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Prevalence of Potentially Severe Drug-Drug Interactions in Ambulatory Patients with Dyslipidaemia Receiving HMG-CoA Reductase Inhibitor Therapy

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Abstract

Background: Drug-drug interactions (DDIs) are a well known risk factor for adverse drug reactions. HMG-CoA reductase inhibitors ('statins') are a cornerstone in the treatment of dyslipidaemia and patients with dyslipidaemia are concomitantly treated with a variety of additional drugs. Since DDIs are associated with adverse reactions, we performed a cross-sectional study to assess the prevalence of potentially critical drug-drug and drug-statin interactions in an outpatient adult population with dyslipidaemia.

Methods: Data from patients with dyslipidaemia treated with a statin were collected from 242 practitioners from different parts of Switzerland. The medication list was screened for potentially harmful DDIs with statins or other drugs using an interactive electronic drug interaction program.

Results: We included 2742 ambulatory statin-treated patients (mean age ± SD 65.1 ± 11.1 years; 61.6% males) with (mean ± SD) 3.2 ± 1.6 diagnoses and 4.9 ± 2.4 drugs prescribed. Of those, 190 patients (6.9%) had a total of 198 potentially harmful drug-statin interactions. Interacting drugs were fibrates or nicotinic acid (9.5% of patients with drug-statin interactions), cytochrome P450 (CYP) 3A4 inhibitors (70.5%), digoxin (22.6%) or ciclosporin (cyclosporine) [1.6%]. The proportion of patients with a potential drug-statin interaction was 12.1% for simvastatin, 10.0% for atorvastatin, 3.8% for fluvastatin and 0.3% for pravastatin. Additionally, the program identified 393 potentially critical non-statin DDIs in 288 patients.

Conclusions: CYP3A4 inhibitors are the most frequent cause of potential drug interactions with statins. As the risk for developing rhabdomyolysis is increased in patients with drug-statin interactions, clinicians should be aware of the most frequently observed drug-statin interactions and how these interactions can be avoided.

Background

Drug-drug interactions (DDIs) are an important cause of adverse drug reactions. It has been estimated that approximately 5% of prescribing errors[1] or of adverse drug reactions [2] are caused by DDIs in hospitalised patients. In a recent investigation, 2.3–7.8% of adverse effects associated with the use of cotrimoxazole (trimethoprim/sulfamethoxazole), digoxin or ACE inhibitors were found to be due to interactions with specific concomitant drugs.[3] Polypharmacy, which is closely associated with the number of diagnoses in a given patient,[4] has been identified as a major risk factor for DDIs. Additionally, the way a drug is metabolised and/or excreted is a major determinant of potential DDIs.[5] Regarding drug metabolism, drugs undergoing degradation by cytochrome P450 (CYP) isoenzymes carry a particularly high risk for DDIs because of the large number of drugs inhibiting or inducing CYP isoenzymes.[5,6] Additionally, clinically relevant DDIs can arise on the level of transport proteins responsible for renal and/or biliary excretion of endogenous and exogenous substances. Examples are interactions involving P-glycoprotein (P-gp), such as interactions between HMG-CoA reductase inhibitors ('statins') and digoxin[7] or clarithromycin and digoxin.[8,9]

Interactions with statins can lead to rhabdomyolysis, a severe adverse reaction which may be fatal.[10,11] A recent study in Ireland estimated that approximately 30% of all users of statins have concomitant drugs prescribed that can inhibit statin metabolism, potentially leading to rhabdomyolysis.[12] It is known that the interaction potential differs between individual statins.[13,14] Atorvastatin, lovastatin and simvastatin are all biotransformed by CYP3A4, the most abundant CYP isoenzyme, which metabolises most drugs undergoing CYP-associated biotransformation.[6,15] Accordingly, the risk for interactions is highest for drugs metabolised by CYP3A4, particularly if no other CYP isoenzymes are involved in their biotransformation. Fluvastatin is primarily metabolised by CYP2C9, an isoenzyme that is less abundant than CYP3A4, making the drug less prone to DDIs.[16,17] Pravastatin is more hydrophilic because of a hydroxyl group allowing conjugation of the drug without previous phase I biotransformation.[13,14] Accordingly, the risk for interactions with pravastatin is estimated to be lower than for statins undergoing CYP-dependent metabolism.[16,17] Because data on the prevalence and risk factors for potential DDIs in ambulatory patients are rare and interactions in patients treated with statins can be associated with severe adverse effects,[10,11,18] we identified potential DDIs in ambulatory patients with hyperlipidaemia treated with a statin to assess the prevalence of potential DDIs in association with statin therapy, to assess the prevalence of other potential DDIs not involving statins and to identify risk factors for potential DDIs in this population.

Methods

Subjects, Study Design and Data Collection

Between February and April 2002, practitioners from different parts of Switzerland were recruited to participate in the cross-sectional SAFE (Swiss Analysis Focused on the Evaluation of potential drug interactions) trial. The participating practitioners screened all patients attending their practice during five consecutive days and completed a data sheet for each patient with dyslipidaemia receiving statin therapy. The form included data on year of birth, sex, the statin prescribed, indication for the statin, main diagnoses and all concomitantly prescribed drugs. Diagnoses were coded according to the International Statistical Classification of Disease and Related Health Problems (ICD-10) and drugs were coded according to the WHO Drug Dictionary (version 01-3, third quarter 2001). All patient data were recorded in an electronic database and all drug profiles were screened using the online version of Drug-Reax® Interactive Drug Interactions (Micromedex™ Healthcare Series Vol. 111-115/Exp 03-12/2002),[19] a drug interaction program that has been used in several previous studies.[20-22] This program has proven to be more sensitive to predict potential DDIs than expert physicians.[22]

Database and Semiautomatic Screening by Drug-Reax®

Drug-Reax®, an interactive electronic drug interaction program with a filter for severity rating (ma-

jor, moderate, minor) that provides referenced information on the clinical picture caused by a given DDI, was used for screening potential DDIs.[19] For this project, a specific software for data management and entry was developed. The software allowed coding of diagnoses according to ICD-10 and of drugs according to the WHO Drug Dictionary. Phenprocoumon and acenocoumarol, the two oral anticoagulants used in Switzerland, were coded as warfarin, because they are not listed in Drug-Reax®. After the entry of all drugs received by a single patient, the software prepared data records for all possible drug-drug combinations for the patient (number of drug pairs/patient = [number of drugs × (number of drugs − 1)/2]). By using the browser object of MS-Access, a semiautomatic search was started in Drug-Reax® and the result was pasted into the database. A systematic parsing procedure analysed the search results, which consequently had to be assigned to the correct drug-drug pair. With this procedure, over 30 000 drug-drug pairs were screened. Drug combinations with the potential of relevant interactions for either compound were separated for further evaluation.

Evaluation of Clinical Relevance of Potential Drug Interactions

Drug-HMG-CoA Reductase Inhibitor ('Statin') Interactions

Each patient and medication profile with a possible drug-statin interaction detected by Drug-Reax® was evaluated by a pharmacist and a clinical pharmacologist for clinical relevance. A drug-statin combination was considered critical or potentially harmful and, therefore, clinically relevant if: the respective statin was combined with a known inhibitor of its metabolism and/or transport; there was at least one published case report describing the interaction; or, the potential adverse effect could have had a serious outcome. Serious outcome was defined as described by the International Conference on Harmonisation (ICH) guidelines for clinical safety data management of adverse drug reactions.[23] In case of disagreement, the specific interaction was discussed until consensus between both assessors was reached.

Non-Statin Drug-Drug Interactions

Each drug profile with a possible non-statin DDI of 'major severity' according to Drug-Reax® or with a DDI not recognised by Drug-Reax® but by manual screening using standard literature,[24,25] an additional online drug interaction database (www.pharmavista.ch) and/or Medline, was evaluated by a pharmacist and a clinical pharmacologist. DDIs were considered as potentially harmful (and therefore clinically relevant) if the potential adverse effect of this interaction could have had a serious outcome. A DDI of 'major severity' according to Drug-Reax® was considered as not being clinically relevant if the interaction did not correspond to the actual clinical situation (e.g. first-dose hypotension of ACE inhibitors in patients receiving long-term treatment with ACE inhibitors and diuretics) or if one of the potentially interacting drugs was administered topically (e.g. treatment with topical ketoconazole in a patient treated with a CYP3A4 substrate).

Statistical Analysis

Possible differences of age, number of diagnoses and number of drugs between the groups of patients treated with the different statins were tested by one-way ANOVA. Categorical variables were tested by Pearson χ^2. The 5% significance level (α-criterion) was adjusted for multiple testing according to Bonferroni-Holm.[26]

Potential drug-statin and non-statin DDIs were analysed by logistic regression analyses using a backward elimination procedure with Wald statistics and likelihood-ratio statistics. The occurrence of potential drug-statin or non-statin DDIs was used as the response variable. Explanatory variables put in the two models of drug-statin and non-statin DDIs included the dichotomous variables male sex, French-speaking part of Switzerland, Italian-speaking part of Switzerland, diagnosis of hypertension, diabetes, coronary heart disease, cardiac failure, arrhythmias, depression/psychiatric disorders, cerebrovascular diseases, rheumatic diseases/diseases of the musculoskeletal system, gout/hyperuricaemia, epilepsy and other diagnoses (table I). The continuous variables included in the model were age (years), number of diagnoses, number of prescribed drugs and number of prescribed pharmacologically

Table I. Patient characteristics and co-morbidities in 2742 patients with dyslipidaemia receiving HMG-CoA reductase inhibitor ('statin') therapy stratified according to individual statins

Patient characteristics	Total (n = 2742)	Atorvastatin (n = 886)	Pravastatin (n = 934)	Simvastatin (n = 763)	Fluvastatin (n = 159)	P-value
Age [y (mean ± SD)]	65.1 ± 11.2	63.7 ± 11.6	65.3 ± 11.2	66.5 ± 10.8	65.6 ± 10.8	<0.05[a]
Females [no. (%)]	1052 (38.4)	334 (37.7)	362 (38.8)	296 (38.8)	60 (37.7)	NS
No. of diagnoses (including dyslipidaemia) [mean ± SD]	3.2 ± 1.6	3.2 ± 1.6	3.2 ± 1.6	3.4 ± 1.5	3.2 ± 1.3	NS
No. of prescribed drugs including statin (mean ± SD)	4.9 ± 2.4	4.7 ± 2.4	4.8 ± 2.4	5.1 ± 2.3	5.1 ± 2.2	<0.05[b]
Hypertension [no. (%)]	1428 (52.1)	441 (49.8)	479 (51.3)	407 (53.3)	101 (63.5)	NS
Diabetes mellitus [no. (%)]	520 (19.0)	170 (19.2)	170 (18.2)	151 (19.8)	29 (18.2)	NS
Coronary heart disease [no. (%)]	1166 (42.5)	372 (42.0)	389 (41.6)	348 (45.6)	57 (35.8)	NS
Cardiac failure [no. (%)]	130 (4.7)	40 (4.5)	35 (3.7)	49 (6.4)	6 (3.8)	NS
Arrhythmias [no. (%)]	188 (6.9)	56 (6.3)	63 (6.7)	61 (8.0)	8 (5.0)	NS
Cerebrovascular diseases (including transitory ischaemic attacks and peripheral arterial occlusive disease) [no. (%)]	461 (16.8)	136 (15.3)	159 (17.0)	139 (18.2)	27 (17.0)	NS
Depression/psychiatric disorder [no. (%)]	423 (15.4)	137 (15.5)	133 (14.2)	125 (16.4)	28 (17.6)	NS
Rheumatic diseases/diseases of musculoskeletal system [no. (%)]	416 (15.2)	124 (14.0)	139 (19.9)	128 (16.8)	25 (15.7)	NS
Gout/hyperuricaemia [no. (%)]	103 (3.8)	42 (4.7)	34 (3.6)	21 (2.8)	6 (3.8)	NS
Epilepsy [no. (%)]	16 (0.6)	4 (0.5)	6 (0.6)	6 (0.8)	0	NS
Other diagnoses [no. (%)]	244 (8.9)	88 (9.9)	94 (10.1)	54 (7.1)	8 (5.0)	NS

a Age: simvastatin > atorvastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm).

b Number of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm).

NS = not significant; **SD** = standard deviation.

active compounds. Explanatory variables were included in the final model, if the p-value was < 0.1.

The final model of drug-statin interactions comprised the following explanatory variables: number of diagnoses, number of prescribed drugs, diagnosis of hypertension, diabetes, cardiac failure, arrhythmias and French-speaking part of Switzerland. The influence of the prescribed statin was assessed by an indicator variable for the use of pravastatin (yes/no), i.e. pravastatin was tested against all other statins. The following parameters were put in the final non-statin DDI model as explanatory variables: male sex, number of prescribed pharmacologically active compounds, diagnosis of diabetes, cardiac failure, arrhythmias, cerebrovascular diseases and gout/hyperuricaemia. The influence on non-statin DDIs was assessed by an indicator variable for the presence of potential drug-statin DDIs. Relative risk estimates are expressed as odds ratios (ORs) with 95% CIs.

Statistical analyses were performed with SPSS for Windows version 10.1.4 (SPSS Inc., Chicago, USA).

Results

Drug-Statin Interactions

From February to April 2002, 242 practitioners (43.0% general practitioners, 41.7% internists, 13.6% cardiologists and 1.7% others) from different parts of Switzerland recorded the medication of 2753 patients with dyslipidaemia treated with a statin. Eleven patients were excluded from the analysis: ten patients were not prescribed a statin and one was receiving cerivastatin, a statin withdrawn from the market in 2000. Patients were recruited in the German- (49.2%), French- (37.9%) or Italian- (12.9%) speaking parts of Switzerland. Pravastatin was prescribed in 34.1% of all patients, atorvastatin in 32.3%, simvastatin in 27.8% and fluvastatin in 5.8%. Patient characteristics are summarised in table I. The 2742 patients included in the study had a total of 8943 diagnoses (mean ± SD 3.2 ± 1.6 per patient) and were prescribed a total of 12 766 drugs (mean 4.9 ± 2.4 drugs per patient, range 1–21). The most prevalent co-morbidities besides dyslipidaemia were arterial hypertension, coronary heart disease, diabetes mellitus, cerebrovascular diseases, psychiatric illnesses, arrhythmias and cardiac failure. In comparison to the other statins, patients treated with simvastatin were significantly older and were prescribed more drugs than other statin users.

The distribution of drugs concomitantly prescribed with statins is shown in table II. Since arterial hypertension and coronary heart disease were the most prevalent co-morbidities, aspirin (acetylsalicylic acid), β-adrenoceptor antagonists (β-blockers), ACE inhibitors, angiotensin receptor antagonists and thiazide or loop diuretics, were the drugs most often prescribed concomitantly. Overall, 122 patients (4.4%) had no additional drug prescribed.

Overall, 190 (6.9%) of the 2742 patients receiving statin therapy had a total of 198 drug combinations with the potential for a critical drug-statin interaction; eight patients had two such drug combinations (table III). The prevalence of potentially critical drug-statin interactions was 12.1% (95% CI 9.7, 14.4) in patients with simvastatin, 10.0% (95% CI 8.0, 12.1) with atorvastatin, 3.8% (95% CI 0.5, 7.1) with fluvastatin and 0.3% (95% CI 0.1, 0.7) with pravastatin. The potentially interacting drugs comprised other lipid-lowering drugs (fibrates, nicotinic acid), known CYP3A4 inhibitors (amiodarone, verapamil, fluoxetine/norfluoxetine, diltiazem, nefazodone, clarithromycin and systemic azole antifungal drugs), or known CYP2C9 inhibitors (fluoxetine/norfluoxetine). Forty-three patients (22.6% of the patients with a potential drug-statin interaction) were concomitantly treated with digoxin, a P-gp substrate.

Logistic regression analysis indicated that the following variables were associated with a statistically increased relative risk for potentially critical drug-statin interactions: number of drugs (adjusted OR 1.3; 95% CI 1.2, 1.4; $p < 0.001$), diagnosis of cardiac failure (adjusted OR 1.8; 95% CI 1.1, 3.1; $p = 0.03$), diagnosis of arrhythmias (adjusted OR 5.6; 95% CI 3.6, 8.5; $p < 0.001$) and being a patient from the French-speaking part of Switzerland (adjusted OR 1.5; 95% CI 1.1, 2.1; $p = 0.018$). The use of pravastatin was associated with a lower risk for potentially critical drug-statin interactions (adjusted OR 0.02; 95% CI 0.01, 0.07; $p < 0.001$) compared with use of other statins.

Table II. Co-medication prescribed in 2742 HMG-CoA reductase inhibitor ('statin') users stratified according to individual statin

Comedication	Total (n = 2742)	Atorvastatin (n = 886)	Pravastatin (n = 934)	Simvastatin (n = 763)	Fluvastatin (n = 159)	P-value
No. of concomitant drugs (mean± SD)	3.9 ± 2.4	3.7 ± 2.4	3.8 ± 2.4	4.1 ± 2.3	4.1 ± 2.2	<0.05[a]
Acetylsalicylic acid (aspirin) [no. (%)]	1258 (45.9)	423 (47.7)	409 (43.8)	369 (48.4)	57 (35.8)	NS
β-adrenoceptor antagonists (β-Blockers) [no. (%)]	1145 (41.8)	373 (42.1)	376 (40.3)	327 (42.9)	69 (43.4)	NT
Thiazide or loop diuretics [no. (%)]	900 (32.8)	272 (30.7)	320 (34.3)	258 (33.8)	50 (31.4)	NS
ACE inhibitors [no. (%)]	778 (28.4)	226 (25.5)	250 (26.8)	252 (33.0)	50 (31.4)	<0.05[b]
Angiotensin receptor antagonists [no. (%)]	551 (20.1)	177 (20.0)	198 (21.2)	147 (19.3)	29 (18.2)	NT
NSAIDs [no. (%)]	427 (15.6)	122 (13.8)	140 (15.0)	132 (17.3)	33 (20.8)	NS
Calcium antagonists [no. (%)] (dihydropyridines)	403 (14.7)	129 (14.6)	130 (13.9)	121 (15.9)	23 (14.5)	NT
Antidepressants[c] [no. (%)]	340 (12.4)	119 (13.4)	88 (9.4)	103 (13.5)	30 (18.9)	<0.05[d]
Oral antidiabetics (other than sulfonylureas [no. (%)]	328 (12.0)	119 (13.4)	111 (11.9)	84 (11.0)	14 (8.8)	NT
Sulfonylureas [no. (%)]	205 (7.5)	70 (7.9)	67 (7.2)	58 (7.6)	10 (6.3)	NT
Phenprocoumon [no. (%)]	201 (7.3)	56 (6.3)	76 (8.1)	62 (8.1)	7 (4.4)	NS
Potassium-sparing diuretics [no. (%)]	161 (5.9)	57 (6.4)	53 (5.7)	38 (5.0)	13 (8.2)	NT
Clopidogrel [no. (%)]	136 (5.0)	43 (4.9)	37 (4.0)	48 (6.3)	8 (5.0)	NT
Insulin [no. (%)]	133 (4.9)	40 (4.5)	40 (4.3)	45 (5.9)	8 (5.0)	NT
Allopurinol [no. (%)]	122 (4.4)	43 (4.9)	42 (4.5)	27 (3.5)	10 (6.2)	NT
Acenocoumarol [no. (%)]	119 (4.3)	27 (3.0)	44 (4.7)	41 (5.4)	7 (4.4)	NS
Calcium antagonists (verapamil or diltiazem) [no. (%)]	100 (3.6)	33 (3.7)	30 (3.2)	31 (4.1)	6 (3.8)	NT
Amiodarone [no. (%)]	82 (3.0)	29 (3.2)	26 (2.8)	23 (3.0)	4 (2.5)	NS
Digoxin [no. (%)]	67 (2.4)	21 (2.4)	19 (2.0)	23 (3.0)	4 (2.5)	NT
Tramadol [no. (%)]	24 (0.9)	12 (1.4)	5 (0.5)	7 (0.9)	0	NT
Hypericum (St John's wort) [no. (%)]	23 (0.8)	8 (0.9)	8 (0.9)	5 (0.7)	2 (1.3)	NT
Ginkgo [no. (%)]	18 (0.7)	5 (0.5)	9 (1.0)	4 (0.5)	0	NT
Fibrates [no. (%)]	17 (0.6)	10 (1.1)	3 (0.3)	3 (0.4)	1 (0.6)	NT
Ciclosporin (cyclosporine) [no. (%)]	8 (0.3)	0	4 (0.4)	3 (0.4)	1 (0.6)	NT
Methotrexate [no. (%)]	6 (0.2)	2 (0.2)	2 (0.2)	0	2 (1.3)	NT
Azathioprine [no. (%)]	4 (0.1)	0	1 (0.1)	3 (0.4)	0	NT
Nicotinic acid [no. (%)]	3 (0.1)	0	2 (0.2)	1 (0.1)	0	NT
Azole antifungals (systemic) [no. (%)]	2 (0.1)	0	0	2 (0.3)	0	NT

a No. of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm).

b ACE inhibitors: simvastatin > atorvastatin; simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm).

c Excluding hypericum extract.

d Antidepressants: atorvastatin > pravastatin; fluvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm).

NS = not significant; **NT** = not tested to avoid multiple testing on the same sample; **SD** = standard deviation.

Table III. List of 198 potential drug-HMG-CoA reductase inhibitor ('statin') interactions in 190 patients with dyslipidaemia treated with a statin; eight patients had two potential interactions (seven in the atorvastatin and one in the simvastatin group)

Potential interactions	Total	Atorvastatin	Pravastatin	Simvastatin	Fluvastatin
Total no. of patients with potential interactions (no.)	190	89	3	92	6
Total no. of potential interactions [no. (%)]	198 (100.0)	96 (100.0)	3 (100.0)	93 (100.0)	6 (100.0)
Other lipid-lowering drugs [no. (%)]	18 (9.1)	10 (10.4)	3 (100.0)	4 (4.3)	1 (16.7)
fibrates	17 (8.6)	10 (10.4)	3 (100.0)	3 (3.2)	1 (16.7)
nicotinic acid	1 (0.5)	0	0	1 (1.1)	0
CYP3A4 inhibitors [no. (%)]	129 (65.2)	66 (68.8)	NA	63 (67.7)	NA
amiodarone	52 (26.3)	29 (30.2)	NA	23 (24.7)	NA
verapamil	40 (20.2)	21 (21.96)	NA	19 (20.4)	NA
diltiazem	5 (2.5)	0	NA	5 (5.4)	NA
fluoxetine/norfluoxetine	24 (12.1)	13 (13.5)	NA	11 (11.8)	NA
nefazodone	3 (1.5)	3 (3.1)	NA	0	NA
clarithromycin	3 (1.5)	0	NA	3 (3.2)	NA
azole antifungal (systemic)	2 (1.0)	0	NA	2 (2.2)	NA
CYP2C9 inhibitors [no. (%)]	5 (2.5)	NA	NA	NA	5 (83.3)
fluoxetine/norfluoxetine	5 (2.5)	NA	NA	NA	5 (83.3)
P-glycoprotein substrates [no. (%)]	43 (21.7)	20 (20.8)	NA	23 (24.7)	NA
digoxin	43 (21.7)	20 (20.8)	NA	23 (24.7)	NA
Others [no. (%)]	3 (1.5)	0	0	3 (3.2)	0
ciclosporin (cyclosporine)	3 (1.5)	0	0	3 (3.2)	0

CYP = cytochrome P450; **NA** = not applicable.

Additional drug-statin combinations were observed, which did not meet the criteria to be classified as potential DDIs with harmful clinical consequences as defined, but which are worth mentioning. Three hundred and twenty patients (11.7% of the study population) were prescribed an oral anticoagulant, either phenprocoumon (CYP3A4 and CYP2C9 substrate; 201 patients or 7.3% of all patients studied) or acenocoumarol (CYP2C9 substrate; 119 patients or 4.3%). In 200 patients (7.3%) oral anticoagulants were administered in combination with atorvastatin, simvastatin or fluvastatin. Since oral anticoagulants are only CYP substrates but not inhibitors, these potential interactions were not included in our analysis. Fifty-four patients (2.0% of all patients studied) were treated with a CYP inducer. Thirty-nine of these patients (1.4%) had a combination that might lead to a decreased plasma concentration of the statin (simvastatin or atorvastatin) and a potential loss of its clinical effect (7 with barbiturates, 15 with carbamazepine, 2 with phenytoin and 15 with hypericum [St John's wort]). Since the clinical relevance of these potential interactions is not clear, they were not included in our analysis. The potential interaction between atorvastatin and clopidogrel, which was initially published in early 2003,[27] remains controversial[28,29] and was therefore not included in our analysis. No patient was reported to have signs or symptoms of myopathy during data collection.

Non-Statin Drug-Drug Interactions

In 288 of the 2742 patients studied (10.5%), 393 drug combinations with non-statin DDIs were identified, corresponding to a mean of 1.36 ± 0.8 interactions per affected patient. Of 288 patients with interactions, 219 (76.0%) had one non-statin DDI, 47 patients (16.3%) had two and 22 patients (7.6%) had three or more non-statin DDIs. The non-statin DDIs that were detected most often are listed in table IV. Patients treated with ACE inhibitors, potassium-sparing diuretics, β-blockers, oral anticoagulants, amiodarone or digoxin were most likely to have potential non-statin DDIs. The underlying mechanism of potential DDIs was pharmacodynamic in 65% of the 393 drug combinations with non-statin DDIs (predominantly among cardiovascular drugs), pharmacokinetic in 14% and in 21% the mechanism was unclear.

Table IV. Description of 393 critical non-HMG-CoA reductase inhibitor ('statin') drug-drug interactions in 288 patients with dyslipidaemia

Interaction	No. (%)	Mechanism and/or potential risk
ACE inhibitor – potassium-sparing diuretic	51 (13.0)	Hyperkalaemia due to increased potassium retention secondary to lowered aldosterone levels caused by ACE inhibitor
Digoxin – loop/thiazide diuretics	42 (10.7)	Secondary digoxin toxicity due to diuretic-induced hypokalaemia and hypomagnesaemia, enhancing Na-K-ATPase inhibition by cardiac glycosides
Allopurinol – ACE inhibitor	40 (10.2)	Unknown mechanism leading to hypersensitivity syndrome
Amiodarone – oral anticoagulants (phenprocoumon, acenocoumarol)	33 (8.4)	Increased bleeding risk due to decreased metabolism of oral anticoagulants
Amiodarone – β-adrenoceptor antagonist (β-blocker)	31 (7.9)	Additive cardiac effects (AV node refractory period prolonged and sinus node automaticity decreased by amiodarone), potentially leading to bradycardia, hypotension or cardiac arrest
Aspirin (acetylsalicylic acid) – oral anticoagulant (phenprocoumon, acenocoumarol)	27 (6.9)	Combination of thrombocyte aggregation inhibition and anticoagulant is associated with increased risk of bleeding
β-Blocker – antidiabetic agents	22 (5.6)	Blockade of β_2-receptors impairs glycogenolysis and peripheral manifestations of hypoglycaemia (described for insulin or sulfonylureas, but not for thiazolidinediones, acarbose or metformin)
Digoxin – β-blocker	21 (5.3)	Additive prolongation of AV-conduction time
		Digoxin toxicity due to competition for intestinal P-glycoprotein (described for talinolol)
Diltiazem /verapamil – β-blocker	18 (4.6)	Additive negative inotropic effects and impaired AV conduction possibly leading to hypotension, bradycardia and conduction blocks
Ginkgo – aspirin/oral anticoagulants (phenprocoumon, acenocoumarol)	16 (4.1)	Increased risk of bleeding due to inhibition of thrombocyte aggregation by ginkgo
NSAID – aspirin	13 (3.3)	Increased risk of gastrointestinal bleeding in patients with NSAID and low-dose aspirin
NSAID – oral anticoagulants (phenprocoumon, acenocoumarol)	11 (2.8)	Increased risk of gastrointestinal bleeding due to gastric erosions, inhibition of platelet aggregation and displacement of anticoagulants from plasma albumin by NSAID
Tramadol – CNS drugs: tricyclic antidepressants, selective serotonin reuptake inhibitors, neuroleptics, monoamine oxidase inhibitors	10 (2.5)	Decreased seizure threshold and enhanced risk for seizures in combination with CNS drugs associated with seizures
		Increased concentration of serotonin in the nervous system and periphery potentially leading to serotonin syndrome
		Hypertensive crisis in combination with monoamine oxidase inhibitors
CYP inducers[a] (phenobarbital, primidone, phenytoin, carbamazepine, hypericum, rifampicin [rifampin]) – critical CYP substrates[a] (phenprocoumon, acenocoumarol, clonazepam, clozapine, antiepileptics)	9 (2.3)	Clearance of CYP substrates increased

Continued next page

Table IV. Contd

Interaction	No. (%)	Mechanism and/or potential risk
CYP inhibitors[a] (amiodarone, fluoxetine, fluvoxamine) – critical CYP substrates[a] (thioridazine, cisapride, verapamil, alprazolam, amitriptyline)	7 (1.8)	Clearance of CYP substrates decreased
Potassium – ACE inhibitors	6 (1.5)	Increased potassium retention and risk for hyperkalaemia secondary to lowered aldosterone levels caused by ACE inhibitor
Potassium – potassium-sparing diuretics	5 (1.3)	Increased potassium retention and risk for hyperkalaemia
Methotrexate – NSAID	5 (1.3)	Increased methotrexate toxicity due to decreased renal methotrexate clearance resulting from NSAID-induced impairment of renal perfusion and competition for tubular secretion
Other	26 (6.6)	NA

a The drugs listed (CYP inducers, CYP substrates, CYP inhibitors) are those that were prescribed during the current study. The list does not, therefore, necessarily include the typical drugs interacting with CYP isoenzymes.

ATPase = adenosine triphosphatase; **AV** = atrio-ventricular; **CYP** = cytochrome P450; **NA** = not applicable.

Logistic regression analysis yielded statistically increased relative risks for the following variables: male sex (adjusted OR 1.4; 95% CI 1.1, 1.9), number of prescribed pharmacologically active compounds (adjusted OR 1.6; 95% CI 1.5, 1.7), diagnosis of cardiac failure (adjusted OR 3.3; 95% CI 2.1, 5.1), diagnosis of arrhythmias (adjusted OR 3.50; 95% CI 2.4, 5.2), diagnosis of cerebrovascular diseases (adjusted OR 1.6; 95% CI 1.1, 2.2) and a diagnosis of gout (adjusted OR 2.9; 95% CI 1.7, 4.9).

Discussion

Our study demonstrates that overall, approximately 7% of all patients prescribed a statin were at risk for a drug-statin interaction. This figure is lower than the one obtained in a recent study in Ireland, where potentially interacting drugs were detected in approximately 30% of patients treated with a statin.[12] This discrepancy may be explained by differences in the prescribing pattern between Ireland and Switzerland and also by differences in the definition of drug-statin interactions. Considering the prescribing pattern, only 3.6% of the patients in our study were treated with the CYP3A4 inhibitors verapamil or diltiazem, whereas 13.1% of the patients in the Irish study were concomitantly treated with these drugs.[12] In the Irish study, inhibitors, inducers and substrates of CYP3A4 and CYP2C9 were regarded as drugs with the potential to interact with statins.[12] In contrast, in our study, only CYP inhibitors, P-gp substrates and other drugs for which case reports or drug interaction studies about a clinically relevant interaction could be identified, were considered as drugs with the potential to interact with statins. Moreover, CYP3A4 and/or CYP2C9 substrates, for which no case reports of clinically relevant drug-statin interactions exist, were not included in the analysis. In addition, CYP inducers (e.g. phenytoin, carbamazepine, rifampicin [rifampin] and hypericum) were not considered as drugs with a clinically significant interaction potential with statins in our study and were, therefore, not included.

Although the participating physicians had been told to transmit the medication lists of the patients entering the study before performing any changes, we cannot exclude the possibility that some practitioners checked the medication list for drug-drug

interactions before transmitting it. The true prevalence of drug-drug interactions may therefore be higher than found in our study.

Approximately 40% of all patients treated with a statin who develop rhabdomyolysis are concomitantly treated with an interacting drug.[18] A recent analysis of reports to the US FDA revealed that mibefradil, fibrates, ciclosporin (cyclosporine), macrolides (erythromycin and clarithromycin), warfarin, digoxin, azole antifungals, nicotinic acid, tacrolimus, chlorzoxazone and nefazodone were the drugs or drug classes considered to be involved in statin-induced rhabdomyolysis. From our data, showing that 7% of patients treated with a statin have the potential for a drug-statin interaction, it can be estimated that drug-statin interactions increase the risk for rhabdomyolysis by a factor of approximately 6. This figure corresponds well with an estimated 10-fold increase in the risk of rhabdomyolysis reported by Omar et al.,[18] confirming our findings and calculations. Statin-induced rhabdomyolysis remains a rare event, occurring in 0.04–0.2% of statin-treated patients, even in the presence of an interacting drug.[18] This is supported by the observation that none of the 2742 patients studied, including the 190 patients with a potential drug-statin interaction, had signs or symptoms of myopathy in our investigation. Despite being a rare adverse reaction, owing to the widespread use of statins and the potentially fatal outcome, statin-associated rhabdomyolysis has become an important clinical problem. This was demonstrated dramatically by the recent withdrawal of cerivastatin from the market.[30]

Our study defines several risk factors associated with the presence of a potentially critical drug-statin interaction. The individual statin chosen for treatment of dyslipidaemia is the most important one. Similar to other epidemiological studies[12,31] and published case series of patients with statin-induced rhabdomyolysis,[18] our study also demonstrates that CYP3A4 inhibitors concomitantly prescribed with simvastatin or atorvastatin (lovastatin is not marketed in Switzerland) are the most frequent combinations of potentially critical drug-statin interactions. Potential drug interactions with fluvastatin are rarer, because this drug is primarily metabolised by CYP2C9;[13,32] CYP2C9 inhibitors are less often used in patients with dyslipidaemia than CYP3A4 inhibitors.[12] For pravastatin, potential interactions seem to be even rarer than for fluvastatin, since this statin is not metabolised by CYP isoenzymes, but is glucuronidated.

Furthermore, the study shows that important additional risk factors for the appearance of potentially critical drug interactions with statins include the number of concomitant drugs a patient is prescribed and a diagnosis of heart failure and/or arrhythmias; these diagnoses are highly correlated with specific drug therapies known to interact with statins. In the case of heart failure, an important interaction is observed between some statins and digoxin, which can increase the plasma digoxin concentration by approximately 30% due to inhibition of P-gp by certain statins. This interaction is observed with P-gp substrates such as simvastatin, lovastatin and atorvastatin.[33] Regarding the narrow therapeutic range of digoxin, this interaction may be clinically relevant for the above-mentioned statins, but not with pravastatin,[34] which does not inhibit P-gp.[33,35]

The group of patients with the highest risk for potential drug-statin interactions are those with cardiac arrhythmias. In Switzerland, patients with cardiac arrhythmias are often treated with verapamil, digoxin or amiodarone, which can all interact with most statins. Verapamil inhibits both CYP3A4 and P-gp,[35,36] and amiodarone is an efficient inhibitor of several CYP isoenzymes, among them CYP3A4 and CYP2C9.[37]

The interactions between statins and fibrates or ciclosporin may be mediated by the inhibition of hepatic transporters, which are involved in the hepatic uptake of statins. Organic anion transporting polypeptide (OATP)-2/OATP-C-mediated transport has been identified not only for pravastatin,[38,39] but also for simvastatin,[38] fluvastatin,[38] atorvastatin[40] and cerivastatin.[41] Shitara et al.[41] showed that ciclosporin can inhibit hepatic uptake of cerivastatin, which was at least partly mediated by ciclosporin-induced inhibition of OATP2, suggesting that increased plasma concentrations of cerivastatin in the presence of ciclosporin are mainly due to the impairment of hepatic uptake rather than inhibition of CYP3A4.[41] The same mechanism may be responsible for the DDI with ciclosporin and pravastatin.[42] Recently, the pharmacokinetic inter-

action between gemfibrozil and pravastatin has been investigated in more detail. The increase in the pravastatin plasma concentration could be explained by a decrease in both renal clearance and hepatic uptake.[43]

As expected and as shown in previous studies,[44,45] we could identify polypharmacy as a risk factor for DDIs. In agreement with these studies, the current work also demonstrates that the risk for potentially serious DDIs increased with the increasing number of drugs used. This may be critical particularly in patients with cardiac diseases, who are generally treated with more than one drug.[46] Accordingly, we identified heart failure as one of the major risk factors associated with potential non-statin DDIs. Regarding the drugs used in heart failure, e.g. ACE inhibitors, digoxin and potassium-sparing and loop diuretics, all rank among the drugs with a high prevalence of potentially serious non-statin DDIs.

Potential non-statin interactions frequently detected in patients with heart failure were those between ACE inhibitors and potassium supplements or potassium-sparing diuretics, which is in accordance with a study of the prevalence of DDIs in the medication of medical patients at hospital discharge.[20] While the administration of potassium supplements in patients treated with ACE inhibitors is well known to be associated with hyperkalaemia,[47,48] the development of hyperkalaemia in patients treated with ACE inhibitors and low-dose spironolactone (i.e. 25–50 mg/day as recommended for the treatment of heart failure[49]) has been reported only recently.[50,51] Renal failure appears to be an additional risk factor for the development of hyperkalaemia in patients treated with ACE inhibitors, particularly when a drug-drug and/or diet-drug interaction is present.[50,52] Concomitant use of loop or thiazide diuretics may diminish the risk of hyperkalaemia associated with ACE inhibitors and potassium supplements or potassium-sparing diuretics, but we still recommend that patients treated with such combinations be followed carefully, particularly if they also have renal failure.

Another group of patients with a high prevalence of non-statin DDIs identified in our study are those with gout. Our data indicate that this is the case particularly because of a potential interaction between allopurinol and ACE inhibitors, which may increase the risk of developing an allopurinol-induced hypersensitivity syndrome.[53] Although evidence for this interaction exists only as case reports,[54-56] the clinical outcome for the allopurinol-associated hypersensitivity syndrome is potentially so serious (fatalities are reported[53,57,58]) that it may be prudent to avoid this drug combination.

Patients with psychiatric disorders, particularly depression, were also identified as a risk group for non-statin DDIs. Whereas tri- and tetracyclic antidepressants are generally not relevant inhibitors or inducers of CYP isoenzymes, this is different for selective serotonin reuptake inhibitors (SSRIs).[59] Significant inhibition of CYP isoenzymes has been described for fluvoxamine (inhibition of CYP1A2, CYP2C19 and CYP3A4), paroxetine (CYP2D6) and fluoxetine (CYP2D6, CYP1A2, CYP3A4 and CYP2C9).[59-61] For all of these SSRIs, DDIs due to CYP inhibition with clinical relevance have been described. This is important to know for physicians caring for patients with cardiovascular disease, since antidepressants are frequently prescribed in this population.[62]

None of the patients included in this study had symptoms or signs of an adverse drug effect due to a statin or non-statin DDI. Regarding other reports in the literature, where approximately 6% of patients with a critical DDI experienced adverse effects,[63,64] some adverse effects in the 190 patients with statin interactions or the 288 patients identified with a critical non-statin DDI would have been expected. However, the aim of the study was to quantify the prevalence of potential DDIs and not of adverse events. Additionally, we did not have direct access to the patient records to identify adverse clinical outcomes in association with a DDI, potentially favouring underreporting of DDI-associated adverse reactions. Moreover, the medication screened included only the drugs prescribed by the physician taking part in the study. It is possible that patients may have seen other physicians prescribing additional drugs that were unknown to the physician treating the patient for dyslipidaemia. Therefore, the prevalence of potential statin or non-statin DDIs in this population may be even higher than the one assessed in this study.

Conclusions

In conclusion, our study shows that CYP3A4 inhibitors are the most frequent cause of potential drug interactions with statins. Although statin-induced rhabdomyolysis is a rare event even in patients with a drug-statin interaction, the possibly severe outcome of rhabdomyolysis favours the concept that potentially interacting drug-statin combinations should be avoided or patients should be monitored more closely. It is therefore important to teach clinicians about the most frequently observed drug-statin interactions and how these interactions can be avoided.

Additionally, serious non-statin DDIs are common in patients with dyslipidaemia, mostly because of co-morbidities for which they are treated concomitantly with numerous additional drugs. Further research is necessary to assess the clinical significance of our findings, e.g. the incidence and clinical significance of adverse effects in patients with potentially serious DDIs.

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