Importance of Drug-Drug Interactions in Drug Safety

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Table of Contents

Summary

Drug-drug interactions (DDIs) are a well known risk factor for adverse drug reactions (ADR). DDIs became an important issue in drug safety in the last few years after the withdrawal of effective and commercially important drugs such as terfenadine, astemizole, mibefradil, cerivastatin, and in the US and UK cisapride. After the world-wide withdrawal of cerivastatin due to an increased incidence of potentially fatal rhabdomyolysis seen in association with interacting drugs, the evaluate of the individual safety profiles of the remaining available statins was mandatory, particularly since their pharmacokinetic (PK) profiles are different.

Statins are a cornerstone in the treatment of dyslipidemic patients, but these patients are concomitantly treated with a variety of additional drugs. In this thesis the prevalence of potential drug-statin interactions and non-statin DDIs in an outpatient adult population with dyslipidemia in different geographical regions in Switzerland was explored in a crossectional investigation. Risk factors and regional differences were analyzed in order to identify the patients carrying the highest risk for potential DDIs. Potential DDIs were analyzed according to the statin used, additional diagnoses, co-medication, clinical speciality and location of the practitioners. Data of patients with dyslipidemia treated with a statins were collected from practitioners from different parts of Switzerland. The medication was screened for potentially harmful DDIs with statins or other drugs using an interactive electronic drug interaction program. The ambulatory statin-treated, mainly elderly patients had approximately 3 diagnoses and 5 drugs prescribed per patient. Of the patients screened, 15% had potentially severe DDIs, 7% had potentially harmful drug-statin interactions, and 10% had potentially critical non-statin DDIs. Drugs interacting with statins were identified to be mainly CYP3A4-inhibitors, followed by digoxin, fibrates, and ciclosporin. More potential drug-statin interactions were found for simvastatin and atorvastatin than for fluvastatin or pravastatin. While for drug-statin interactions predominantly pharmacokinetic interactions were identified, non-statin DDIs were mainly pharmacodynamic interactions between cardiovascular drugs. The number of drugs per patient and a diagnosis of arrhythmia or heart failure were factors associated with an increased risk for DDIs. Patients were screened from the German, French, and Italian part of Switzerland. The distribution of the practitioners participating and the prevalence of potential DDIs were similar among geographic regions. The prescribing pattern, however, differed slightly. Identified risk factors for drug-statin interactions were the number of drugs prescribed, a diagnosis of arrhythmias or heart failure. The number of diagnoses and subsequently the number of drugs prescribed increased with age. In accordance with the fact that polypharmacy is a strong risk factor for DDIs, the prevalence of DDIs increased with age, particularly for patients ≥ 70 years. For non-statin DDI additional risk factors were male sex and a diagnosis of cerebrovascular disease. The French speaking part of Switzerland was associated with an increased risk for drug-statin interactions. They prescribed the same amount of drug combinations potentially leading to DDIs, although significantly less drugs per patient in a younger study population were used. The exact reasons for the increased risk for drug-statin interactions in the French part are mainly unknown and could not be fully explained by the data available from this study.

Concluding, potentially harmful drug combinations were common in patients with dyslipidemia due to drug treatment of their co-morbidities. CYP3A4 inhibitors were the most frequent cause for potential

interactions with statins. Despite the fact that drug-statin interactions may increase the risk of statin-induced rhabdomyolysis by 6-10-fold, it remains a rare event, even in the presence of an interacting drug. Nevertheless, due to the widespread use of statins and the potentially fatal outcome, statin-associated rhabdomyolysis will remain an important clinical problem, and action should be taken to minimize the risk.

In general, polymedication should be reduced where possible to an aim of ≤ 6 drugs per patient with dyslipidemia. Special attention should be drawn to patients with a higher risk for potential DDIs and drug-statin interactions i.e. polymorbid and elderly patients with polymedication, and patients with a diagnosis of arrhythmia or heart failure. If a potentially harmful drug-statin combination can not be avoided, the patients should be monitored very closely.

In this thesis the true clinical significance of potential DDIs was not investigated. In the literature, the occurrence of symptomatic DDIs was shown to be up to 10%. The incidence and clinical significance of adverse effects in patients with potentially serious DDIs among statin users should be elucidated. An ongoing diploma thesis is therefore investigating the importance of drug-statin interactions among all statin-associated ADRs spontaneously reported to the Swiss National Pharmacovigilance Center (PVC), Swissmedic.

In the past, DDIs, drug-herb or drug-food interactions had mainly been detected by publications of case reports and signals from national pharmacovigilance centers. These reports have led to the close investigation of the mechanism of the DDIs, to the identification of potential risk factors, or to the withdrawal from the market, as mentioned above. Therefore, two cases of adverse DDIs from the drug information unit (Klinisch-pharmakologischer Service, [KLIPS]) and regional pharmacovigilance center (RPVC) of the Clinic of Pharmacology, University Hospital Basel, were published, in order to generate signals of vitally important safety concerns for other healthcare providers and scientist.

A case of irregular bleeding during oral contraceptive (OC) treatment in combination with St. John's wort (SJW), which had been a query to KLIPS, was published. An overview of potentially hazardous SJW drug-herb interactions (cellular rejection of pancreas- / kidney- as well as heart transplants with ciclosporin; rise of the international normalized ratio (INR) with oral anticoagulants; break-through through bleeding with OCs; reduction of plasma concentration of digoxin, indinavir, amitriptyline and theophylline) were presented, and the underlying mechanisms of the SJW-OC interaction were discussed. Over-the-counter preparations of SJW are widely used as 'natural' herbal medicine alternatively to traditional antidepressants due to their favorable safety profile compared to conventional prescribed antidepressants. However, the risk of untoward adverse effects and/or interactions with other compounds have been underestimated or were not widely recognized.

In a second case report, the objective was to report the occurrence of a so far not well recognized and poorly documented interaction between lithium and rofecoxib. Only a few cases of reversible lithium intoxication as a result of a possible DDI with a COX-2 selective inhibitor have so far been reported. The mechanism of the interaction between lithium and COX-2 selective inhibitors were discussed, and possible risk factors were postulated. It was concluded that the co-administration of rofecoxib and lithium may result in life-threatening lithium intoxication, especially in patients with a pre-existing decrease in renal function and/or decreased intravascular volume.

Aims of the thesis

The **major** goal of this thesis was to elucidate the possible importance of drug-drug interactions (DDIs) as a contributing factor towards drug safety.

The **main** focus of this thesis was to identify clinically relevant potential DDIs in ambulatory, hyperlipidemic patients treated with a statin in Switzerland, and to assess the prevalence of drug-statin interactions as well as non-statin DDIs. The statins were chosen as the drug group for investigation because DDIs with statins had become a world-wide health issue following the withdrawal of cerivastatin. However, the members of the statin family have different metabolic and pharmacokinetic profiles. These differences highlight the potential for different DDI-profiles and risk for interactions within a drug group. Data from Ireland have shown a relatively high co-prescribing of potentially interacting drugs with statins. Differences in prescribing habits among countries and regions, however, may influence the occurrence of potential DDIs.

In order to contribute to the issues mentioned above, a crossectional investigation was performed with practitioners who provided the relevant patient data and drug profiles on dyslipidemic patients treated with a statin.

The following questions were assessed during this investigation:

- Is there a differences in the prevalence of potential drug-statin interactions and non-statin DDIs across the spectrum of prescribed statins?
- Is any of the statins used more susceptible to potentially dangerous DDIs?
- Which are identifiable risk factors for potential DDIs in this population? Postulated possible risk factors were concomitant illnesses, additional drug treatments, the medical speciality of the attending practitioner, living in a specific part of Switzerland, number of diagnoses, or age.
- Are practitioners who prescribe less drug-statin interactions generally more aware of and avoid the prescription of drug combinations potentially leading to DDIs?

The answer to these questions could help to identify those patients that might be at higher risk for clinically relevant ADRs due to DDIs (such as rhabdomyolysis in the case of statins) to which more attention should be drawn.

A **second** focus of the thesis was to illustrate the role of a drug information unit and RPVC in investigating DDIs which were initially raised as query to KLIPS and which appeared to be clinically relevant DDIs. In addition to reassure the healthcare provider who raised the query, two case reports of the observed, potentially important safety concerns were published in order to generate a signal of a safety-issue and increase the awareness of other care providers and scientists for potentially harmful DDIs.

Abbreviations

ACE	Angiotensin-converting enzyme
ADE	Adverse drug event
ADR	Adverse drug reaction
ALAT	Alanin aminotransferase
ASAT	Aspartat aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BZD	Benzodiazepine
CAR	Constitutive androstan receptor
CK	Creatine kinase
c_{max}	Maximal serum/plasma concentration
CNS	Central nervous system
COX	Cyclooxygenase
CYP	Cytochrome P-450 isoenzyme
DDI	Drug-drug interaction
DEI	Drug-excipient interaction
DNA	Deoxyribonucleic acid
e.g.	For example
EM	Extensive metabolizer
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration, USA
FSH	Follicle stimulating hormone
GABA	Gamma-aminobutyric acid
GSH	Reduced glutathion
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
i.e.	it est (this is, these are)
i.v.	Intravenous
ICU	Intensive care unit
IKS	Interkantonale Kontrollstelle für Heilmittel (intercantonal board of drug control) Switzerland
INR	International normalized ratio
KLIPS	Klinisch-pharmakologischer Service (clinical pharmacological service)
LDL	Low density lipoprotein
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MDR	Multi-drug resistance
MRP	Multi-drug resistance associated protein
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OC	Oral contraceptive
OCT	Organic cation transporter
PDA	Personal digital assistance
P-gp	P-glycoprotein
PK	Pharmacokinetic
PM	Poor metabolizer
PRX	Pregnane X receptor
PT	Prothrombin time
PV	Pharmacovigilance
PVC	Pharmacovigilance center
RPVC	Regional pharmacovigilance center
SANZ	Schweizerische Arzneimittel-Nebenwirkungs-Zentrale (Swiss center for reporting adverse drug reactions)

SGCI	Schweizerische Gesellschaft für Chemische Industrie (Swiss association for chemical industry)
SJW	St. John's wort
SSRI	Selective serotonin reuptake inhibitors
syn.	Synonym
TDM	Therapeutic drug monitoring
Tdp	Torsade de pointes
UDP-GT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 Drug safety

1.1.1 Background

Drug safety comprises the evidence of the innocuousness of a drug and the quality of the product, including the proof of its effectiveness in a given indication. No drug is completely free of any risk. The safety of a drug is interpreted as the acceptance of a certain risk for harm, or the probability of an adverse drug event (ADE). For approval, the drug authorities can accept a positive risk-benefit balance from the data of preclinical studies and the clinical trials phases I-III *(Hartmann, 2003)*. Yet, the safety record of clinical trials phase I-III provides only limited possibilities to observe adverse drug reactions (ADRs). Limitations of pre-approval clinical trials are the relatively small number of subjects and patients studied (3000-5000 subjects), the narrow study population (children, elderly, and women were often excluded), the narrow indication which does not represent the evolving uses in every day practice, and the short duration (1-3 years, preventing to see ADR with a long latency). According to the 'rule of three', to detect for sure a rare ADR (incidence 0.01-0.1%; i.e. 1 case in 1000-10'000 subjects treated) at least 3000-30'000 patients must be studied. After approval, further investigations on drug safety are therefore necessary, including post-marketing trials (clinical trials phase IV) and post-marketing surveillance studies, national and international spontaneous adverse reaction reporting, pharmacoepidemiological studies (case-control-studies; cohort studies such as population-oriented Hospital Drug Monitoring and Medical Record Linkage or drug-oriented Prescription Event Monitoring; descriptive studies such as case series and cohort studies without control). Data collections for other purposes, such as routine statistics or from prescriptions-outcome databases, may also be used.

The post-approval reevaluation of drug safety lead to withdrawal of up to 10% of approved new drug entities (shown for the years 1972-1994). Withdrawal occurred mainly during the first few years after launching. In 50% of the safety related withdrawals world-wide it occurred after less than 5 years, and in 31% after less than 2 years *(Rägo, 2002)*. Another, for a long time ignored and neglected aspect of drug safety is the counterfeit of pharmaceutical products, estimated to be 5% of the world trade. It may lead to a great health risk as there is complete absence of quality control of these products. Pharmaceutical counterfeit may contain the correct ingredient in incorrect quantities, an incorrect active compound with toxic effect, or no active drug. Examples therefore are 100 cases of fatal kidney failure in children following ingestion of a cough syrup heavily contaminated by antifreeze in Haiti, and the vaccination of 60'000-80'000 children with inactive vaccine in Niger which may have lead to more than 100 fatal infections. Although the majority of the cases come from the South Eastern and the Western Pacific, and Africa, approximately 15% of the reports come also from North America and Europe *(ten Ham, 2003)*. A recent report from the national pharmacovigilance center of Switzerland, Swissmedic, however, warned about the dramatically increasing number of counterfeit due to uncontrollable internet trading *(dgy, 2004)*.

1.1.2 History of drug safety monitoring

The first activities in drug safety date back to 1893 when the first commission was initiated that collected notifications about side effects, and already in 1906, the US Federal Food and Drug Act required that pharmaceuticals should be 'pure' and 'free of any contamination' *(Rägo, 2002)*. In general, the development of systematic pharmacovigilance (PV) has mainly been driven by drug-catastrophes with a huge echo in the media. They led to regulatory or legal adjustments and to the introduction of surveillance-systems. Milestones in drug surveillance started in 1939, after 107 lethal cases due to diethylenglycol as a solubilizer for sulphanilamides. Subsequently the law was modified requiring toxicological studies. The whole ethos of drug safety monitoring or PV as it is known today, however, came into being through the tragedy of thalidomide. Between 1959 and 1962, the thalidomide disaster produced an estimated 10,000 deformed children born in those countries in which the drug was taken by women in the early stages of pregnancy. The thalidomide tragedy lead to the introduction of national and international survey systems for ADR in 1961. In 1962, the Kefauver-Harrise-Amendment was launched in the USA, requiring the proof of safety and efficacy before marketing a drug. A further milestone was the start of the 'Yellow Cards' system (spontaneous ADR reporting) in England in 1964, which is still in use today. In 1968, The World Health Organization (WHO) set up an International Drug Monitoring Programme, which has been carried out by the Uppsala Monitoring Centre (UMC) in Sweden since 1978 and which has become the cornerstone of international drug safety today. In 1969, the occurrence of the syndrome of subacute myelo-optico neuropathy (SMON) after clioquinol in Japan *(Egashira & Matsuyama, 1982; Konagaya et al., 2004)* lead to the attention of ethnic susceptibilities of ADR and pharmacogenetics in drug safety. The oculo-mucocutan syndrome under practotol in 1975 lead to the introduction of 'Prescription Event Monitoring' in England and to the registration of all ADEs in clinical trials *(Rawson et al., 1990)*. After the appearance of blood dyscrasias and gastrointestinal bleedings under the treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in the 1980 ies, the first steps towards pharmacoepidemiology were undertaken. Due to the need to harmonize the world-wide activities in the field of drug safety, in 1990 the International Committee for Harmonisation (ICH) initiated to elaborate guidelines for drug safety. In 1995, the European Medicines Evaluation Agency (EMEA) started its activities as European drug regulation authority and launched binding guidelines in PV for the members of the European Union (EU) such as the 'Rapid-Alert' System (RAS) in 1996. Today, PV consists of a world-wide network of regional and national pharmacovigilance centers (PVC), PV departments of drug companies and the UMC. The UMC is responsible for the collection of data about ADR from around the world, particularly from 72 countries which joined the WHO Drug Monitoring Program. From the common centralized database with over 3 million case reports, new ADR signals are identified and analyzed *(Hartmann, 2003; Rägo, 2002; UMC, 2003)*. A problem with spontaneous reporting remains, which is underreporting: only less than 10% of all serious and 2-4% of non-serious ADRs are reported *(Einarson, 1993; Smith et al., 1996)*

1.1.3 Spontaneous adverse drug reaction reporting system in Switzerland

In Switzerland, only in 1979 the spontaneous adverse drug reaction reporting center (Schweizerische Arzneimittel-Nebenwirkungs-Zentrale; SANZ), was initialized through the initiative of the Swiss Medical

Association (FMH) and the Swiss association for chemical industry (SGCI). ADR reports from medical doctors were assessed and sent to the respective pharmaceutical companies by SANZ. At that time, the former drug regulation authority of Switzerland, the Interkantonale Kontrollstelle für Heilmittel (IKS), did not participate in the project. The effectiveness and competence of the SANZ was very high and acceptance was very good among healthcare providers, the pharmaceutical industry, the Swiss Drug Regulation Authority, and scientists. After ten years, in 1991, SANZ and IKS signed an agreement of collaboration on a scientific basis and for the exchange of data in the interest of uniformity within PV. In the following years, SANZ expanded its collaborations to build up a hemovigilance (1995), and with the division of vaccinations of the Swiss federal office of healthcare (1999) *(Giger, 2001)*. In 2000, the Swiss national assembly and the council of states passed a new federal law on drugs and medical devices (Heilmittelgesetz, HMG) *(Anonymous, 2000a)*. It included an obligation of reporting ADR for healthcare providers and companies (HMG, article 59) and integrated the PV into the new federal institute of drugs (HMG, article 58) called Swissmedic. IKS was completely integrated into the new institute. SANZ, however, was obliged to renounce the funding of the pharmaceutical industry and was tought to become one of the regional pharmacovigilance centers (RPVC) together with the divisions of pharmacology and drug information units of the University hospitals of Basel, Bern, Geneva, Lausanne and Zürich and since 2002 Lugano. The foundation board of SANZ did not support this development and SANZ was closed in June 2001 *(Giger, 2001)*.

The RPVCs are responsible for data entry, coding, writing narratives and assessments, and electronical transmission of ADR reports to the Swiss PVC of Swissmedic. Swissmedic collects all national ADR-reports from RPVCs and pharmaceutical companies and transmits them to the collaborating sites (WHO Collaboration Center UMC, pharmaceutical company) as shown in Figure 1. The Swiss PVC as well as UMC detect national and international signals, and communicate their findings to the collaborating institutions.

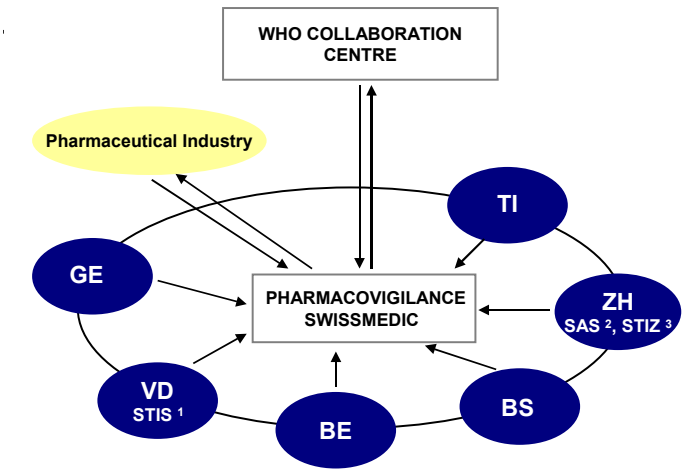

Figure 1 *Organization of PV in Switzerland 2003 adapted from (Morant, 2004)*. Dark circles = regional PVC; BE = Bern; BS = Basel; GE = Geneva; TI = Lugano; VD = Lausanne; ZH = Zürich; [1] STIS = Swiss teratogen information service, drug risk in pregnancy; [2] SAS = foundation for drug safety, systematic recording of ADR in an university hospital setting; [3] STIZ = Swiss toxicological information center

1.1.4 Importance of drug-drug interactions in drug safety

In recent years, effective and commercially important drugs have been withdrawn from the market because of preventable, severe adverse DDIs, which had been detected and had contributed to drug safety only after launching the drug. In early 1997, the second generation H1-antagonist terfenadine, known for dose-dependent QT interval prolonging properties causing dysrhythmias such as torsade de pointes (Tdp), was withdrawn for the US market *(Gottlieb, 1999)*. The withdrawal of astemizole, showing similar properties as terfenadine, followed in 1999 *(Gottlieb, 1999)*. Although not confirmed by the manufacturers, DDIs leading to increased terfenadine plasma concentrations by azole antifungals such as itraconazole probably played a role *(Pohjola-Sintonen et al., 1993)*. The novel calcium antagonist mibefradil, a substrate of cytochrome P-450 (CYP) 3A4 and inhibitor of CYP3A4 and CYP2D6, was voluntarily withdrawn by Roche in June 1998 due to serious pharmacokinetic and pharmacodynamic interactions (which also contributed to a trend of increased mortality with mibefradil). Although the company had changed the labelling including a warning from the combination with other drugs such as astemizole, cisapride, terfenadine, lovastatin and simvastatin *(Krayenbühl et al., 1999; SoRelle, 1998; Welker et al., 1998)*, mibefradil was continued to be combined with these drugs leading to harmful events. Cisapride, a cholinergic-gastrokinetic drug with QT interval prolongation properties leading to Tdp and ventricular tachycardia was withdrawn form the UK and US marked in the summer of 2000 *(Griffin, 2000)*. Contributing factors were the dose dependency of the ADR occurring with higher dosage forms and with enzyme inhibiting drugs like macrolide antibiotics, human immunodeficiency virus (HIV) protease inhibitors and azole antifungals *(Anonymous, 2000b; Hoover et al., 1996; 2000)*. In August 2001, cerivastatin was voluntarily withdrawn world-wide because of disproportionate numbers of reports of rhabdomyolysis-associated deaths (10 to 80 times higher than for other statins), which were possibly related to serious drug interactions, particularly with gemfibrozil *(Charatan, 2001; Furberg & Pitt, 2001; Marwick, 2003)*. Although the dangers of the potential harmful interactions were communicated in most of the above described cases, labelmodifications and traditional risk communication strategies like 'dear health care professional' letters were ineffective means to sufficiently communicate risk with the intention to change behavior. The reasons for this are not understood. Possible explanations and questions were whether the prescribers received and read the messages, whether they understood and believed the information, and whether they incorporated the knowledge into practice *(Huang et al., 2004)*.

1.2 Adverse drug reactions

1.2.1 Epidemiology of adverse drug reactions

Despite efforts to reduce the incidence of medication-related adverse events, morbidity and mortality from drug-induced disease continue to be high and represent an important public health problem. They may be so severe that patients require hospitalization and some of these patients die. Although drugs with higher selectivity are developed, they are not completely free of ADRs. *(Calis & Young, 2001)*. ADRs can be idiosyncratic and unpredictable (type B reactions, 'bizarre', not dose-dependent, high mortality, genetic

abnormalities play a role, 10-20% of all ADRs), others, however, can be predicted based on knowledge of a drug's clinical pharmacology (type A reactions, dose-dependent, toxic, known or unknown abnormal pharmacological effects, 60-80% of all ADRs) *(Rawlins, 1981)*. Extension of this classification of Rawlins and Thompson include type C (chemical), D (delayed) and E (end of treatment) reactions, however this is not universally accepted. Further ADR may be classified following immune-mediated hypersensitivity reactions to drugs, or simply according to the onset (acute, sub-acute, latent) or for the severity (mild, moderate, severe) of the ADR *(Calis & Young, 2001)*. Clinically relevant ADR may be symptomatic, or relevant abnormalities of laboratory values may remain asymptomatic *(Fattinger et al., 2000)*. Ineffectiveness is also an unintended and potentially harmful response to a drug. Approximately half of medicine-related hospital admissions are due to ineffectiveness, which can be secondary to inappropriate use (wrong dose, wrong duration, wrong indication), but can also be a warning sing in PV, e.g. an interaction or a pharmaceutical defect, a counterfeit product, and tolerance or resistance development *(Meyboom et al., 2000)*.

The overall incidence of drug-related complications in ambulatory patients, including ADR, is approximately 20% *(Gandhi et al., 2000)*. In an outpatient population > 65 years of age, 10% ADR were found, of which another 10% (0.7% of the studied population) were sent to hospital *(Chrischilles et al., 1992)*. ADRs are cause of 3-15% of hospitalizations *(Bates et al., 1995; Beard, 1992; Einarson, 1993; Fattinger et al., 2000; Lazarou et al., 1998; Moore et al., 1998; Pouyanne et al., 2000; Prince et al., 1992)*. Reasons for the variation of the rates may be in part the methods of detection (ADR-definition, computerized or manual surveillance) and case ascertainment (all hospitalized patients, focussed hospital unit surveillance) *(Classen et al., 1997)*. During hospitalization, the ADR incidence may rise up to 11-35%, according to methodology and the definitions of ADR *(Davis, 1977; Fattinger et al., 2000; Lazarou et al., 1998; Schlienger et al., 1999)*. Approximately 1-4% of the patients experience a serious ADR *(Classen et al., 1997; Fattinger et al., 2000; Lazarou et al., 1998; Schlienger et al., 1999)*. Having an ADR increases the risk of death by 2-fold *(Classen et al., 1997)*. Fatality was reported to be 1.4-5% in patients, which were hospitalized due to an ADR, or who experienced an ADR during hospitalization *(Einarson, 1993; Fattinger et al., 2000; Lazarou et al., 1998)*. ADRs represent relevant additional health costs by hospitalization itself, increased time spent in an intensive care unit (ICU) and prolongation of hospital stay (by 1.2-2.2 days, or even more for severe ADEs) *(Bates et al., 1997; Classen et al., 1997; Fattinger et al., 2000; Moore et al., 1998)*. For Switzerland, it was estimated that the direct consequences of ADRs would cost 6650.- SFr per case and overall about 70-100 million SFr per year *(Lepori et al., 1999)*. An estimated 30-60% of ADRs, mainly type A reactions, were considered to be potentially preventable *(Bates et al., 1995; Classen et al., 1997; Dartnell et al., 1996; Evans et al., 1994; Lazarou et al., 1998; Leape et al., 1991)*. Of 50% of ADRs considered to be potentially preventable, 42% were attributed to missed dose adjustment in patients with impaired renal function, 1.5% to known drug allergies of the patient, 1% to medication errors, and 4.6% to known DDIs *(Classen et al., 1997)*.

Besides ADR, other medication related events may occur and have an impact on overall safety of a drug. In combination, they are often studied as ADE, i.e. all injuries resulting from a drug use, including medication errors such as errors in prescribing, dispensing, patient adherence, monitoring, and ADR not related to an error *(Bates et al., 1995; Gurwitz et al., 2000; Leape et al., 1995; Leape et al., 1999)*. A recent study with outpatients found a rate of 50 ADE in 1000 patient years, of which 27.6% were preventable *(Gurwitz et al., 2003)*. Reasons for preventability were inadequate patient monitoring by health care

providers (36.6%), prescription error (wrong medication / wrong indication; 27.1%), wrong dose (24.0%), patient non-compliance (21.1%), and in 13.3% established DDIs. In a study in Switzerland, it was shown that patient mistakes as cause of hospitalization due to ADE are relatively rare *(Lepori et al., 1999)*. In this study, a high percentage of the ADR were type A reactions, and therefore predictable and potentially preventable. The majority of ADE were iatrogenic (88%) and were caused by overdose, wrong indication, or interaction. As a large amount of ADRs and ADEs are preventable, more attention should be addressed to prevention management.

1.2.2 Reasons and risk factors for adverse reactions

Known risk factors predisposing for clinically relevant ADRs are gender, age, polypharmacy and average length of a hospital stay *(Classen et al., 1997; Fattinger et al., 2000; Kando et al., 1995; Lazarou et al., 1998)*. Other factors include dose, pharmaceutical variation in drug formulation, pharmacokinetic (absorption, distribution, metabolism, excretion) or pharmacodynamic abnormalities, as well as DDIs *(Pirmohamed et al., 1998)*. Although older patients experience a disproportionate large number of ADRs, chronological age as true independent risk factor has been debated *(Gurwitz & Avorn, 1991)*. Sophisticated studies considering all relevant aspects of aging are missing. Age is possibly rather an indicator of altered pharmacokinetics in the elderly (altered volume of distribution due to higher fat content, impaired metabolism and excretion due to impaired liver and renal function) leading to relative overdosing when administering standard doses as proposed for the usually studied population in clinical trials (dysfunctional prescribing). Elderly may also be more or less sensitive to pharmacological effects of drugs, or start from another 'baseline value' for a certain drug effect. Elderly patients have more diagnosis and the number of diagnoses is correlated with the number of drugs prescribed *(Gurwitz & Avorn, 1991)*. Other factors proposed to have an effect on ADR rate are renal function, hepatic function, alcoholism, smoking, drug abuse and severity of underlying illness *(Lazarou et al., 1998)*. Concomitant host disease may also influence the susceptibility to ADR, as has been shown for HIV-disease, *(Koopmans et al., 1995; van der Ven et al., 1991)*.

Variation in genes for drug-metabolizing enzymes, drug receptors, and drug transporters have been associated with individual variability in the efficacy and toxicity of drugs. Pharmacogenetic studies have revealed genetic polymorphisms in different enzymatic systems and patient groups of poor (PM) or extensive metabolizers (EM) for certain enzymes were identified. Accordingly, these patients show differing pharmacokinetic profiles for substrate drugs of the respective enzymes. Increased or decreased metabolism or other enzymatic activities can change the concentrations of a drug as well as those of its active, inactive or toxic metabolites, which can lead to unexpected drug effects like hemolysis in glucose-6-phosphate dehydrogenase deficiency. Polymorphism in receptors may alter clinical response and frequency of ADRs (e.g. β-Blocker response in asthma patients). Consequently, genetic polymorphisms have an impact on the safety profile of a drug in the respective patient groups. In general, PM will be relatively overdosed and be at higher risk for drug toxicity. In case of a pro-drug, PM will be relatively underdosed and may be considered as non-responder do to lack of effect. The debrisoquin polymorphism of CYP2D6 (5-10% PM, 1-10% ultra-rapid metabolizers) is one of the best studied polymorphic genes of pharmacological interest. Other known polymorphic enzymes are CYP2C9 (14-28% PM), CYP2C19 (3-6% whites, 8-23% asians), dihydropyrimidine

dehydrogenase (0.1% PM, relevant for fluorouracil toxicity), N-aceyltransferase (1.5% PM, prolonged apnoea under succinylcholine), N-aceyltransferase (40-70% whites and 10-20% asians are PM), thiopurinmethyl transferase (0.3% PM, relevant for mercaptopurine and azathioprine toxicity), and uridine diphosphate glucuronosyltransferase (UDP-GT) (10-15% PM). Other genetic polymorphisms regarding multidrug resistance gene MDR1 (syn.: P-gp; 24%) and LQT 1-5 mutations on 5 genes coding for cardiac ion channels (long-QT syndrome, leading to sudden cardiac death) *(Meyer, 2000)*. Genetically determined alterations in drug metabolizing enzymes can predispose to both pharmacological and idiosyncratic toxicity *(Park et al., 1995)*. Single gene defects account for only a minority of ADRs. For most ADR, particularly the idiosyncratic ones, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors *(Park et al., 1995; Pirmohamed et al., 1994)*.

1.3 Interactions

An interaction occurs when the effects of one drug are changed by the presence of another drug, food, drink or environmental chemical agent. The outcome can be harmful if the interaction causes an increased toxicity of the drug. However, the reduction in efficacy due to an interaction may be just as harmful as an increase (e.g. decreased anticoagulation from warfarin when combined with an inducer). While these interactions are unwanted and represent adverse and undesirable drug reactions, others can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics in order to achieve a better antihypertensive effect. Drug interactions do not include physico-chemical reactions in mixtures for intravenous (i.v.) administration, or for interferences for drugs with chemical assays with body fluids, for which the term 'pharmaceutical incompatibilities' is more appropriate. Drug interactions may be similar within the same group of drugs, however they may also be different within individual drugs within the same group (e.g. warfarin versus phenprocoumon; simvastatin versus pravastatin) and therefore interactions may not be extrapolated uncritically to all members of the same group *(Stockley, 2002)*.

1.3.1 Epidemiology and clinical relevance of drug-drug interactions

DDIs may only be theoretical or clinically trivial, or they may become clinical relevant and may even lead to hospitalization or death. The prevalence of potential clinically important DDIs varies tremendously and is described to be 4.7%-88% *(Bjorkman et al., 2002; Gronroos et al., 1997; Herr et al., 1992; Ishikura & Ishizuka, 1983; Jankel & Speedie, 1990; Lipton et al., 1992; Shinn et al., 1983; Smith et al., 1966)*. In outpatients, prevalences of 25-27% *(Bergendal et al., 1995; Costa, 1991; Kurfees & Dotson, 1987)* or up to 46% in elderly outpatients *(Bjorkman et al., 2002)* have been reported. Differences in study designs, methodologies, reference sources to categorize DDI, denominator, definitions of clinical significance, and study population (e.g. elderly, nursing homes, emergency rooms) contribute to the considerable variation in reported prevalences. Not all of these interactions may lead to actual clinical problems *(Mitchell et al., 1979)*. The percentage of patients which actually experience problems may only be 1% *(Herr et al., 1992; Puckett & Visconti, 1971)* up to 11% *(Haumschild et al., 1987; Jankel & Speedie, 1990)* of the patients with potential

DDIs. Clinical relevance may also be judged differently. While pharmacists detected 39.2-64.4% moderately severe to severe potential DDI in three different ward types, only in 2-22% of the cases the interactions were found to be clinically relevant by the physicians *(Wiltink, 1998)*. DDI, however has been identified as a leading cause for ADR *(Borda et al., 1968; Schneider et al., 1992)*.

ADR as a reason for hospital admission was shown to have a prevalence of 1.1 - 18.3% in 9 selected studies. Of the ADR-related hospital admissions, 1.3 - 21.2%, or up to 2.8% of all hospital admissions, were judged to be due to a DDI. However, none of the studies analyzed was free of methodological flaws, and the reasons for the DDI were not elucidated (e.g. improper use, avoidability) *(Jankel & Fitterman, 1993)*. The same authors found only a few studies attempting to determine whether patients actually experienced symptoms that could be attributed to the DDI. They found 0-10% symptomatic patients due to DDIs *(Jankel & Speedie, 1990)*, which corresponds to 5% found by others *(Anonymous, 1972)*. Recent studies in different countries analyzed the prevalence of hospitalization associated with adverse DDIs. Among patients visiting an Emergency Department in Italy, 4% experienced an ADE, of which another 4% were due to a DDI *(Raschetti et al., 1999)*. The ADE lead to hospitalization in 19% of all patients who had suffered an ADE, of which 11% were caused by a DDI. The incidence of DDI-associated hospital admission per 100 admissions was 0.27%. In a study in Switzerland, 21% of ADR-associated hospital admissions (6.4% of all admissions) were caused by a DDI (ca. 1.3% of all admissions) *(Lepori et al., 1999)*. A study from Australia showed that 4.4% of drug-related hospital admissions were due to DDIs *(Stanton et al., 1994)*. In Germany, 56% of patients with coronary heart disease or chronic obstructive lung disease had a potential interaction at hospital admission *(Kohler et al., 2000)*. A mean of 2.8 interactions per patient were reported. Of these, 70% were judged to demand clinical attention, and 1-2% were life threatening. In these studies, drug classes that were often involved in DDI identified at hospital admission were angiotensin-converting enzyme (ACE) inhibitors, kaliuretic diuretics, anticoagulants, aggregation inhibitors, NSAIDs, and digitalis glycosides *(Kohler et al., 2000; Lepori et al., 1999)*.

Increased risk for clinically relevant DDIs is associated with age *(Herr et al., 1992)*. However, age itself does not seem to be an independent predictor of the incidence of potential DDIs, as it correlates with the number of drugs prescribed, which in turn has been shown to increase the risk for experiencing DDIs *(Heininger-Rothbucher et al., 2001; Kohler et al., 2000)*. The risk for DDIs increases exponentially with the number of drugs prescribed *(Cadieux, 1989)*. The number of prescribing physicians is another risk factor for DDIs, whereas a single primary care physician or the use of a single dispensing pharmacy decreases the risk, particularly among certain drug groups such as cardiovascular and psychotropic drugs *(Tamblyn et al., 1996)*. A consistent finding is, that more dependent, institutionalized patients score highly for potential DDIs. Reasons therefore may be more severe polymorbidity, or over-prescribing by the physicians *(Seymour & Routledge, 1998)*. As the number of drugs is an important risk factor for DDI, patients with disease states for multiple therapy such as HIV, tuberculosis, cancer, and others, may be at risk for potential DDIs. Other risk factors for specific DDIs may be related to individual drugs or treatments, as has been shown for women and patients with hepatic failure for DDIs with cerivastatin *(Davidson, 2002)*.

1.3.2 Mechanisms of interactions

Mechanistically, interactions are generally divided into pharmacodynamic (PD) and PK drug interactions. Among PK interactions, the CYPs in the liver and gut wall, as well as the drug transporter P-gp play a predominant role, but also other enzymes and transport systems may be involved. Interactions may alternatively be classified based on their severity (minor, i.e. limited clinical consequences, no change in therapy; moderate, i.e. toxicity known but overcome with close monitoring; severe, i.e. serious toxicity requiring change in dose, drug, or dosing schedule) and their probability to be caused by a drug (established, probable, suspected, possible, or unlikely). The probability is generally established by documentation of similar interactions in clinical trials, case reports, pre-clinical studies, anecdotes, and by *in vitro* studies. Interactions may additionally be classified according to the time course of their occurrence (immediately, delayed) *(Alfaro & Piscitelli, 2001; Stockley, 2002)*

1.3.2.1 Pharmacodynamic interactions

The effects of one drug may be changed by the presence of another drug at its site of actions. The drugs may directly compete for receptors (competition for receptor binding; agonist-antagonist reaction) like opiate μ-receptor agonist and partial antagonist. Sometimes they interact more indirectly interfering with physiological mechanisms such as diuretics and ACE-inhibitors in antihypertensive therapy. Antagonism or opposing interactions (e.g. warfarin and vitamin K; levodopa and neuroleptic drugs) may impede pharmacologic response to a treatment. The effects of two drugs may also just be additiv effects (syn.: potentiation) leading to increased toxicity, like additive QT interval prolongation, additive anticholinergic effects, serotonin syndrome with two serotoninergic drugs, additive central nervous system (CNS) depression with alcohol and CNS depressive drugs. Although they are not interactions in the sense of the definition, they may be equally harmful and should therefore be considered. Also disturbances in fluid and electrolyte balance may result in increased susceptibility to a drug like for example digoxin and K^+-depletion through thiazide and loop diuretics, or in altered pharmacokinetics such as decreased Li^+-clearance with thiazide diuretics, predisposing the patient for more ADR *(Stockley, 2002)*.

1.3.2.2 Pharmacokinetic interactions

1.3.2.2.1 Absorption

Numerous mechanisms can affect drug absorption. They include a change in gastric pH influencing the passive diffusion, which depends upon the extent of non-ionized lipid-soluble form of the drug (e.g. antacids and ketoconazole leading to reduced absorption), adsorption (e.g. charcoal), chelation / complexation (e.g. di-/trivalent metallic ions and tetracycline; cholestyramine and oral anticoagulants, digoxin, or vitamin K) keeping the drug in the intestine and reducing bioavailability and therapeutic effect. But also a change in gastrointestinal motility induced by drugs like anticholinergics (decreased gut motility which increases the absorption of some drugs by increased time for dissolution and absorption), or alteration in gut flora (e.g. enteric bacteria and digoxin: digoxin area under the concentration-tim curve (AUC) reduced; addition of antibiotics: digoxin AUC increased; gut flora hydrolyzing steroid conjugates and antibiotics: enterohepatic cycling of steroids reduced) may occur. Most of these interactions result in reduced rather than

increased absorption *(Alfaro & Piscitelli, 2001; Stockley, 2002)*. Other mechanisms altering the absorption may be the inhibition or intestinal enzymes, mainly CYP3A4, and the modulation of transport proteins expressed in the intestine like P-gp. They are the most widely studied concerning DDIs at this level. Other intestinally located transporters, for instance the multidrug resistance associated proteins (MRPs), organic cation transporters (OCT1 and OCTN2), breast cancer resistance protein (BCRP), or organic anion-transporting polypeptides (OATP) *(Koepsell et al., 1999; Lecureur et al., 2000; Russel et al., 2002; Wagner et al., 2001; Watkins, 2001)*, might also be involved. An inhibition of the intestinal efflux pump P-gp, which transports substrates from the enterocyte back into the gut lumen, may lead to and increased absorption an bioavailability (e.g. erythromycin or grapefruit juice and talinolol) *(Schwarz et al., 2000; Spahn-Langguth & Langguth, 2001)*), while an induction of P-gp may lead to a decreased bioavailability of P-gp substrates (e.g. rifampicin and talinolol) *(Westphal et al., 2000)*. Table 1 gives an overview of relevant P-gp substrates, inducers and inhibitors.

P-gp Substrates		P-gp Inhibitors		P-gp Inducers
Amitriptyline	Estradiol	Amiodarone	Itraconazole	Amitriptyline
Amoxicillin	Indinavir	Atorvastatin	Lovastatin	Dexamethasone
Atorvastatin	Lovastatin	Clarithromycin	Mibefradil	Doxorubicin
Carbamazepine	Mibefradil	Ciclosporin	Nifedipine (?)	Efavirenz
Colchicine	Morphine	Desetylamiodarone	Omeprazole (?)	Lopinavir
Corticosteroids	Phenytoin	Diltiazem	Quercetin	Nefazodone
Ciclosporin	Quinidine	Erythromycin	Quinidine	Phenobarbital
Daunorubicin	Talinolol	Fluoxetin	Ritonavir	Ritonavir
Dexamethasone	Terfenadine	Grapefruit juice	Saquinavir	Rifampicin
Digoxin	Verapamil	Garlic	Sertraline	St. John's wort
Diltiazem	Vinca alcaloids	Green tea	Simvastatin	
Doxorubicin		Haloperidol	Terfenadine	
		Ketoconazole	Verapamil	

Table 1 Selection of P-gp substrates, inhibitors and inducers, adapted from Oesterheld *(Oesterheld, 2003)*

Intestinal CYP3A4, which is expressed with a high variability in the enterocytes, will metabolize CYP3A4 substrates before reaching the portal vein and reduce bioavailability contributing to presystemic first pass elimination. Induction of CYP3A4 will further reduce, while inhibition of CYP3A4 will increase bioavailability of the parent compound. In case of activating an inactive prodrug to the active metabolite by CYP3A4, the effects will be vice versa *(Stockley, 2002)*. P-gp and CYP3A4 are also located in other organs (kidneys, liver, endothelial cells of the blood-brain barrier and liver, respectively). Further possible interactions at the level of CYPs and P-gp are discussed in the corresponding Chapters 1.3.2.2.3 through 1.3.2.2.5.

1.3.2.2.2 Protein binding

Protein binding displacement of highly protein bound drugs resulting in clinically relevant DDI have long been over-emphasized. The increase of free concentration is transient as the free drug is subsequently cleared. The transient increase only becomes relevant for high extraction drugs and drugs with a small volume of distribution, a long elimination half-life and a narrow therapeutic index like phenytoin, phenprocoumon, and tolbutamide *(Alfaro & Piscitelli, 2001; Brüggmann, 2003; Stockley, 2002)*.

1.3.2.2.3 Metabolism

Interactions affecting drug metabolism by induction or inhibition of drug metabolizing enzymes may occur at the level of phase I metabolic reactions (dealkylation, deamination and hydroxylation by microsomal CYP family) as well as phase II reactions (glucuronidation by microsomal UDP-GT, sulfatation by cytosolic sulfotransferases). An enzyme induction may lead to decreased drug plasma concentrations and loss of effectiveness, while an enzyme inhibition may lead to increased plasma concentrations and increased risk for ADRs. It should be noted, that metabolites may also be active or toxic and an enzyme induction may therefore lead to increased clinical effect or toxicity. *(Alfaro & Piscitelli, 2001; Brüggmann, 2003; Stockley, 2002)*. The most important CYP isoenzymes for drug metabolism are CYP1A2, CYP2B6, CYP2C9, CYP2C19, CPY2D6, CYP2E1 and CYP3A4 (most abundant), which are the most studied concerning drug interactions. There are many tables listing drugs as substrates, inhibitors and/or inducers of the various CYPs *(DeLuca & Gysling, 2001; Flockhart, 2004; Michalets, 1998; Oesterheld & Osser, 1997-2004; Tatro, updated January 2004)*. They base on *in vitro* or/and *in vivo* investigations on drug metabolism and interactions. The may be used as a basic guide to predict DDIs. However the potency of the individual drugs to lead to clinically relevant DDIs, e.g. expressed as an inhibition constant k_i, is not always given, and final conclusions are difficult to be drawn. Table 2 gives an overview of some important drugs and their relation to CYPs. They were selected in consideration oft the relevant results described in Chapters II and III.

The net effect of CYP induction is increased DNA-transcription and synthesis of the CYP enzymes. The time course of induction depends on the elimination half-life of the inducer, the time required for new enzyme production and enzyme degradation and may take days up to 2-3 weeks to fully develop. As mechanisms, induction by the aryl hydrocarbon receptor, ethanol, peroxisome proliferators, the constitutive androstan receptor (CAR) and the pregnane X receptor (PRX) were identified. For drugs, CAR and PXR seem to be primarily affected. PXR is mostly involved with CYP3A4 induction *(Alfaro & Piscitelli, 2001)*.

CYP inhibition may be characterized as reversible, quasi irreversible and irreversible. Competitive reversible inhibition is the most common type in DDI, besides non-competitive and un-competitive inhibition. While competitive inhibition occurs when two substrates compete for the active site of the free enzyme, with non-competitive and un-competitive inhibition the inhibitor binds to the enzyme-substrate leading to a non-functional inhibitor-enzyme-substrate complex. The onset and time course is generally more rapid and may take a few days to fully develop. When evaluating potential DDI mediated by CYP inhibition, the toxic potential and the therapeutic index of the substrate drug should be considered, as well as possible other pathways involved in substrate metabolism, through which the substrate could alternatively be cleared. The role of the metabolite (active metabolite including therapeutic effect, e.g. codeine / metabolite morphine; toxic metabolite leading to increased toxicity, e.g. nefazodone / meta-chlophenylpiperazine (mCPP) metabolite

associated with anxiety) and the possibility of genetic polymorphism (EM or PM) should also be considered *(Alfaro & Piscitelli, 2001; Stockley, 2002)*.

Substrates						
CYP1A2	**CYP2B6**	**CYP2C9**	**CYP2C19**	**CYP2D6**	**CYP2E1**	**CYP3A4**
Amitriptyline	Amitriptyline	Amitriptyline	Amitriptyline	Codein	Acetaminophen	Alprazolam
Caffeine	Diazepam	Celecoxib	Citalopram	Desipramine	Ethanol	Atorvastatin
Estradiol	Midazolam	Fluoxetine	Imipramine	Dextromethor-phan	Halothane	Cerivastatin*
Fluvoxamine	Nevirapine	Fluvastatin	Omeprazole	Fluoxetine	Theophylline	Lovastatin
Imipramine	Testosteron	Diclofenac	Pantoprazole	Fluvoxamine		Ritonavir
Theophylline	Valproic acid	Ibuprofen	Phenytoin	Haloperidol		Saquinavir
Verapamil	Verapamil	Phenytoin	Progesterone	Nortriptyline		Sertraline
R-warfarin		S-warfarin	Propranolol	Risperidon		Sildenafil
		(Cerivastatin*; CYP2C9/2C8)	R-warfarin	Tramadol		Simvastatin
				Venlafaxin		Tacrolimus
						Verapamil
Inhibitors						
Amiodarone	Amiodarone	Amiodarone	Cimetidine	Amiodarone	Disulfiram	Amiodarone
Cimetidine	Ketoconazole	Fluconazole	Felbamate	Celecoxib		Ciclosporine
Ciprofloxacin	Tranylcypro-mine	Fluoxetine	Fluoxetine	Chlorpheniramine		Cimetidine
Fluvoxamine	Troglitazone	Fluvastatin	Fluvoxamine	Cimetidine		Ciprofloxacin
Mibefradil*	Troleandomycin	Fluvoxamine	Indomethacin	Clomipramine		Diltiazem
Norfloxacin		Isoniazid	Ketoconazole	Fluoxetine		Erythromycin
Ticlopidine		Lovastatin	Lansoprazole	Methadone		Fluconazole
		Paroxetine	Omeprazole	Mibefradil*		Fluoxetine
		Sertraline	Oxcarbazepine	Paroxetine		Gestodene
		Zafirlukast	Paroxetine	Quinidine		Grapefruit juice
			Topiramate	Ritonavir		Indinavir
				Terbinafine		Itraconazole
						Ketoconazole
						Mibefradil*
						Nefazodone
						Ritonavir
						Saquinavir
Inducers						
Char-grilled meat	Dexam-methasone	Rifampicin	Norethindrone	None	Ethanol	Barbiturates
Omeprazole	Phenobarbital	Secobarbital	Prednison		Isoniazide	Carbamazepine
Tabacco	Rifampicin		Rifampicin			Efavirenz
	Valproat					Glucocorticoids
						Nevirapine
						Oxcarbazepine
						Phenobarbital
						Phenytoin
						Rifampicin
						St. John's wort

Table 2 Selection of CYP substrates, inhibitors and inducers, adapted from *(Alfaro & Piscitelli, 2001; Flockhart, 2004; Michalets, 1998)*; * withdrawn from market

Besides interactions on CYP metabolism, other enzyme systems may be affected by DDIs. Examples are the well documented increased myelotoxicity of azathioprine and 6-mercaptopurine when combined with allopurinol, a xanthine oxidase inhibitor, leading to potentially life-threatening pancytopenia *(Cummins et al., 1996)*. Another example is the increased clinical effect and toxicity of serotonin, adrenalin, or noradrenalin which are metabolised by monoaminoxidase (MAO), in combination with MAO-inhibitors *(Livingston & Livingston, 1996)*. Although there is some information on inhibitory and inducing effects of drugs on serum aspirin esterase *in vitro (Gupta et al., 1979)*, and on inhibitory effects on paracetamol-gucuronidation in humans *(Itoh et al., 2001; Itoh et al., 2002; Markowitz et al., 2002)*, the clinical relevance of these findings is unkown.

1.3.2.2.4 Elimination

Renal elimination: It is known that free, unbound drug or metabolite are filtered through the pores of the glomerular membrane into the lumen of the renal tubules. Filtration rate is mainly dependent on the flow of blood through the glomeruli. As blood flow is partially controlled by the production of renal vasodillatory prostaglandines, an inhibition of these prostaglandines will reduce renal filtration of drugs *(Stockley, 2002)*. The decreased lithium excretion with NSAIDs is at least partly explained by this mechanism. At the level of the tubules there are several possibilities to influence the fate of the drug. Weak bases or acids are present in their non-ionized lipid soluble, reabsorbable form depending on urinary pH. The presence of drugs may influence urinary pH thereby influencing the elimination rate of certain drugs. However, there are only a few clinically significant examples of this type of interaction, e.g. antacids, salicylates or quinidine. The concept of deliberately change of pH-dependent tubular reabsorption, however, may be used in intoxication to accelerate elimination of the toxic drug. Another mechanism for interactions at the level of the kidney may be competition at active excretory carrier transporters in the kidney tubules. A competition may result in decreased active secretion and increased plasma concentration of one or each of the involved the drugs *(Stockley, 2002)*. Active transporters which are identified in the renal proximal tubule cell are P-gp, MRPs, organic anion transporters (OATs, OATPs, OCT2, OCTNs, and peptide transporters (PEPTs) *(Koepsell et al., 1999; Lecureur et al., 2000; Russel et al., 2002; Watkins, 2001)*. Clinically relevant interactions involved with active excretion into the tubule are probenecid and methotrexate (MTX) *(Basin et al., 1991)* or penicillin *(Somogyi, 1996)*. Latter was formerly beneficially used to increase penicillin concentration and effectiveness *(Somogyi, 1996)* and is at least in parts mediated by inhibition of OAT-mediated secretion *(Masuda et al., 1997)*. The interaction between MTX and probenecid is possibly mediated by probenecid induced inhibition of MRP2 (syn.: canicular multispecific organic anion transporter [cMOAT]) *(Kato et al., 2002)* and/or OATs *(Takeda et al., 2002)*. Salicylates and other NSAIDs in combination with MTX may result in serious MTX toxicity *(Stockley, 2002)*. This relevant PK interaction, however, is debated particularly for low dose MTX, as clinical studies failed to show altered PK profiles of low dose MTX in combination with NSAIDs *(Iqbal et al., 1998; Karim et al., 1999)*. *In vitro* investigations suggest that the interaction is due to NSAID-mediated inhibition of MTX-excretion by OAT1 and 3 *(Takeda et al., 2002)*. Digoxin is a P-gp substrate, whose linear and nearly complete oral absorption does not seem to be influenced by intestinal P-gp *(Chiou et al., 2001)*. Examples of interactions with digoxin, which are at least in part mediated by P-gp at the level of the kidney tubules, are documented for the P-gp inhibitors quinidine *(Fromm et al., 1999)*, ciclosporin *(Okamura et al.,*

1993), amiodarone *(Kakumoto et al., 2002)*, verapamil *(Takara et al., 2002)*, atorvastatin *(Boyd et al., 2000)*, and itraconazole *(Jalava et al., 1997)* and may lead to increased digoxin plasma concentrations *(Kakumoto et al., 2002)*.

Biliary excretion: Unchanged drugs and their metabolites or glucuronides may be excreted into the bile and eliminated fecally. Numerous transport proteins are involved in the uptake of drugs from the blood into hepatocytes such as OAT2, OATP, OCT1, and in the excretion from hepatocyte into the biliary caniculi like P-gp, MDR3, MRP2 and sister of P-gp (SPGP, syn.: bile salt export pump) *(Kato et al., 2002; Koepsell et al., 1999; Kullak-Ublick, 1999; Lecureur et al., 2000; Russel et al., 2002; Watkins, 2001)*. Biliary excretion by MRP2 of glucuronide- and GSH-conjugates and non-conjugated anionic drugs like pravastatin has been demonstrated in animals *(Tokui et al., 1999; Yamazaki et al., 1997)* and *in vitro* studies showed transport of anti-viral agents by MRP2 *(Adachi et al., 2002; Gutmann et al., 1999)*. Although *in vivo* and *in vitro* investigations on biliary elimination of P-gp substrates indicate that DDI may occur at the level of hepatobiliary drug transporters *(Speeg & Maldonado, 1994; Tsai et al., 2002; Wu & Benet, 2003)*, clinically relevant DDIs have not been studied largely.

1.3.2.2.5 Enterohepatic Shunt

Unchanged drugs or (conjugated) metabolites, which are excreted via the bile into the gut may be metabolized or hydrolyzed by the gut flora to (parent) compounds, which may by reabsorbed. This reabsorption contributes to a prolongation of the parent drug's elimination half-life. Disturbances of the gut flora by antibiotics like penicillins and tetracyclines may alter the reabsorption rate and decrease enterohepatic shunt of drugs, contributing to decreased drug plasma concentrations as has been illustrated by therapeutic failure of oral contraceptive (OC) therapy *(Back et al., 1981)*. However, any other mechanism which decreases gastrointestinal absorption, could lead to a DDI at the level of enterohepatic shunt, if the drug undergoes relevant enterohepatic cycling. An example thereof is phenprocoumon and cholestyramine, which should be consumed with a two-hours interval because of complex-binding of phenprocoumon. However, cholestyramine may also increase drug clearance: e.g. clearance of phenprocoumon or warfarin is increased by binding them and interrupting the enterohepatic cycling. The fatal thrombosis in a very compliant patient with a prosthetic valve treated with phenprocoumon and cholestyramine demonstrates the potential severity of such interactions *(Balmelli et al., 2002)*.

1.3.2.3 Drug-excipient interactions

Excipients are substances 'without' pharmacologic effects. They are thought to be inert and solely used for formulation of a pharmacologically active compound into a stable pharmaceutical product. Interactions between a drug and the excipient (drug-excipient interaction [DEI]) leading to an altered pharmacokinetic profile were over a long time not considered. However, DEI may occur at all levels of PK by changing solubility and stability of the drug in the gastrointestinal fluids, by influencing permeability through biological membranes, intestinal and hepatic metabolism, transport mechanisms (e.g. P-gp), or plasma protein binding. Synthetic surfactants such as Tween 80 *(Lo et al., 1998)*, Cremophor EL *(Shono et al., 2004)*, Solutol HS 15 *(Komarov et al., 1996)*, and vitamin E-TPGS *(Rege et al., 2002)* have been shown to be inhibitors of P-gp. DEI have been mainly studied in cancer chemotherapy. Tumor resistance to anticancer

drugs has been revealed to be P-gp mediated and Cremophor EL and Tween 80 have been shown to modulate P-gp-mediated anticancer multidrug resistance *(Friche et al., 1990)*, and to increase doxorubicin antitumor activity in mice *(Badary et al., 1998)*. Solutol HS 15 has been shown to be a weak inhibitor of CYP3A4 *in vitro (Bravo Gonzalez, 2003)*. The same has been shown for Tween 20 and Tween 80 *(Mountfield et al., 2000)*. Surfactants may lead to increased absorption and altered PK profiles of P-gp or CYP3A4 substrates as was shown in animal studies for ciclosporin *(Bravo Gonzalez et al., 2002)* and colchicine *(Bittner et al., 2003; Bittner et al., 2002)*. Surfactants may also interact with biomembranes and lead to increased drug absorption. Surfactants are mainly used to solubilize poorly soluble drugs for intravenous administration. For instance Tween 80 is used for amiodarone [Cordarone®] and Cremophor EL for paclitaxel [Taxol®] *(Morant, 2004)*. But they are also used to increase oral bioavailability of a drug with low and variable bioavailability, like Cremophor EL for ciclosporin [Sandimmun® neoral] *(Morant, 2004)*. They are investigated in altering the bioavailability of antitumor agents *(Malingre et al., 2001)*, or studied in clinical trials to increase bioavailability of ciclosporin *(Drewe et al., 1992)*, saquinavir *(Martin-Facklam et al., 2002)* and talinolol *(Bogmanm et al., 2004)*. Little is known, however, on their real impact in clinically relevant DDI in patients.

1.3.2.4 Drug-herbal and drug-food interactions

Besides classical DDIs, interactions between a drug and food like grapefruit juice *(Bailey et al., 1998)* and brussels sprouts *(Pantuck et al., 1984; Pantuck et al., 1979)*, excipients like Cremophor EL and Tween 80 *(Wagner et al., 2001)*, herbal products like SJW, gingko, and ginseng *(Fugh-Berman, 2000; Huang et al., 2004; Izzo & Ernst, 2001; Miller, 1998)*, environmental factors like smoking and ethanol intake with clinical relevance were described *(Alfaro & Piscitelli, 2001; Stockley, 2002)*. Table 3 shows the most important interactions associated with herbs and foods. With few exceptions, like SJW *(Durr et al., 2000; Moore et al., 2000; Pfrunder, 2003; Wang et al., 2001)*, there is still a lack of scientific data from carefully designed and conducted investigations between drugs and molecules that may represent the active or inactive ingredient of botanical-derived alternative medicines. An unsolved issue is also the lack of quality of many herbal products and the lack of their standardization.

Herb or food	Mechanism	Affected Drugs	Effect
Grapefruit juice (furanocoumarins, naringenin)	CYP3A4 inhibition, P-gp inhibition (intestinal)	Calcium channel blockers	Hypotension, dizziness, syncope
		Terfenadine	AUC increased, QT prolongation
		Saquinavir	AUC increased
		Ciclosporin	
		Statins	Myalgia, rhabdomyolysis
Garlic (allium sativa)	Reduced platelet aggregation	Warfarin	INR increased, PT increased
St. John's wort (hypericum perforatum; hyperforin)	CYP3A4 induction, P-gp induction	Oral contraceptives	Break-through bleeding, pregnancies
		Ciclosporin, tacrolimus	Organ rejection, reduced plasma levels
		Warfarin, phenprocoumon	INR decreased
		Digoxin; indinavir; Amitriptyline; midazolam; Simvastatin	AUC reduced
		Methadone	Withdrawal symptoms
	Inhibition of serotonin reuptake	Antidepressants (trazodone, sertraline, nefazodone)	Mild serotonin syndrome
Ginkgo (ginkgo biloba)	PAF induced reduced platelet aggregation	Warfarin	Haemorrhage (intracerebral)
Ginseng (panax spec.)	unknown	Warfarin	INR decrease
		Phenelzine, other MAOIs	Headache, manic episode
Kava (piper methysticum)	Possible interaction with BZD metabolism	Alprazolam	Semicomatose state
		Levodopa	Increased 'off' periods
Ethanol intake (chronic)	CYP1A2 induction	Paracetamol	Increased hepatoxicity by increased formation of toxic metabolite

Table 3 Selected examples of drug-food and drug-herb interactions, according to *(Fugh-Berman, 2000; Huang et al., 2004; Izzo & Ernst, 2001; Miller, 1998)*. INR = international normalized ratio; PT = prothrombin time; BZD = benzodiazepine; AUC = area under the plasma concentration-time curve; PAF = platelet activating factor; MOAI = monoamine oxidase inhibitor

1.3.3 Screening for drug-drug interactions

Manual screening for potential DDIs within a given drug profile of a patient may reveal very thorough results, but is time consuming. Besides the need of a profound knowledge of pharmacodynamic and pharmacokinetic properties of drugs, many excellent literature sources must be consulted and literature researches on databases such as MEDLINE or EMBASE need to be done to cover the whole spectrum of possible DDIs.

The standard books on drug interactions 'Drug interactions' by Stockley *(Stockley, 2002)*, 'Drug interaction analysis and management' by Hansten & Horn *(Hansten & Horn, 1999)*, 'Drug interaction facts' by Tatro *(Tatro, updated January 2004)*, and 'Metabolic drug interactions' by Levy et al. *(Levy et al., 2000)* may be quoted. Review articles may give very good overview on selected DDI topics such as interactions with antiepileptic drugs *(Anderson, 1998; Levy, 1995; Riva et al., 1996)*, herbal drug interactions *(Fugh-Berman, 2000)*, CYP interactions *(Lin & Lu, 1998; Michalets, 1998)*, drug interactions with psychoactive drugs *(Ereshefsky et al., 1995; Markowitz et al., 1999; Tanaka & Hisawa, 1999)*, antidepressants *(Richelson, 1998; Spina & Scordo, 2002)*, selective serotonin reuptake inhibitors *(Hemeryck & Belpaire, 2002; Sproule et al., 1997)*), immunosuppressive agents *(Mignat, 1997)*, or with class III antiarrythmic drugs *(Yamreudeewong et al., 2003)*.

Tables of substrates, inhibitors and inductors of P-gp or CYPs may help to interpret a potentially interacting drug combination. Electronic CYP tables are provided by Flockhart at http://medicine.iupui.edu/flockhart *(Flockhart, 2004)*, by DeLuca & Gysling at http://www.infomed.org/pharma-kritik/pk21d-98.html *(DeLuca & Gysling, 2001)*, and by Oesterheld & Osser at http://www.mhc.com/ *(Oesterheld & Osser, 1997-2004)*. An excellent overview of transporters and their inhibitors and inducers is provided by Watkins at http://bigfoot.med.unc.edu/watkinslab/ *(Watkins, 2001)*. These information sources rely on previously published *in vitro* and *in vivo* animal data as well as on human experiences considering a certain CYP or P-gp. Oesterheld & Osser provide a CYP Drug Interaction Program *(Oesterheld & Osser, 1997-2004)* which allows the introduction of drug profiles and gives a prediction of possible effects regarding the metabolic pathways of the drugs. A problem which arises with all these tables is that *in vivo* animal and *in vitro* data cannot always be extrapolated to what will happen in clinical situations in humans. The interpretation of a drug combination will remain theoretical. Flockhart resolved the problem by providing a CYP table with drugs for which clinically relevant interactions have been observed.

Besides the manual checking of a drug profile, some electronic interaction programs allow to screen drug profiles for potential DDIs by interaction modules. They may be offered online or offline either as CD-Rom or for Palm / Pocket-PC. While some online programs are accessible for free, others will charge an annual license fee. Table 4 gives an incomplete list of some freely accessible, except for Drug-Reax®, online interaction tools. Comments are given on the overview and manageability of the results they yield, on an existing rating scale, on overall quality of the given information, as well as on the completeness of detected drug interactions. Latter arise from the results with an invented drug profile with known drug-statin interactions (simvastatin with amiodarone, clofibrate, verapamil, nefazodone, clarithromycin, digoxin, ciclosporin, carbamazepine, SJW, and phenytoin). Other, not freely accessible programs are the ABDA-

database of the federal organization of the German pharmacist associations (which is the basis of the Pharmavista DDI program), Stockley's Drug Interactions (CD-ROM, book-version with some search tools), Medical Letter Adverse Drug Interactions Program, as well as DrugIx™-Adverse Drug Interactions Program and Tarascon Pocket Pharmacopoeia® Deluxe for personal digital assistance (PDA) from the Medical Letter Inc. Main, USA.

While it has been shown that computerized screening is faster and more sensitive than expert physician to predict potential DDIs *(Dambro & Kallgren, 1988; Langdorf et al., 2000)*, and while Drug-Reax® has been used in several studies *(Egger et al., 2003; Gaddis et al., 2002; Geppert et al., 2003; Langdorf et al., 2000)*, very limited information is available on the evaluation of these programs. After an evaluation of six computerized drug interaction screening programs ('Medicom Micro Plus', 'Medical Letter', S-O-A-P, 'Drug Interactions' by Hansten, 'Drug Therapy Screening System' (DTSS), and 'RxTriage') a panel of pharmacists concluded that none of them was ideal. Only two out of six were able to detect all of the potential drug interactions tested ('Medicom Micro Plus', DTSS). But their presentation of information was considered weak. Those who ranked highest in user friendliness and efficiency ('RxTriage', 'Drug Interactions' by Hansten) missed two interactions *(Jankel & Martin, 1992)*. Strain et al. *(Strain et al., 2002)* compared three electronic DDI tools for psychotropic DDI identification, i.e. 'ePocrates Rx' for the hand held computer PalmPilot, the software 'Interact' endorsed by the American Psychiatric Association, and the 'Mount Sinai multiple source for the evaluation of DDI' developed by Strain et al. *(Strain et al., 1999)*. Every program had disadvantages (no severity rating, missing interactions, no references, not portable, no updates, or only one drug search possible at the time). Only recently, DDI software for PDA was evaluated, indicating that the Products 'iFacts' and 'Lexi-Interact' are the most competent, complete and user friendly compendia, followed by 'Mosby's Drug Consult' and 'Mobile Micromedex', while 'ePpocrates Rx' remained far behind *(Barrons, 2004)*.

	Drug-Reax*®	Lexi-Interact™	ePocrates MultiCheck	Interactions by British National Formulary	DrugDigest	BIAM	Pharmavista
Access	(not free of charge)	http://www.utdol.com/crlsql/interact/frameset.jsp	https://www.epocrates.com/multiCheck.do	http:\\bnf.org -> BNF46	http://www.drugdigest.org/DD/Interaction/ChooseDrugs	http://www.biam2.org/ordonn.html	http://www.pharmavista.ch/
Overview of results, handling	+++	++	NE	+	++	++	++
Rating	Severity: minor moderate, major	Severity: minor moderate, major Risk rating A-X	NE	2 not defined categories	Severity: minor moderate, major	Counseling: to prevent, to monitor, possibly useful	Importance: severe, moderate, poor, inconsiderable external statement
Rating on the quality of the documentation	Poor, good, fair	None	NE	None	None	None	(Included in 'importance'?)
Overall quality of information	Thorough	Group effects described, general (particularly for CYP and P-gp)	NE	Very short, main information	Short, main information and recommendation	Very short	Thorough, sometimes general
Completeness of result within tested drug profile	++ (8/10)	++ (7/10)	NE	- (2/10)	+ (6/10)	- (3/10)	+ (6/10)
References	Given	Mostly given	NE	Not given	Not given	Given	Given

Table 4 Selected examples of online interaction programs with integrated interactions module. All except Drug-Reax® are free of charge. Comments on a given drug profile with 10 known drug interactions of simvastatin with amiodarone, clofibrate, verapamil, nefazodone, clarithromycin, digoxin, ciclosporin, carbamazepine, hypericum, and phenytoin: +++ very good, ++ good, + acceptable, -poor, NE = not evaluable

1.4 Drug safety of HMG-CoA reductase inhibitors

1.4.1 Pharmacokinetic and physicochemical characteristics of HMG-CoA reductase inhibitors

Although the HMG-CoA reductase inhibitors (statins) exhibit the same pharmacodynamic mechanism to alter the lipid profile, i.e. the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase, which is the rate limiting step of cholesterol-biosynthesis in the liver, the statins have different chemical structures and vary in their pharmacokinetic properties. The chemical structures of the existing statins are shown in Figure 2.

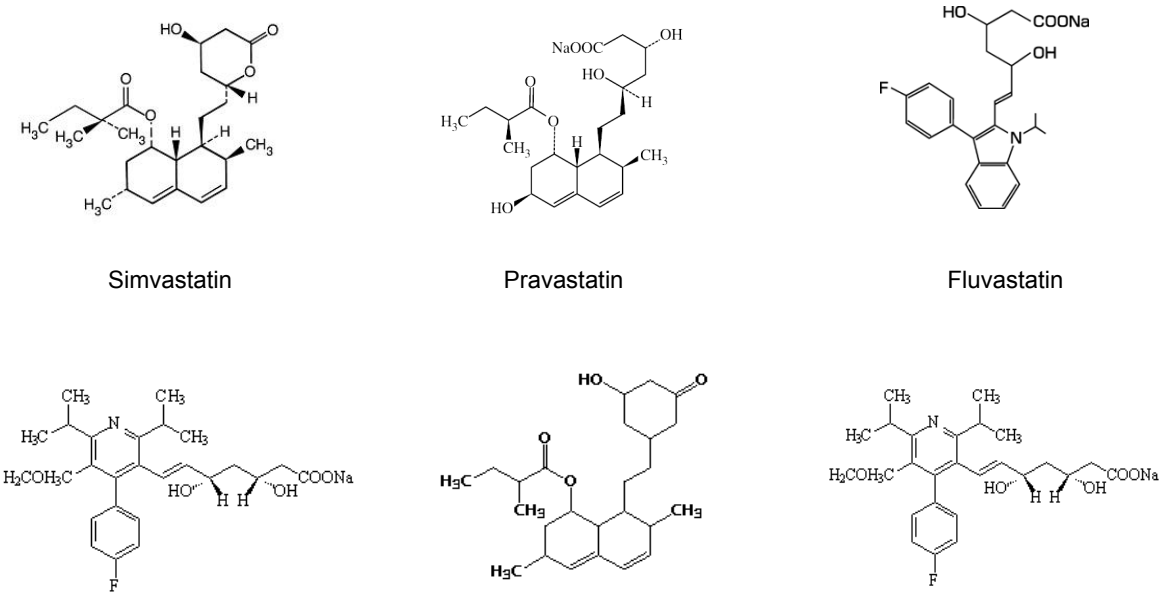

Figure 2 Structural differences among statins (simvastatin, pravastatin, fluvastatin and atorvastatin available in Switzerland, lovastatin available in the USA). * withdrawn from the market

The pharmacokinetic and physicochemical characteristics of the statins are shown in Table 5. The different pharmacokinetic profiles of the statins may contribute to their differing, individual DDI profile and DDI risk. The most important feature therefore is probably the different CYP-mediated metabolism. It is estimated, that pravastatin, which is not metabolized by CYPs to a relevant extent, may have a minor risk for CYP-induced DDIs. OATP2, exclusively expressed in the liver, has been identified as the transporter of

pravastatin, lovastatin, simvastatin and atorvastatin, which is thought to be the reason for hepatic uptake, particularly for the hydrophilic pravastatin *(Hsiang et al., 1999)*.

	Simvastatin	Atorvastatin	Pravastatin	Fluvastatin	Lovastatin	Cerivastatin
Origin	Semisynthetic	Synthetic	Semisynthetic	Synthetic	Microbial	Synthetic
Lactone prodrug	Yes	No	No	No	Yes	No
Lipohilicity	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic
Crosses BBB	Lactone	NA	No	No	Lactone	NA
Absorption (%)	60-85	30	35	98	31	>98
Bioavailability (%)	<5	12	17	10-35	<5	60
Relative potency	6	12	2	1	3	200
Dosage (mg/d)	5-80	10-80	5-40	20-80	10-80	0.1-0.8
Protein binding (%)	95	>98	48	>99	95	>99
Elimination half-life (h)	~ 3	~ 15	~ 2	~ 3	~ 2	~ 3
Renal elimination (%)	13	<2	20-60	6	30	30
CYP metabolism: major	CYP3A4	CYP3A4	Not relevant	CYP2C9	CYP3A4	CYP2C8, 3A4
minor	CYP2D6, 2C9		CYP2C9, 3A4	CYP2D6, 3A4	CYP2D6, 2C9	
P-gp inhibition	Yes	Yes	No	No	Yes	NA

Figure 5 Pharmacokinetic and physicochemical properties of statins. Adapted by *(Christians et al., 1998; Horsmans, 1999; Igel et al., 2001; Oesterheld, 2003; Williams & Feely, 2002)*. BBB = blood brain barrier, NA = not available

1.4.2 Adverse drug reaction profile

The lipid-lowering statins, which have been proven to have a favorable benefit for virtually all patients with cardiovascular risks mainly by reducing low density lipoprotein (LDL) cholesterol levels, are well tolerated over short- and long-term and have a low incidence of adverse events (<2%). Early reports indicated a potential for statins to alter a number of CNS parameters, including sleep and cognition, as well as inducing lens opacity and cataract. However, ophthalmic toxicity was not demonstrable in larger studies, and it appears that statin cause few, if any, changes in sleep and cognitiive pattern when compared to placebo. General gastrointestinal discomfort including constipation, flatulence and dyspepsia are commonly reported, and arthralgia have been observed. Hepatic dysfunction with a mild, asymptomatic and reversible elevation in alanin aminotransferase (ALAT) and aspartat aminotransferase (ASAT) > 3-fold upper limit of normal (ULN) is dose-dependent and is observed < 2% with all statins; possibly the least for pravastatin and cerivastatin *(Farmer & Torre-Amione, 2000; Williams & Feely, 2002)*.

ADRs on skeletal muscles, including myopathy, is a group effect of statins. It may lead to severe, potentially fatal rhabdomyolysis, defined as clinical syndrome and creatine kinase (CK) elevation up to > 1000 IU/L *(Farmer & Torre-Amione, 2000)*. The incidence of myopathy is 0.1-0.5%, and rhabdomyolysis is very rare wit an incidence of 0.02-0.04% *(Omar & Wilson, 2002)*. Muscular ADR frequency associated with statins is dose-related *(Ucar et al., 2000)*. Different hypotheses considering the mechanism of statin-induced

muscle toxicity were suggested, as for example a deficit of ubichinone (coenzyme Q) in the muscle cell, which disturbs cellular respiration resulting in cell death. However, the exact mechanisms are still unknown. From *in vitro* investigations, it was postulated that lipophilic statins, which have a higher penetration into muscular cells, are more myotoxic. However, this was not confirmed in clinical praxis *(Farmer & Torre-Amione, 2000)*. A study conducted in England analyzed the frequency of spontaneous reports of skeletal muscular associated ADR per prescribed statins. A similar incidence was found for simvastatin (0.004%), pravastatin (0.003%), fluvastatin (0.005%) und atorvastatin (0.003%) and only for cerivastatin (0.01%) the incidence was higher *(Evans & Rees, 2002)*. Risk factors for statin-associated myotoxicity are suggested to be age, female gender, combination with fibrates, liver and kidney dysfunction, as well as certain comorbidities like diabetes mellitus and hypothyroidism *(Evans & Rees, 2002; Williams & Feely, 2002)*. Due to the dose-dependency, potential PK interactions, which lead to increased statin plasma concentrations, are important risk factors for statin induced myopathies *(Omar & Wilson, 2002; Thompson et al., 2003)*. Therefore, patients with hyperlipidemia which require polymedication, such as patients with coronary heart disease, diabetes, hypertension, organ transplants, or HIV *(Corsini, 2003)* may be at higher risk. However, other factors, such as genetic predisposition, may also play a role *(Evans & Rees, 2002; Williams & Feely, 2002)*.

1.4.3 Drug-statin interactions

The different DDI profiles of the statins has been well described in the review of Williams & Feely *(Martin & Krum, 2003; Williams & Feely, 2002)*. Martin & Krum give a good overview of clinically relevant CYP-mediated statin DDIs *(Martin & Krum, 2003)*.

1.4.3.1 CYP3A4 and simvastatin, atorvastatin, lovastatin and cerivastatin

Simvastatin, atorvastatin, lovastatin are predominantly, and cerivastatin, also a CYP2C8 substrate, is partly metabolized by CYP3A4. Therefore, they are susceptible to interactions with CYP3A4 inhibitors (see Table 2), leading to increased statin plasma concentrations. The combination of a statin with CYP3A4 inhibitors has been shown to increase the risk for myopathy *(Gruer et al., 1999)*. Clinically relevant interactions between the potent CYP3A4 inhibitor erythromycin have been shown for simvastatin and cerivastatin *(Muck et al., 1998)*. For other CYP3A4 inhibitors like azole antifungals (ketoconazole and itraconazole), DDIs with simvastatin, lovastatin and to a smaller amount with atorvastatin *(Kivistö et al., 1998; Neuvonen & Jalava, 1996; Neuvonen et al., 1998)* were observed. Further examples of CYP3A4 mediated statin DDIs are mibefradil, verapamil, nefazodone, HIV-protease inhibitors ritonavir and nelfinavir, and grapefruit juice with simvastatin *(Cheng et al., 2002; Kantola et al., 1998a; Lilja et al., 1998; Schmassmann-Suhijar et al., 1998; Thompson & Samuels, 2002)*, Diltiazem with lovastatin *(Azie et al., 1998)*, grapefruit with lovastatin *(Kantola et al., 1998b)*, and atorvastatin *(Lilja et al., 1999)*, and nelfinavir with atorvastatin *(Hsyu et al., 2001)*. The Interaction with ciclosporin is probably not mediated by CYP3A4, as ciclosporin is not a CYP3A4 inhibitor *(DeLuca & Gysling, 2001; Flockhart, 2004)*. A feasible mechanism is the inhibition of OATP2-mediated hepatic uptake of statins by cyclosporin, leading to increased statin plasma concentrations *(Hsiang et al., 1999; Shitara et al., 2003)*.

1.4.3.2 CYP2C9 and fluvastatin

For fluvastatin, which is predominantly metabolized by CYP2C9, less interactions have been seen. Itraconazol and fluconazole were found to significantly increase fluvastatin AUC up to 200% in a pharmacokinetic study *(Kantola et al., 2000)*. A moderate and probably not clinically relevant increase of fluvastatin plasma concentration (27-70%) and AUC (20-40%) have been reported for cimetidine, erythromycin, omeprazole, ranitidine, and phenytoin. The mechanism of the unexpected interaction between fluvastatin and phenytoin, however, is unknown *(Klasco & Moore, 1974 - 2002.)*.

1.4.3.3 Fibrates and statins

The interaction between statins and fibrates is complex. Although the metabolism of fibrates is attributed to CYP3A4, other metabolic pathways are still debated. Myotoxicity and rhabdomyolysis are a known complication of gemfibrozil in combination with statins. The precise mechanisms are unknonw. Besides a additive myotoxic effect of both drugs, it may be partly mediated by CYP3A4 and CYP2C8/9 inhibition by gemfibrozil *(Fujino et al., 2003; Wen et al., 2001)*, but also other pharmacokinetic mechanisms like inhibition of glucuronidation *(Prueksaritanont et al., 2002)* or inhibition of statin uptake into the liver by OATP *(Kyrklund et al., 2003; Shitara et al., 2003)* are discussed. The activation of the peroxisome proliferation activated family of nuclear receptors (PPAR), and the hypolipidemic effect of fibrates itself influences the regulation of CYP2, 3, and 4 and may therefore contribute to the increased risk of interactions with statins *(Schoonjans et al., 1996)*.

1.4.3.4 CYP inducers and statins

The clinical significance of DDI between CYP inducers and statins leading to decreased statin plasma concentrations is not known *(Williams & Feely, 2002)*. Drug-statin interactions with inducers have been described between fluvastatin and rifampicin leading to fluvastatin bioavailability reduction by 50% *(Jokubaitis, 1994)*, and SJW decreased the AUC of simvastatin *(Sugimoto et al., 2001)*.

1.4.3.5 Statin-drug interaction, including P-gp mediated interactions

Besides DDI affecting the statins, statins themselves may alter the pharmacokinetics of other drugs. Interactions have been observed with simvastatin, fluvastatin as well as pravastatin and warfarin, leading to variable INR. Mechanisms alterating CYP-mediated metabolism as well as protein binding displacement are discussed *(Williams & Feely, 2002)*. Fluvastatin is an inhibitor of CYP2C9 and has been shown to increase phenytoin, oral anticoagulants, oral hypoglycemic agents, and NSAIDs in some healthy volunteers *(Transon et al., 1995)*, however it is unknown, whether there are clinically important effects in patients. Additionally, the co-administration of atorvastatin or simvastatin with digoxin have shown to increase digoxin plasma concentrations by 15% and 20%, respectively *(Williams & Feely, 2002)*. Statins, particularly simvastatin and lovastatin, and to a lesser extent atorvastatin and fluvastatin, have been shown to inhibit P-gp *(Bogman et al., 2001; Sakaeda et al., 2002; Wang et al., 2001)*. The mechanism of this interaction may involve P-gp inhibition and subsequently decreases digoxin clearance.

CHAPTER II

CROSS-SECTIONAL INVESTIGATION

IN PRIVATE PRACTICE ON

THE PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS

IN DYSLIPIDEMIC PATIENTS

IN SWITZERLAND

2.1 Prevalence of potentially severe drug-drug interactions in ambulatory dyslipidemic patients treated with a statin

Drug interactions in dyslipidemic patients

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Drug Safety (submitted on March 16th 2004)

2.1.1 Summary

DDIs are a well known risk factor for ADR. Statins are a cornerstone in the treatment of dyslipidemic patients, and patients with dyslipidemia are concomitantly treated with a variety of additional drugs. Since DDIs are associated with adverse reaction, 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 dyslipidemia. Data of patients with dyslipidemia treated with a statin were collected from 242 practitioners from different parts of Switzerland. The medication was screened for potentially harmful DDIs with statins or other drugs using an interactive electronic drug interaction program. In total, 2742 ambulatory statin-treated patients were included (mean age 65.1 ± 11.1 years; 61.6% males) with 3.2 ± 1.6 (mean±SD) 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), CYP3A4-inhibitors (70.5%), digoxin (22.6%) or ciclosporin (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. Concluding, CYP3A4 inhibitors were the most frequent cause for potential interactions with statins. As the risk for developing rhabdomyolysis is increased in patients having drug-statin interactions, clinicians should be aware of the most frequently observed drug-statin interactions and how these interactions can be avoided.

2.1.2 Introduction

DDIs are an important cause for ADRs. It has been estimated that approximately 5% of prescribing errors *(Fijn et al., 2002)* or of ADRs *(Classen et al., 1997)* are due to DDIs in hospitalized patients. In a recent investigation, 2.3% to 7.8% of adverse effects in association with the use of co-trimoxazole, digoxin or ACE-inhibitors were found to be due to interactions with concomitant drugs *(Juurlink et al., 2003)*. Polypharmacy, which is associated with the number of diagnoses in a given patient *(Grymonpre et al., 1988)*, has been identified as a major risk factor for DDIs. Considering individual drugs, the way a drug is metabolized and/or excreted is a major determinant of potential DDIs *(Herrlinger & Klotz, 2001)*. Drugs metabolized by CYPs have a particularly high risk for DDIs because of the large number of drugs inhibiting or inducing CYPs *(Herrlinger & Klotz, 2001; Meyer, 2000)*. 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-gp, e.g. interactions between statins and digoxin *(Hoffman, 1992)*, or clarithromycin and digoxin *(Tanaka et al., 2003; Wakasugi et al., 1998)*.

Interactions with statins can lead to rhabdomyolysis, a severe adverse reaction which may be fatal *(Federman et al., 2001; Weise & Possidente, 2000)*. A recent study in Ireland estimated that approximately 30% of all users of statins have concomitant drugs prescribed, which can influence statin metabolism, potentially leading to rhabdomyolysis *(Heerey et al., 2000)*. It is known that the interaction potential differs between individual statins *(Farmer & Torre-Amione, 2000; Horsmans, 1999)*. Atorvastatin, lovastatin and

simvastatin are all biotransformed by CYP3A4, the most abundant CYP isozyme, which metabolizes most drugs undergoing CYP-associated biotransformation *(Meyer, 2000; Rogers et al., 2002)*. Accordingly, the risk for interactions is highest for drugs metabolized by CYP3A4, particularly if no other CYP isozymes are involved in their biotransformation. Fluvastatin is primarily metabolized by CYP2C9, an isozyme by which less drugs are metabolized than by CYP3A4, making this drug less prone to DDIs *(Chong et al., 2001; Igel et al., 2001)*. Pravastatin is more hydrophilic due to a hydroxyl group, allowing conjugation of the drug without previous phase I biotransformation *(Farmer & Torre-Amione, 2000; Horsmans, 1999)*. Accordingly, the risk for interactions with pravastatin is estimated to be lower than for statins undergoing CYP-dependent metabolism *(Chong et al., 2001; Igel et al., 2001)*.. 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 *(Federman et al., 2001; Omar & Wilson, 2002; Weise & Possidente, 2000)*, we identified potential DDIs in ambulatory, hyperlipidemic patients treated with a statin to assess (1) the prevalence of potential DDIs in association with statin therapy, (2) to assess the prevalence of other potential DDIs not involving statins, and (3) to identify risk factors for potential DDIs in this population.

2.1.3 Methods

2.1.3.1 Subjects, study design and data collection

Between February to April 2002, practitioners from different parts of Switzerland were recruited to participate in the 'Swiss Analysis Focused on the Evaluation of Potential Drug Interactions' (SAFE). The participating practitioners screened all patients attending their practice during five consecutive days and completed a data sheet of each dyslipidemic patient with 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 according to the WHO Drug Dictionary (Version 01-3, third quart 2001). All patient data were recorded in an electronic database and all drug profiles were screened by the online version of Drug-Reax®Interactive Drug Interactions (Micromedex™ Healthcare Series Vol. 111-115 / Exp. 03-12/2002) *(Klasco & Moore, 1974 - 2002.)*, a drug interaction program that was used in several previous studies *(Egger et al., 2003; Gaddis et al., 2002; Langdorf et al., 2000)*. This program has proven to be more sensitive to predict potential DDIs than expert physicians *(Langdorf et al., 2000)*.

2.1.3.2 Database and semiautomatic screening by Drug-Reax®

Drug-Reax®, an interactive electronic drug interaction program with a filter for severity rating (major, moderate, minor) and providing referenced information on the clinical picture caused by a given DDI, was used for screening potential DDIs (Klasco & Moore, 1974 - 2002.). 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 of one single patient, the software prepared data records for all possible drug-drug

combinations for the patient (number of drug pairs/patient = (number of drugs x (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 analyzed 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.

2.1.3.3 Evaluation of clinical relevance of potential drug interactions

2.1.3.3.1 Drug-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 1) the respective statin was combined with a known inhibitor of its metabolism and/or transport; 2) there was at least one published case report describing this interaction, or 3) the potential adverse effect could have had a serious outcome. Serious outcome was defined as described by the ICH guidelines for clinical safety data management of adverse drug reactions *(Steering Committee ICH, 1994)*. In case of disagreement, the specific interaction was discussed until consensus between both assessors was reached.

2.1.3.3.2 Non-statin DDIs

Each drug profile with a possible non-statin DDI of 'major severity' according to Drug-Reax® or with a DDI not recognized by Drug-Reax®, but by manual screening using standard literature *(Stockley, 1999; Tatro, updated January 2003)*, 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. Serious outcome was defined as described by the ICH guidelines for clinical safety data management of adverse drug reactions *(Steering Committee ICH, 1994)*. 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 having 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). In case of disagreement between the two assessors, the specific interaction was discussed until consensus was reached.

2.1.3.4 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 *(Holm, 1979)*.

Potential drug-statin and non-statin DDIs were analyzed 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 / hyperuricemia, epilepsy, and other diagnoses (see Table 6). The continuous variables included in the model were age (years), number of diagnoses, number of prescribed drugs, and number of prescribed pharmacologically 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 / hyperuricemia. 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% confidence intervals (95% CI).

Statistical analyses were performed with SPSS for Windows version 10.1.4 (SPSS Inc., Chicago, Illinois 60606).

2.1.4 Results

2.1.4.1 Drug-statin interactions

From February through 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 2,753 dyslipidemic patients treated with a statin. Eleven patients were excluded from the analysis: ten patients were not prescribed a statin and one patient was on 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 part 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 summarized in Table 6. The 2,742 patients included had a total of 8,943 diagnoses (mean 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 beside dyslipidemia 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.

Patients	Total (n=2742)	Atorvastatin (n=886)	Pravastatin (n=934)	Simvastatin (n=763)	Fluvastatin (n=159)	p-value
Age, yrs (mean ± SD)	65.1 ± 11.2	63.7 ± 11.6	65.3 ± 11.2	66.5 ± 10.8	65.6 ± 10.8	<.05*
Females, n (%)	1052 (38.4)	334 (37.7)	362 (38.8)	296 (38.8)	60 (37.7)	ns
Number of diagnoses (including dyslipidemia) (mean ± SD)	3.2 ± 1.6	3.2 ± 1.6	3.2 ± 1.6	3.4 ± 1.5	3.2 ± 1.3	ns
Number 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	<.05 †
Hypertension, n (%)	1428 (52.1)	441 (49.8)	479 (51.3)	407 (53.3)	101 (63.5)	ns
Diabetes mellitus, n (%)	520 (19.0)	170 (19.2)	170 (18.2)	151 (19.8)	29 (18.2)	ns
Coronary heart disease, n (%)	1166 (42.5)	372 (42.0)	389 (41.6)	348 (45.6)	57 (35.8)	ns
Cardiac failure, n (%)	130 (4.7)	40 (4.5)	35 (3.7)	49 (6.4)	6 (3.8)	ns
Arrhythmias, n (%)	188 (6.9)	56 (6.3)	63 (6.7)	61 (8.0)	8 (5.0)	ns
Cerebrovascular diseases (including transitory ischemic attacks and peripheral arterial occlusive disease), n (%)	461 (16.8)	136 (15.3)	159 (17.0)	139 (18.2)	27 (17.0)	ns
Depression / psychiatric disorder, n (%)	423 (15.4)	137 (15.5)	133 (14.2)	125 (16.4)	28 (17.6)	ns
Rheumatic diseases / diseases of musculoskeletal system, n (%)	416 (15.2)	124 (14.0)	139 (19.9)	128 (16.8)	25(15.7)	ns
Gout / hyperuricemia, n (%)	103 (3.8)	42 (4.7)	34 (3.6)	21 (2.8)	6 (3.8)	ns
Epilepsy, n (%)	16 (0.6)	4 (0.5)	6 (0.6)	6 (0.8)	0	ns
Other diagnoses, n (%)	244 (8.9)	88 (9.9)	94 (10.1)	54 (7.1)	8 (5.0)	ns

Table 6 Patient characteristics and co-morbidities in 2742 dyslipidemic patients with statin therapy stratified according to individual statins. * age: simvastatin > atorvastatin, pravastatin > atorvastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm); † Number of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm); ns = no significant difference

The distribution of drugs concomitantly prescribed with statins is shown in Table 7. Since arterial hypertension and coronary heart disease were the most prevalent co-morbidities, acetylsalicylic acid, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, and thiazide or loop diuretics were the drugs most often prescribed concomitantly. Overall, 122 patients (4.4%) had no additional drug prescribed.

	Total (n=2742)	Atorvastatin (n=886)	Pravastatin (n=934)	Simvastatin (n=763)	Fluvastatin (n=159)	p-value
Number 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†
Acetylsalicylic acid, n (%)	1258 (45.9)	423 (47.7)	408 (43.7)	366 (48.0)	57 (35.8)	ns
Beta-blockers, n (%)	1145 (41.8)	373 (42.1)	376 (40.3)	327 (42.9)	69 (43.4)	nt
Thiazide or loop diuretics, n (%)	900 (32.8)	272 (30.7)	320 (34.3)	258 (33.8)	50 (31.4)	ns
ACE-inhibitors, n (%)	778 (28.4)	226 (25.5)	250 (26.8)	252 (33.0)	50 (31.4)	<0.05&
Angiotensin receptor antagonists, n (%)	551 (20.1)	177 (20.0)	198 (21.2)	147 (19.3)	29 (18.2)	nt
Nonsteroidal anti-inflammatory drugs, n (%)	427 (15.6)	122 (13.8)	140 (15.0)	132 (17.3)	33 (20.8)	ns
Calcium antagonists, n (%) (dihydropyridines)	403 (14.7)	129 (14.6)	130 (13.9)	121 (15.9)	23 (14.5)	nt
Antidepressants*, n (%)	340 (12.4)	119 (13.4)	88 (9.4)	103 (13.5)	30 (18.9)	<0.05$
Oral antidiabetics (other than sulfonylureas, n (%)	238 (12.0)	119 (13.4)	111 (11.9)	84 (11.0)	14 (8.8)	nt
Sulfonylureas, n (%)	205 (7.5)	70 (7.9)	67 (7.2)	58 (7.6)	10 (6.3)	nt
Phenprocoumon, n (%)	201 (7.3)	56 (6.3)	76 (8.1)	62 (8.1)	7 (4.4)	ns
Potassium sparing diuretics, n (%)	161 (5.9)	57 (6.4)	53 (5.7)	38 (5.0)	13 (8.2)	nt
Clopidogrel, n (%)	136 (5.0)	43 (4.9)	37 (4.0)	48 (6.3)	8.0 (5.0)	nt
Insulin, n (%)	133 (4.9)	40 (4.5)	40 (4.3)	45 (5.9)	8 (5.0)	nt
Allopurinol, n (%)	122 (4.4)	43 (4.9)	42 (4.5)	27 (3.5)	10 (6.2)	nt
Acenocoumarol, n (%)	119 (4.3)	27 (3.0)	44 (4.7)	41 (5.4)	7 (4.4)	ns
Calcium antagonists (verapamil or diltiazem), n (%)	100 (3.6)	33 (3.7)	30 (3.2)	31 (4.1)	6 (3.8)	nt
Amiodarone, n (%)	82 (3.0)	29 (3.2)	26 (2.8)	23 (3.0)	4 (2.5)	ns
Digoxin, n (%)	67 (2.4)	21 (2.4)	19 (2.0)	23 (3.0)	4 (2.5)	nt
Tramadol , n (%)	24 (0.9)	12 (1.4)	5 (0.5)	7 (0.9)	--	nt
St. Johns wort, n (%)	23 (0.8)	8 (0.9)	8 (0.9)	5 (0.7)	2 (1.3)	nt
Gingko, n (%)	18 (0.7)	5 (0.5)	9 (1.0)	4 (0.5)	--	nt
Fibrates, n (%)	17 (0.6)	10 (1.1)	3 (0.3)	3 (0.4)	1 (0.6)	nt
Ciclosporin, n (%)	8 (0.3)	--	4 (0.4)	3 (0.4)	1 (0.6)	nt
Methotrexate, n (%)	6 (0.2)	2 (0.2)	2 (0.2)	--	2 (1.3)	nt
Azathioprin, n (%)	4 (0.1)	--	1 (0.1)	3 (0.4)	--	nt
Nicotinic acid, n (%)	3 (0.1)	--	2 (0.2)	1 (0.1)	--	nt
Azole antifungals (systemic), n (%)	2 (0.1)	--	--	2 (0.3)	--	nt

Table 7 Co-medication prescribed in 2742 statin users stratified according to individual statin. *excluding St. Johns wort extract; † Number of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm); & ACE-inhibitors: simvastatin > atorvastatin; simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm); $ Antidepressants: atorvastatin > pravastatin; fluvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm); nt = not tested to avoid multiple testing on the same sample; ns = no significant difference;

Overall, 190 (6.9%) of the 2742 patients with 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 (see Table 8). The prevalence of potentially critical drug-statin interactions was 12.1% (95% CI 9.7 to 14.4%) in patients with simvastatin, 10.0% (95% CI 8.0 to 12.1%) with atorvastatin, 3.8% (95% CI 0.5 to 7.1%) with fluvastatin, and 0.3% (95% CI 0.1 to 0.7%) with pravastatin. The potentially interacting drugs comprised other lipid lowering drugs (fibrates, nicotinic acid), known CYP 3A4 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.

Potential interactions	Total	Atorvastatin	Pravastatin	Simvastatin	Fluvastatin
Total number of patients with potential interactions, n	190	89	3	92	6
Total number of potential interactions, n (%)	198 (100.0)	96 (100.0)	3 (100.0)	93 (100.0)	6 (100.0)
Other lipid lowering drugs, n (%)	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)	--	--	1 (1.1)	--
CYP3A4 inhibitors, n (%)	129 (65.2)	66 (68.8)	NA	63 (67.7)	NA
Amiodarone	52 (26.3)	29 (30.2)	--	23 (24.7)	--
Verapamil	40 (20.2)	21 (21.96)	--	19 (20.4)	--
Diltiazem	5 (2.5)	--	--	5 (5.4	--
Fluoxetine / Norfluoxetine	24 (12.1)	13 (13.5)	--	11 (11.8)	--
Nefazodone	3 (1.5)	3 (3.1)	--	--	--
Clarithromycin	3 (1.5)	--	--	3 (3.2)	--
Azole antifungal (systemic)	2 (1.0)	--	--	2 (2.2)	--
CYP2C9 inhibitors, n (%)	5 (2.5)	NA	NA	NA	5 (83.3)
Fluoxetine / Norfluoxetine	5 (2.5)	--	--	--	5 (83.3)
P-gp substrates, n (%)	43 (21.7)	20 (20.8)	NA	23 (24.7)	--
Digoxin	43 (21.7)	20 (20.8)	--	23 (24.7)	--
Others, n (%)	3 (1.5)	--	--	3 (3.2)	--
Ciclosporin	3 (1.5)	--	--	3 (3.2)	--

Table 8 List of 198 potential drug-statin interactions in 190 dyslipidemic patients treated with a statin; eight patients had two potential interactions (7 in the atorvastatin and 1 in the simvastatin group). NA = not applicable; ns = no significant difference

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 to 1.4, $p < 0.001$), diagnosis of cardiac failure (adjusted OR 1.8; 95% CI 1.1 to 3.1, $p = 0.03$),

diagnosis of arrhythmias (adjusted OR 5.6; 95% CI 3.6 to 8.5, p < 0.001), and being a patient from the French speaking part of Switzerland (adjusted OR 1.5; 95% CI1.1 to 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% confidence interval 0.01 to 0.07, p < 0.001) compared to use of other statins.

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 (CYP 2C9 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 which 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 SJW). 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 *(Clarke & Waskell, 2003)* remains controversial *(Saw et al., 2003; Wienbergen et al., 2003)* and was therefore not included in our analysis. No patient was reported to have signs or symptoms of myopathy during data collection.

2.1.4.2 Non-statin drug-drug interactions

In 288 patients of 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 which were detected most often are listed in Table 9. Patients treated with ACE-inhibitors, potassium sparing diuretics, beta-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), 14% were pharmacokinetic, and in 21% the mechanism was unclear.

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

Interaction	n (%)	Mechanism and/or potential risk
ACE-inhibitor – potassium sparing diuretic	51 (13.0)	Hyperkalemia 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 hypokalemia and hyomagnesemia, enhancing Na^+-K^+-ATP-ase 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 – beta-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 – oral anticoagulant (phenprocoumon, acenocoumarol)	27 (6.9)	Combination of thrombocyte aggregation inhibition and anticoagulant is associated with increased risk of bleeding
Beta-blocker – antidiabetic agents	22 (5.6)	Blockade of β_2-receptors impairs glycogenolysis and peripheral manifestations of hypoglycemia (described for insulin or sulfonylureas, but not for thiazolidindiones, acarbose or metformin)
Digoxin – beta-blocker	21 (5.3)	Additive prolongation of AV-conduction time. Digoxin toxicity due to competition for intestinal P-gp (described for talinolol)
Diltiazem / verapamil – beta-blocker	18 (4.6)	Additive negative inotropic effects and impaired AV conduction possibly leading to hypotension, bradycardia and conduction blocks
Gingko – aspirin / oral anticoagulants (phenprocoumon, acenocoumarol)	16 (4.1)	Increased risk of bleeding due to inhibition of thrombocyte aggregation by gingko
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 †	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 MAOI
CYP inducers* – critical CYP substrates**	9 (2.3)	Clearance of CYP substrates increased
CYP inhibitors*** – critical CYP substrate****	7 (1.8)	Clearance of CYP substrates decreased
Potassium – ACE-inhibitors	6 (1.5)	Increased potassium retention and risk for hyperkalemia secondary to lowered aldosterone levels caused by ACE-inhibitor
Potassium – potassium sparing diuretics	5 (1.3)	Increased potassium retention and risk for hyperkalemia
Methrotrexate - NSAID	5 (1.3)	Increased MTX toxicity due to decreased renal methotrexate clearance due to NSAID induced impairment of renal perfusion and competition of tubular secretion
other	26 (6.6)	NA

Table 9 Description of 393 critical non-statin DDIs in 288 patients with dyslipidemia. * - *** = the drugs listed (CYP inducers, CYP substrates, CYP inhibitors) contain the drugs, which were prescribed during the current study. The list does, therefore, not necessarily contain the typical drugs interacting with CYPs. NA = not applicable; MAOI = monoamine oxidase inhibitors; * phenobarbital, primidone, phenytoin, carbamazepine, SJW, rifampicin; ** phenprocoumon, acenocoumarol, clonazepam, clozapine, antiepileptics; *** amiodarone, fluoxetine, fluvoxamine; **** thioridazine, cisapride, verapamil, alprazolam, amitriptyline; † tricyclic antidepressants, selective serotonine reuptake inhibitors (SSRI), neuroleptics, MAOI

2.1.5 Discussion

Our study demonstrates that overall, approximately 7% of all patients prescribed a statin have a potentially critical 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 *(Heerey et al., 2000)*. 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 *(Heerey et al., 2000)*. In the Irish study, inhibitors, inducers and substrates of CYP3A4 and CYP2C9 were regarded as drugs potentially interacting with statins *(Heerey et al., 2000)*. 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 potentially interacting with statins. Moreover, CYP3A4 and/or CYP 2C9 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 and SJW) 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 DDIs before transmitting it. The true prevalence of DDIs 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 *(Omar & Wilson, 2002)*. A recent analysis of FDA reports on statin-associated rhabdomyolysis revealed that mibefradil, fibrates, ciclosporin, macrolides (especially erythromycin, clarithromycin), warfarin, digoxin, azole antifungals, nicotinic acid, tacrolimus, chlorzoxazone and nefazodone were the drugs or drug classes most often involved as potential interacting drugs in patients with statin-induced rhabdomyolysis. From our data, showing that 7% of patients treated with a statin have a potential drug-statin interaction, it can be estimated that drug-statin interactions increase the risk for rhabdomyolysis approximately 6-fold. This figure corresponds well with an estimated 10-fold increase in the risk of rhabdomyolysis reported by Omar et al *(Omar & Wilson, 2002)*, confirming our findings and calculations. Statin-induced rhabdomyolysis remains therefore a rare event, occurring in 0.04-0.2% of statin treated patients, even in the presence of an interacting drug *(Omar & Wilson, 2002)*. 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, due 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 *(Wooltorton, 2001)*.

Our study defines several risk factors associated with the presence of a potentially critical drug-statin interaction. The individual statin chosen for treatment of dyslipidemia is the most important one. Similar to other epidemiological studies *(Einarson et al., 2002; Heerey et al., 2000)* and published case series of

patients with statin-induced rhabdomyolysis *(Omar & Wilson, 2002)*, 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 metabolized by CYP2C9 *(Horsmans, 1999; Williams & Feely, 2002)*; CYP2C9 inhibitors are less often used in dyslipidemic patients than CYP3A4 inhibitors *(Heerey et al., 2000)*. For pravastatin, potential interactions seem to be even rarer than for fluvastatin, since this statin is not metabolized by CYP450 enzymes, 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 statins and digoxin, which can increase the plasma digoxin level 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 *(Sakaeda et al., 2002)*. Regarding the narrow therapeutic range of digoxin, this interaction may be clinically relevant for the above mentioned statins, but not with pravastatin *(Triscari et al., 1993)*, which does not inhibit P-gp *(Bogman et al., 2001; Sakaeda et al., 2002)*

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 *(Bogman et al., 2001; Yeo & Yeo, 2001)*, and amiodarone is an efficient inhibitor of several CYPs, among them CYP3A4 and CYP2C9 *(Yamreudeewong et al., 2003)*.

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. OATP2/OATP-C-mediated transport has been identified not only for pravastatin *(Hsiang et al., 1999; Nakai et al., 2001)*, but also for simvastatin *(Hsiang et al., 1999)*, fluvastatin *(Hsiang et al., 1999)*, atorvastatin *(Lennernas, 2003)*, and cerivastatin *(Shitara et al., 2003)*. Shatira et al. 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 levels of cerivastatin in the presence of ciclosporin are mainly due to impairment of hepatic uptake than inhibition of CYP3A4 *(Shitara et al., 2003)*. The same mechanism may be responsible for the DDI with ciclosporin and pravastatin *(Regazzi et al., 1993)*. Recently, the PK interaction between gemfibrozil and pravastatin has been investigated in more detail. The increase in the pravastatin plasma concentration could be explained by both a decrease in renal clearance and in hepatic uptake *(Kyrklund et al., 2003)*.

As expected and as shown in previous studies *(Hohl et al., 2001; Rosholm et al., 1998)*, 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 in particular in patients with cardiac diseases, who are generally treated with more than one drug *(Cleland et al., 2000)*. 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, for instance ACE-inhibitors, digoxin, and potassium-sparing and loop diuretics, they all rank among the drugs with a high prevalence of potentially serious non-statin DDIs.

Potential non-statin DDIs 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 *(Egger et al., 2003)*. The administration of potassium supplements in patients treated with ACE-inhibitors is well known to be associated with hyperkalemia *(Burnakis & Mioduch, 1984; Chan & Critchley, 1992)*. The development of hyperkalemia in patients treated with ACE-inhibitors and low dose spironolactone, i.e. 25-50 mg daily as recommended for the treatment of heart failure *(Pitt et al., 1999)*, has been reported only recently *(Schepkens et al., 2001; Wrenger et al., 2003)*. Renal failure appears to be an additional risk factor for the development of hyperkalemia in patients treated with ACE-inhibitors, in particular when a drug-drug and/or diet-drug interaction is present *(Shlipak, 2003; Wrenger et al., 2003)*. Concomitant use of loop or thiazide diuretics may diminish the risk of hyperkalemia of ACE-inhibitors and potassium supplements or potassium-sparing diuretics, but we still recommend that patients treated with such combinations should be followed carefully, in particular 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 *(Lupton & Odom, 1979)*. While examples for this interaction only exist as case reports *(Ahmad, 1995; Pennell et al., 1984; Samanta & Burden, 1984)*, the clinical outcome for the allopurinol-associated hypersensitivity syndrome is potentially so serious (fatalities are reported *(Kumar et al., 1996; Lupton & Odom, 1979; Singer & Wallace, 1986)*) that it may be prudent to avoid this drug combination.

Patients with psychiatric disorders, in particular depression, were also identified as risk group for non-statin DDIs. While tri- and tetracyclic antidepressants are generally not relevant inhibitors or inducers of CYPs, this is different for SSRIs *(Richelson, 1997)*. Significant inhibition of CYPs have been described for fluvoxamine (inhibition of CYP1A2, CYP2C19 and CYP3A4), paroxetine (CYP2D6) and fluoxetine (CYP2D6, CYP1A2, CYP3A4 and CYP2C9) *(Richelson, 1997; Skerritt et al., 1997; Sproule et al., 1997)*. 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 *(Guck et al., 2003)*.

None of the patients included in this study had symptoms or signs of an ADR due to a statin or non-statin DDI. Regarding other reports in the literature, where approximately 6% of patients with a critical DDI have adverse effects *(Puckett & Visconti, 1971; Schuster et al., 1982)*, some ADR 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 ADR. Additionally, we did not have direct access to the patient records to identify adverse clinical outcomes in association with a DDI, potentially favoring underreporting of DDI-associated ADR. Moreover, the medication screened included only those drugs prescribed by the physician taking part in the study. It is possible that patients may have visited other physicians prescribing additional drugs that were unknown to the physician treating the patient for dyslipidemia. Therefore, the prevalence of potential statin or non-statin DDIs in this population may be even higher than the one assessed in this study.

2.1.6 Conclusions

In conclusion, our study shows that CYP3A4 inhibitors are the most frequent cause of potential DDIs with statins. Although statin-induced rhabdomyolysis is a rare event even in patients having a drug-statin interaction, the possibly severe outcome of rhabdomyolysis favors 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 dyslipidemia, mostly due to 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.

2.2 The prevalence of potential drug-drug interactions in ambulatory patients with dyslipidemia in different parts of Switzerland

Drug interactions in dyslipidemic patients

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2.2.1 Summary

The aim of this investigation was the assessment of the prevalence of DDIs in dyslipidemic patients from different parts of Switzerland. Data of dyslipidemic patients treated with a statin were collected from 242 practitioners in Switzerland. The medication was screened electronically for potentially harmful DDIs. DDIs were analyzed according to the statin used, additional diagnoses, co-medication, and speciality and location of the practitioners. The 2742 statin-treated patients screened originated from the German (53.3%), French (36.0%), or Italian (10.7%) part of Switzerland, had a mean age of 65.1 ± 11.2 years, 3.2 ± 1.6 diagnoses and 4.9 ± 2.4 drugs prescribed. The speciality of the practitioners showed no regional differences, but the prescribing pattern differed slightly among regions. Of the patients screened, 401 (14.6%) had 591 potentially severe DDIs. Hereof, 190 patients (6.9%) had potential statin DDIs and 288 (10.5%) potential non-statin DDIs, mainly with pharmacodynamic mechanisms. The prevalence of potential DDIs was similar between regions, except for a tendency for a higher prevalence of drug-statin interactions in the French speaking part. There were no significant differences in the prevalence of potential DDIs among the specialities of the practitioners. The number of drugs per patient and a diagnosis of arrhythmia or heart failure were risk factors for DDIs. In conclusion, drug combinations with potentially severe DDIs are common in patients with dyslipidemia due to treatment of their co-morbidities. Special attention should be drawn to patients with an increased risk for potential DDIs, namely those with ≥7 drugs, and patients with heart failure or arrhythmias.

2.2.2 Introduction

DDIs are an important cause for ADRs. It has been estimated that approximately 5% of prescribing errors *(Fijn et al., 2002)* or of ADRs *(Classen et al., 1997)* are due to DDIs in hospitalized patients. In a recent investigation, 2.3% to 7.8% of ADR in association with the use of co-trimoxazole, digoxin or ACE-inhibitors were found to be due to interactions with concomitant drugs *(Juurlink et al., 2003)*. Polypharmacy, which is associated with the number of diagnoses in a given patient *(Grymonpre et al., 1988)*, has been identified as a major risk factor for DDIs. Considering individual drugs, the way a drug is metabolized and/or excreted is a major determinant of potential DDIs *(Herrlinger & Klotz, 2001)*. Drugs metabolized by CYPs have a particularly high risk for DDIs because of the large number of drugs inhibiting or inducing CYPs *(Herrlinger & Klotz, 2001; Meyer, 2000)*. 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-gp, e.g. interactions between statins and digoxin *(Hoffman, 1992)* or clarithromycin and digoxin *(Tanaka et al., 2003; Wakasugi et al., 1998)*.

Interactions with statins can lead to rhabdomyolysis, a severe ADR which may be fatal *(Federman et al., 2001; Weise & Possidente, 2000)*. A recent study in Ireland estimated that approximately 30% of all users of statins have concomitant drugs prescribed, which can influence statin metabolism, potentially leading to rhabdomyolysis *(Heerey et al., 2000)*. It is known that the interaction potential differs between individual statins *(Farmer & Torre-Amione, 2000; Horsmans, 1999)*. Atorvastatin, lovastatin and simvastatin

are all biotransformed by CYP3A4, the most abundant CYP isozyme, which metabolizes most drugs undergoing CYP-associated biotransformation *(Meyer, 2000; Rogers et al., 2002)*. Accordingly, the risk for interactions is highest for drugs metabolized by CYP3A4, particularly if no other CYP isozymes are involved in their biotransformation. Fluvastatin is primarily metabolized by CYP2C9, an isozyme by which less drugs are metabolized than by CYP3A4, making this drug less prone to DDIs *(Chong et al., 2001; Igel et al., 2001)*. Pravastatin is more hydrophilic due to a hydroxyl group, allowing conjugation of the drug without previous phase I biotransformation *(Farmer & Torre-Amione, 2000; Horsmans, 1999)*. Accordingly, the risk for interactions with pravastatin is estimated to be lower than for statins undergoing CYP-dependent metabolism *(Chong et al., 2001; Igel et al., 2001)*. Because data about the prevalence and about risk factors of potential DDIs in ambulatory patients are rare and because DDIs in patients treated with statins can lead to severe adverse effects *(Federman et al., 2001; Omar & Wilson, 2002; Weise & Possidente, 2000)*, we identified potential DDIs in ambulatory, dyslipidemic patients treated with a statin. Specific aims were to assess the prevalence of potential DDIs in association with statin therapy (drug-statin interactions) and of potential DDIs not involving statins (non-statin DDIs), and to identify regional differences and risk factors for potential DDIs in this population.

2.2.3 Methods

2.2.3.1 Subjects, design, data collection and data managing

Between February to April 2002, practitioners from different parts of Switzerland screened all patients attending their practice during five consecutive days and filled out a data sheet of each dyslipidemic patient treated with a statin. The collection and management of the data, and screening for potential DDIs with Drug-Reax® *(Klasco & Moore, 1974 - 2002.)*, an electronic drug interaction detection program, have been described in detail elsewhere *(Rätz Bravo et al., 2004)*. Shortly, information on year of birth, sex, main diagnoses and all concomitantly prescribed drugs were collected. All patient data were recorded in an electronic database and all drug profiles were screened semiautomatically by the online version of Drug-Reax®. Over 30'000 drug-drug pairs were screened and cases with a severe DDIs were individually evaluated.

2.2.3.2 Evaluation of clinical relevance of potential non-statin drug-drug interactions

Each drug profile with a possible drug-statin interaction of any severity or a non-statin DDI of major severity according to the severity rating of the interaction program was evaluated by a pharmacist and a clinical pharmacologist for its clinical relevance. In addition, DDIs not recognized by the interaction program, but by manual screening of the drug profile using standard literature *(Stockley, 1999; Tatro, updated January 2003)*, an additional online drug interaction database (www.pharmavista.ch) and/or Medline, were also evaluated. DDIs were considered as potentially harmful (and therefore clinically relevant), if the potential adverse effect of this interaction could have had a serious outcome as defined by the ICH guidelines for clinical safety data management of adverse drug reactions *(ICH, 1994)*. The procedure of evaluation of the clinical relevance of the observed potential DDIs is described in more detail elsewhere *(Rätz Bravo et al., 2004)*..

2.2.3.3 Statistical analysis

Data are presented as mean±SD unless specified otherwise. All statistical analyses were performed with the SPSS for Windows software package version 10.1.4 (SPSS Inc., Chicago, Illinois 60606).

Possible differences in the number of drugs per patient according to geographical region, and differences between DDIs stratified for statins, geographical region or speciality of the practitioner were tested by one-way ANOVA, or Pearson's χ^2 in the case of categorical variables. The 5%-significance level (α-criterion) was adjusted for multiple testing according to Bonferroni-Holm *(Holm, 1979)*.

Potential drug-statin and non-statin DDIs were analyzed further by logistic regression 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 or 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 / hyperuricemia, epilepsia, other diagnoses, general practitioner, internist, cardiologist, and other speciality. The continuous variables included in the model were age (years), number of diagnoses and number of prescribed drugs. 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. Explanatory variables were included in the final model, if their p-value was < 0.1 to detect trends. Relative risks are expressed as odds ratios (ORs) with the corresponding confidence interval (95% CI).

2.2.4 Results

From February through April 2002, 242 practitioners from different parts in Switzerland (53.3% from the German, 36.0% from the French, and 10.7% from the Italian speaking part) recorded medications and diagnoses of 2742 patients treated with a statin for dyslipidemia. When stratified for geographical region, there were no significant differences in the specialities of the participating physicians (data not shown).

The 2742 patients studied were 65.1±11.2 years old, had an average of 3.2±1.6 diagnoses and were prescribed 4.9±2.4 drugs. Thirty-eight percent of the patients were female, 49% were recruited from the German, 38% from the French, and 13% from the Italian part of Switzerland. Important diagnoses in addition to dyslipidemia were arterial hypertension (52.1% of the patients studied), coronary heart disease (42.5%), diabetes mellitus (19.0%), peripheral arterial occlusive disease (16.8%), psychiatric illnesses (15.4%), rheumatic diseases / diseases of the musculoskeletal system (15.2%), arrhythmias (6.9%), and heart failure (4.7%).

As shown in Figure 3A, there was a linear correlation between the number of diagnoses per patient and the number of drugs prescribed. For the first diagnosis, an average of 2.9 drugs are prescribed and 0.9 additional drugs for each following diagnosis. The prescribing pattern for drugs relevant for interactions was slightly different between the regions of Switzerland investigated (Table 10). Acetylsalicylic acid, clopidogrel, and angiotensin receptor blockers were prescribed less often in the Italian, and beta-blockers and dihydropyridine calcium channel blockers less often in the French speaking part of Switzerland. Patients in

the Italian part of Switzerland were treated more often with psychotropic drugs like antidepressants or benzodiazepines. Phenprocoumon is the anticoagulant used predominantly in the German speaking part, while acenocoumarol is used primarily in the French part of Switzerland. Concomitant medication not considered relevant for interactions, and therefore not listed in Table 10, accounted for 22% of all drugs prescribed. Onehundred-twentytwo patients (4.4%) had no drug prescribed in addition to the statin.

Overall, 591 drug combinations with the potential for a critical DDI were detected in 401 patients (14.6% of the patients studied). In 190 patients (6.9%), there were 198 drug combinations with the potential for a critical drug-statin interaction, and, 393 drug combinations with a critical non-statin DDI were detected in 288 patients (10.5%). While potential statin DDIs were predominantly pharmacokinetic interactions involving CYPs, potential non-statin DDIs where mostly pharmacodynamic interactions involving cardiovascular drugs. As shown in Table 11, patients prescribed pravastatin or fluvastatin had less drug-statin or total DDIs than patients prescribed atorvastatin or simvastatin. A detailed analysis of these data has revealed that this is due to a reduced number of interactions with CYP3A4 inhibitors in patients treated with pravastatin or fluvastatin *(Rätz Bravo et al., 2004)*. Interestingly, the prevalence of non-statin DDIs was not different when stratified per statin prescribed.

Stratification of the number of DDIs according to the geographical region revealed a tendency for more total and non-statin DDIs in the Italian, and more drug-statin interactions in the French speaking part of Switzerland (Table 12). While the mean number of diagnoses per patient was the same in the different parts of Switzerland, the mean number of drugs prescribed per patient was significantly lower in the French speaking part. As shown in Table 13, the prevalence of potential DDIs was not different when stratified according to the speciality of practitioners.

Logistic regression analysis indicated that the following variables were associated with an increased relative risk for potentially critical non-statin DDIs in the final regression model: Diagnosis of arrhythmias (adjusted OR 3.50; 95% CI 2.4 to 5.2, $p < 0.001$), heart failure (adjusted OR 3.3; 95% CI 2.1 to 5.1, $p < 0.001$), gout (adjusted OR 2.9; 95% CI 1.7 to 4.9, $p < 0.001$) or cerebrovascular diseases (adjusted OR 1.6; 95% CI 1.1 to 2.2, $p = 0.007$), number of prescribed drugs (adjusted OR 1.6; 95% CI 1.5 to 1.7, $p < 0.001$) and male sex (adjusted OR 1.4, 95% CI 1.1 to 1.9, $p = 0.017$). Considering potential drug-statin interactions, the number of drugs per patient, and heart failure and/or arrhythmias were also risk factors, but not cerebrovascular diseases or gout. In addition, being a patient from the French speaking part of Switzerland was identified as a risk factor for statin DDIs (adjusted OR 1.5; 95% CI 1.1 to 2.1, $p = 0.018$) and the use of pravastatin was associated with a lower risk for potentially critical statin DDIs (adjusted OR = 0.02, 95% confidence interval 0.01 to 0.07, $p < 0.001$) when compared to the use of other statins. The speciality of the practitioner was not associated with a higher risk for potentially critical statin or non-statin DDIs. As suggested by the regression analysis, the number of drugs per patient shows a strong correlation with the prevalence of critical drug-statin or non-statin DDIs (Figure 3B).

As shown in Figure 4A, the number of diagnoses and, consequently, the number of drugs prescribed per patient increase with age. Since polypharmacy is a strong risk factor for DDIs (Figure 4B and (Grymonpre et al., 1988)), the prevalence of potential DDIs shows also an increase with age. Twenty percent of the dyslipidemic patients ≥70 years have one or more potentially severe DDI.

	Switzerland overall	German speaking part	French speaking part	Italian speaking part	p-value
Patients, n (%)	2742 (100.0)	1349 (100.0)	1040 (100.0)	353 (100.0)	
Mean number of drugs per patient (±SD)	4.9 (2.4)	5.0 (2.4)	4.6 (2.3)	5.2 (2.3)	< 0.05
Statins (overall)					< 0.05
Atorvastatin, n (%)	866 (32.2)	452 (33.5)	334 (32.1)	100 (28.3)	
Pravastatin, n (%)	934 (33.9)	447 (33.1)	382 (31.5)	105 (29.7)	
Simvastatin, n (%)	763 (27.7)	391 (29.0)	280 (26.9)	92 (26.1)	
Fluvastatin, n (%)	159 (5.8)	59 (4.4)	44 (4.2)	56 (15.9)	
Acetylsalicylic acid, n (%)	1258 (45.9)	701 (52.0)	426 (41.0)	131 (37.1)	< 0.05
Beta-blockers, n (%)	1145 (41.8)	633 (46.9)	358 (34.4)	154 (43.6)	< 0.05
Thiazide or loop diuretics, n (%)	900 (32.8)	482 (35.7)	319 (30.7)	99 (28.0)	ns
ACE-inhibitors, n (%)	778 (28.4)	403 (29.9)	264 (25.4)	111 (31.4)	ns
Angiotensin receptor antagonists, n (%)	551 (20.1)	256 (19.0)	239 (23.0)	56 (15.9)	< 0.05
Benzodiazepine, n (%)	499 (18.2)	191 (14.2)	200 (19.2)	108 (30.6)	< 0.05
NSAIDs, n (%)	427 (15.6)	190(14.1)	157 (15.1)	80 (22.7)	ns
Calcium antagonists (dihydropyridines), n (%)	403 (14.7)	224 (16.6)	116 (11.2)	63 (17.8)	< 0.05
Antidepressants*, n (%)	340 (12.4)	142 (10.5)	142 (13.7)	56 (15.9)	< 0.05
St. John's wort, n (%)	23 (0.8)	19 (1.4)	1 (0.1)	3 (0.8)	nt
Oral antidiabetics (other than sulfonylureas), n (%)	328 (12.0)	157 (11.6)	132 (12.7)	39 (11.0)	nt
Sulfonylureas, n (%)	205 (7.5)	100 (7.4)	79 (7.6)	26 (7.4)	nt
Insulin, n (%)	133 (4.9)	79 (5.9)	40 (3.8)	14 (4.0)	nt
Phenprocoumon, n (%)	201 (7.3)	169 (12.5)	14 (1.3)	18 (5.1)	nt
Acenocoumarol, n (%)	119 (4.3)	12 (0.9)	88 (8.5)	19 (5.4)	nt
Potassium sparing diuretics, n (%)	161 (5.9)	91 (6.7)	54 (5.2)	16 (4.5)	nt
Clopidogrel, n (%)	136 (5.0)	56 (4.2)	44 (4.2)	36 (10.2)	< 0.05
Allopurinol, n (%)	122 (4.4)	59 (4.4)	48 (4.6)	15 (4.2)	nt
Neuroleptics, n (%)	98 (3.6)	39 (2.9)	32 (3.1)	27 (7.6)	nt
Calcium antagonists (verapamil or diltiazem), n (%)	100 (3.6)	54 (4.0)	34 (3.3)	12 (3.4)	nt
Amiodarone, n (%)	82 (3.0)	41 (3.0)	30 (2.9)	11 (3.1)	nt
Digoxin, n (%)	67 (2.4)	37 (2.7)	23 (2.2)	7 (2.0)	nt
Tramadol, n (%)	24 (0.9)	11 (0.8)	11 (1.1)	2 (0.6)	nt
Gingko, n (%)	18 (0.7)	13 (1.0)	2 (0.2)	3 (0.8)	nt
Fibrates, n (%)	17 (0.6)	7 (0.5)	9 (0.9)	1 (0.3)	nt

Table 10 Drug therapy of the patients included according to geographical region. Data are given as the number of patients treated with a specific drug (percentage of patients in the respective geographical region in parenthesis). Drugs prescribed in less than 10 patients or without relevant interactions (accounting for 2953 drugs or 22% of all drugs prescribed) are not shown in this Table. nt = not tested to avoid multiple testing on the same sample; ns = no significant difference

	Total	Atorvastatin	Pravastatin	Simvastatin	Fluvastatin	p-value
Patients, n (%)	2742 (100.0)	886 (100.0)	934 (100.0)	763 (100.0)	159 (100.0)	
Total number of patients with interactions, n (%)	401 (14.6)	146 (16.5)	94 (10.1)	136 (17.8)	25 (15.7)	< 0.005
Number of patients with drug-statin interactions, n (%)	190 (6.9)	89 (10.0)	3 (0.3)	92 (12.1)	6 (3.8)	< 0.005
Number of patients with DDIs other than statins, n (%)	288 (10.5)	96 (10.8)	91 (9.7)	82 (10.7)	19 (11.9)	ns

Table 11 Overall prevalence of potential DDIs in dyslipidemic patients stratified by individual statin. Data are given as the number of patients with the respective DDI (percentage of patients in the respective group in parenthesis). ns = no significant difference

	Switzerland overall	German speaking part	French speaking part	Italian speaking part	p-value
Patients, n (%)	2742 (100.0)	1349 (100.0)	1040 (100.0)	353 (100.0)	
Mean number of diagnoses per patient (± SD)	3.2 (1.55)	3.3 (1.57)	3.2 (1.51)	3.3 (1.52)	ns
Mean number of drugs per patient (± SD)	4.9 (2.4)	5.0 (2.4)	4.6 (2.3)	5.2 (2.3)	< 0.05
Total number of patients with interactions, n (%)	401 (14.6)	200 (14.8)	144 (13.8)	57 (16.1)	ns
Number of patients with drug-statin interactions, n (%)	190 (6.9)	86 (6.4)	78 (7.5)	26 (7.4)	ns
Number of patients with DDIs other than statins, n (%)	288 (10.5)	154 (11.4)	93 (8.9)	41 (11.6)	ns

Table 12 Prevalence of potential DDIs in dyslipidemic patients from different parts of Switzerland. Data are given as the number of patients with the respective DDI (percentage of patients in the respective group in parenthesis). ns = no significant difference

	Total	General practitioner	Internist	Cardiologist	Others	p-value
Practitioners, n	242	104	101	33	4	
Patients, n (%)	2742 (100)	1125 (100)	1167 (100)	412 (100)	38 (100)	
Patients with a DDI, n (%)	401 (14.6)	158 (14.0)	167 (14.3)	72 (17.5)	4 (10.5)	ns
Patients with a drug-statin interaction, n (%)	190 (6.9)	79 (7.0)	80 (6.9)	30 (7.3)	1 (2.6)	ns
Patients with a non-statin DDI, n (%)	288 (10.5)	110 (9.8)	120 (10.3)	54 (13.1)	4 (10.5)	ns
Patients with both interactions, n (%)	77 (2.8)	31 (2.8)	33 (2.8)	12 (2.9)	1 (2.6)	ns

Table 13 Number of drugs and percentage of patients with DDIs stratified by the speciality of participating physicians. ns = no significant difference

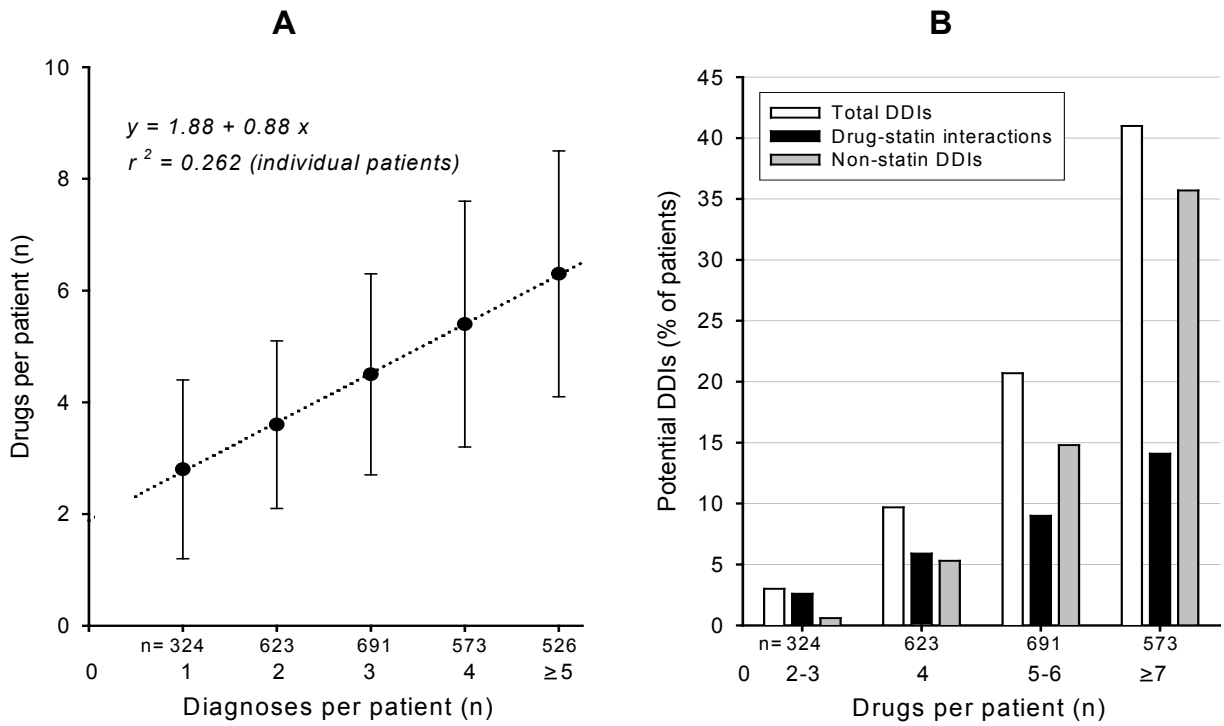

Figure 3 Relationship between diagnoses and drugs (A) and between drugs and potential DDIs per patient (B). There is a linear relationship between the number of diagnoses and the number of drugs a patient is treated with. Polypharmacy is a clear risk factor the the prevalence of potentially severe DDIs.

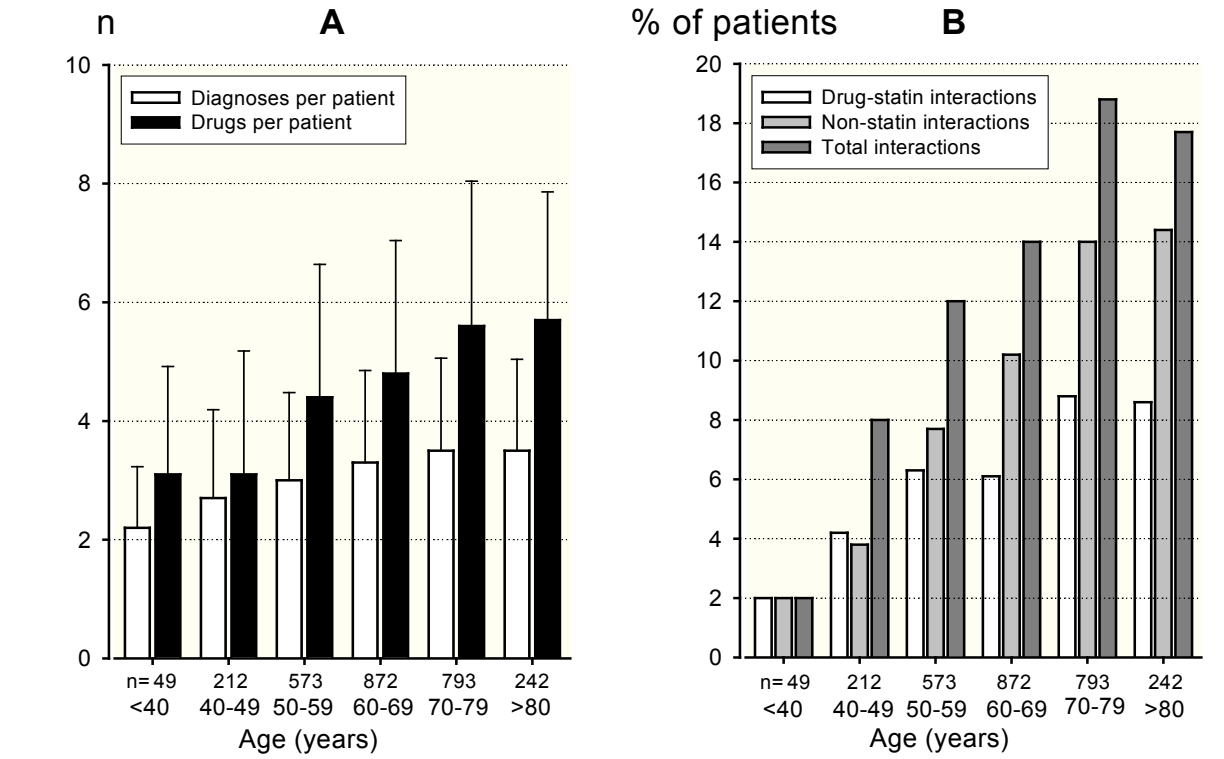

Figure 4 Age-dependency of diagnoses and drugs per patient (A) and prevalence of DDIs (B). The number of diagnoses and drugs increase with age. Accordingly, also the prevalence of DDIs shows and age-dependent increase.

2.2.5 Discussion

Our investigation demonstrates that overall, approximately 15% of all dyslipidemic patients prescribed a statin have a potentially critical DDI and that in approximately 40% of these interactions (7% of the patients studied), a statin is involved.

This prevalence is lower than in a recent Irish study, where potentially interacting drugs were detected in approximately 30% of patients treated with a statin *(Heerey et al., 2000)*. This discrepancy can be explained by different definitions of DDIs (in the Irish study, all potential DDIs were included, while we included only potentially severe interactions) and by differences in the prescribing pattern between Ireland and Switzerland. For instance, 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 treated with these drugs *(Heerey et al., 2000)*.

Statins have been shown to be associated with 3 different types of DDIs, namely inhibition of their metabolism by CYP inhibitors (leading to an increased statin plasma concentration) *(Martin & Krum, 2003)*, inhibition of P-gp (leading to an increase in the plasma concentration of P-gp substrates such as digoxin)*(Williams & Feely, 2002)*, and inhibition of the hepatic uptake of statins by ciclosporin or gemfibrozil (leading to an increased statin plasma concentration)*(Hsiang et al., 1999; Kyrklund et al., 2003; Shitara et al., 2003)*. The first two interaction types affect atorvastatin, simvastatin and lovastatin, whereas all statins are affected by the third type. As described by us *(Rätz Bravo et al., 2004)* and by others *(Grymonpre et al., 1988)*, CYP3A4 inhibitors are quantitatively the most important drug class interacting with statins, followed by digoxin, fibrates and ciclosporin. Strong risk factors for the presence of drug-statin interaction were therefore the choice of the individual statin, and a diagnosis of heart failure and/or arrhythmias. Since concomitant treatment with a CYP3A4 inhibitor is the most frequent DDI with statins *(Grymonpre et al., 1988)*, and fluvastatin and pravastatin are no CYP3A4 substrates *(Grymonpre et al., 1988)*, it is evident that patients treated with one of these statins have less potential statin DDIs than patients treated with simvastatin or atorvastatin (Table 2). In Switzerland, many patients with heart failure are still treated with digoxin, and patients with arrhythmias are often teated with verapamil and/or amiodarone, both inhibitors of CYP3A4 *(Michalets, 1998; Yeo & Yeo, 2001)*, explaining why heart failure and arrhythmias are risk factors for potential DDIs with statins.

Important risk factors for potentially severe non-statin DDIs included the number of concomitant drugs, and the diagnosis of heart failure and/or arrhythmias, cerebrovascular disease or gout. Polypharmacy is a well known risk factor for DDIs *(Grymonpre et al., 1988)*, as demonstrated also in our study (see Figure 1B). Our data suggest that dyslipidemic patients treated with ≥7 drugs have a prevalence of approximately 40% for one or more potential DDIs. In dyslipidemic patients treated with ≥7 drugs, any additional drug should therefore be screened thoroughly for being associated with potential DDIs. Since the number of diagnoses correlates with the number of drugs prescribed (*(Grymonpre et al., 1988)*, Figure 1A), and the number of diagnoses (and therefore also the number of drugs) is increasing with age (Figure 2A), elderly dyslipidemic patients have more potential DDIs than younger ones (Figure 2B). It is well established that renal and hepatic elimination processes are impaired in the elderly *(Swift, 2003)*, putting them at a high risk for developping adverse effects from potential DDIs which are associated with increased drug levels.

Similar to potential DDIs with statins, cardiovascular diseases were also risk factors for potential non-statin DDIs. In addition to the above mentioned CYP3A4 inhibitors and/or digoxin used in these patients, many interactions were due to the combination of ACE-inhibitors or angiotensin receptor blockers with potassium sparing diuretics and/or potassium supplements. While the combination of low dose spironolacton with ACE-inhibitors has been shown to reduce mortality in patients with heart failure *(Pitt et al., 1999)*, this combination has been described to be associated with potentially life-threatening hyperkalemia, particularly in patients with potassium supplements and/or impaired renal function *(Svensson et al., 2003)*. Another population at risk for potential non-statin DDIs are patients with gout. Allopurinol has been associated with a potentially severe DDI with ACE-inhibitors *(Ahmad, 1995; Pennell et al., 1984; Samanta & Burden, 1984)*, possibly by interfering with the renal elimination of allopurinol metabolites *(Hande et al., 1984)*. This combination can lead to a hypersensitivity syndrome associated with allopurinol *(Lupton & Odom, 1979)*, and is therefore best avoided.

While the prevalence of potential statin DDIs and of total DDIs was clearly dependent on the statin prescribed, this was not the case for non-statin DDIs. Physicians who prescribe statins with a lower interaction potential (pravastatin, fluvastatin) are therefore not more careful in avoiding non-statin DDIs than physicians prescribing statins with a higher interaction potential. Reasons other than the low interaction potential may therefore influence the prescription of pravastatin and fluvastatin.

Considering potential non-statin DDIs and total DDIs, there were no significant differences when stratified for geographical region or speciality of the practitioners included. Since the treatment of dyslipidemia and of the often associated cardiovascular diseases is quite standardized, this finding is not unexpected. Cardiologists had a tendency for prescribing more drug combinations which may result in DDIs than other specialists. This observation may be explained by referral of complex patients with complex drug lists to cardiologists.

Treatment in the French speaking part of Switzerland beeing a risk factor for a potential drug-statin interaction suggests the existence of regional differences in drug prescription. The finding reached statistical significance only in the logistic regression analysis, but not in the direct comparisons made in Table 12, which is explained by the different statistical techniques used. Although patients treated in the French speaking part were younger and were treated with a lower number of drugs as compared to the other regions, there was a tendency for a higher prevalence of drug-statin interactions. The exact reasons for this finding are not completely evident from the data in Table 10, but may be related to a higher use of fibrates in the French speaking part.

2.2.6 Conclusions

In conclusion, our study shows that potentially severe DDIs are frequent among dyslipidemic patients treated with a statin. Major risk factors include polymedication and accompanying cardiovascular diseases such as heart failure or cardiac arrhythmias. Patients at high risk are elderly, polymorbid patients with cardiovascular diseases. In Switzerland, there are no clinically significant differences in the prevalence of potential DDIs in dyslipidemic patients when stratified per geographical region or speciality of the

practitioners. Further investigations should address the question of how to prevent the prescription of potentially harmful DDIs and of the incidence of ADRs in patients with potentially severe DDIs.

CHAPTER III

CASE REPORTS OF

CLINICAL RELEVANT DRUG INTERACTIONS AND

ADVERSE EFFECTS

FROM A PHARMACOVIGILANCE CENTRE AND

DRUG-INFORMATION UNIT

IN SWITZERLAND

3.1 St. John's wort: A herbal drug with a high potential for drug interactions

Case report and review of the literature

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3.1.1 Summary

Over-the-counter preparations of SJW (hypericum perforatum L.) are widely used as ‘natural’ herbal medicine alternatively to traditional prescribed antidepressants. The antidepressive effect has been shown in numerous placebo-controlled studies. The mechanism of action is assumed to be at least in part, similar to conventional antidepressants, due to pre-synaptic serotonin reuptake inhibition as well as GABA-modulation and inhibition of monoaminoxidases. Because of its favorable safety profile compared to conventional antidepressants, the use of SJW preparations has gained high acceptance among practitioners and patients. However, any biologically active compound contains a certain risk of untoward adverse effects and/or interactions with other compounds, which are often unknown or not widely recognized, particularly in the instance of herbal remedies. Thus, practitioners, pharmacists, and patients might feel themselves in taking such compounds at present under a false sense of security. Recently, a variety of case reports on potentially hazardous interactions due to drug combinations with SJW have been published (e.g. cellular rejection of pancreas- / kidney- as well as heart transplants with ciclosporin; rise of INR with oral anticoagulants; break-through bleeding with oral contraceptives [OCs]); reduction of plasma concentration of digoxin, indinavir, amitriptyline, and theophylline). We report herein a case of irregular bleeding with oral-contraception and discuss the drug-herb interactions and the underlying mechanisms.

3.1.2 Introduction

The use of herbal medicines is often considered as ‘mild’ and ‘harmless’. Therefore, they are highly accepted and, today, are becoming more and more popular among patients sensitized for the risks of drug therapy. For these reasons, herbal medicines are frequently used as over-the-counter medication. From the classical medicine's point of view they have been insufficiently documented with regard to their efficacy and safety for many years. With the potentially beneficial effects of taking such herbal medicines based mostly on field reports and on studies, which were methodologically / scientifically debatable (for example non-randomised, non-placebo-controlled trials). In the practical experience of prescribing, practitioners prescribe them conservatively. By contrast, preparations of SJW pertain to the herbal preparations for which efficacy and safety has been investigated comparably well in the recent years. Its antidepressive efficacy has been well-documented in placebo-controlled trials, as well as in controlled trials, comparing its efficacy with tricyclic antidepressants or SSRIs. Preparations of SJW in the incidence of mild to moderate depression are used in ambulatory care as a herbal alternative to conventional antidepressants. The increasing consumption of SJW preparations is documented by rising sales from the USA and Europe. The market sales in the USA increased by 2800% within one year in 1998 *(Brevoort, 1998)*. In Germany, the volume of sales was approximately 6 mrd. USD in 1998 *(Harrison, 1998)* and in Switzerland around 8 million Swiss francs (prescriptions as well as over-the-counter sales, including tee) [personal communication, Zeller AG, CH-8590 Romanshorn]. Adverse effects of SJW preparations are clearly less frequent than with conventional antidepressants and are limited predominantly to mild gastrointestinal disturbances, tiredness, or phototoxicity. Recently, more and more case reports and clinical studies have reported interferences when conventional drug therapies were combined with SJW preparations, e.g. acute cellular rejection in transplant

patients treated with ciclosporin *(Barone et al., 2000; Bon et al., 1999; Ruschitzka et al., 2000)*, decreased plasma concentrations of HIV-protease inhibitors *(Piscitelli et al., 2000)*, decreased anticoagulation of phenprocoumon or warfarin *(Brenner et al., 2000; Martinek, 2000; Ruschitzka et al., 2000)*, decreased plasma concentration of theophylline *(Nebel et al., 1999)*, and cases of menstrual break-through bleeding with OCs *(Yue et al., 2000)*. Extracts of SJW may have an impact on the pharmacokinetic profile of digoxin. In a placebo-controlled trial with SJW and digoxin, a significant decrease in digoxin AUC and trough levels were measured, while no effect on digoxin half-life was observed *(Johne et al., 1999)*. Possible mechanisms for the interactions with SJW could be an induction of CYP3A4, 1A2 and 2C9 as well as of P-gp, an important transport protein for the absorption, elimination and distribution of drugs, are discussed. We report a case of menstrual bleeding and amenorrhea in a patient with OC treatment after introducing a SJW preparation for mild depression. The mechanisms of the interaction are discussed.

3.1.3 Case report

We describe a 33 years old patient who was taking OCs for many years. For approximately 1½ years her prescribed contraception consisted of a combination of ethinyl estradiol 0.03 mg and desogestrel 0.15 mg/day. She ingested the tablets for 21 days starting on Fridays, followed by a 7 day intermittence resulting in regular cycles with menstrual bleedings beginning on Monday mornings. Mid February 2000 the patient was complaining of depressive mood disorders. She started a self-medication with a sedative herbal preparation for approximately three days, possibly a SJW preparation. Subsequently she was prescribed a therapy with 3 x 300 mg of SJW extract Li 160, standardized on 0.03% hypericine, combined with 12.5 mg trimipramine each evening before bed time. The day to take the last OC pill would have been approximately two weeks later, followed by an expected menstrual bleed three days thereafter. However, she had spotting already on the day before her last OC to be taken. She skipped the last dose and the oral contraception was not resumed. Three weeks later she still had no menstrual bleeding. Other causes for the bleeding disorder such as diarrhea, vomiting, other co-medication or incorrect intake of the OC, i.e. non-compliance, were excluded. Other diagnoses of the patient were a mitral valve prolapse with need of prophylactic treatment for endocarditis, as required. She had tendencies for hypotension and, as gynecological finding, a myoma, which, however, was controlled for two years and had never led to bleeding complications. Pregnancy tests performed on two different days after the incident were negative. Due to her depression, therapy with SJW and trimipramine was continued. The OC remained abandoned and other contraceptive methods, involving chemical and mechanical methods, were employed. After one month the patient spontaneously had a normal menstrual bleeding followed by a normal menstrual cycle.

3.1.4 Discussion

3.1.4.1 Effectiveness of St. John's wort

SJW preparations consist of a spectrum of ingredients of more than ten compounds such as flavonoids, xanthones, bioflavonides and naphthodiantronens *(Ruschitzka et al., 2000)*. Findings could not

identify yet the exact ingredient responsible for the antidepressant effect *(Wurglics et al., 2000)*. The effectiveness and relative beneficial ADR profile of SJW in comparison to conventional antidepressants were demonstrated in several placebo-controlled studies and by a meta-analysis *(Wurglics et al., 2000)*. The results were confirmed by Linde et al. *(Linde et al., 1996)*, who evaluated 23 randomised studies (20 of which double-blind) with a total of 1757 patients with mild to moderate depression, who were treated with SJW for 4 to 8 weeks, according to the individual study protocols. In all groups, an improvement of the symptoms according to the Hamilton Depression Scale or the Global Clinical Impression Scale was observed. In most placebo-controlled studies, this therapeutic effect was significant. In controlled trials, the comparison of the clinical improvement of the treatment with SJW versus the tricyclic antidepressants amitriptyline (900 mg/day SJW versus 75 mg/day amitriptyline) and imipramine (1800 mg/day SJW versus 150 mg/day imipramine, respectively), and versus the SSRI sertraline (900 mg/day SJW versus 75 mg/day sertraline) and fluoxetine (500 mg/day of the ethanolic SJW extract Ze 117 versus 20 mg/day fluoxetine) showed no significant difference *(Brenner et al., 2000; Fugh-Berman & Cott, 1999)*. However, there was a difference in the frequency of ADR. In the study with fluoxetine, 23% of the patients treated with fluoxetine reported ADRs compared to 8% of patients treated with SJW. Classical dose finding studies do not exist for SJW extracts. However, for minor depression a daily dose of 500 to 900 mg of the respective SJW extract has been established *(Schrader, 2000)*.

3.1.4.2 Mechanism of action / pharmacology

The mechanism of action of SJW has not yet been completely defined. An inhibition of serotonin reuptake as well as an inhibition of noradrenalin and dopamin reuptake had been observed *(Meier, 1999)*. Receptor binding studies had shown a distinct affinity to receptors, among others gamma-aminobutyric acid $GABA_A$ and $GABA_B$ *(Cott, 1997; Fugh-Berman & Cott, 1999; Müller et al., 1997; Pepping, 1999; Simmen et al., 1999; Wheatley, 2000)*. An inhibition of the monoamine oxidase (MAO) by flavonoides and xanthones was observed. However, the clinical significance of this finding is inconclusive to date, due to the low concentrations, especially of the xanthones, in the extracts used *(Bladt & Wagner, 1994)*. It is possible, that hyperforin plays a more important role towards the therapeutic effect of SJW than hypericine, for which the extracts are standardized *(Laakmann et al., 1998)*.

3.1.4.3 Adverse drug reactions

ADR occur less often and are usually milder with SJW preparations than with traditional antidepressants. The most frequent ADR in the fluoxetine-controlled study *(Schrader, 2000)* were agitation (8%), gastrointestinal discomfort (6%), vomiting (4%), dizziness (4%), tiredness, anxiety and erectile dysfunction (3% each) compared to 5% gastrointestinal discomfort for SJW. Other ADR were reported in less than 2% of the patients. In light-skinned persons, with higher hypericine doses, photosensitive erythema was observed *(Brockmöller et al., 1997)*. Isolated case reports of lethargy *(Gordon, 1998)*, paralytic ileus *(Tran, 1997)*, acute neuropathy *(Bove, 1998)* and two unpublished cases with serotonin syndrome *(Demott, 1998)* exist. The causality between ADR and SJW was not established in all cases. Toxicological animal studies indicate a low toxicity for SJW *(Garrett et al., 1982; Leuschner & Rimpler, 1990)*. However, in the study of Garrett et al. *(Garrett et al., 1982)* an induction of liver enzymes was measured, indicating a potential for

interactions at the level of an increased metabolism or first-pass effect of those drugs, which are metabolized through the respective enzymes.

3.1.4.4 Drug-drug interactions with St. John's wort

In the last years, an increasing number of case reports with decreased therapeutic effects of drugs combined with SJW preparations were published and are summarized in Table 1. The former Swiss center for reporting adverse drug reactions (Schweizer Arzneimittel-Nebenwirkungs-Zentrale, SANZ) had received eight spontaneous reports of suspected ADR related to SJW until 1999 *(Bon et al., 1999)*. Of these, three involved bleeding disorders in women, who had been taking OCs without complications for a long time. The unexplained bleeding disorders occurred one week after initiating treatment with a SJW preparation in two cases, and after three months in the other case. From 1999 until mid 2000 seven additional cases with prolonged bleeding of more than 7 days (metrorrhagia) were reported to the inter-cantonal board of drug control of Switzerland (Interkantonale Kontrollstelle für Heilmittel, IKS) *(Martinek, 2000)*. In Sweden, eight similar cases were reported to the public health department until the beginning of 2000 *(Yue et al., 2000)*. At least four published cases regard interactions with ciclosporin *(Barone et al., 2000; Bon et al., 1999; Ruschitzka et al., 2000)*. Ruschitzka et al. described two acute heart transplant rejections *(Ruschitzka et al., 2000)*. The ciclosporin plasma concentration was reduced three weeks after the start of SJW extract treatment (3 x 300 mg/day) and endomyocardial biopsies revealed acute cellular transplant rejection. In both cases, ciclosporin concentrations normalized after abstaining from taking the SJW preparation. The third case was a patient with lung fibrosis treated with ciclosporin and prednisone. Upon commencing SJW therapy, ciclosporin plasma concentration decreased and the ciclosporin dose had to be increased accordingly *(Bon et al., 1999)*. After the withdrawal of SJW treatment, the ciclosporin dose had to be decreased again. The fourth case was a patient with combined renal and pancreas transplantation with stable ciclosporin therapy and plasma concentrations for 3 ½ years *(Barone et al., 2000)*. The ciclosporin concentration decreased to $^1/_3$ of the initial value for unknown reasons over a period of two months, followed by a cellular transplant rejection. The ciclosporin dose was increased accordingly and self-medication with SJW was stopped simultaneously. The ciclosporin concentration increased disproportionally. After a subsequent ciclosporin reduction the original doses with stable ciclosporin plasma concentrations were achieved. The cellular transplant rejection was reversible, however developed to a chronic graft rejection and the patient had to subsequently return to dialysis therapy. Pischitelli et al. described a pharmacokinetic interaction study between the HIV protease inhibitor indinavir and a SJW preparation in a dose of 3 x 300 mg extract in eight healthy volunteers *(Piscitelli et al., 2000)*. A statistically significant reduction in AUC of indinavir of 57% was observed. C_{max} decreased by 28%, however, this did not reach statistical significance. There were several cases reporting a diminished anticoagulative effect of coumarin derivatives, four cases with phenprocoumon *(Martinek, 2000; Ruschitzka et al., 2000)* and seven cases with warfarin *(Yue et al., 2000)*. An adjustment of the coumarin dose was necessary, and the effect was reversible after withdrawal of the SJW preparation. Nebel et al. described a patient with a marked decrease of theophylline plasma concentration and the need for a tremendous increase of the theophylline dose *(Nebel et al., 1999)*. An evaluation of the potential interactions of her medication revealed that the self-medication with a SJW preparation was the only new drug in a long list of long-term co-medication. After withdrawal of SJW, the

theophylline dose could be reduced to previous dosage levels. Johne et al. investigated in a single-blind, placebo-controlled parallel study the influence of a SJW extract on the pharmacokinetics of digoxin *(Johne et al., 1999)*. After 5 days, a significantly decreased AUC (-25%) as well as decreased trough levels were observed. The half-life of digoxin was not affected. Therefore, an interaction at the level of absorption or distribution was assumed to be causative. Five cases of mild serotonin syndrome in elderly patients as a result of a pharmacodynamic interaction between an SSRI and SJW preparations were observed [*(Lantz et al., 1999)* cited in *(Ernst, 1999)*].

No. cases	Medication	Adverse effect of drug interaction	Commentary / mechanism
18	Oral contraceptive*	Bleeding disorders	Substrate of CYP3A4
4	Phenprocoumon	INR-increase, risk for thromboembolic processes	Substrate of CYP2C9, CYP3A4 (?)
7	Warfarin	INR-increase, risk for thromboembolic processes	
4	Ciclosporin	Decreased plasma concentration up to 70%. Acute cellular graft rejection after pancreas, renal and cardiac transplantation	Ciclosporin is a substrate of CYP3A4 as well as P-gp
8**	Indinavir	57% reduction of indinavir AUC, risk for development of resistance and jeopardising therapeutic success.	Indinavir is a substrate of CYP3A4 as well as P-gp
13**	Digoxin	25% reduction of digoxin AUC and 26% reduction of C_{trough}	Digoxin is a substrate of P-gp, NOT CYP3A4
1	Theophylline	Reduction of theophylline plasma concentration	Induction of CYP1A2 (?)
5	SSRIs (sertraline, nefazodone)	Mild serotonin syndrome	Pharmacodynamic interaction

Table 15 Clinical relevant interactions with SJW preparations. * Ethinylestradiol 0.02-0.03 mg / desogestrel 0.15 mg; ** within a study; INR = international normalized ratio; AUC = area under the plasma concentration-time curve

In Switzerland, SJW preparations with extracts obtained from differing extraction procedures, with different ingredient spectras, and with different dosing recommendations are sold. The most often used extracts are Ze 117 and Li 160. The Ze 117 extract (brands: ReBalance®, Remotiv®, Hyperval®) is an ethanol / water extract containing less than 0.1% hyperforin, and daily doses of 500 mg are recommended. The Li 160 extract (brand: Jarsin®), however, is a methanolic extract containing approximately 4% hyperforin (batch dependent), and daily doses of 900 mg are recommended *(Meier, 1999; Wurglics et al., 2000)*. Other extracts showed a 4-fold variation of hyperforin content between different batches *(Wurglics et al., 2000)*. In this context it seems interesting, that 22 of the 23 cases spontaneously reported to the IKS with a possible SJW interaction concerned the extract Li 160, which contains higher hyperforin concentrations and which is used in higher therapeutic doses *(Martinek, 2000)*. In an unpublished study, the interaction between OCs

and the extract Ze 117 was studied [personal communication, Zeller AG, CH 8590, Romanshorn]. During the study, no bleeding disorders were observed, which would have indicated a possible interaction. Therefore, it cannot be excluded that the problem of pharmacokinetic interactions of SJW is a dose-dependent and extract-specific phenomenon. The identification of the ingredients responsible for the interactions has not yet been successful. Nevertheless, some of our *in vitro* investigations with cell cultures and *in vivo* studies in healthy volunteers showed that SJW extract Ze 117 in a daily dose of 900 mg induced the expression of CYP3A4 as well as of P-gp in a dose-dependent manner *(Drewe et al., 2000)*.

3.1.4.5 Discussion of the case

OCs are roughly divided into two groups, i.e. combinations of an estrogen with gestagen and gestagen-only preparations. The steroid hormones exert a negative feedback on the hypothalamic-hypophysic axes. Gestagens lead to an inhibition of the luteinising hormones (LH) and consequently inhibit the ovulation, they increase the density of the cervix mucus (prevention of sperm penetration), and inhibit endometrial proliferation (prevention of nidation of a fertilized egg). Estrogens inhibit the formation of the follicle stimulating hormone (FSH) and consequently the maturation of mature follicles *(Hardman & Limbird, 1996; Parfitt, 1999)*. Today's monophasic gestagen / estrogen combinations exert the contraceptive effect predominantly by the gestagen effect. Estrogens ensure a stable menstrual cycle [personal communication, Organon AG, Pfäffikon]. Smear and break-through bleedings are ADR of all types of OCs *(Hardman & Limbird, 1996)*. This is believed to occur for two reasons: (1) They are due to a too low estrogen / gestagen ratio, either due to low estrogen or high gestagen doses. No stable endometrium can be developed and a change of the preparation is indicated *(Isselbacher et al., 1994; Parfitt, 1999)*. In this case, the primary problem lies at the level of the endometrium, and smear bleeding is no indication for a contraceptive failure. Alternatively, (2) with smear and break-through bleedings, which are due to postponing the treatment, irregular intake of the OC with a delay of more than 36 hours between tablets, vomiting or diarrhea, other illnesses, or possible DDIs, it can not be assumed that the problem is restricted only to the endometrium. This is particularly true if there were regular cycles with the OC before the event [personal communication Schering AG, Organon AG]. Drugs known to impair the inhibition of ovulation by OCs are enzyme-inducing agents like phenytoin, primidone, barbiturates, carbamazepine, rifampicin and griseofulvin. But also antibiotics, especially penicillins and its derivative's as well as tetracyclines, may impair contraception, possibly by interruption of the enterohepatic cycle of ethinyl estradiol *(Morant & Ruppanner, 2000)*. As steroid hormones are metabolized mainly by CYP3A4 *(Bertz & Granneman, 1997; Michalets, 1998)* and as there is an overlap between CYP3A4 substrates an P-gp modulation, a pharmacokinetic interaction between the steroid hormones of the OC with an as yet unidentified component of the SJW extract may be a possible explanation for the smear and break-through bleeding. Trimipramine is a substrate of CYP2D6 *(Bolaji et al., 1993)*, like many other tricyclic antidepressants *(Bertz & Granneman, 1997)*. Trimipramine is not known to exhibit CYP inducing or inhibiting properties *(Bertz & Granneman, 1997; Bonnabry et al., 1997; Flockhart, 2002; Michalets, 1998)*. Therefore, the bleeding disorders are unlikely to be caused by an interaction between the OC and trimipramine. As no other reason for the bleeding disorder could be identified, is seems most probable to have been due to an interaction between the SJW preparation and the OC, possibly via an induction of CYP3A4 and/or P-gp. In this instance, contraception may not be warranted and additional

mechanical contraceptive methods should be recommended. In the case of withdrawal of the inducing agent, additional contraceptive precautions up to approximately four weeks after stopping administration of the inducing agent, may be necessary.

3.1.5 Conclusions

Due to the known mechanism of the interaction of SJW preparations, particularly with the methanolic Li 160 extract in high doses, interactions with drugs which are metabolized by CYP3A4 or which are substrates of P-gp, leading to a decreased effect, must be expected. As SJW is an over-the-counter herbal remedy, patients treated with ciclosporin, oral anticoagulants, digoxin, theophylline, HIV protease inhibitors, or OCs (particularly micro-preparations) should be informed on the possible consequences of these combinations. They should be encouraged to report their over-the-counter co-medication to their physician or to abstain from self-medication. Self-medication with SJW preparations should be recorded for these patients. After the beginning with, or after withdrawal of SJW, ciclosporin, theophylline, digoxin concentrations should be monitored closely via therapeutic drug monitoring, and doses should be adjusted accordingly. INR should be monitored closely in patients treated with oral coumarin derivatives. Women taking low dose OCs should use mechanical and/or local chemical contraceptive methods instead, or should abstain from self-medication with SJW preparations *(Gordon, 1998)*.

3.2 Lithium intoxication as a result of a drug-drug interaction with rofecoxib

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3.2.1 Summary

The objective was to report the occurrence of lithium intoxication in a patient with bipolar disorder after adding rofecoxib to the medication regimen. A 68-year old woman with bipolar disorder under long-term treatment with lithium, carbamazepine, pipamperone and mirtazapine was prescribed rofecoxib for the treatment of leg pain. Within one week, she showed progressive hypokinesia and tremor, which was treated with propranolol. Subsequently, she developed bradycardia, necessitating treatment with isoproterenol. Her lithium serum concentration had doubled compared to those before rofecoxib and her renal function had detoriated. After stopping lithium and rofecoxib, her laboratory values and neurological signs improved or normalized within 2 days. An objective causality assessment revealed a probable relationship between concomitant use of the drugs and the resulting symptoms. So far, only three cases of reversible lithium intoxication as a result of a possible DDI with rofecoxib or celecoxib have been previously reported. The mechanism of the interaction between lithium and COX-2 selective inhibitors is most probably related to inhibition of renal synthesis of prostaglandins, which are important for the maintenance of renal perfusion and tubular function. Impairment of renal blood flow, leading to a decrease in the glomerular filtration rate, and increased proximal tubular absorption are the most likely mechanisms by which COX-2 selective inhibitors reduce lithium clearance. Concluding, coadministration of rofecoxib and lithium may result in life-threatening lithium intoxication, especially in patients with a preexisting decrease in renal function and/or decreased intravascular volume.

3.2.2 Introduction

Selective cyclooxygenase (COX) 2 inhibitors are frequently used to treat acute and chronic inflammatory diseases and pain because they appear to have a lower risk for gastrointestinal toxicity compared to conventional nonsteroidal anti-inflammatory drugs (NSAIDs) *(Bombardier et al., 2000)*. However, the expectation that COX-2 selective inhibitors could also reduce untoward renal effects compared with conventional NSAIDs could not be met *(Gambaro & Perazella, 2003)*. Considering the reviews about the effects of selective COX-2 inhibitors on the kidneys, it appears that their nephrotoxicity is similar to that of nonselective COX-2 inhibitors *(Brater, 1999; Gambaro & Perazella, 2003)*. COX-2, initially thought to be expressed primarily in inflamed tissues, has been shown to also play a role in physiological processes, including maintenance of renal function. This is particularly the case in conditions involving increased renal prostaglandin dependence such as decreased sodium intake, volume depletion, renal artery stenosis, liver cirrhosis, and heart failure *(Gambaro & Perazella, 2003; Noroian & Clive, 2002)*. Renal expression of COX-2 is increased in the conditions mentioned above to maintain renal blood flow and glomerular filtration rate, as well as tubular functions involved in sodium, potassium and water homeostasis. Acute renal failure associated with COX-2 selective inhibitors has been reported in patients with the same risk factors as reported for conventional NSAID-associated renal adverse effects *(Gambaro & Perazella, 2003; Noroian & Clive, 2002)*.

Lithium is an established treatment for patients with bipolar disorders. Due to its toxicity, the lithium serum concentration must be maintained within a narrow range. Neurologic manifestations of toxicity are dose-dependent and may begin with nausea / vomiting, drowsiness, lethargy, coarse hand tremor, and muscular weakness, followed by nystagmus, ataxia, confusion, dysarthria, and myoclonic twitches, finally resulting in impaired consciousness, seizures, coma, and death. Electrocardiographic changes (flat or inverted T waves) may also be observed *(Finley et al., 1995)*.

The pharmacokinetic properties of lithium and its DDIs have been reviewed *(Finley et al., 1995)*. Lithium is absorbed rapidly and completely from the upper gastrointestinal tract, is not bound to plasma proteins, is distributed evenly in the body water (showing a volume of distribution of 0.7 L/kg), and is eliminated almost entirely by the kidneys. Lithium is filtered by the glomerulus, and approximately 75% of the amount filtered is reabsorbed in parallel to sodium, mostly in the proximal tubule *(Timmer & Sands, 1999)*. Several drug classes, including diuretics (particularly thiazides), ACE-inhibitors and NSAIDs have been shown to decrease renal lithium clearance and to increase lithium serum concentrations *(Tyrer, 1996)*.

Since selective COX-2 inhibitors show similar effects on the kidney as those of conventional NSAIDs *(Gambaro & Perazella, 2003; Noroian & Clive, 2002)*, COX-2 inhibitors could also decrease renal lithium clearance. However, to the best of our knowledge, only few cases of possible interactions of lithium with celecoxib *(Gunja et al., 2002; Slordal et al., 2003)* or rofecoxib *(Lundmark et al., 2002)* have so far been described in the literature. Most recently, Phelan et al. *(Phelan et al., 2003)* described 18 patients with increased serum lithium concentrations associated with the addition of a COX-2 inhibitor to their medication regimen; these cases had been reported to the Food and Drug Administration.

3.2.3 Case Report

A 68-year old woman with bipolar disorder, who had been on a stable treatment regimen with lithium 200 mg twice daily since 12 years (serum concentrations between 0.74 - 0.94 mEq/L), was hospitalized due to pain in the left leg after an accidental fall 3 months earlier. Additionally, she had been prescribed carbamazepine 400 mg twice daily (for 12 years), pipamperone 60 mg daily and zopiclone for sleeping (for 6 years) and mirtazapine 30 mg daily (for 3 months). There was no history of previous use of NSAIDs or aspirin. X-ray investigations revealed osteochondrosis at L5-S1, but no direct cause for the pain in the left limb. Physical examination revealed kyphosis of the thoracic vertebral column and hyperlordosis. Since the woman had pain upon compression of the lumbar and pelvic musculature, a diagnosis of lumbospondylogenic syndrome was made. Additional diagnoses were chronic pancytopenia of unknown origin and impaired renal function (reason not known, first diagnosis 3 years before presentation), with calculated creatinine clearance approximately 40 mL/min. On the day of hospitalization, her serum creatinine concentration was 1.25 mg/dL, heart rate 68 beats/min, and blood pressure 90/60 mm Hg, a normal value for her.

To treat the pain, administration of 25 mg rofecoxib twice daily was started. On the second day of hospitalization, the patient's serum lithium concentration was just above the upper therapeutic range (0.81 mEq/L, range 0.5-0.8). On day 3, she started to develop hand tremor. She was examined by a neurologist,

who diagnosed an extrapyramidal syndrome consisting of tremor, rigor and hypokinesia, possibly associated with neuroleptic treatment. On day 8 at 11:00, the patient was treated with a single dose of 40 mg propranolol, because her tremor had worsened. In the late afternoon, approximately 6 hours after administration of propranolol, the patient reported headache, nausea and vomiting. An electrocardiogramm showed sinus bradycardia and intermittent complete atrioventricular block with sinus arrests up to 4 seconds, but no signs of heart failure. She was transferred to the ICU for supervision.

Upon admission at the ICU, her heart rate was 40 beats/min, and blood pressure was 90/40 mm Hg (Table 1); no atrioventricular block or signs of heart failure were noted. She was alert, her speech was slurred, she exhibited tremor of her hands at rest, and intermittent periods of drowsiness occurred. Neither nystagmus nor asterixis were present. Intravenous isoproterenol was administered, resolving bradycardia and increasing blood pressure. During the whole episode, the patient's urine output had been >70 mL/hour, indicating that renal perfusion had been maintained. In comparison with her value obtained 6 days earlier, the lithium serum concentration had doubled (1.67 mEq/L), reaching the toxic range. As shown in Figure 1, this increase could partially be explained by a drop in the clearance of lithium, since the calculated creatinine clearance was 27 mL/min at this time. An electrocardiogram revealed inversion of the T wave, compatible with increased lithium serum concentration. Rofecoxib, lithium and carbamazepine were stopped on day eighth. After rofecoxib was stopped, the creatinine clearance reached prehospitalization level over 2 days, with a parallel fall in the serum lithium concentration to 0.92 mEq/L over the same period.

Parameter	Day 1[a]	Day 2	Day 7	Day 8[b]	Day 9 (01:45)	Day 9 (12:51)	Day 10 (06:45)	Day 10 (13:30)
Lithium concentration (therapeutic range: 0.5-0.8 mEq/L)		0.81		1.67		1.32	0.92	
Carbamazepine concentration (therapeutic range: 4-10 mg/L)						12.7		
SCr concentration (reference range: 0.5-1.0 mg/dL)		1.25		1.77	1.58	1.59	1.33	1.24
Calculated Cl_{Cr} (mL/min)		41		28		28	38	41
Potassium level (reference range: 3.5-5.0 mEq/L)		4.3		5.4	5.3	4.3	4.5	4.3
Blood pressure (mm Hg)	90/60	120/60	120/68	90/40	102/68	112/90	118/48	104/54

Table 16 Clinical signs and laboratory values in a patient treated with lithium and rofecoxib. Cl_{Cr} = creatinine clearance; SCr = serum creatinine; [a]rofecoxib started; [b]single oral dose of propranlol was administered; rofecoxib and lithium were stopped.

The patient was discharged from the ICU on the tenth day of hospitalization (3 days after entering the ICU) with a normal heart rate, normal electrocardiogram, and clearly improved tremor. After the reintroduction of lithium and carbamazepine at the same dosage as before and initiation of acetaminophen as analgesic, the patient had no further complications. Using the Naranjo probability scale, a probable

relationship was found for lithium intoxication and an interaction between lithium and rofecoxib *(Naranjo et al., 1981)*.

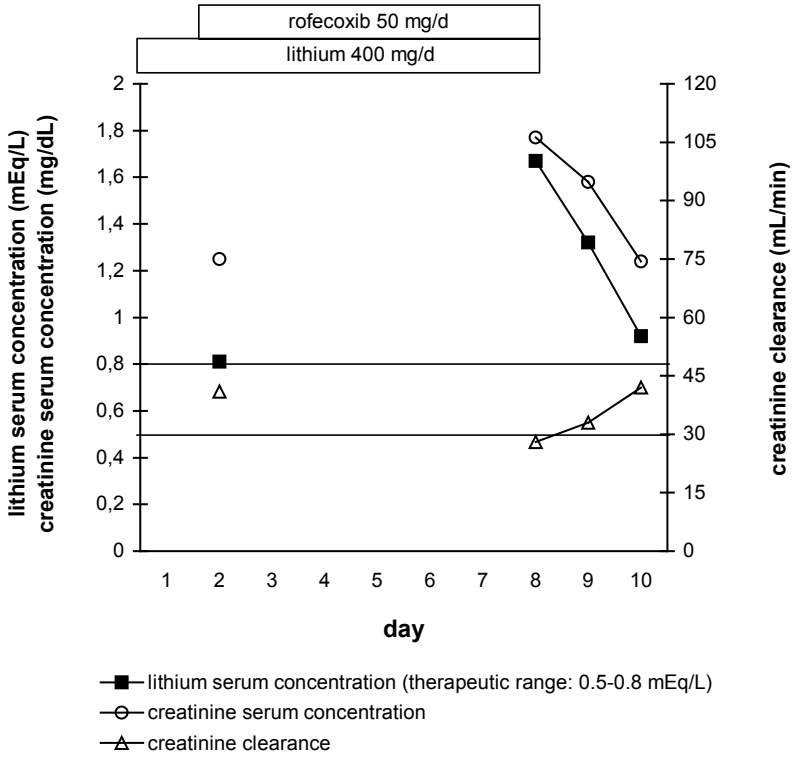

Figure 4 Lithium and creatinine serum concentrations, and creatinine clearance during concomitant rofecoxib therapy.

3.2.4 Discussion

Three cases of an interaction between COX-2 inhibitors (celecoxib or rofecoxib) with lithium, resulting in increased serum lithium concentrations and lithium toxicity, have been reported in detail *(Gunja et al., 2002; Lundmark et al., 2002; Slordal et al., 2003)*. All of these cases are comparable with the one we describe here. All patients were elderly, had been treated with lithium and other drugs for many years, and had maintained serum lithium concentrations within the therapeutic range. All patients developed signs of lithium intoxication (confusion, tremor, gait disturbance) leading to hospitalization a few days up to 3 months after beginning treatment with a COX-2 inhibitor. In all patients, toxic serum lithium concentrations (> 1.2 mEq/L) and elevated serum creatinine values were measured. After withdrawal of lithium and the COX-2 inhibitor, all patients recovered within one week, and the lithium and creatinine serum concentrations returned to the values prior to administration of the COX-2 inhibitor. Our patient was also treated with carbamazepine, which has been reported to have a pharmacodynamic interaction with lithium *(Finley et al.,*

1995). Such an interaction may therefore have contributed to the neurologic symptoms experienced by our patient.

A case series published in abstract form included 10 patients on lithium therapy who were treated with 50 mg rofecoxib for 5 days due to various pain states *(Sajbel et al., 2001)*. In 9 of these patients, the serum lithium levels increased and one of them developed signs of mild lithium toxicity. After stopping treatment with rofecoxib, the lithium concentrations of all patients returned to near to baseline.

Of 20 cases of lithium intoxication reported spontaneously to the Swiss Agency for Therapeutic Products between 1996 and 2003 (including the patient described here), one additional patient was treated with rofecoxib (10% of the reported cases) and 6 patients received conventional NSAIDs (ibuprofen, diclofenac, mefenaminic acid, aspirin; 30% of the reported cases). Most of these patients were on stable, long-term therapy with lithium, and signs and symptoms of lithium intoxication occurred a few days after introduction of the NSAID or COX-2 inhibitor. Three patients (including ours) had relevant comorbidities such as preexisting renal failure and/or dehydration.

Most recently, Phelan et al. *(Phelan et al., 2003)* found 18 possible cases of lithium interaction with COX-2 inhibitors: 13 with rofecoxib and 5 with celecoxib. The increase of the serum lithium concentration after the addition of celecoxib ranged from 56 to 99% and, after rofecoxib was introduced, from 58 to 448%. Unfortunately, the case series lacks information about preexisting renal disorder, concomitant drug use, and medical history of the patients.

As mentioned above, approximately 75% of the filtered lithium ions are reabsorbed by the renal tubules and collecting ducts. The major part of this reabsorption occurs in the proximal tubule (up to 70% of the lithium filtered) *(Hayslett & Kashgarian, 1979; Timmer & Sands, 1999)*, and minor amounts are reabsorbed in the loop of Henle and in the collecting ducts *(Atherton et al., 1991; Koomans et al., 1989)*. Although the mechanism of proximal tubular reabsorption of lithium is debated *(Greger, 1990; Leyssac et al., 1994)*, it competes with the reabsorption of sodium and may be driven by the sodium-hydrogen exchanger *(Timmer & Sands, 1999)*. This is compatible with the observation that administration of sodium to patients with lithium intoxication is associated with increased lithium clearance. Reabsorption of lithium in the loop of Henle is bumetanide sensitive and proposed to be accomplished by the sodium-potassium-chlorid cotransporter *(Atherton et al., 1991)* and, in the collecting ducts, by the sodium channel *(Timmer & Sands, 1999)*. Dehydration is associated with reduced clearance of lithium primarily due to impaired renal perfusion resulting in reduced lithium filtration, but also due to increased reabsorption of lithium *(Okusa & Crystal, 1994; Timmer & Sands, 1999; Tyrer, 1996)*. It has been shown that age-related changes in the glomerular filtration rate may explain the prolonged plasma half-life of lithium in the elderly *(Sproule et al., 2000)*.

The interaction between NSAIDs and lithium is well established and, appearingly, the effect on lithium clearance differs among the individual NSAIDs (e.g, the effect of aspirin and sulindac is less pronounced than with other NSAIDs) *(Ragheb, 1990; Tyrer, 1996)*. However, the mechanism of the interaction between NSAIDs and lithium leading to increased lithium serum concentrations is not fully understood *(Stockley, 2002)*. COX-2 is constitutively expressed in the thick ascending limb of the kidney, in interstitial cells of the papilla, and in cells of the macula densa *(Gambaro & Perazella, 2003; Noroian & Clive, 2002)*. Although the role of COX-2 in the kidney is not completely clear, it seems to be important for the regulation of the renal

function, more so than COX-1 *(Kömhoff et al., 1997)*. Vasodilating prostaglandins, predominantly prostaglandin E_2 (PGE_2), play an important role in the maintenance of renal blood flow, particularly in patients with decreased sodium intake, volume depletion, renal artery stenosis, or heart failure *(Gambaro & Perazella, 2003; Noroian & Clive, 2002)*. Administration of an NSAID or COX-2 inhibitor to such patients may therefore cause a sharp decrease in renal blood flow, possibly leading to acute renal failure *(Brater, 1999; Noroian & Clive, 2002; Tyrer, 1996)*. In addition, PGE_2 may play a role in controlling renal salt and water reabsorption, and reduced renal PGE_2 levels may be associated with increased reabsorption of sodium and lithium in patients treated with NSAIDs *(Brater, 1999; Ragheb, 1990; Tyrer, 1996)*.

3.2.5 Conclusions

Similar to nonselective COX inhibitors, the administration of COX-2 selective inhibitors to patients treated with lithium may result in increased lithium serum concentrations and lithium intoxication. The lithium serum concentration may increase rapidly (within days) after introduction of the COX-2 selective inhibitors. Patients at risk are those with conditions of increased prostaglandin dependence of renal perfusion, such as those with reduced sodium intake, volume depletion, impaired renal function, liver cirrhosis or heart failure.

In patients treated with lithium, NSAIDs or COX-2 inhibitors should therefore be avoided, particularly in the presence of risk factors. If anti-inflammatory treatment with COX-2 inhibitors or NSAIDs is considered to be necessary in such patients, lithium concentrations should be monitored closely and lithium doses should be adjusted accordingly. If anti-inflammatory treatment is stopped, the reverse reaction will occur, and lithium doses have should be increased to prevent exacerbation of bipolar disorder.

CHAPTER IV

DISCUSSION, CONCLUSIONS AND OUTLOOK

4.1 Discussion

In the last 7 years, DDIs became an important issue in drug safety after the withdrawal of effective and commercially important drugs, like terfenadine, astemizole, mibefradil, cisapride in the UK and USA, and cerivastatin. Preventable, severe adverse DDIs played a major role in the reassessment of the safety of these drugs. In most cases, potentially harmful DDIs had been revealed only after launching the drug, mainly by signals, either from national PVCs or from the companies themselves. After the world-wide withdrawal of cerivastatin due to an increased incidence of potentially fatal rhabdomyolysis also seen in combination with interacting drugs, a focus was addressed to evaluate the individual safety profiles of the members of the statin family, particularly due to their differing PK profiles. Other DDIs or drug-food interactions were detected by publications of case reports and signals from national PVC, like interactions with SJW or grapefruit juice. They lead to the close investigation of the mechanism of the DDIs and to the identification of the herfore responsible compounds of the foods and herbs. Therefore PV plays an important role in identifying and communicating health issues due to DDIs.

In this thesis, the prevalence of potential drug-statin interactions and non-statin DDIs in ambulatory dyslipidemic patients in different geographical regions in Switzerland was explored in a crossectional investigation in private practice. Risk factors and regional differences were analyzed in order to identify the patients most at risk for potential DDIs. Additionally, cases of adverse DDIs from the drug information unit and regional pharmacovigilance center were published, in order to generate signals for other healthcare providers and scientist on potentially harmful DDIs.

The crossectional investigation in private practice is described in **Chapter II**. Overall, potentially critical DDI in dyslipidemic patients prescribed a statin were frequent (15%). A lower prevalence of potentially critical *drug-statin interactions* was identified than in a recent study in Ireland (7% versus 30%, respectively). The difference was attributed to differences in the prescribing pattern, e.g. in Switzerland less CYP3A4-inhibitors verapamil and diltiazem were prescribed to the studied population, and in the definition of drug-statin interactions as discussed in **Chapter 2.1**. In accordance to others, it was found that the individual statin chosen for the treatment of dyslipidemia was one of the most important risk factor for potential drug-statin interactions. The CYP3A4 substrates simvastatin and atorvastatin bore a higher risk than the CYP2C9 substrate fluvastatin for potential drug-statin interactions, and pravastatin (no relevant CYP metabolism). The latter showed the lowest risk. Additional risk factors for the appearance of potentially critical drug-statin or statin-drug interactions were a diagnosis of arrhythmias with an approximately 5.6-fold increased risk, followed by the number of concomitant drugs and/or a diagnosis of heart failure, and being treated in the French part of Switzerland. Arrhythmias and heart failure are highly correlated with specific drug therapies known to interact with statins, such as amiodarone, verapamil or diltiazem as well as digoxin. It was demonstrated, that dyslipidemic patients had an average of 2.2 additional diagnoses with a need for drug treatment. The studied population received on average 4.9 drugs. It will therefore be important to try to reduce the number of drugs and to screen the drug profile for potential DDIs before administering a new drug in order to decrease the risk for adverse drug-statin interactions, especially in patients with arrhythmia and heart failure. It was concluded that drug-statin interactions increased the risk for rhabdomyolysis. Nevertheless, rhabdomyolysis remains a rare event, occurring in 0.04-0.2% of statin treated patients, even in

the presence of an interacting drug. This is supported by the fact that in this investigation, no signs or symptoms of myopathy had been reported.

The prevalence of and the drugs mainly involved in potential *non-statin DDIs* is also described in **Chapter 2.1**. The prevalence of non-statin DDIs was similar to those found in other studies. The drugs most often involved in potential non-statin DDIs were cardiovascular drugs such as ACE-inhibitors, potassium supplements or potassium-sparing diuretics, spironolactone, loop or thiazide diuretics, but also NSAIDs, drug affecting hemostasis (i.e. phenprocoumon and acetylsalicylic acid), tramadol, and CNS-drugs such as SSRIs. Latter is an important information for physicians, since antidepressants are frequently prescribed for patients with cardiovascular diseases and may interact with the comedication. Risk factors were similar as for statin-drug interactions, with a diagnosis for arrhythmias and/or heart failure increasing the risk for non-statin DDIs approximately 3-fold, each. Additionally, male sex and the diagnosis of cerebrovascular disease and gout were identified risk factors. Why male sex was found to be associated with a higher risk for DDIs could not be answered by the current dataanalysis. Patients with gout treated with allopurinol were found to have high prevalence of non-statin DDIs due to a poorly documented, debatable, severe, possible interaction between allopurinol and ACE-inhibitors, leading to a hypersensitivity syndrome. Although it may be prudent to avoid this drug combination or to monitor the patient closely if the combination is given, more information should be available to judge the importance of this DDI, as it may bias the results of studies like the one described in this thesis.

Not all potential DDIs will lead to clinical problems. In the literature, only up to 10% of patients with potential DDIs were reported to become symptomatic. Therefore, up to 4 cases with an DDI-associated ADR would have been expected in this study population. However, no ADR was reported. It has to be emphasized that studying symptomatic adverse DDIs was not an aim of the investigation and was therefore not requested. The finding of no ADR report in this study is in accordance with known underreporting of ADR within spontaneous ADR-reporting systems. Additionally, the participating physicians attended the patient only at one occasion during the investigation, and the ADR might not have been apparent at this particular moment. However, it could have occurred afterwards, or even before, and action has already been taken for its management. This could also be in accordance with suggested explanation for the low incidence of symptomatic DDIs, which were that many experienced physicians accommodate the effects without consciously recognizing that what they were seeing an ADR or an altered plasma concentration in TDM was the result of an interaction. Other reasons for the lower than expected rate of ADR reports may have been, that patients tolerated ADR well.

Regarding the mechanisms of the potential DDIs observed in this investigation, there were differences between drug-statin interactions and non-statin DDIs. While the majority of drug-statin interactions were PK interactions, PD interactions predominated among non-statin DDIs. The latter accounted for approximately two third of potential DDIs and were detected mainly between cardiovascular drugs. Only for a small part, the exact mechanism was undetermined. Most potential DDIs detected were preventable by screening the drug profiles, and DDI-associated ADR would be preventable by adequate management, like dose adjustment, monitoring of the patient, or selection of a not interacting drugs.

In **Chapter 2.2**, regional differences of potential DDIs among statin users, and differences among practitioners were analyzed. The prevalence of potential DDIs was the same among the different practitioners and geographical regions. By logistic regression analysis, dyslipidemic patients treated with a statin in the French part of Switzerland were found to be at higher risk for being prescribed a potential drug-statin interaction. The finding reached statistical significance only in the logistic regression analysis. In the direct comparisons between geographical reagions no significant difference was see. This is explained by the different statistical techniques used. Although patients treated in the French speaking part were younger and were treated with a lower number of drugs as compared to the other regions, there was a tendency for a higher prevalence of drug-statin interactions. The exact reasons for this finding are not completely evident from the data of the study, but may be related to a higher use of fibrates in the French speaking part.

While the prevalence of drug-statin interactions was different between statins, this was not the case for non-statin DDIs. Physicians who prescribe statins with a lower interaction potential (pravastatin, fluvastatin) are therefore not more careful in avoiding non-statin DDIs than physicians prescribing statins with a higher interaction potential. This could be interpreted in that practitioners who prescribe less statin-drug interactions were not more aware of potential DDIs. The prescription of the less interacting statins might therefore just be by chance, or other reasons than the low interaction potential might have governed the prescription of pravastatin and fluvastatin by these practitioners. Furthermore, knowledge and warnings of potentially harmful statin-drug combination may not have reached or may simply have been ignored.

Like in other studies, polypharmacy was shown to be a risk factor for DDIs and reaches 40% with ≥ 7 drugs. Therefore, dyslipidemic patients should not be treated with more than 6 drugs. Particular attention should be drawn to elderly, polymorbid patients with other risk factors such as arrhythmias and cardiovascular diseases.

This crossectional study was designed to investigate the prescription pattern of practitioners and to analyze the prevalence of, and risk factors for potential DDIs. Some valuable information to complete the investigation was not explored, and the study design shows some weaknesses. For example as the participating practitioners were untrained 'study doctors' and screened their patients and completed the data sheets themselves, data may be missing. This had been proven for the incompleteness of recorded diagnoses in this study. Furthermore, doses, over-the-counter drugs, or drugs prescribed by other physicians were not systematically screened, and it is unknown, how many other doctors the patients attended. This missing information might highly influenced the results, and the prevalence of potential DDIs may have been underestimated in this study. Further, as the investigation occurred only at one time point within the patients treatment, and as there is no information of and access to a drug history, possible ADRs with subsequent dose adjustments, the relevant outcome thereof considering the potential DDIs, remained undetectable. Concerning the methodology, two other practical points should be stressed and should be considered for futur studies. First the choice of the WHO-dictionary for drug-coding and second the choice of a dynamic online DDI-screening program revealed to be considerably time consuming regarding data clearing for final statistical analysis. The use of generic names and a non-dynamic version, e.g. CD-ROM of Drug-Reax®, might have been advantageous.

The case of the drug-herbal interaction between SJW and an OC described in **Chapter III, 3.1**, was one of many signals that lead to the profound investigation of the mechanisms and involved ingredients of SJW interactions. It was postulated, that a dose-dependent, and therefore extract-dependent, PK interaction between the steroid hormones of the OCs with a not yet identified component of the SJW extract at the level of CYP3A4 and P-gp might have caused the interaction. Our case report contributed to the revelation of the underlying mechanism of interactions with SJW, in particular with OCs. The SJW interactions had become an important research topic. Subsequent *in vitro* investigations and a clinical study revealed hypericine and hyperforin both inducing P-gp and CYP3A4 transcriptional expression, and quercitrin having a tendency to induce CYP3A4 mRNA expression *(Pfrunder, 2003)*. Hyperforin was shown to be a potent activator of PXR *(Moore et al., 2000)*, and hypericine was an inductor of P-gp expression *(Perloff et al., 2001)*. Pfrunder has shown in her thesis that CYP3A4 induction by different SJW extracts was concentration-dependent on hyperforin, and up-regulation of MDR1 gene expression was dose-dependent, but differen for different SJW extracts tested *(Pfrunder, 2003)*. Therefore, apart from hyperforin, additional constituents of the extracts were suggested to be involved in the transcriptional induction. In a subsequent controlled clinical trial studying the interaction between SJW extract LI 160 and low-dose OC treatment was studied. In cycles where OC was combined with SJW extract LI 160, the SJW extract responsible for most adverse interactions reported in Switzerland, higher incidences of intracyclic bleeding episodes were reported than in concrol cycles with OC-monotherapy *(Pfrunder et al., 2003)*. No alterations in progesterone and ethinyl estradiol serum concentrations curves were detected and no ovulation had occurred, but a decrease in AUC, t_{max} and $T_{1/2}$ of 3-ketodesogestrel was observed. It was concluded, that rather inhibition of CYP2C9/2C19 than induction of CYP3A4 or P-gp were responsible for the findings, which are in conflict with other observations.

The interaction between NSAIDs and lithium is well established. Nevertheless, it appears that these drugs continue to be co-prescribed leading to lithium intoxications, which are still a problem of lithium safety. The effect on lithium clearance differs among the individual NSAIDs, e.g. the effect of aspirin and sulindac is less pronounced as compared to the other NSAIDs. Unaware of the effects of COX-2 inhibitors on the kidney, one could easily presume that lithium therapy could be safe in combination with COX-2 inhibitors. The lithium intoxication after combination with rofecoxib described in **Chapter 3.2.** is one signal among a few other published case reports and some more cases known to have been reported to the national PVC of increased lithium concentrations or intoxication in combination with a COX-inhibitor. For practitioners, it is important to know, that COX-2 inhibitors interact with lithium clearance equal to NSAIDs and to recognize possible risk factors such as relevant comorbidities like preexisting renal failure and/or dehydration.

4.2 Conclusions

Serious potential DDIs (drug-statin interactions and non-statin DDIs) have been shown to be common in patients with dyslipidemia treated with a statin, mostly due to co-morbidities for which they are treated concomitantly with numerous additional drugs. These potential DDIs may possibly increase the occurrence of ADRs. Potential DDI among statin users increase with the number of drugs prescribed, and subsequently with the number of diagnoses and increasing age. Patients at risk, i.e. polymorbid and elderly patients with

polymedication, and patients with diagnoses of arrhythmia or heart failure should be prescribed as few drugs as possible in order to reduce the risk of adverse DDIs.

Despite the fact that statin-drug interactions may increase the risk of statin-induced rhabdomyolysis by 6-10-fold, it remains a rare event, occurring in 0.04-0.2% of statin treated patients, even in the presence of an interacting drug. Although it remains a rare adverse reaction, due to the widespread use of statins and the potentially fatal outcome, statin-associated rhabdomyolysis will remain an important clinical problem, and action should be taken, to minimize the risk.

Our study showed that CYP3A4 inhibitors were the most frequent cause of potential drug interactions with statins, and most important risk factors were a diagnosis of arrhythmias, the number of drugs prescribed and a diagnosis of heart failure. To reduce the risk of adverse drug-statin interactions, it will therefore be important to reduce the number of drugs to a possible minimum in dyslipidemic patients with other comorbidities, and to screen the drug profile for potential DDIs before administering a new drug, particularly in patients with arrhythmias and heart failure. Combinations of CYP3A4 inhibitors with simvastatin and atorvastatin, of CYP2C9 inhibitors with fluvastatin, or P-gp substrates with simvastatin, atorvastatin and fluvastatin should be avoided by choosing another drug combination in order to prevent potential drug-statin or statin-drug interactions. Patients with arrhythmia and heart failure are treated with drugs known to interact with statins, such as amiodarone, verapamil or diltiazem as well as digoxin. For these patients it may be prudent to choose pravastatin as alternative statin, which does not interact with the medication needed to treat the potentially life threatening underlying diseases. If a potentially harmful drug-statin interaction can not be avoided, the patients should be monitored very closely. Reasons for the increased risk for drug-statin interactions in the French part are mainly unknown and can not be fully explained by the data available by this study.

The publication of case reports of DDIs are important signals which may lead to thorough investigations on the mechanism of DDIs and to a better understanding of the interactions. It hopefully helps to prevent potentially harmful DDIs.

4.3 Outlook

In this thesis the prevalence of potential DDIs among statin users has been evaluated. The true clinical significance of our findings however is unknown. Further research is necessary to elucidate the incidence and clinical significance of adverse effects in dyslipidemic patients with potentially serious DDIs, as well as in other patient groups.

⇒ A first approach to elucidate this topic is made by an ongoing diploma thesis, where the importance of drug-statin interactions among all statin-associated ADRs reported to the Swiss national PVC, Swissmedic is assessed.

⇒ Future studies on DDIs should include the study of the patient history, the management of possibly symptomatic DDI, and clinical outcome of potential DDI in order to assess whether the potential DDI leads to clinical symptoms and to assess the true clinical significance of potential adverse DDIs. This

would require different study designs and might be conducted in different patient populations, i.e. ambulatory versus hospitalized patients. As practitioners will probably not have enough time themselves for time consuming chart review and patient follow up, an external person would need to receive the authorization to screen patient charts for an ambulatory setting.

⇒ The clinical significance of DDIs could also be assessed in individual DDI-pairs such as the DDI between allopurinol and ACE-inhibitors in patients with gout. This DDI showed a high prevalence in our study population. However, it is poorly documented and debatable, but a potentially severe DDI and its importance should be further investigated. This could be done by analyzing vigilance data or by conducting other pharmacoepidemiologic studies. As it is suspected to be a rare event, a high number of patients studied will be needed to reveal any valid results.

Further investigation should be addressed to investigate the reasons why potentially harmful DDIs are continued to be prescribed. This would be of particular interest concerning drug-statin interactions in the French part of Switzerland. Questioning practitioners could be a possible first approach. A focus should then be addressed to the question on the management of how to prevent potentially harmful DDIs, for example by teaching, or by offering reliable automatic interactions screening programs.

Furthermore, health care providers should be encouraged to report adverse DDIs to RPVCs, and RPVCs should not hesitate to publish case reports, which can serve as an important safety signal within drug safety. This holds true for our RPVC as we try to encourage the involved parties to publish the case of a fatal intreraction between the 5-fluorouracil (5-FU) prodrug capecitabin and the antiviral drug brivudine. This interaction is known and labelled, but insufficently documented in Medline.

CHAPTER V

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