ORIGINAL RESEARCH ARTICLE

Drug Safety 2006; 29 (1): 79-90
0114-5916/06/0001-0079/$39.95/0

The Prevalence of Potential Drug-Drug Interactions in Patients with Heart Failure at Hospital Discharge

Bernhard Straubhaar,[1] *Stephan Krähenbühl*[1,2] and *Raymond G. Schlienger*[1,2]

1 Department of Pharmaceutical Sciences, Institute of Clinical Pharmacy, University of Basel, Basel, Switzerland

2 Division of Clinical Pharmacology and Toxicology, University Hospital of Basel, Basel, Switzerland

Abstract

Background/objective: Pharmacotherapy for heart failure is complex and, due to polypharmacy, is associated with a large risk of potential drug-drug interactions (DDIs). The objective of the present study was to assess the prevalence of potential DDIs in the medication of hospitalised heart failure patients and to evaluate their clinical relevance.

Study design/methods: The medication of 400 patients was retrospectively analysed for potential DDIs at hospital admission and discharge using a computerised drug interaction program. Main inclusion criteria were the diagnosis of heart failure and a minimum of two drug prescriptions at discharge.

Results: In the study population of 400 heart failure patients (median age 79 years, 55.5% men), the median number of drugs per patient was lower at admission than at discharge (6 [interquartile range {IQR} 4–9] vs 8 [IQR 6–10]; $p < 0.001$). At hospital admission, a total of 863 potential DDIs were detected in 272 patients (68.0%; 95% CI 63.4, 72.6). At discharge, 1171 potential DDIs were detected in 355 patients (88.8%; 95% CI 85.7, 91.8). This corresponds with a significant increase in the median number of potential DDIs per patient from admission to discharge (1.5 [IQR 0–3] vs 3 [IQR 1–4]; $p < 0.001$). Of the 1171 potential DDIs at discharge, 432 (36.9%) were prevalent at admission and 739 (63.1%) resulted from a medication change during the hospital stay. Of these 739 new potential DDIs, the severity of the potential adverse effect was rated as 'major' in 190 (25.7%) patients, 'moderate' in 482 (65.2%) and 'minor' in 67 (9.1%). The 190 potential DDIs with major severity were recorded in a total of 145 patients (36.3%; 95% CI 31.5, 41.0%). Hyperkalaemia was the most prevalent potential adverse effect of major severity ($n = 93$) and the combination of an ACE inhibitor with a potassium-sparing diuretic was recorded in 64 (16.0%) patients.

Conclusions: The study shows that hospitalisation of patients with heart failure results in an increase in the number of drugs prescribed per patient and, thereby, also in the number of potentially interacting drug combinations per patient. Although electronic drug interaction programs are a valuable tool to check for

potential DDIs, the clinical relevance of most potential DDIs can only be judged by assessment of the individual patient.

Background

Because of the complexity of the pharmacotherapy, patients with heart failure are at risk for drug-drug interactions (DDIs). In addition to therapy for heart failure itself, the treatment of underlying causative factors and comorbidities such as hypertension, coronary artery disease, diabetes mellitus and dyslipidaemia increases the number of pharmacological agents considered necessary for many patients with heart failure.[1] This ultimately translates into polypharmacy,[2,3] which is a major risk factor for DDIs.[2,4-6] Cardiovascular drugs in particular are often involved in DDIs.[5-8]

Additionally, the majority of heart failure patients are >60 years of age.[2,9] There are several age-related changes in pharmacokinetics that can increase plasma drug levels and potentially result in adverse drug reactions. Moreover, pharmacodynamic interactions are of particular relevance in the elderly. Because of reduced homeostatic mechanisms, elderly patients are more sensitive to the additive effects of two drugs and an adverse event can be more severe than in younger, healthier patients.[4]

Numerous studies have assessed the prevalence of potential DDIs in inpatients and outpatients with varying underlying diseases.[5-8,10-15] However, we are unaware of any study that has tried to specifically analyse potential DDIs in patients with heart failure. With the present study, we aimed to assess the prevalence of potential DDIs in the medication of heart failure patients at hospital admission and discharge, to determine the number of new potential DDIs due to a medication change during the hospital stay, and to analyse the interactions in more detail with regard to their clinical relevance.

Methods

Study Design, Patients and Data Collection

The study was conducted at the University Hospital of Basel and approved by the local ethical committee. The hospital is a 763-bed teaching institution providing primary and tertiary care to an urban population of approximately 200 000 inhabitants; it also serves as a tertiary care referral centre for Northwest Switzerland.

We enrolled 400 consecutive heart failure patients who were discharged from the general medical wards, intensive medical care unit, coronary care unit, ward for acute geriatric medicine and inpatient emergency ward between October 2002 and January 2004. Patients diagnosed with heart failure, either as the main diagnosis or as an additional diagnosis, were identified using the International Classification of Diseases – 10th Edition (ICD-10) codes I50.0, I50.1 and I50.9. If a patient had several hospitalisations during the study period, only the most recent hospital stay was analysed. Patients who had less than two drugs prescribed at hospital discharge, for whom no information was available on the medication at hospital admission or who died during the hospital stay were excluded from the study.

Information on drugs prescribed at hospital admission and discharge was retrieved from clinical records and the hospital discharge letter. For each patient, the number of drugs, pharmacologically active compounds, new drugs and drugs stopped during the hospital stay were recorded. Drugs were classified according to the anatomical therapeutic chemical (ATC) classification system.

Demographic information (age, sex and weight), length of hospital stay, main diagnosis (according to the ICD-10 classification) and the number of additional diagnoses were obtained from the clinical records. Comorbidities often associated with heart failure (i.e. arterial hypertension, ischaemic heart disease, cardiac arrhythmias, diabetes, dyslipidaemia) were also recorded.

To assess the clinical relevance of certain potential DDIs, laboratory data were collected (last available value before discharge) as follows: (i) serum potassium level; (ii) serum creatinine level to estimate the creatinine clearance (using the Dettli equation[16]); and (iii) prothrombin time expressed as international normalised ratio (INR). Additionally, the patients' discharge status was also recorded (e.g.

whether the patient was discharged home or to an institutional setting, such as a nursing home, rehabilitation centre or to another hospital).

Classification of Potential Drug-Drug Interactions (DDIs)

Each medication regimen at hospital admission and discharge was retrospectively screened for potential DDIs using the interactive, online drug interaction information system Drug-Reax® (Thomson Micromedex™, Greenwood Village, CO, USA),[17] a drug interaction program that was used for this purpose in several previous studies.[6,8,11,18,19] The program has proven to be more sensitive to predict potential DDIs than expert physicians.[19] For each potentially interacting drug combination, it provides information on the clinical consequence or the adverse effects of the potential DDI, severity and latency period, as well as the possible mechanism and how well the potential DDI is documented. The provided information is drug specific rather than class specific to aid in the interpretation of the data. In addition, the program features summaries of the reviewed literature for each potential DDI, and provides references for further reading. The program classifies the severity of a potential DDI in four categories: 'contraindicated', 'major', 'moderate' and 'minor'. The grade of documentation gives information about the quality of the available data and ranges from 'excellent' to 'unlikely'.

In this study, potential DDIs of all severities and documentation grades, except unlikely potential DDIs, were included for analysis. At hospital admission and discharge the total number of potential DDIs and the pairs of interacting pharmacologically active compounds were recorded. New potential DDIs resulting from a medication change during hospital stay and potential DDIs that were present at admission but were not present at discharge were listed separately. In addition, information on severity, onset, documentation grade, potential adverse effects and affected system organ classes according to the WHO Adverse Reaction Terminology (WHO-ART) of all potential DDIs at discharge were recorded. The mechanism of a potential DDI, if known, was classified as pharmacokinetic or pharmacodynamic.

Statistical Analysis

Descriptive data are expressed as medians with the corresponding interquartile range (IQR) or as proportions; laboratory data are expressed as means with the corresponding standard deviation. Numerical variables were tested for normal distribution using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. For paired two-sample comparisons, the non-parametric Wilcoxon signed-rank test was performed. The non-parametric Mann-Whitney-U test was used for unpaired two-sample comparisons. Nominal data in dependent groups were compared with the McNemars test. A two-sided p-value < 0.05 was considered statistically significant. Statistical tests were performed with the SPSS for Windows software package version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

The characteristics of the 400 patients enrolled are displayed in table I. The median age of the patients was 79 years with the majority (86.3%) being ≥65 years; slightly more than half of the patients were male. At discharge, patients had a median of 7 (IQR 6–9) diagnoses. The majority of patients (75.3%) were discharged from hospital with a main diagnosis related to the cardiovascular system; 175 patients (43.8%) had heart failure and 59 (14.8%) had an acute myocardial infarction as the main diagnosis.

In addition to the heart failure diagnosis, patients had a median of 2 (IQR 2–3) comorbidities associated with heart failure. Approximately two-thirds of the patients had ischaemic heart disease and more than half had hypertension and/or cardiac arrhythmias. Diabetes was present in slightly less than one-third of the patients and dyslipidaemia in one-quarter (table I). Ten patients had no diagnosis for any of the analysed comorbidities.

Prescribed Drugs

The 400 patients were prescribed a total of 2482 drugs at hospital admission and 3174 drugs at hospital discharge. At discharge, the median number of

Table I. Characteristics of 400 hospitalised heart failure patients

Demographic data	Value
Age in years [median (IQR)]	79 (71–85)
<65 years [no. (%)]	55 (13.8)
≥65 years [no. (%)]	345 (86.3)
Sex (male) [no. (%)]	222 (55.5)
Weight in kg [median (IQR)]	69 (58–80)
Length of hospital stay in days [median (IQR)]	12.5 (7–19)
Diagnoses	
Number of diagnoses [median (IQR)]	7 (6–9)
Main diagnosis [no. (%)]	
infectious and parasitic diseases	16 (4.0)
neoplasms	13 (3.3)
diseases of the circulatory system	301 (75.3)
diseases of the respiratory system	32 (8.0)
others, <2 % frequency	38 (9.5)
Cardiovascular/metabolic comorbidities [no. (%)]	
Hypertension	226 (56.5)
Ischaemic heart disease	269 (67.3)
Cardiac arrhythmias	234 (58.5)
Diabetes mellitus	118 (29.5)
Dyslipidaemia	104 (26.0)
Medication [median (IQR)]	
Number of drugs at hospital admission	6 (4–9)
Number of drugs at hospital discharge	8 (6–10)

IQR = interquartile range.

drugs per patient was significantly higher than the number of drugs at admission (8 [IQR 6–10] vs 6 [IQR 4–9]; $p < 0.001$). Because some drugs were combined preparations (i.e. ≥2 pharmacologically active compounds), the total number of active compounds was 2690 at admission and 3449 at discharge. At hospital admission, 11 patients (2.8%) had no drug prescriptions and 19 (4.8%) patients were prescribed one drug. There was no difference in the number of drugs prescribed between male and female patients.

Figure 1 displays the drug classes most often prescribed at admission and discharge. According to the ATC classification system, the majority were drugs affecting the cardiovascular system (45.2% of all drugs at admission, 45.7% at discharge). The three other most prevalent anatomical main groups were drugs affecting the alimentary tract and metabolism (admission 16.5%, discharge 15.6%), the blood and blood-forming organs (admission 13.9%, discharge 16.8%) and the nervous system (admission 12.4%, discharge 9.0%). These four groups represented 88.0% of all drugs at hospital admission and 87.1% at discharge.

At discharge, all drug classes – except drugs affecting the musculoskeletal and the nervous system – had a higher prescription prevalence than at admission. An additional 160 patients were prescribed antithrombotic agents at discharge, 127 patients had an additional prescription for a diuretic, 107 patients received an ACE inhibitor or an angiotensin receptor antagonist and 100 additional patients were discharged with a β-adrenoceptor antagonist (β-blocker). In contrast, digoxin and calcium channel antagonists were significantly less prevalent at discharge than at admission (i.e. 49 vs 32 patients for digoxin [$p < 0.01$] and 64 vs 32 for calcium channel antagonists [$p < 0.001$]).

At discharge, 395 (98.8%) patients had been prescribed at least one drug affecting the cardiovascular system. Drugs affecting the blood and blood-forming organs (e.g. platelet aggregation inhibitors, vitamin K antagonists, heparin or heparinoids) were prescribed to 371 (92.8%) patients. In the group of drugs affecting the alimentary tract, proton pump inhibitors, drugs for diabetes and mineral supplements were most prevalent. Drugs affecting the nervous system were prescribed to 169 (42.3%) patients. In addition, 88 (22.0%) patients were prescribed drugs that affected the respiratory system, 58 (14.5%) patients were prescribed anti-infectives for systemic use, 54 (13.5%) patients were prescribed systemic hormonal preparations (e.g. thyroid therapy or corticosteroids for systemic use) and 45 (11.3%) patients were prescribed drugs that affected the musculoskeletal system. Eighty-seven (21.8%) patients were prescribed drugs that acted on other organ systems (representing a total of 124 drugs). Table II displays the fifteen drug classes most often prescribed at discharge.

Potential DDIs in General

The prevalence of potential DDIs at admission and discharge is shown in detail in table III. At admission, 68.0% (95% CI 63.4, 72.6) of the patients had at least one potentially interacting drug combination in their medication. The median number of potential DDIs per patient was 1.5 (IQR 0–3). If only the 370 patients at risk for potential DDIs were taken into account (i.e. patients with ≥2 drugs

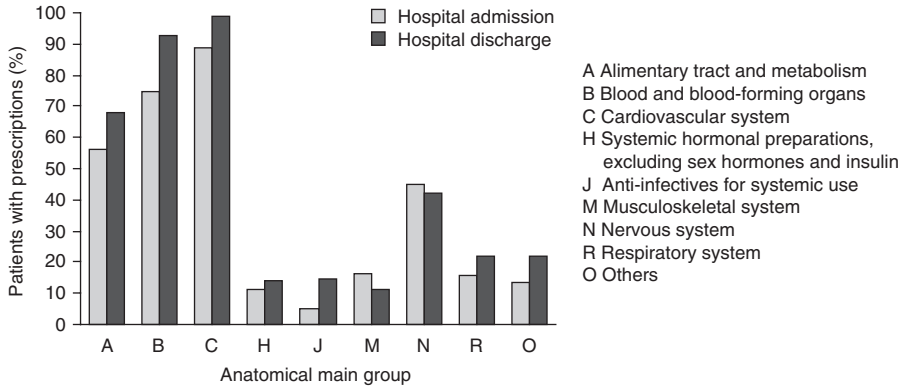

Fig. 1. Drug classes (classified according to the anatomical therapeutic chemical classification system) most often prescribed at hospital admission and discharge in 400 patients with heart failure.

prescribed at admission), the median number of potential DDIs per patient rose to 2 (IQR 0–4). At discharge, a total of 1171 potential DDIs were detected in 355 patients (88.8%; 95% CI 85.7, 91.8%), which corresponded to a median of 3 (IQR 1–4) potential DDIs per patient. In patients at risk for potential DDIs, the median number of potential DDIs per patient at discharge was significantly higher ($p < 0.001$) than the number of potential DDIs per patient at admission.

Patients with one or more potential DDIs at discharge were prescribed significantly more drugs than those without potential DDIs (median number of drugs 8 vs 5, $p < 0.001$); the same was observed at admission (7 vs 3, $p < 0.001$). Of the 1171 potential DDIs at discharge, a total of 432 (36.9%) potential DDIs were already present at admission, while 739 (63.1%) resulted from a medication change during hospital stay (new potential DDIs). These were detected in 299 patients (74.8%; 95% CI 70.5, 79.0). The overall number of potential DDIs at admission and discharge was unchanged in 109 (27.3%) patients. In contrast, 205 (51.3%) patients had more potential DDIs at discharge than at admission, while the number of potential DDIs at discharge decreased in 86 (21.5%) patients compared with the number at admission. At discharge, male patients had significantly more potential DDIs than female patients (median number of potential DDIs 3 vs 2, $p < 0.001$).

The following results refer to the 739 new potential DDIs due to a medication change during the

Table II. The 15 drug classes most often prescribed at hospital discharge in 400 hospitalised heart failure patients

Therapeutic class	Examples of often prescribed drugs	Patients with prescriptions [no. (%)]
High-ceiling diuretics	Torasemide	318 (79.5)
ACE inhibitors, including combinations	Ramipril, enalapril	272 (68.0)
β-adrenoceptor antagonists	Metoprolol, bisoprolol	261 (65.3)
Platelet aggregation inhibitors	Aspirin (acetylsalicylic acid), clopidogrel	193 (48.3)
Vitamin K antagonists	Phenprocoumon	175 (43.8)
HMG-CoA reductase inhibitors	Pravastatin, simvastatin	136 (34.0)
Potassium-sparing diuretics, including combinations	Spironolactone	121 (30.3)
Vasodilators used in cardiac diseases	Nitroglycerin	115 (28.8)
Mineral supplements	Calcium carbonate, potassium chloride	102 (25.5)
Proton pump inhibitors	Omeprazole, esomeprazole	101 (25.3)
Drugs used in diabetes mellitus	Glibornuride, insulin	99 (24.8)
Drugs for obstructive airway diseases	Salbutamol/ipratropium	76 (19.0)
Heparin group	Dalteparin sodium	67 (16.8)
Benzodiazepines and benzodiazepine-related drugs	Oxazepam, zolpidem	66 (16.5)
Laxatives	Lactitol	65 (16.3)

Table III. The prevalence of potential drug-drug interactions (DDIs) in 400 heart failure patients at hospital admission and discharge

Parameter	Value
Hospital admission	
Number of patients with potential DDIs (%)	272 (68.0)
Total number of potential DDIs	863
Number of potential DDIs per patient [median (IQR)]	1.5 (0–3)
Hospital discharge	
Number of patients with potential DDIs [no. (%)]	355 (88.8)
Total number of potential DDIs	1171
Number of potential DDIs per patient [median (IQR)]	3 (1–4)
Total number of new potential DDIs due to a medication change (%)	739 (63.1)
Number of patients with potential DDI with major severity (%)	193 (48.3)
Total number of potential DDIs with major severity (%)	284 (24.3)
Total number of new potential DDIs with major severity due to a medication change (%)	190 (16.2)
Number of patients with new potential DDI due to a medication change (%)	299 (74.8)
Number of patients with new potential DDI with major severity due to a medication change (%)	145 (36.3)

hospital stay. The severity of the potential adverse effect was rated as 'major' in 190 (25.7%) potential DDIs, 'moderate' in 482 (65.2%) and 'minor' in 67 (9.1%). In 535 potential DDIs (72.4%) the underlying mechanism was a pharmacodynamic interaction and in 129 (17.5%) a pharmacokinetic interaction. Both mechanisms were involved in 25 potential DDIs (3.4%) and in 50 (6.8%) the mechanism was unknown. A possible potentiation of the effects of one or both drugs involved in the interaction was assigned to 587 potential DDIs (79.4%) and a reduced effectiveness to 86 (11.6%). In 66 potential DDIs (8.9%) the potential influence on the therapeutic effect was of a different nature (e.g. increased risk of ACE inhibitor-associated hypersensitivity in combination with allopurinol or increased risk of amoxicillin-induced rash in combination with allopurinol).

The onset of the potential adverse outcome of the DDI was classified as 'delayed' in 432 (58.5%), 'rapid' in 250 (33.8%) and 'not specified' in 57 (7.7%). For 32 (4.3%) potential DDIs the documentation was classified as 'excellent', 'good' for 145 (19.6%), 'fair' for 459 (62.1%) and 'poor' for 103 (13.9%).

The potential adverse effects concerned platelet, bleeding and clotting disorders in 32% of the patients, the cardiovascular system in general in 27%, metabolic and nutritional disorders in 21%, general disorders in 9% and disorders of other organ systems in 11%. An increased risk of bleeding was the most frequently listed potential adverse effect (n = 197; 26.7%).

Table IV lists the ten most prevalent potentially interacting drug combinations, which account for 57.8% of all new 739 potential DDIs at discharge. Drug classes often involved in major potential DDIs were ACE inhibitors, potassium-sparing diuretics, vitamin K antagonists and heparins. Amiodarone, prescribed to 59 patients, was involved in 27 new major potential DDIs.

DDIs Potentially Resulting in Hyperkalaemia

At discharge, there were a total of 93 new major potential DDIs recorded that may potentially lead to hyperkalaemia. Of the 82 affected patients, the majority (92.7%) had one drug combination potentially resulting in hyperkalaemia, one patient had two, and five patients had three (table V). The mean serum potassium level of the 82 affected patients at discharge was 4.1 (± 0.7, range 2.2–5.4) mmol/L. Three patients had a potassium level of 5.0 mmol/L and five patients had a potassium level of >5 mmol/L, but none of the patients had a level of >5.4 mmol/L. The mean estimated creatinine clearance of the 82 affected patients at discharge was 59.2 (± 27.3, range 17.1–140) mL/min. Nine patients had impaired renal function with an estimated creatinine clearance of <30 mL/min. Of these, two had a serum potassium level of >5 mmol/L at discharge. A potassium-wasting diuretic (loop diuretic and/or

thiazide) was included in the medication regimen of 75 (91.5%) of the 82 patients.

Fifty-six percent of the 82 patients were discharged to their own home, 28% were transferred to another hospital and the remaining to a nursing home or a rehabilitation centre.

Amiodarone plus β-Adrenoceptor Antagonists

At discharge, 13 patients were newly prescribed the combination of amiodarone with a β-blocker (12 patients with metoprolol, one patient with bisoprolol). This potential DDI may result in bradycardia, cardiac arrest or hypotension with a rapid onset of the potential adverse effects. To assess if any patient experienced these potential adverse effects, the clinical records of 12 patients (one record was not available for review) were reviewed for episodes of bradycardia (heart rate <60 beats per minute [bpm]) and hypotension while in hospital. One patient had several episodes of heart rates <60 bpm recorded with a minimum of 54 bpm, but no information on symptomatic bradycardia could be found in the clinical records. Before treatment with amiodarone was added to a pre-existing therapy with 100mg extended release metoprolol daily, the lowest recorded heart rate was 72 bpm in that patient.

Low Molecular Weight Heparin plus Phenprocoumon

The combination of phenprocoumon with a low molecular weight heparin (LMWH) was prescribed to 21 patients at hospital discharge. Both drugs affect homeostasis by different mechanisms and may increase the risk of bleeding. The majority (66.7%) of these patients were discharged to their own home and the others to an institutional setting.

The mean INR of the affected patients at discharge was 1.6 (± 0.5, range 1.1–3.0). No value was available for one patient. Of 20 patients, 17 (85%) had an INR of <2, two patients had an INR between 2 and 2.9, and one patient had an INR of 3.0.

Discussion

Our study shows that both the number of drugs prescribed per patient and the number of potential DDIs per patient increased significantly during the hospital stay. Furthermore, every fourth potential DDI at discharge could have resulted in an adverse event of major severity. Because most patients no longer benefit from close medical monitoring after hospital discharge, the discharge medication should have a low risk of potential DDIs. This is especially important for potential DDIs with a delayed onset of the associated adverse outcome that may only become clinically apparent after the patient has been discharged. For that reason, potentially interacting drug combinations that were newly introduced during the hospital stay are of special interest.

The increase in potential DDIs can be partly explained by the increase in the number of prescribed drugs per patient. On the other hand, newly prescribed drugs themselves were often involved in potential DDIs. ACE inhibitors, loop diuretics, spironolactone and β-blockers were among the most often added drugs during hospitalisation and among the most prevalent interacting drugs.

Table IV. The ten most prevalent drug combinations of 739 potential drug-drug interactions new at discharge

Drug-drug combination	Severity	Potential adverse effect	Patients with potential DDI [no. (%)]
ACEI + diuretic (loop or thiazide)	Moderate	Postural hypotension	151 (37.8)
ACEI + potassium-sparing diuretic	Major	Hyperkalaemia	64 (16.0)
Phenprocoumon + spironolactone	Moderate	Decreased anticoagulant effectiveness	37 (9.3)
Aspirin (acetylsalicylic acid) [low dose] + LMWH	Moderate	Increased risk of bleeding	34 (8.5)
Antidiabetes agent + β-adrenoceptor antagonist	Moderate	Decreased diabetic control	30 (7.5)
Aspirin (low dose) + clopidogrel	Minor	Increased risk of bleeding	30 (7.5)
Clopidogrel + torasemide	Moderate	Torasemide toxicity	22 (5.5)
LMWH + phenprocoumon	Major	Increased risk of bleeding	21 (5.3)
ACEI + potassium	Major	Hyperkalaemia	20 (5.0)
Amiodarone + phenprocoumon	Moderate	Increased risk of bleeding	18 (4.5)

ACEI = angiotensin converting enzyme inhibitor; **LMWH** = low molecular weight heparin.

Table V. Drug combinations with potential major adverse effects due to a medication change during hospitalisation that were identified in five or more patients at discharge

Drug combination	Potential adverse effect	Patients with potential DDI [no. (%)]
ACEI + potassium-sparing diuretic	Hyperkalaemia	64 (16.0)
LMWH + phenprocoumon	Increased risk of bleeding	21 (5.3)
ACEI + potassium	Hyperkalaemia	20 (5.0)
Amiodarone + β-adrenoceptor antagonist	Bradycardia, cardiac arrest	13 (3.3)
Omeprazole + phenprocoumon	Increased risk of bleeding	10 (2.5)
Aspirin (acetylsalicylic acid) [low dose] + vitamin K antagonist	Increased risk of bleeding	7 (1.8)
Clopidogrel + LMWH	Increased risk of bleeding	7 (1.8)
Potassium + spironolactone	Hyperkalaemia	6 (1.5)
Amiodarone + antipsychotic	Increased risk of QT interval prolongation, torsades de pointes and cardiac arrest	5 (1.3)

ACEI = angiotensin converting enzyme inhibitor; **DDI** = drug-drug interaction; **LMWH** = low molecular weight heparin.

Patients with heart failure in which an ACE inhibitor is added to a pre-existing diuretic therapy are at some risk for first-dose hypotension.[20-22] Generally, this is not a major problem if ACE inhibitor therapy is started during the hospital stay and the patient's blood pressure is regularly monitored. In the long term, patients will generally tolerate the combination of an ACE inhibitor with a diuretic.[23] However, it was shown that in practice ACE inhibitor therapy is often discontinued in the first year after hospitalisation.[24] Therefore, an eventual restart of the therapy in an ambulatory setting with a high ACE inhibitor dose may result in symptomatic hypotension.

Antithrombotic agents (vitamin K antagonists, platelet aggregation inhibitors) were the group of drugs with the most manifest change of the exposure prevalence during hospital stay and were involved in six of the ten most prevalent new potential DDIs. The combination of low-dose aspirin (acetylsalicylic acid) [100 mg/day] with another antithrombotic agent, potentially resulting in an increased risk of bleeding, was accountable for two of the most frequent potential DDIs due to a medication change. Classified as a DDI with potentially moderate adverse effects, the concomitant administration of low-dose aspirin and a LMWH is standard treatment for unstable angina pectoris and non-Q-wave myocardial infarction, in order to reduce the risk of reinfarction or death.[25] Nevertheless, this combination is associated with an increased risk of haemorrhagic complications[26] and special attention is necessary for patients with impaired renal function because of the reduced renal elimination of LMWHs.[27]

The concomitant use of LMWHs and oral anticoagulants may result in an increased risk of bleeding because both drugs inhibit blood coagulation by different mechanisms.[17] In this study, 21 patients were discharged with a prescription for phenprocoumon and a LMWH and were therefore exposed to a potential risk of bleeding. However, the majority of patients had an INR of <2 at discharge with a very low risk of bleeding, even in the presence of a LMWH. Oral anticoagulants, such as phenprocoumon, inhibit the vitamin K-dependent hepatic carboxylation of clotting factors. Because already carboxylated clotting factors are not altered in their activity and phenprocoumon has a long half-life, it takes approximately 5–7 days to be fully effective.[28] In order to achieve the desired anticoagulation, the concomitant use of heparins during this period is necessary. Therefore, it can be assumed that patients discharged with this combination will have to use the LMWH only until the INR has reached its target value. Therefore, close monitoring has to be guaranteed after hospital discharge in order to stop the LMWH when the INR is therapeutic. This is especially important because two-thirds of these patients were discharged home and further monitoring has to be arranged with their general practitioner.

However, it should be emphasised that even though we identified several drug combinations that may increase the risk of haemorrhage, the majority of these combinations are standard and the clinical

benefit often outweighs the modest potential risk increase.

Hyperkalaemia may develop during treatment with several drugs, including ACE inhibitors, potassium-sparing diuretics and potassium supplements, and occurs frequently in patients with altered renal function.[29] Because impaired renal function is common in patients with heart failure,[30] these patients may be at an increased risk of developing hyperkalaemia, especially with the concomitant use of two or more drugs that potentially result in hyperkalaemia. In the present study, 20.5% of the patients were exposed to a potential DDI that may have resulted in hyperkalaemia. Potassium levels at hospital discharge did not exceed values >5 mmol/L in most patients. Five patients did have a potassium level >5 mmol/L, but none of the patients were discharged with serious hyperkalaemia (defined as serum potassium level of >6 mmol/L).[31] All five patients with a potassium level of >5 mmol/L at discharge were prescribed the combination of an ACE inhibitor with spironolactone. In most cases it was not known if spironolactone was primarily prescribed for the treatment of advanced heart failure or to prevent hypokalaemia due to concomitant treatment with a potassium-wasting diuretic.

Drug combinations potentially resulting in hyperkalaemia need special attention from physicians and pharmacists because hyperkalaemia is relatively prevalent in outpatients, especially in those receiving spironolactone[32] or ACE inhibitor therapy.[33] It is noteworthy in this context, that after publication of the RALES (Randomized Aldactone Evaluation Study) trial, which showed that spironolactone significantly improved outcomes in patients with severe heart failure,[34] it was shown by Juurlink and colleagues[35] that the rates of prescriptions for spironolactone, as well as the rates of hyperkalaemia-associated morbidity and mortality, abruptly increased. Close monitoring of potassium levels and renal function is therefore essential to prevent unnecessary hospital admissions. Special caution is indicated in elderly patients with impaired renal function and worsening heart failure.[32,36]

The concomitant use of amiodarone and β-blockers is not recommended because of the additive negative inotropic and negative dromotropic effects. There is one published case report of severe sinus bradycardia and hypotension after the concomitant use of amiodarone and metoprolol.[37] Furthermore, a pharmacokinetic interaction is theoretically possible because amiodarone is an inhibitor of cytochrome P450 (CYP) 2D6[38] and several β-blockers, such as metoprolol and carvedilol, are CYP2D6 substrates. If arrhythmias (e.g. tachycardic atrial fibrillation) cannot be adequately treated with monotherapy alone, a combination therapy may be considered after careful evaluation of the benefit-risk ratio and under careful cardiac monitoring. In fact, a *post hoc* meta-analysis of the two Myocardial Infarct Amiodarone Trials (EMIAT [European Myocardial Infarct Amiodarone Trial] and CAMIAT [Canadian Amiodarone Myocardial Infarction Trial]) showed lower relative risks for all-cause mortality and cardiac death in the group receiving amiodarone and a β-blocker than the group receiving a β-blocker alone.[39] Another retrospective study in patients with chronic heart failure concluded that amiodarone and carvedilol may be used concomitantly without the expectation of increased adverse effects or loss of clinical efficacy.[40] If amiodarone is indicated in heart failure patients, it is recommended by some authors to use it in combination with a β-blocker.[23]

The majority of potential DDIs had a pharmacodynamic underlying mechanism with mainly additive effects on the cardiovascular system, platelet function or blood coagulation. It can be assumed that most of the potentiations of the therapeutic effect were intended by the prescribing physician in order to achieve the desired therapeutic effects. But from the collected data in this study it is not known what the exact indications for the prescribing of potentially interacting drug combinations were. Furthermore, it is unknown if the physicians were always aware of the increased risk of potential adverse effects and if necessary precautions or therapy monitoring were arranged.

Study Limitations

The present study has several limitations, mostly because of the retrospective design of the study and the methods used. First, the analysis of medication regimens by a computer program only allows the detection of 'potential' interactions. This does not mean that possible adverse effects become clinically

manifest in all patients with a potential DDI. In contrast, it is known that only a small proportion of potential DDIs actually result in clinically relevant events with negative consequences for the patient.[4,41-43] In addition, some patients may benefit from interacting drug combinations because the additive effects may be necessary to adequately treat a disease or symptom. The computer program cannot discriminate between beneficial and dangerous potential DDIs because the exact indications for the prescription of an interacting drug combination are not included in an electronic interaction check. However, it can be assumed that many of the potentially interacting drug combinations identified in our analysis were prescribed on purpose (e.g. the amiodarone/β-blocker combination to treat sustained ventricular arrhythmias) because the benefit of the combination may outweigh the potential risk of an adverse effect. Additionally, the clinical relevance of potential DDIs can only be assessed if the proportion of patients, in whom the adverse event indeed clinically occurs, is known. In order to evaluate the clinical relevance of selected potential DDIs with major severity, we recorded some laboratory and clinical parameters in this study to assess any adverse outcome. However, we are aware that the relevance of these data is limited. Therefore, based on the results of this study, only statements about the prevalence and nature of potential DDIs are possible.

Another limitation of the study lies in the nature of the interaction program chosen for this study or rather in electronic drug interaction programs in general. Because the program was from an American publisher, certain drugs common in continental Europe, but not in the US, had to be substituted by an analogous drug listed in the program. The substitutes were selected according to pharmacokinetic, pharmacodynamic and chemical properties. The most prevalent substituted drug was the vitamin K antagonist phenprocoumon.

Potential DDIs may be highly dependent on the dose of the individual drugs administered. For instance, in this study, aspirin was only prescribed as a platelet aggregation inhibitor in a daily dose of 100mg. None of the patients were prescribed a higher dose (e.g. 300 mg/day) to inhibit platelet aggregation and none were prescribed aspirin as an analgesic. It is known that some potential DDIs with aspirin are only clinically relevant if it is administrated in analgesic doses, but the drug interaction program used to evaluate the patients' medication regimen is not able to distinguish between the two different dose schemes and produces a signal whenever aspirin is involved in a potential DDI. Therefore, potential DDIs involving aspirin that were regarded as clinically irrelevant if the dosage of aspirin did not exceed 100 mg/day (e.g. combination of low-dose aspirin with an ACE inhibitor, which potentially results in a decreased antihypertensive effect) were not included in the analysis. In total, 195 potential DDIs including low-dose aspirin at admission and a total of 280 potential DDIs at discharge were not included. Additionally, the exposure prevalence of NSAIDs was remarkably low in our study population and, therefore, the potential DDI of NSAIDs with ACE inhibitors – potentially leading to a decreased antihypertensive and natriuretic affect of the ACE inhibitors or even acute renal failure especially in patients predisposed to or with pre-existing nephropathy[17] – was a negligible problem. This may be explained by the fact that NSAIDs are indeed only rarely prescribed to medical inpatients in our institution. If only analgetic therapy is needed (without any anti-inflammatory component), paracetamol (acetaminophen) or a weak opioid (e.g. tramadol) are preferentially prescribed.

Electronic drug interaction programs are very helpful tools to check for potential DDIs. They generally produce a high number of signals but do in fact overestimate the risk of potential DDIs,[44] which makes it necessary to interpret the provided information in the context of their clinical relevance.

Conclusions

The high prevalence of potential DDIs in the discharge medication of heart failure patients is a consequence of the complex pharmacotherapy of heart failure and associated comorbidities. However, many of those potentially interacting drug combinations are standard therapy in patients with heart failure and even though the combinations may bear some risk for an adverse outcome, the benefit generally far outweighs the potential risk. Nevertheless, drug combinations potentially resulting in hyper-

kalaemia or haemorrhage are of major importance for physicians and pharmacists; the former because the incidence of hyperkalaemia in outpatients is relatively high and the adverse effects may be serious, the latter because bleedings are characteristically insidious and delayed. Careful monitoring and adherence to evidence-based prescribing are important preventive measures to minimise the risk of these interactions.

Acknowledgements

The present study was not funded. None of the authors have any conflicts of interest directly relevant to the content of this study.

References

1. Masoudi FA, Krumholz HM. Polypharmacy and comorbidity in heart failure. BMJ 2003; 327 (7414): 513-4
2. Ledwidge M, Travers B, Ryder M, et al. Specialist care of heart failure improves appropriate pharmacotherapy at the expense of greater polypharmacy and drug-interactions. Eur J Heart Fail 2004; 6 (2): 235-43
3. Martinez-Selles M, Garcia Robles JA, Munoz R, et al. Pharmacological treatment in patients with heart failure: patients knowledge and occurrence of polypharmacy, alternative medicine and immunizations. Eur J Heart Fail 2004; 6 (2): 219-26
4. Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. Drugs Aging 1998; 12 (6): 485-94
5. Köhler GI, Bode-Boger SM, Busse R, et al. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 2000; 38 (11): 504-13
6. Ratz Bravo A, Tchambaz L, Krähenbühl-Melcher A, et al. The prevalence of potentially critical drug-drug interactions in ambulatory dyslipidemic patients treated with statins. Drug Saf 2005; 28 (3): 263-75
7. Bjerrum L, Andersen M, Petersen G, et al. Exposure to potential drug interactions in primary health care. Scand J Prim Health Care 2003; 21 (3): 153-8
8. Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58 (11): 773-8
9. Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. Lancet 2003; 362 (9378): 147-58
10. Rosholm JU, Bjerrum L, Hallas J, et al. Polypharmacy and the risk of drug-drug interactions among Danish elderly: a prescription database study. Dan Med Bull 1998; 45 (2): 210-3
11. Bergk V, Gasse C, Rothenbacher D, et al. Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther 2004; 76 (1): 85-96
12. Bergendal L, Friberg A, Schaffrath A. Potential drug-drug interactions in 5,125 mostly elderly out-patients in Gothenburg, Sweden. Pharm World Sci 1995; 17 (5): 152-7
13. Björkman IK, Fastbom J, Schmidt IK, et al. Drug-drug interactions in the elderly. Ann Pharmacother 2002; 36 (11): 1675-81
14. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993; 9 (1): 51-9
15. Di Castri A, Jacquot JM, Hemmi P, et al. Intéractions médicamenteuses: etudes de 409 ordonnances établies à l'issue d'une hospitalisation gériatrique. Therapie 1995; 50 (3): 259-64
16. Dettli L. Drug dosage in patients with renal disease. Clin Pharmacol Ther 1974; 16 (1): 274-80
17. Klasco RK, Moore LE. Drug-Reax® System. Greenwood Village (CO): MICROMEDEX, 2004
18. Gaddis GM, Holt TR, Woods M. Drug interactions in at-risk emergency department patients. Acad Emerg Med 2002; 9 (11): 1162-7
19. Langdorf MI, Fox JC, Marwah RS, et al. Physician versus computer knowledge of potential drug interactions in the emergency department. Acad Emerg Med 2000; 7 (11): 1321-9
20. Meredith PA. Is postural hypotension a real problem with antihypertensive medication? Cardiology 2001; 96 Suppl. 1: 19-24
21. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. Drug Saf 1995; 12 (5): 334-47
22. Tan LB, Williams SG, Goldspink DF. From CONSENSUS to CHARM: how do ACEI and ARB produce clinical benefits in CHF? Int J Cardiol 2004; 94 (2-3): 137-41
23. Klein L, O'Connor CM, Gattis WA, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations. Am J Cardiol 2003; 91 (9A): 18F-40F
24. Bouvy ML, Heerdink ER, Leufkens HG, et al. Patterns of pharmacotherapy in patients hospitalised for congestive heart failure. Eur J Heart Fail 2003; 5 (2): 195-200
25. Ageno W, Turpie AG. Low molecular weight heparins in the treatment of unstable angina. Minerva Cardioangiol 2002; 50 (6): 643-51
26. Shullo MA, Rose ML, Vivas C, et al. Hemorrhagic complications of enoxaparin and aspirin in patients with kidney transplants. Pharmacotherapy 2002; 22 (2): 184-7
27. Farooq V, Hegarty J, Chandrasekar T, et al. Serious adverse incidents with the usage of low molecular weight heparins in patients with chronic kidney disease. Am J Kidney Dis 2004; 43 (3): 531-7
28. Haustein KO. Pharmacokinetic and pharmacodynamic properties of oral anticoagulants, especially phenprocoumon. Semin Thromb Hemost 1999; 25 (1): 5-11
29. Perazella MA. Drug-induced hyperkalemia: old culprits and new offenders. Am J Med 2000; 109 (4): 307-14
30. McAlister FA, Ezekowitz J, Tonelli M, et al. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004; 109 (8): 1004-9
31. Schepkens H, Vanholder R, Billiouw JM, et al. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med 2001; 110 (6): 438-41
32. Svensson M, Gustafsson F, Galatius S, et al. How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? J Card Fail 2004; 10 (4): 297-303
33. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors: how much should we worry? Arch Intern Med 1998; 158 (1): 26-32
34. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341 (10): 709-17
35. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351 (6): 543-51
36. Morimoto T, Gandhi TK, Fiskio JM, et al. An evaluation of risk factors for adverse drug events associated with angiotensin-

converting enzyme inhibitors. J Eval Clin Pract 2004; 10 (4): 499-509
37. Leor J, Levartowsky D, Sharon C, et al. Amiodarone and beta-adrenergic blockers: an interaction with metoprolol but not with atenolol. Am Heart J 1988; 116 (1 Pt 1): 206-7
38. Yamreudeewong W, DeBisschop M, Martin L, et al. Potentially significant drug interactions of class III antiarrhythmic drugs. Drug Saf 2003; 26 (6): 421-38
39. Boutitie F, Boissel JP, Connolly SJ, et al. Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. The EMIAT and CAMIAT Investigators. Circulation 1999; 99 (17): 2268-75
40. Krum H, Shusterman N, MacMahon S, et al. Efficacy and safety of carvedilol in patients with chronic heart failure receiving concomitant amiodarone therapy. Australia/New Zealand Heart Failure Research Collaborative Group. J Card Fail 1998; 4 (4): 281-8
41. Herrlinger C, Klotz U. Drug metabolism and drug interactions in the elderly. Best Pract Res Clin Gastroenterol 2001; 15 (6): 897-918
42. Juurlink DN, Mamdani MM, Kopp A, et al. A population-based assessment of the potential interaction between serotonin-specific reuptake inhibitors and digoxin. Br J Clin Pharmacol 2005; 59 (1): 102-7
43. Chen YF, Avery AJ, Neil KE, et al. Incidence and possible causes of prescribing potentially hazardous/contraindicated drug combinations in general practice. Drug Saf 2005; 28 (1): 67-80
44. Egger T, Dormann H, Ahne G, et al. Identification of adverse drug reactions in geriatric inpatients using a computerised drug database. Drugs Aging 2003; 20 (10): 769-76

Correspondence and offprints: Dr *Raymond G. Schlienger*, Division of Clinical Pharmacology and Toxicology, University Hospital of Basel, Markgräflerhof, Hebelstrasse 2, Basel, CH - 4031, Switzerland.