Interaktionen der medikamentösen Therapie bei Metabolischem Syndrom

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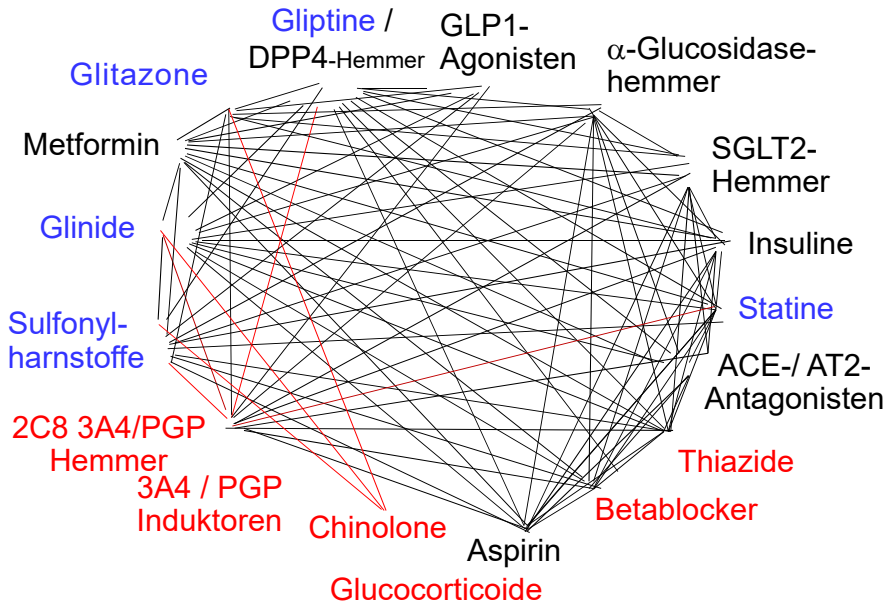


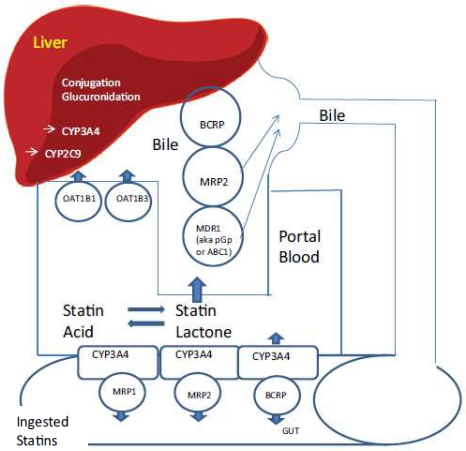
HMG COA HEMMER: CYP450 & P -GLYCOPROTEIN/MDR1

	Bioverfügbarkeit (%)	CYP 2C8	CYP 2C9	CYP 3A4	PGP	unverändert renal
Atorvastatin (Sortis®)	12					
Fluvastatin (Lescol®)	30				?	
Pravastatin (Selipran®)	18					~50%
Rosuvastatin (Crestor®)	20					~10%
Simvastatin (Zocor®)	<5					

PJ Neuvonen et al., Clin Pharmacol Ther. 2006;80:565

Curr Atheroscler Rep (2017) 19: 65

Fig. 1 Metabolic fate(s) of ingested statins



K. Kellick, Curr Atheroscler Rep 2017; 19: 65

Table 2 Transporters and enzymes affecting statins [6]

Statin	Transporters and enzymes affecting metabolism
Simvastatin lovastatin	CYP3A4 (intestinal and hepatic) OAT1B1 p-glycoprotein MDR1 BCRP
orvastatin	BCRP (intestinal) CYP3A4 (intestinal and hepatic) OAT1B1 and OAT2B1 p-glycoprotein
suvastatin	BCRP (intestinal) CYP2C9 (minor) OAT1B1 andOAT1B3 NTCP OAT2B1
avastatin	BCRP (intestinal) OAT1B1 and OAT1B3 OAT2B1
vastatin	BCRP (intestinal) OATP1B1 OAT1B3 OAT2B1 CYP2C9 CYP3A4
avastatin	BCRP (intestinal) MDR1 OAT1B1 andOAT1B3 OATP2B1 CYP2C9 (minor)

BCRP breast cancer resistant protein, *CYP* cytochrome P450, *MDR1* multidrug resistant protein, *OAT* organic anion transporters, *OATP* organic anion-transporting polypeptides

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INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine ciprofloxacin cimetidine amiodarone efavirenz fluoroquinolones fluvoxamine furafylline[1] interferon methoxsalen mibefradil ticlopidine	clopidogrel thiotepa ticlopidine[2] voriconazole	gemfibrozil[2] trimethoprim[2] glitazones montelukast[1] quercetin[1]	fluconazole[2] amiodarone efavirenz fenofibrate fluconazole fluvastatin fluvoxamine[2] isoniazid lovastatin metronidazole paroxetine phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole[1] teniposide voriconazole zafirlukast	PPIs: esomeprazole lansoprazole omeprazole2 pantoprazole Other: chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin isoniazid ketoconazole modafinil oral contraceptives oxcarbazepine probenicid ticlopidine2 topiramate voriconazole	bupropion cinacalcet fluoxetine paroxetine quinidine[1] duloxetine sertraline terbinafine amiodarone cimetidine celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine haloperidol histamine H1 receptor antagonists	diethyl-dithiocarbamate[2] disulfiram	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole[1] ketoconazole nefazodone saquinavir suboxone telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil[2] diltiazem cimetidine amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine

http://www.drug-interactions.com
http://medicine.iupui.edu/flockhart/table.htm

Table 1

Antimicrobial Drugs Studied and the Existing Evidence for Interaction With Sulfonylureas

	Hypoglycemia	
Antimicrobial Drug[a]	**Mechanism**	**Evidence**
Ciprofloxacin	Inhibits ATP K+ channels in pancreatic B-cells initiating insulin secretion[10,11] Enhances glucose-induced insulin secretion[10,11]	Shown to cause hypoglycemia in a cohort study[12]
Clarithromycin	May increase sulfonylurea level by inhibiting P-glycoprotein in the intestinal wall[13,14]	Shown to cause hypoglycemia in cohort studies[8,15]
Fluconazole	CYP2C9 inhibitor interfering with sulfonylurea metabolism[16]	Shown to cause hypoglycemia in cohort study[8]
Levofloxacin	Inhibits ATP-sensitive K+ channels affecting insulin release[10,11] May serve as P-glycoprotein inhibitor, which can increase concentrations of sulfonylureas[14,17]	Displayed hypoglycemic drug interactions with sulfonylureas in multiple studies[8,12,18]
Metronidazole	CYP2C9 inhibitor interfering with sulfonylurea metabolism[19,20]	May have lowered fasting plasma glucose level in hospitalized patients taking sulfonylureas[19]
Moxifloxacin	Enhances glucose-induced insulin secretion[10]	Conflicting evidence from cohort studies[19,21]
Sulfamethoxazole-trimethoprim	CYP2C9 inhibitor, interfering with sulfonylurea metabolism[8,22]	Hypoglycemia in cohort studies[8,9]

Abbreviation: ATP, adenosine triphosphate.

[a]No evidence of interaction with metabolizing enzymes and no prior reports linked to hypoglycemia for the following drugs: amoxicillin[23,24]; azithromycin[25,26]; cefdinir[27]; cefuroxime[28]; cephalexin[9,24]; clindamycin[23]; doxycycline[24]; nitrofurantoin[24]; penicillin V.[24]

T. M. Parekh, JAMA Intern Med. 2014; 174(10): 1605–1612.

VERGLEICH VON 3 QUELLEN ZU INTERAKTIONEN

Table 2. Pairwise comparison showing number of overlapping clinical drug pairs (numbers in thousands) between KBs

KB2 / KB1			FDB				Micromedex				Multum			
		Total (KB1) (%)	Sev1 (%)	Sev2 (%)	Sev3 (%)	Not found (%)	Sev1 (%)	Sev2 (%)	Sev3 (%)	Not found (%)	Sev1 (%)	Sev2 (%)	Sev3 (%)	Not found (%)
FDB	Sev1	101 (100)					49 **(48)**	20 (20)	4 (4)	28 (28)	35 **(34)**	11 (11)	6 (6)	49 (48)
	Sev2	390 (100)					22 (6)	129 **(33)**	92 (24)	147 (38)	19 (5)	73 (19)	78 **(20)**	219 (56)
	Sev3	1102 (100)					3 (<1)	201 (18)	297 **(27)**	602 (55)	2 (<1)	90 (8)	331 **(30)**	680 (62)
Micromedex	Sev1	191 (100)	49 **(25)**	22 (11)	3 (1)	119 (62)					49 **(25)**	4 (2)	10 (5)	129 (67)
	Sev2	2119 (100)	20 (1)	129 (6)	201 **(9)**	1770 (84)					8 (<1)	176 (8)	454 **(21)**	1481 (70)
	Sev3	2139 (100)	4 (<1)	92 (4)	297 **(14)**	1747 (82)					0.9 (<1)	30 (1)	446 **(21)**	1663 (78)
Multum	Sev1	100 (100)	35 **(34)**	19 (19)	2 (2)	45 (45)	49 **(48)**	8 (8)	0.9 (<1)	43 (42)				
	Sev2	368 (100)	11 (3)	73 (20)	90 **(24)**	195 (53)	4 (1)	176 **(48)**	30 (8)	159 (43)				
	Sev3	4302 (100)	6 (<1)	78 (2)	331 **(8)**	3887 (90)	10 (<1)	454 **(11)**	446 (10)	3392 (79)				

Each pairwise comparison is outlined by thick borders. The percentages are based on row totals (KB1). The highest percentage (excluding "not found") in each severity category is highlighted in bold type. Shaded boxes are those in which the severity rankings in 2 KBs agree (sev1 = contraindicated, sev2 = major/severe, sev3 = moderate).

KW Fung et al, Journal of the American Medical Informatics Association, 24(4), 2017, 806–812

FAZIT

- Interaktionen (und UAW) sind häufig, vor allem bei mehrfachkranken Patienten und bei Polypharmazie
- pharmakokinetische Interaktionen oft durch Induktoren oder Hemmer von Enzymen und/oder Transportproteinen
- anfällig auf Interaktionen sind Medikamente mit enger therapeutischer Breite (z.B. orale Antidiabetika), tiefer Bioverfügbarkeit (z. B. Statine) & wenn einzelnes Protein (z.B. CYP3A4) die Ausscheidung dominiert
- auch alternative Arzneien wie z. B. Johanniskraut als Ursache in Betracht ziehen, gezielt auch nach diesen Therapien fragen
- Unsere Kenntnisse sind limitiert: seien Sie auf Überraschungen gefasst (z.B. Chinolone) !
- Interaktionschecks stellen zusätzliche Informationen zur Verfügung
- Spezifizität und Sensitivität der Signale im Hinblick auf ein relevantes Problem zum Teil fraglich, dies kann verunsichern.