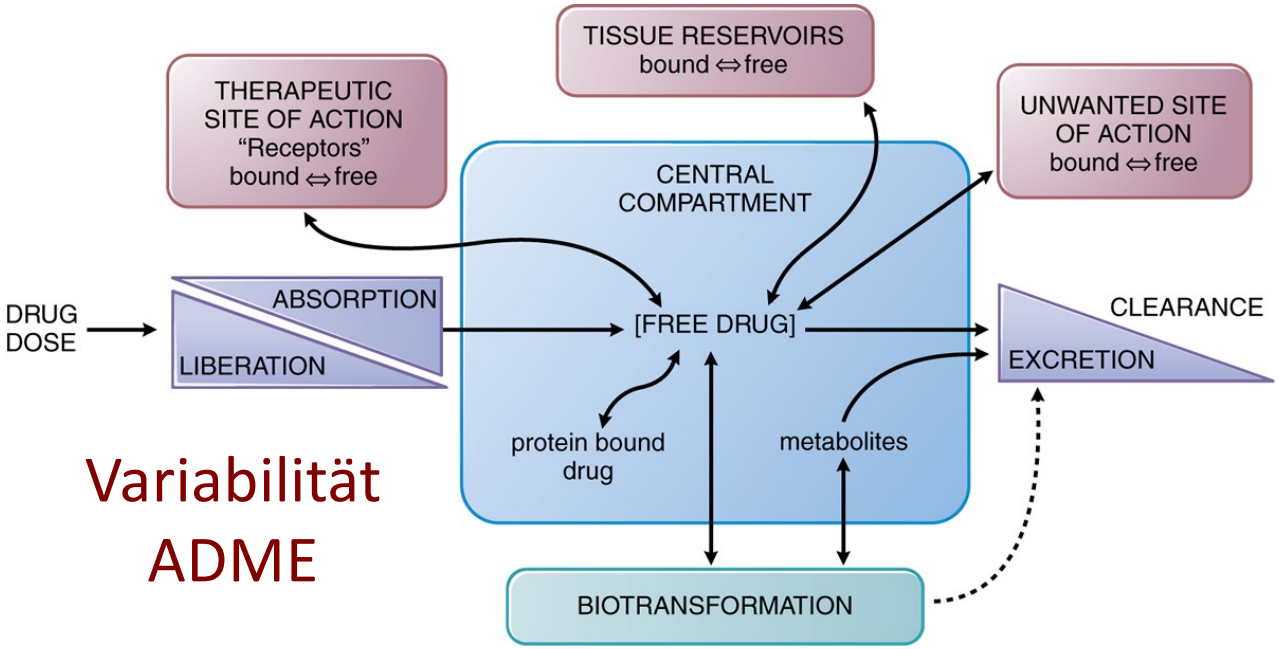
Eine Liste mit den signifikanten Transporter DDIs

Warum nicht?

Prinzip der Arzneimitteltherapie

📖 Derendorf & Meibohm, Pharm Res. 1999 Feb;16(2):176-85.

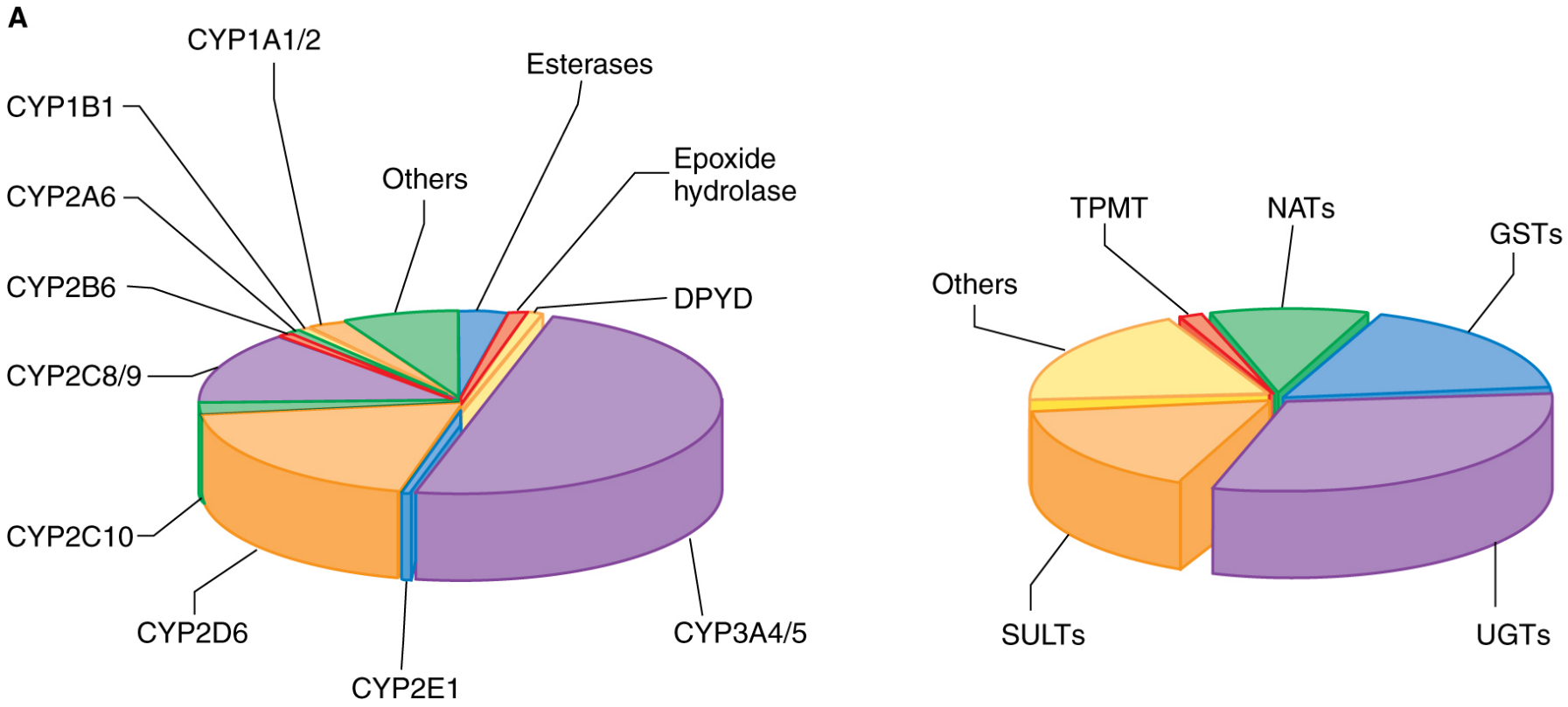




Variabilität
ADME

📖 Goodman & Gilman's: The Pharmacological Basis of Therapeutics , 12th Edition 2011, McGraw-Hill.

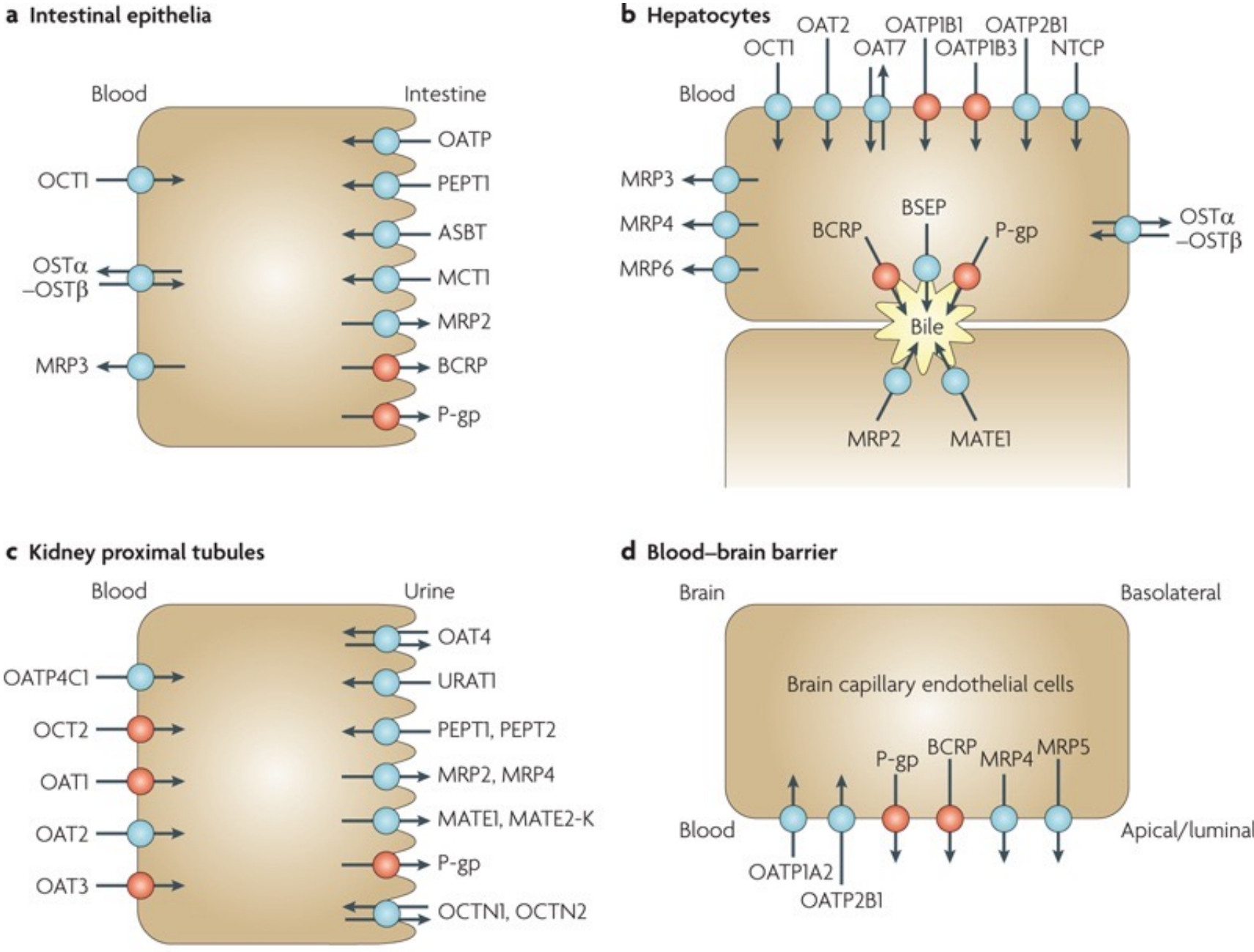
Arzneimittel-abbauende Enzyme



The fraction of clinically used drugs metabolized by the major phase 1 and phase 2 enzymes. The relative size of each pie section represents the estimated percentage of drugs metabolized by the major phase 1 (panel A) and phase 2 (panel B) enzymes, based on studies in the literature. In some cases, more than a single enzyme is responsible for metabolism of a single drug. CYP, cytochrome P450; DPYD, dihydropyrimidine dehydrogenase; GST, glutathione-S-transferase; NAT, N-acetyltransferase; SULT, sulfotransferase, TPMT, thiopurine methyltransferase; UGT, UDP-glucuronosyltransferase.

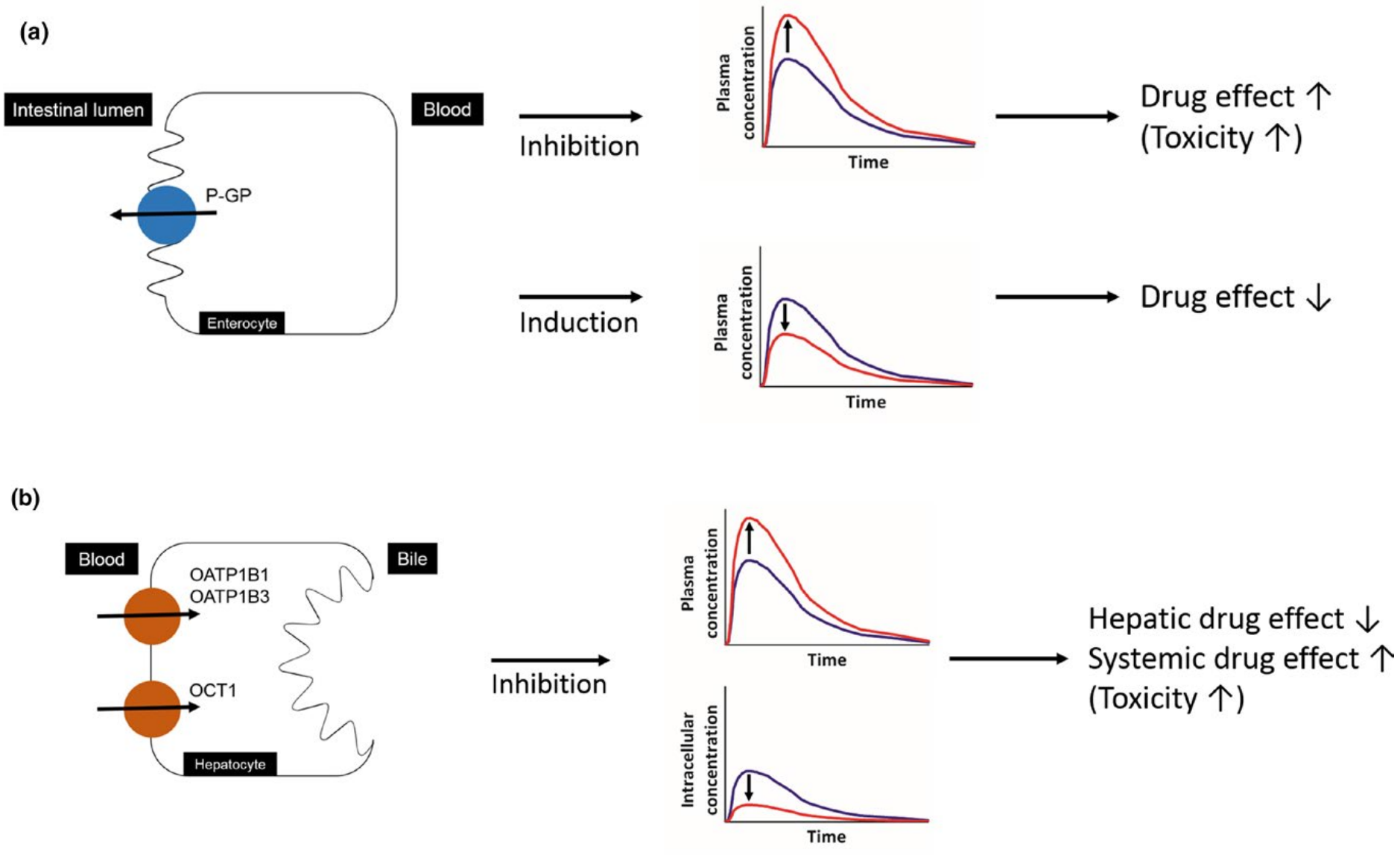
Goodman & Gilman's: The Pharmacological Basis of Therapeutics , 12th Edition 2011, McGraw-Hill.

Arzneimittel-Transporter



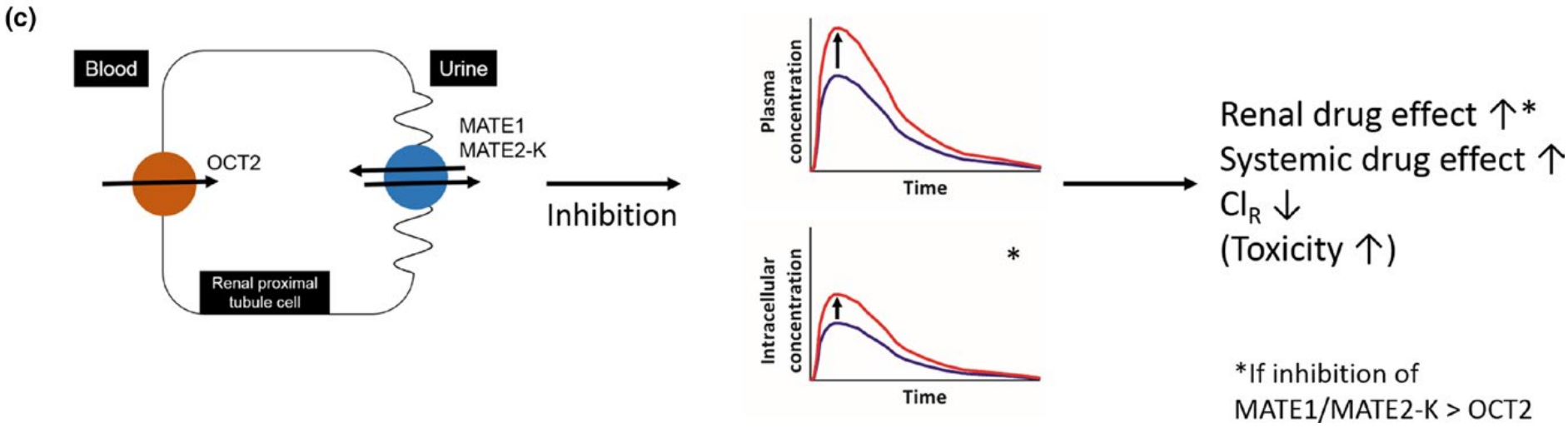
International Transporter Consortium, Giacomini KM et al., Nat Rev Drug Discov. 2010 Mar;9(3):215-36.

Prinzip der Transporter DDI



📖 Gessner A et al., CPT 2019, 105: 1386

Prinzip der Transporter DDI

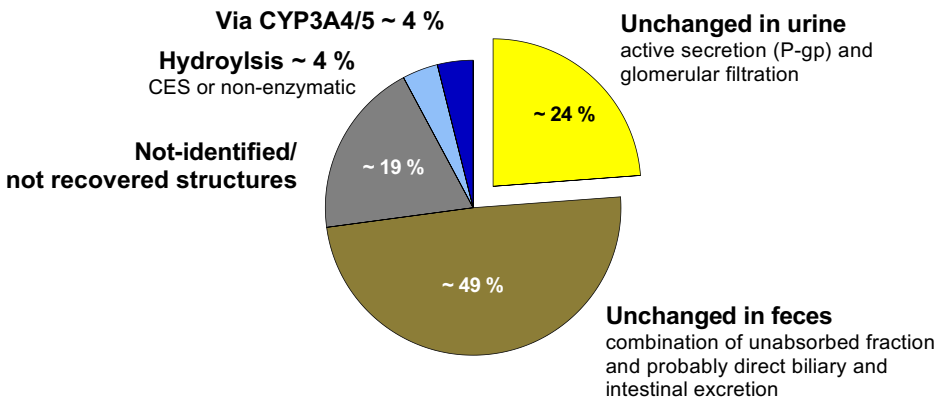


Die Disposition von nur wenigen Arzneimitteln hängt – wenn überhaupt – nur von einem einzigen Transporter ab. Meistens sind Arzneimittel Substrate für mehrere Influx- oder Effluxtransporter und werden zusätzlich durch ein oder mehrere Phase-I- und/oder Phase-II-Enzymen metabolisiert.

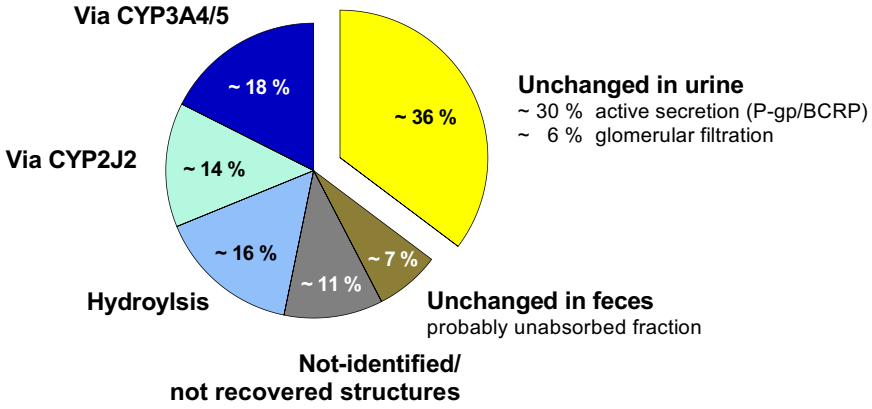
📖 Gessner A et al., CPT 2019, 105: 1386

Arzneimittel ADME

Edoxaban (p.o.)



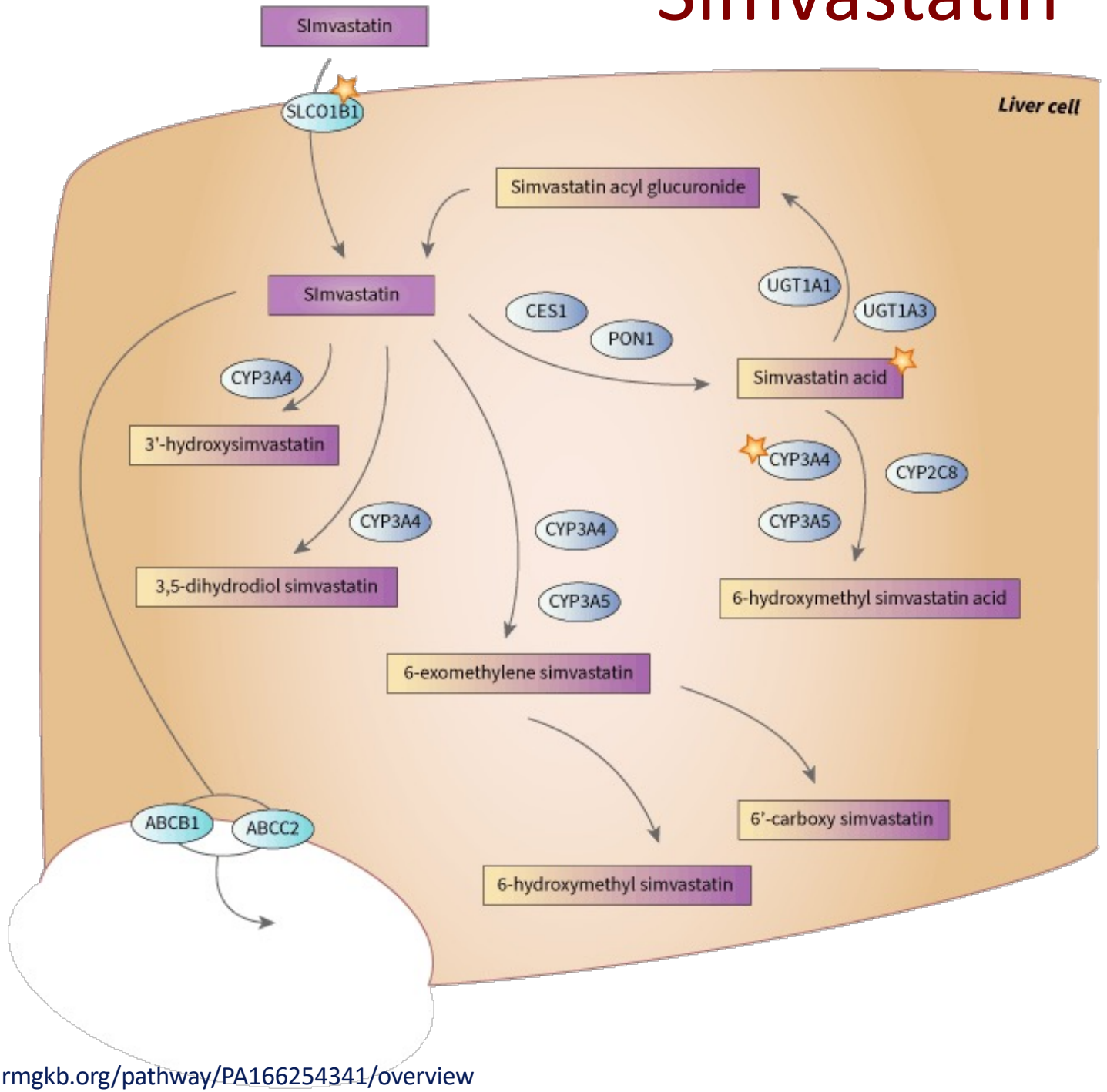
Rivaroxaban (p.o.)



- Jedes Arzneimittel hat unterschiedliche Beteiligung von Enzymen und Transportern mit hoher interindividueller Variabilität
- Genetische Charakterisierung hat oft nichts mit Aktivität zu tun
- Interagierende Arzneimittel sind häufig nicht spezifisch für einzelne Prozesse
- Lokalisation der Interaktion ist wichtig, hohe Konzentrationen im GI-Trakt, geringe Konzentrationen in der Niere
- Keine geeigneten Marker zur Aktivitätsbestimmung verfügbar
- -> Prädiktionen *noch* schwierig bis unmöglich

📖 Förster KF et al., Clin Pharmacokin 2020, 59: 967-980

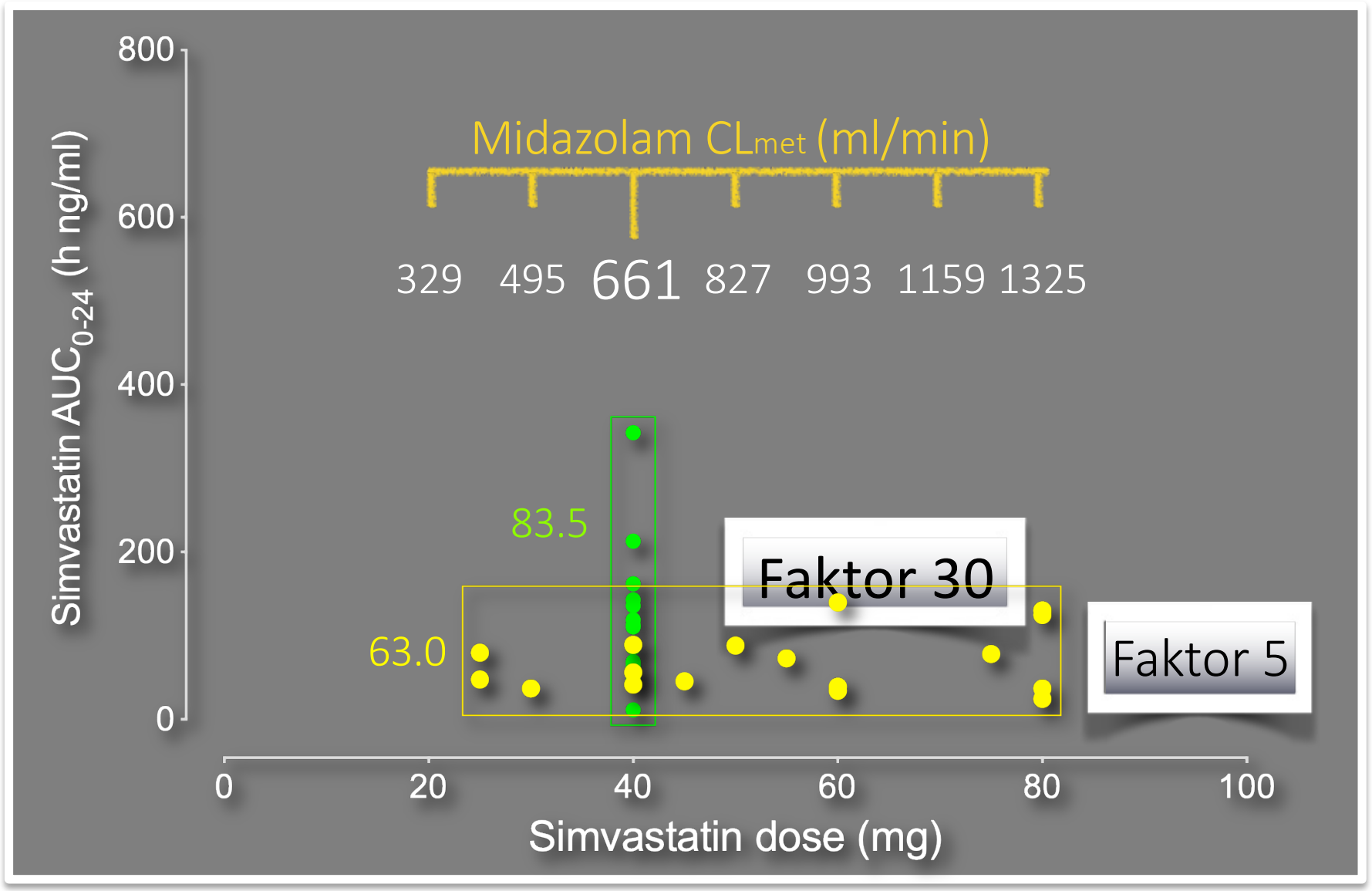
Simvastatin



https://www.pharmgkb.org/pathway/PA166254341/overview

Simvastatin

nur CYP3A



Stoll et al., J Clin Pharmacol 2013, 53: 1199-1204.

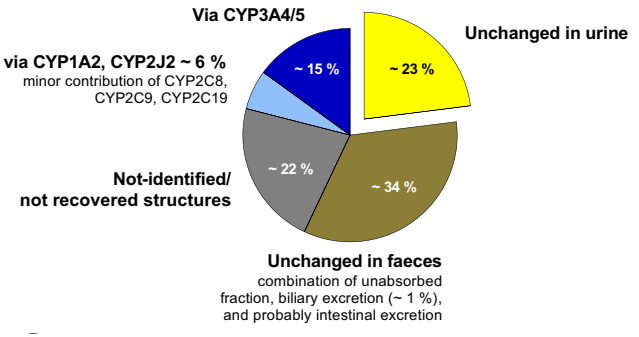
Beispiele Transporter DDI

Table 1 Examples of transporter-mediated drug–drug interactions occurring at leas

Victim drug	Perpetrator drug	Intestinal transporter involved	PK change of victim drug		
Apixaban	Ketoconazole (400 mg/day for 6 days)	P-gp	AUC ↑ (twofold)		
Dabigatran etexilate	Dronedarone (1 × 400 mg)	P-gp	AUC[a] ↑ (2.1-fold)		
Dabigatran etexilate	Ketoconazole (1 × 400 mg)	P-gp	AUC[a] ↑ (2.4-fold)		
Edoxaban	Erythromycin (4 × 500 mg/day for 8 days)	P-gp	AUC ↑ (+ 85%)		
Edoxaban	Cyclosporin (1 × 500 mg)	P-gp	AUC ↑ (+ 73%)	Higher rate of adverse effects	69
Digoxin	Quinidine	P-gp	AUC ↑ (~ twofold)	Higher rate of adverse effects	23,70,71
Rivaroxaban	Ritonavir (2 × 600 mg/day for 5 days)	P-gp	AUC ↑ (2.5-fold)	Higher rate of adverse effects	71,72
Apixaban	Rifampin (1 × 600 mg/day for 11 days)	P-gp	AUC ↓ (– 54%)	Reduced therapeutic effects	66,71
Dabigatran etexilate	Rifampin (1 × 600 mg/day for 7 days)	P-gp	AUC[a] ↓ (– 67%)	Reduced therapeutic effects	68,73
Digoxin	Rifampin (1 × 600 mg/day for 10 days)	P-gp	AUC ↓ (– 30%)	Reduced therapeutic effects	21
Rosuvastatin	Eltrombopag (1 × 75 mg/day for 9 days)	BCRP	AUC ↑ (+ 55%)	Higher rate of adverse effects	28,74

AUC, area under the plasma/serum concentration–time curve; BCRP, breast cancer resistance protein; P-gp, P-glycoprotein; PK, pharmacokinetic.
[a]Total dabigatran AUC.

Apixaban (p.o.)



📖 Gessner A et al., CPT 2019, 105: 1386

Beispiele Transporter DDI

Table 2 Examples of transporter-mediated drug–drug interactions occurring at least in part in hepatocytes

Victim drug	Perpetrator drug	Hepatic transporter involved	PK change of victim drug	Possible change in victim drug effect or toxicity	References
Bosentan	Clarithromycin (2 × 500 mg/day for 4 days)	OATP1B1, OATP1B3	AUC ↑ (3.7-fold)	Higher rate of adverse effects	75
Pitavastatin	Cyclosporine (1 × 2 mg/kg)	OATP1B1, OATP1B3, OATP2B1	AUC ↑ (4.6-fold)	Higher rate of adverse effects, decreased therapeutic hepatic effects	71
Pravastatin	Clarithromycin (2 × 500 mg/day for 8 days)	OATP1B1, OATP1B3, OATP2B1	AUC ↑ (twofold)	Higher rate of adverse effects, decreased therapeutic hepatic effects	76
Rosuvastatin	Cyclosporine (2 × 75 mg/day to 2 × 200 mg/day)	OATP1B1, OATP1B3, OATP2B1	AUC ↑ (7.1-fold heart transplant recipients vs. healthy controls)	Higher rate of adverse effects, decreased therapeutic hepatic effects	77
Rosuvastatin	Gemfibrozil (2 × 600 mg/day for 7 days)	OATP1B1	AUC ↑ (1.9-fold)	Higher rate of adverse effects, decreased therapeutic hepatic effects	78
Rosuvastatin, pitavastatin	Rifampin (1 × 600 mg)	OATP1B1, OATP1B3, OATP2B1	AUC ↑ (5.7-fold, 4.4-fold)	Higher rate of adverse effects, decreased therapeutic hepatic effects	32
Metformin	Verapamil (1 × 180 mg/day for 3 days)	OCT1	C_{max}, AUC unchanged	Glucose-lowering effect ↓	8,38
Metformin	Famotidine (1,000 mg in 6 divided doses)	MATE1	C_{max}, AUC unchanged, estimated F ↑, Cl_R ↑	Glucose-lowering effect ↑	8,39

The information in this table is partially from respective data shown in Table 6 of ref. 16.
AUC, area under the plasma/serum concentration–time curve; Cl_R, renal clearance; C_{max}, maximum serum/plasma concentration; F, bioavailability; MATE, multidrug and toxin extrusion; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PK, pharmacokinetic.

📖 Gessner A et al., CPT 2019, 105: 1386

Beispiele Transporter DDI

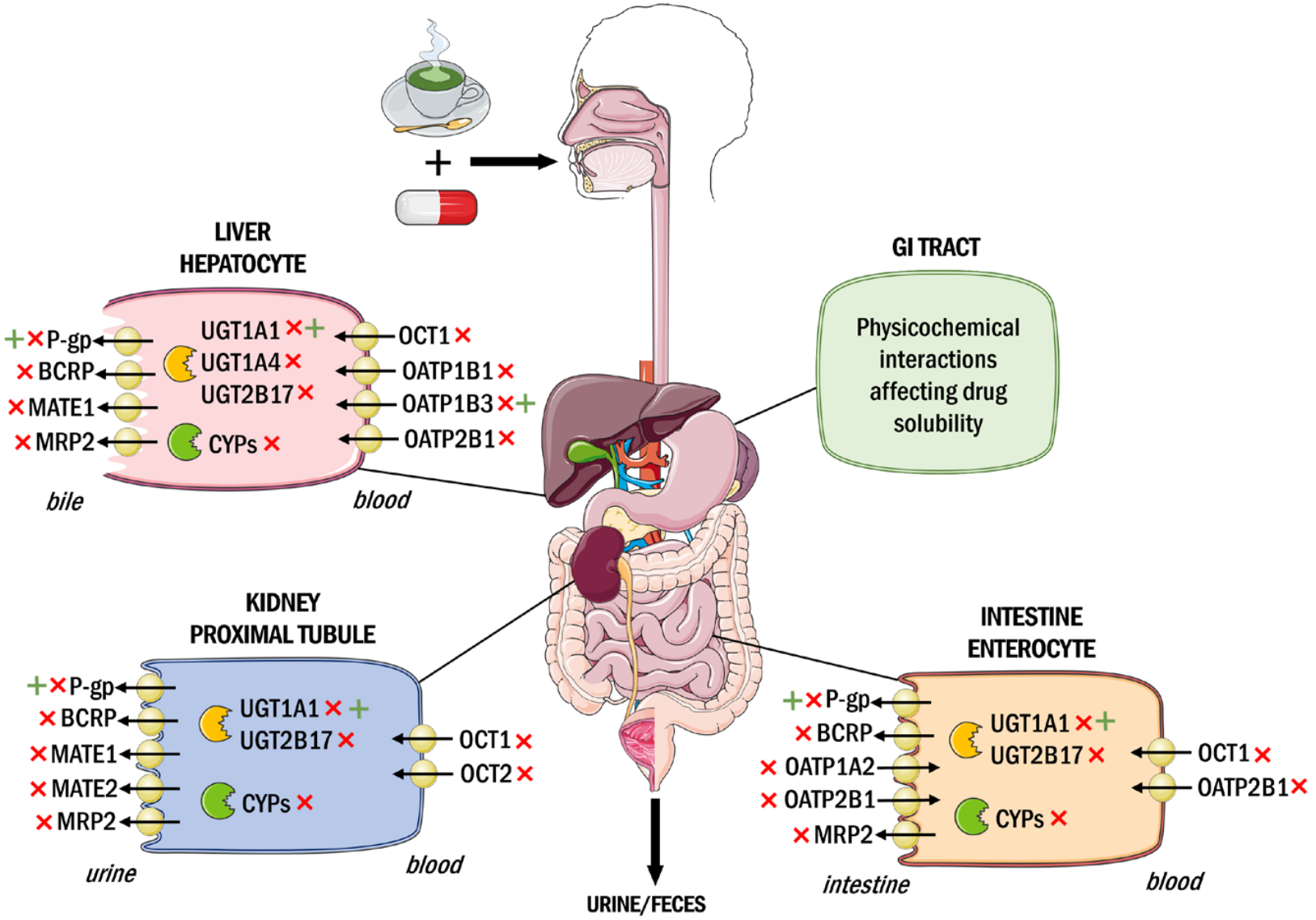
Table 3 Examples of transporter-mediated drug–drug interactions occurring at least in part in renal proximal tubular cells

Victim drug	Perpetrator drug	Renal transporter involved	PK change of victim drug	Possible change in victim drug effect or toxicity	References
Digoxin	Quinidine	P-gp	AUC ↑ (~ twofold) Cl_R ↓ (– 54%)	Higher rate of adverse effects	24,71
Digoxin	Clarithromycin (2 × 250 mg/day for 3 days)	P-gp	AUC ↑ (1.7-fold) Cl_R ↓ (– 17%)	Higher rate of adverse effects	79
Metformin	Cimetidine (2 × 400 mg/day for 5 days)	OCT2, MATE1, MATE2-K	AUC ↑ (1.5-fold) Cl_R ↓ (– 27%)	Higher rate of adverse effects	9
Metformin	Pyrimethamine (1 × 50 mg)	MATE1, MATE2-K	C_{max} ↑ (1.4-fold) AUC ↑ (1.4–fold) Cl_R ↓ (– 33 to – 35%)	Higher rate of adverse effects	80
Metformin	Trimethoprim (2 × 200 mg/day for 5 days)	OCT2, MATE1, MATE2-K	C_{max} ↑ (1.2-fold to 1.4-fold) AUC ↑ (1.3-fold to 1.4-fold) Cl_R ↓ (– 26%)	Higher rate of adverse effects; plasma lactate ↑	81,82
Metformin	Dolutegravir (2 × 50 mg/day for 7 days)	OCT2, MATE1, MATE2-K	C_{max} ↑ (2.1-fold) AUC ↑ (2.5-fold)	Higher rate of adverse effects	83
Amantadine	Quinine (1 × 200 mg), quinidine (1 × 200 mg)	OCT2, MATE1	Cl_R ↓ (– 27% and – 33%, only in men but not in women)	Higher rate of adverse effects	84
Lamivudine	Trimethoprim/sulfamethoxazole (1 × 160/180 mg/day for 5 days)	OCT2, MATE1, MATE2-K	AUC ↑ (1.4-fold) Cl_R (– 35%)	Higher rate of adverse effects	85,86
Chloroquine	Cimetidine (1 × 400 mg/day for 4 days)	MATE1	Cl_0 ↓ (– 53%) Ae ↓ (– 43%)	Higher rate of adverse effects	87,88

📖 Gessner A et al., CPT 2019, 105: 1386

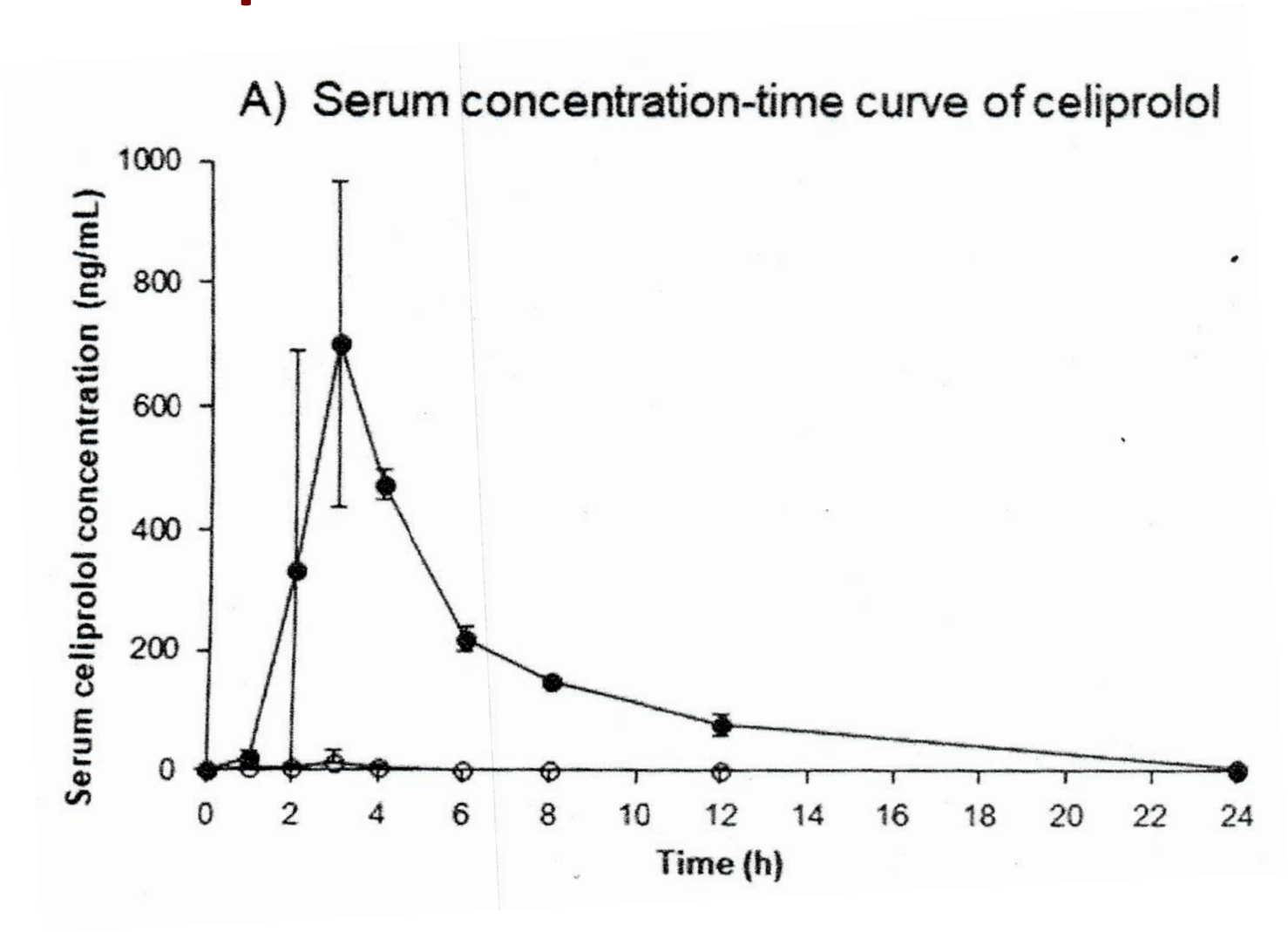
Green Tea Catechins as Perpetrators of Drug Pharmacokinetic Interactions

Nicki M. Kyriacou[1], Annette S. Gross[1] and Andrew J. McLachlan[1,*]



📖 Kyriacou NM et al., CPT 2024, doi:10.1002/cpt.3547

Celiprolol Arzneimittelinteraktion



Green tea intake decreased the area under the serum concentration-time curve of celiprolol by **98.6 %**

Intestinal OATP1A2 inhibition

📖 Sonoda J et al., Int J Clin Pharmacol Ther 59, 198–201 (2021)

Transporter Arzneimittelinteraktionen

Vorsicht bei Extrapolation von *in vitro* DDI

Reduzierte Wirksamkeit - Toxizität?

Welche Mechanismen sind wichtig?

Welche Grenzen gibt es?

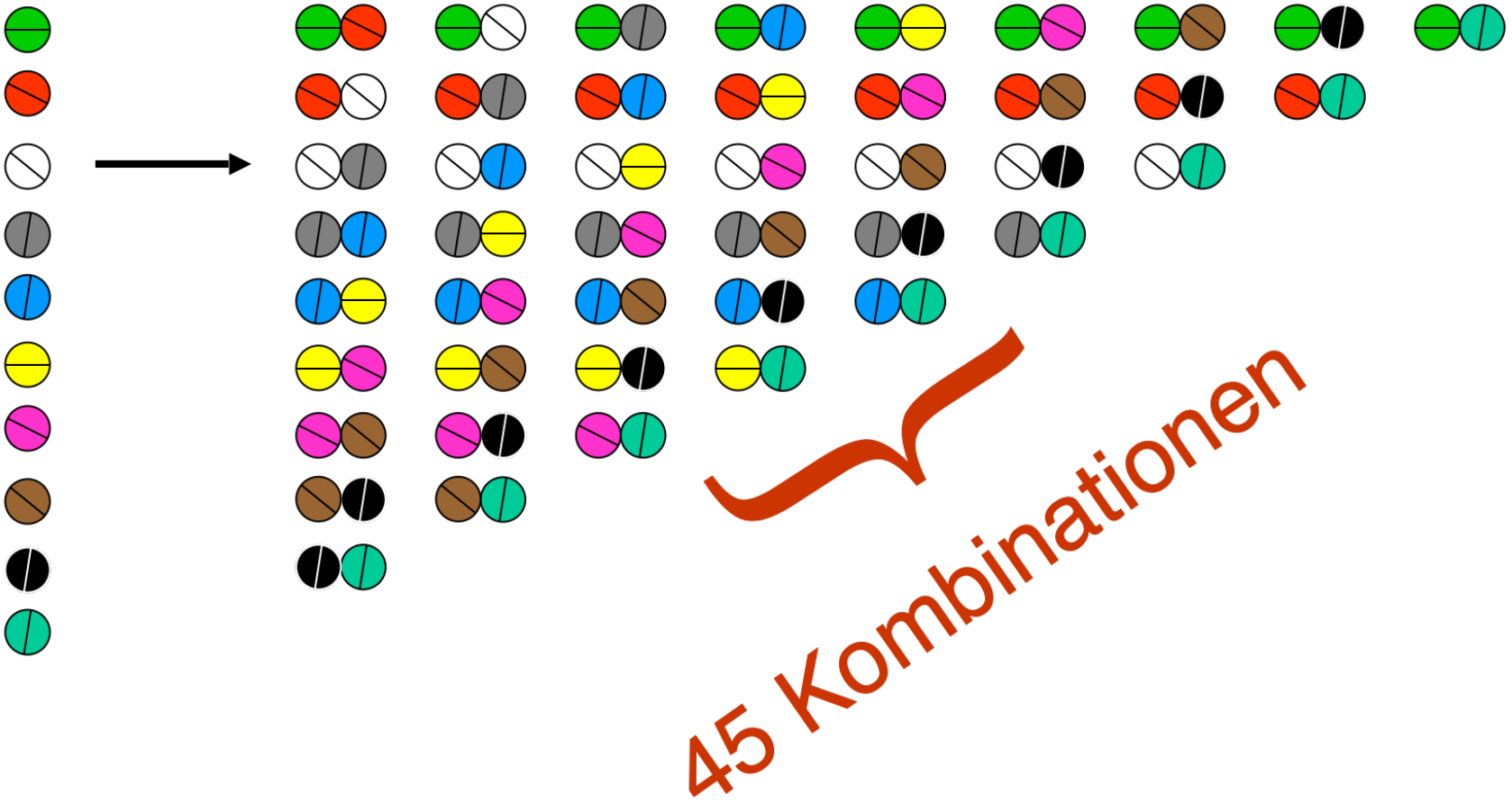
50% Reduktion? 2-facher Anstieg?

Wie kann man das klinisch beherrschen?

Wie ist das Vorgehen bei einem individuellen Patienten?

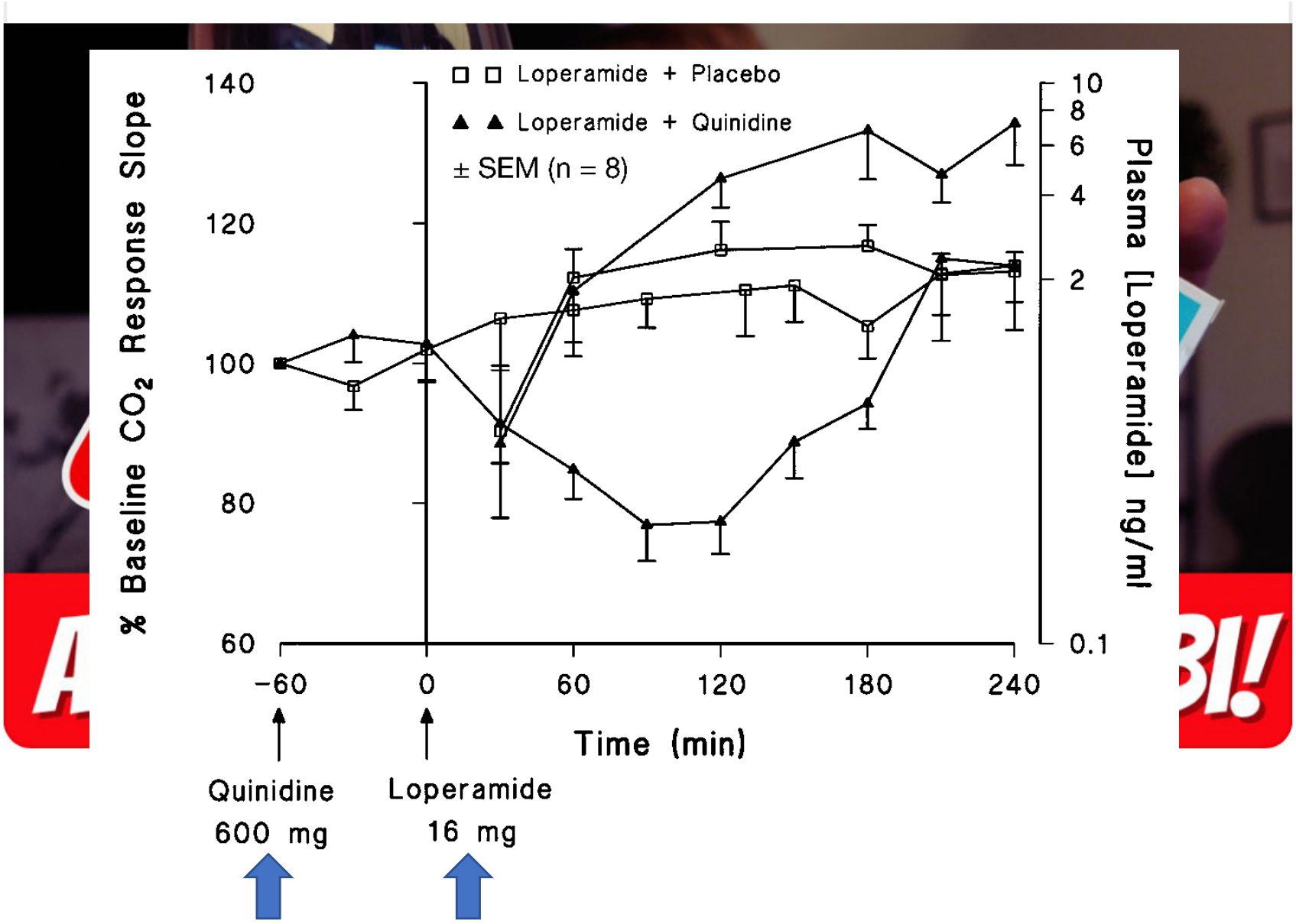
?

10 verschiedene verschriebene Medikamente



pharmakokinetische und -dynamische Wechselwirkungen

Fake News



📖 Sadeque AJM et al., CPT 2000, 68: 231

Arzneimittelinteraktionen

Die meisten Interaktionen sind beherrschbar:

Monitoring

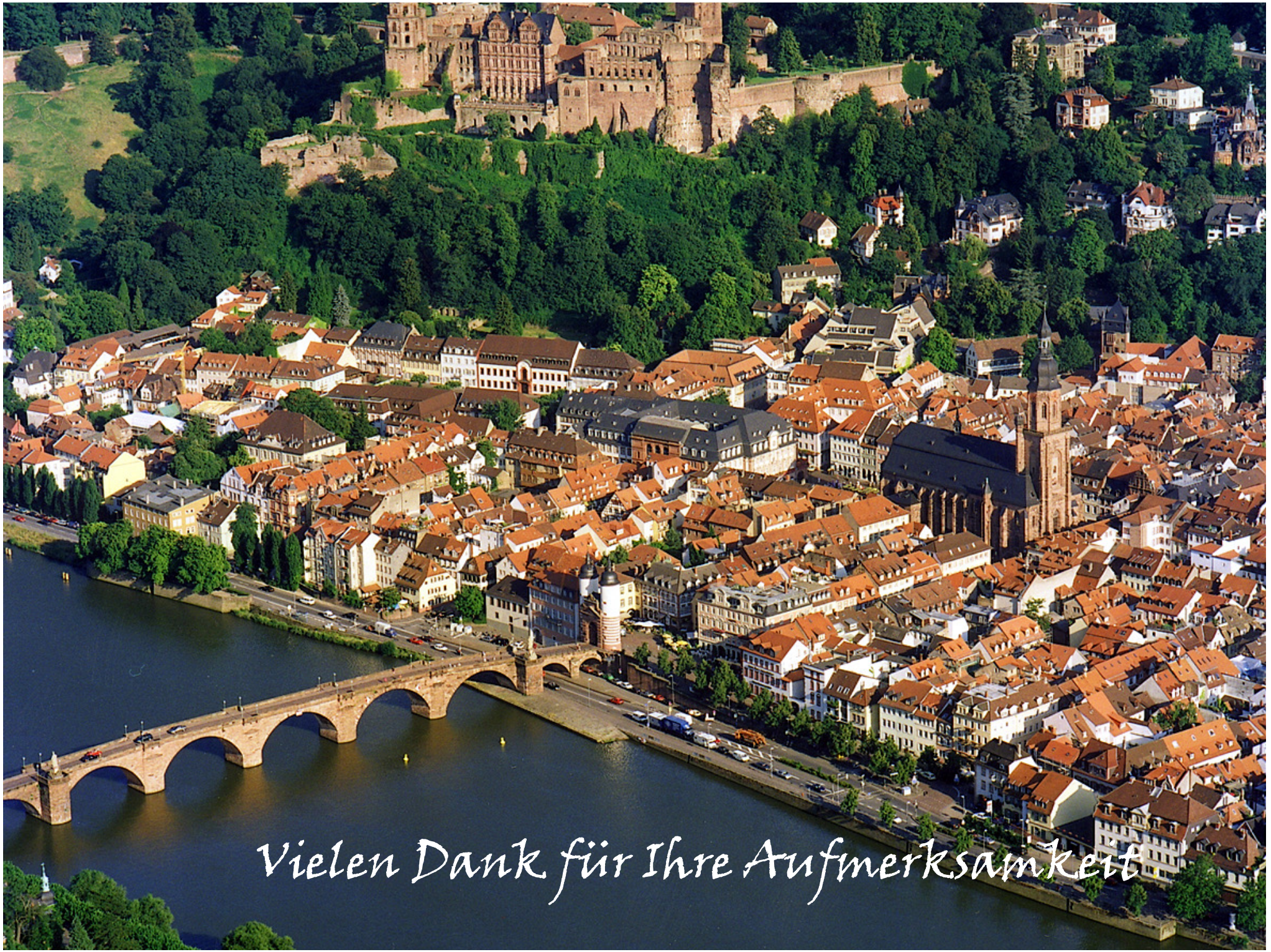
Dosisanpassung

Dosierungszeitpunkte

bei denjenigen, die dem Mittelwert der Population entsprechen

Lösung

- Charakterisierung der Eliminations- und Transportwege von Arzneimitteln
- Durchführung von mehr Interaktionsstudien
- Post Marketing Studien zur Etablierung der pharmakokinetischen Variabilität
- Pharmakogenetik???
- Ideen zur individualisierten Therapie??


Vielen Dank für Ihre Aufmerksamkeit