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Adverse drug reactions caused by drug-drug interactions in cardiovascular disease patients: introduction of a simple prediction tool using electronic screening database items

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Adverse drug reactions caused by drug-drug interactions in cardiovascular disease patients: introduction of a simple prediction tool using electronic screening database items

Objective: Cardiovascular disease (CVD) drugs have been frequently implicated in adverse drug reaction (ADR)-related hospitalisations. Drug-drug interactions (DDIs) are common preventable cause of ADRs, but the impact of DDIs in the CVD population has not been investigated. Hence, the primary aim of the study was to identify DDIs associated with ADRs in CVD patients at hospital admission. The second aim was to develop a simple tool to identify high-risk patients for DDI-related adverse event.

Methods: An observational study was conducted on Cardiology ward of University Clinical Hospital Center. Data were obtained from medical charts. A clinical panel identified DDIs implicated in ADRs, using LexiInteract database and Drug Interaction Probability Score. Statistics were performed using PASW 22 (SPSS Inc.).

Results: DDIs contributed to hospital admission with a total prevalence of 9.69%. DDI-related ADRs affected mainly cardiac function (heart rate or rhythm, 41.07%); bleeding and effect on blood pressure were equally distributed (17.86%). Non-cardiovascular ADRs were found in 23.21% of DDIs. After the admission, 73% of the identified DDIs led to changes in prescription. Prediction ability of calculated DDI-adverse event probability scores was rated as good (AUC=0.80, $p<0.001$).

Conclusions: CVD patients are highly exposed to adverse DDIs; about one in ten patients hospitalized with CVD might have a DDI contributing to the hospitalisation. Given the high prevalence of CVD, DDI-related harm might be significant burden worldwide. Identification of patients with high DDI-adverse event risk might ease the recognition of DDI-related harm and improve the use of electronic databases in clinical practice.

Keywords: drug-related side effects and adverse reactions; drug interactions; patient safety; hospitalization

Introduction

Drug safety has become a public health issue, earning significant and wide interest at all levels of health care. [1] The benefit-risk ratio of a particular drug has become more complex to assess and interpret, due to an increased number of drugs in therapy in the ageing population, and the volume of knowledge about drug-drug and drug-disease interactions. [2] Besides its challenging aspect in achieving effective and safe therapy for an individual patient, drug-related harm substantially contribute to health care costs. [3, 4] An adverse drug reaction (ADR) is defined as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". [5] ADRs can occur in appropriately prescribed, dispensed or administered drugs (considered as nonpreventable), but they can also be caused by drug-drug interactions (DDIs) when an altered drug effect emerge in a presence of the precipitant drug. DDIs are identified as a preventable cause of ADRs, irrespective of the study setting. [6, 7] DDIs accounted for 16.6-49% of ADR-related hospitalisations [7-10], and were present in about 44% of cases reported as drug-related deaths in a university hospital. [11] Epidemiological data derived from meta-analysis estimated the total median prevalence rate of DDI-related hospital admissions to about 1.1%. [7] However, it was reported that the low incidence of DDIs might be an indication of a lack of understanding and recognition of DDIs. [12] Other authors also stated that the true extent of DDI-related harm is not well established. [13, 14] Nevertheless, both researchers and health professionals agree upon the need for generating new evidence on DDIs, to reach improvements in drug safety. [15, 16]

Drugs used for cardiovascular disease (CVD) lead the list of ADRs and DDIs causative agents, identified both through a detailed medical charts exploration in epidemiological research, as well as through spontaneous reporting. A comprehensive review by Al Hamid et al. reported that |each and every study| assessing hospitalisation resulting from ADRs, reported CVD medicines,

with a median of 33.9% (interquartile range 19.9–58.6%). [17] Furthermore, a large French study on more than 6.9 million outpatient dispensings revealed dominant involvement of CVD drugs in DDIs: four out of five most represented contraindicated drug pairs, and all of the five most represented discommended drug pairs involved cardiovascular drugs. [18] In addition, patients with CVD are at higher risk and exposure to DDIs because of the multiple medications, as well as the administration of drugs with narrow therapeutic index, such as warfarin or digoxin. [1, 19] Prescribing of several drugs is common in CVD, which is the main reason for the reported high prevalence of potential DDIs: 91.1-93.7% of hospitalised cardiac patients had at least one potential clinically significant DDI regardless of the type of severity. [20, 21] The DDI-related harm in general, as well as their impact on hospital admissions in the population of CVD patients has not been well examined. Studies carried out in CVD patients investigated iatrogenic adverse events emerging during hospitalization in the coronary care unit, assessing both those resulting from medical procedures and the medication use. [22, 23] Others provided general prevalence rates of drug-related problems in CVD patients during hospital stay [24], or DDIs were assessed only in the cohort of heart failure patients. [25, 26]Another issue in assessing DDIs impact is the causality assessment. The only available tool so far is a 10-item Drug Interaction Probability Scale (DIPS), proposed by Horn and colleagues. [27] The DIPS purpose is to ease the judgement of the contributory role of a potential DDI to a specific patient outcome, in comparison to other potential causes. Electronic databases can be easily applied in DDIs screening, giving the opportunity to quickly assess potential problems in patients therapy. However, significant override rates have been reported for DDIs alerts (up to 72.8 %), due to alert fatigue caused by a high frequency of generated alerts in computerized physician order systems, or intended prescriptions. [28] Therefore, the primary aim of the study was to identify DDI-related ADRs, suspected to cause or contribute to the clinical findings obtained at the moment of hospital admission in CVD patients. The second aim was to develop a simple prediction tool based on existing LexiInteract® monograph items [29], to identify patients having high cumulative risk for

the occurrence of an adverse event due to DDI.

Methods

Study design and setting

An analytical observational study was conducted investigating consecutive patient admissions on Cardiology ward of University Clinical Hospital Center Bežanijska Kosa, Belgrade, Serbia. University Center is a state-owned, non-profit, general hospital with 400 beds. It is located in the capital of Serbia, providing care to the patients from Belgrade as well as to more complex patients from the other parts of Serbia, who needed more specific diagnostic or interventional procedures. Cardiology ward is a department of Internal medicine Clinic, which receives adults with acute and chronic cardiovascular disorders for admission as well as for outpatient examination and treatment. The Ethics committee of the University Clinical Hospital Center Bežanijska Kosa approved this study (No 222/3).

Patient data

Patients demographic and clinical data were obtained from medical charts. All patients having complete data, including demographic data such as age and gender, medical history, reason for hospitalisation, clinical and laboratory parameters noted at the admission, as well as the therapy used before and during hospitalisation were included in the study. Additionally, in case of noted physician suspicion on the adherence, those patients were excluded from the study. We collected data on complete therapy used in the outpatient setting prior to admission to hospital (including medications, supplements, and OTC products), which were used at least a month before the admission. An exact time of introduction in therapy was noted for antiinfective agents.

Identification of potential DDIs

Screening for potential DDIs was performed using LexiInteract electronic database (Lexi-Comp, Inc., Hudson, Ohio). [29] Risk rating classes X, D, and C were considered as potential clinically significant DDIs (risk rating scale presented in Table 1). Additionally, LexiInteract monograph was used to extract data on proposed mechanism, severity and reliability of a DDI. Severity indicators include: minor (effects would be considered tolerable in most cases - no need for medical intervention); moderate (medical intervention needed to treat effects; effects do not meet criteria for major); and major (effects may result in death, hospitalization, permanent injury, or therapeutic failure). LexiInteract gives a brief presentation of published data referring to the observed/presumed interaction in the Discussion section of DDI monograph, with medical literature citations. Depending on the type and quality of published evidence for a certain DDI, reliability was defined as poor, fair, good, or excellent.

Table 1

Identification of ADRs associated with DDIs

In the next step, a clinical panel consisted of a cardiologist (22 years clinical experience as a specialist in internal medicine, 8 years clinical experience as a subspecialist in cardiology), a clinical pharmacist (7 years clinical experience, with 2 years on cardiology ward), and a PhD student in clinical pharmacy (1 year experience on cardiology ward) reviewed the patients medical charts. Data on clinical findings reported at the admission were thoroughly discussed, estimating the impact of potential DDIs on patients clinical and laboratory parameters. Causality between the adverse event and the suspected DDI were assessed using Drug Interaction Probability Scale (DIPS) introduced by Horn et al. The Naranjo scale, which estimates the probability that an ADR was caused by a single drug, was used as a basis for the DIPS. [27] The application of the DIPS to a potential DDI requires knowledge of the pharmacologic, pharmacokinetic and pharmacodynamic properties of the object and precipitant drug. DIPS uses

a series of 10 questions to assess the probability that a causal relationship exists between an event observed in a patient and the coadministration of two drugs. The scale comprises the evaluation of DDI in terms of: (1) previous credible reports; consistency with the known properties of (2) precipitant or (3) object drug; (4) time course; (5) dechallenge; (6) rechallenge; (7) alternative causes; (8) concentration of object drug in blood or other fluids; (9) other objective evidence, other than drug concentration; (10) change in the interaction with precipitant drug dose change. Each question is answered with a "yes," "no," or "unknown/not applicable" response, with assigned numeric score for each question. The total score is used to estimate the probability that the interaction is causally related to the patient event. In our study, potential DDIs with the estimated at least probable causality (DIPS score ≥2) with the adverse event reported in the medical charts, and upon the agreement of all the panelists, were coded as adverse DDIs.

Statistical analysis

Descriptive and inferential statistics were performed using PASW 22 (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as the number of patients with percentage, ordinal as the median value with interquartile and total range, and continuous as the mean value ± standard deviation with total range. Chi-square (or Fisher's exact test, where appropriate) and Mann Whitney tests were used to assess the difference in patients characteristics between groups with and without DDI-related ADR. Binary logistic regression was used to investigate the factors associated with the occurrence of DDIs involved in ADRs. Odds ratios, both crude and adjusted for the number of drugs, were reported. A two-tailed p value <0.05 was considered statistically significant. Estimated odds ratios were further used as the scoring points in calculating the DDI-adverse event (DDI-AE) probability score. DDI-AE score is based on LexiInteract monographs, which reference to published studies on DDIs (in vitro, animal or human studies, where available), or rely on data given in the summary of products characteristics. Even though a

certain extent of drug-adverse effect relationship might be suspected from the LexiInteract monograph, a causality in an individual patient is assumed to be assessed after the calculation of DDI-AE score, i.e. only in patients with calculated high cumulative risk of DDI manifestation. Therefore the score was named for the term „event“. Diagnostic accuracy of the DDI-AE probability score was tested using receiver operating characteristic (ROC) analyses. Performance was defined as acceptable when AUC=0.70-0.79, excellent when AUC=0.80-0.89, and AUC ≥0.9 is considered outstanding. [30]

Results

A total of 421 consecutive medical records were retrieved, where 54 patients (12.8%) had incomplete data on therapy used before the admission, and 16 patients (3.8%) were marked as non-adherent, according to open-form notes made by the accountable physician at the admission. Finally, a total of 2089 drug prescriptions were found in 351 patients at the moment of admission. The median number of drugs per patient was 6 (interquartile range 4-8, total range 1-15). Polypharmacy (≥5 drugs) was present in 68.95% and ≥10 drugs were found in 8.83% of patients. Patients were mainly older (aged ≥65 years; 254, 72.36%), and 48.43% (170) were females. Table 2 presents the demographic and clinical characteristics of the study population.

Table 2

Potential DDIs

Given the number of drugs, a total of 5908 drug pairs were tested for potential DDIs. Potential clinically significant DDIs (X, D and C class) were identified in 1606 drug pairs (27.18%). The vast majority of drug pairs were in C class (1452, 90.41%), 143 (8.90%) DDIs were in D class, and only 11 (0.68%) were in X class, accordingly to risk rating. The total prevalence of potential clinically significant DDIs was estimated to 83.19% (292 patients).

Adverse drug reactions associated with DDIs

The clinical panel identified a total of 56 drug pairs being suspected to cause or contribute to clinical findings obtained at the moment of hospital admission. According to LexiInteract, those adverse interacting drug pairs actually corresponded to 30 unique DDIs implicated in ADRs. ADRs attributed to DDIs were identified in 34 patients, with a total prevalence of 9.69% in the studied population. In patients having at least one potential DDI at admission, the prevalence of ADRs attributed to DDIs was calculated to 11.64%. Most frequent

adverse DDIs were C class (40 DDIs,71.43%), followed by D class (14 DDIs,25%), and only 2 DDIs (3.57%) were assigned an X class risk rating. Severity, as graded by LexiInteract was assessed as moderate in 35 DDIs (62.5%), and major in 21 DDIs (37.5%). Regarding DDI reliability stated in the LexiInteract monograph, there were only 7 DDIs (12.5%) reported as excellent, 12 (21.43%) reported as good, and 37 (66.07%) reported as fair based on the published reports. In total, 41 different drugs (INN) from seven ATC classes were involved in actual DDI-related ADRs. The highest frequency was observed for cardiovascular system drugs (ATC class C, 46 out of 112), with mainly involved ACE inhibitors (10 times). Table 3 shows the frequency of ATC classes with class members implicated in DDI-related ADRs.

Table 3

Detailed data on identified ADRs attributed to DDIs are given in Table 4. ADRs most frequently involved effect on cardiac function (41.07%) –tachycardia or irregular heart rhythm (N=20, 35.7%), and much less frequent bradycardia (N=3, 5.36%). Bleeding and effect on blood pressure were equally distributed (N=10, 17.86%), whereas hypotension was more frequent, than hypertension. Non-cardiovascular events were found in 23.21% of cases, including hyperkalemia, low red cell count, elevated liver enzymes, epigastric pain, and hyperthermia. After the admission, 14 (25%) DDIs remained during the hospitalisation without dose adjustments of either object or precipitant drug, in one case (2%) the dose of object drug was decreased, and 41 (73%) of identified DDIs led to changes in prescription.

Table 4

Calculation of DDI-AE probability score

Among patients characteristics, the prevalence of adverse DDIs was not associated with gender or older age (Table 5). Statistical significance was shown only for the number of drugs, with the odds ratio estimated to 1.42 (95 % CI 1.23-1.63), $p<0.001$. Characteristics of potential

DDIs, such as risk rating class, severity and the underlying DDI mechanism, were significantly associated with the adverse outcome of DDIs in the studied population (Table 5). Odds ratios presented in Table 5, were used to calculate the DDI-AE probability score. Items with the proposed points are presented in Table 6. Two DDI-AE probability scores were tested, DDI-AE 1 including only DDIs features, and DDI-AE 2 including both DDIs features and the number of drugs.

Table 5

Table 6

Prediction ability of DDI-AE probability score

Performance of DDI-AE probability scores was rated as good, with the results comparatively presented in Table 7. DDI-AE 1 score differed significantly between patients with and without DDI-related ADR at admission: median 9.00 [IQR 7.75-11], and 6 [IQR 0-7] ($p<0.001$), respectively. Median values for DDI-AE 2 score were 21.60 [IQR 15.80-23.70] in patients with DDI-related ADR, compared to 13 [IQR 5.60-18.20] ($p<0.001$) in patients without adverse DDI implicated in admission. ROC analyses to evaluate the diagnostic accuracy of DDI-AE 1 and DDI-AE 2 probability score yielded an AUC of 0.800 (95% CI 0.744-0.856) and 0.811 (0.750-0.872), respectively. In spite of slightly lower AUC value, DDI-AE 1 score (not including the number of drugs in the score estimation) showed somewhat better sensitivity and specificity features. The suggested cut-off of 7 points for DDI-AE score 1 demonstrated 76.5% sensitivity and 77.9% specificity in predicting the occurrence of adverse drug event given the characteristics for potential DDIs stated in the LexiInteract monograph.

Table 7

Discussion

To our knowledge, the prevalence of DDI-related hospitalisations and the identification of adverse DDIs have not been previously investigated in CVD patients. Our study revealed the prevalence of DDI-related ADRs in 9.69% of CVD admissions to the cardiology service of our hospital. ADRs related to DDIs were uncommon and usually not major, but it is likely that in non-academic hospitals and non-specialty services the frequency may be substantially higher. In our study, adverse DDIs mainly affected cardiac function (41.07%) – causing tachycardia or irregular heart rhythm (35.7%), and much less frequent bradycardia (5.36%). Bleeding and effect on blood pressure were equally distributed (17.86%), whereas non-cardiovascular events were found in 23.21% of adverse DDIs. Gastrointestinal tract bleeding (33-40%), hyper- and hypotension (18%), and cardiac rhythm disturbances (18-30%) were identified to be the most frequent adverse events resulting from DDIs. [7, 12] The study setting might hold the explanation for the discrepancy in gastrointestinal tract bleeding frequency, as those patients might be more frequently admitted through emergency department or hospitalised at gastroenterology ward.

Interestingly, the proportion of patients with liver or renal disease in anamnesis was significantly lower in the group with adverse DDI (Table 2). It might reflect the increased and existing awareness on drugs prescribing in patients with known decrease in liver or renal function, as a well known risk of ADRs occurrence. Still, harmful drug combinations have been identified in about 10% of CVD patients. Nevertheless, a higher prevalence of adverse DDIs might be expected in CVD patients, due to interacting potential of CVD drugs. [1] Additionally, it was reported CVD itself might increase the risk of ADRs, by altering renal and hepatic perfusion, or causing hypoxia. [31] Hence, drug elimination and tolerability may be further compromised in CVD patients, irrespective of other risk factors. [31, 32] Other studies dealing with cardiac inpatients reported ADR occurrence in 34% of patients during hospital stay [33], whereas the incidence of clinically important DDIs in cardiology department was reported to about

15%.[34] Further, the wide variety of non-CVD drugs involved in DDIs were identified in our study, which assert the benefit of using DDI screening tools. Cardiologists are certainly well trained for CVD drugs and the expected effect of their concomitant use. However, drugs used in other therapeutic areas such as neurology, mental disease, respiratory disease, and urogenital disease, may have quite specific pharmacokinetic and pharmacodynamic and PD characteristics, which certainly require an electronic base support in assessing drugs interacting potential. It was confirmed that potential DDIs arise more often as a result of prescriptions from multiple prescribers than from a single caregiver prescribing multiple drugs. [35]

Previous studies underlined that DDIs represent a real problem in clinical practice. [6] The main strategy for reducing DDIs is to use electronic decision support tools, which usually present DDIs as interruptive alerts. [36] Inevitably, alert fatigue and high rates of alert override are well-recognized consequences of receiving a high volume of DDI alerts. The issues of electronic alert fatigue and override rates were briefly described in the literature [28, 37], carrying the risk that prescribers may miss warnings of potentially serious adverse events. [36] The most frequently proposed strategy to combat alert fatigue is to reduce the total number of DDI alerts, by elimination of minor and/or moderate DDIs. [36, 38, 39] However, our study demonstrated that the majority of adverse DDIs were classified as C class (about 71%), attributed the lowest risk rating among all potential clinically significant DDIs, which is highly expected to be neglected in most of the DDI alerts. In addition, severity was graded as moderate in 62.5% and 37.5% of adverse DDIs. Given the high prevalence of potential clinically significant DDIs with 83%, other strategies have to be employed to deal with the alert fatigue in CVD patient population. We aimed to develop DDI-AE probability score to decrease the possibility for alert overrides through presenting a cumulative risk of DDIs, ‘‘displaying’’ only high-risk patients during the electronic prescribing process. The items used in calculating DDI-AE probability score are

already incorporated in the LexiInteract monograph. Thus, the proposed score could be easily calculated as an add-on feature in the LexiInteract database. Although the number of drugs have been independent risk indicator for adverse DDI occurrence, better results were obtained for DDI-AE 1 score (cut-off value ≥7 points). Furthermore, a statistically significant higher median values for both DDI-AE 1 and DDI-AE 2 score were found in patients with adverse DDI, reflecting the possible additive or synergistic risk of multiple DDIs, in causing adverse outcome. The LexiInteract monograph denotes interacting/noninteracting members of a specific pharmacological group, giving the opportunity to improve patient's therapy through avoiding potentially harmful DDIs. Furthermore, medical charts review presents significant workload for clinicians, to search for the evidence and occurrence of DDIs. [40] That is one of the main reason why DDI-related outcomes are still underinvestigated and underreported. Nowadays, different data mining strategies are being developed in identifying ADRs and DDI-related ADRs, to get closer to their real burden. [41, 42] Validation of the DDI-AE probability score is certainly needed in a larger population, however, the idea of stratifying patients according to DDI-related risk might ease future research, as well as the clinical practice.

General recommendations for future research to improve DDI alerts have been given. One of them is a requirement to determine frequencies and clinical consequences of DDIs. [43] In line with that, the main strength of the study is the identification of adverse DDIs that caused or contributed to hospital admission in patients with CVD. Detailed data at the admission and during the hospital stay were collected, which enabled comprehensive evaluation of adverse DDIs. On the other hand, our results are derived from 351 patient sample, which is the main limitation of the study. DDIs were underreported in this population, nevertheless, due to the number and nature of drugs used in CVD therapy, a higher risk might be expected. Lack of information in this area can easily result in over, as well as underestimation of the clinical consequences of DDIs. [12] Apparently, our results regarding the estimated prevalence of adverse

DDIs should be interpreted with caution due to small sample size. It has been recognized that the studies with a larger sample size showed low incidences and studies with a smaller size showed high incidences of adverse outcomes due to DDIs. Results from studies with a smaller sample size have a larger standard error, and outliers to higher numbers occur more often, wrongly presenting a higher incidence. Further, it is possible that in the smaller studies medication histories were studied in more detail than in the larger ones, and were therefore more readily able to recognise adverse patient outcomes due to DDIs. On the other hand, this may indicate that the percentages found in the larger studies are an underestimation of the true risk.[12] It was also confirmed that a higher rates for adverse events have been found if active strategy was applied in data acquisition, compared to spontaneous reporting, which was the case in our research. [44] Moreover, this is a single-center study exploring the outcomes of the patients admitted to the academic hospital ward. It is likely that the reported results might be unrepresentative for other settings, such as non-academic, non-speciality or outpatient setting. Therefore, the proposed tool for identification of high-risk patients needs to be tested and validated in other settings or in other populations. Further research is needed in the larger sample to obtain the generalizability of the findings, and to improve prospective risk measures to deal with DDI-related adverse therapy outcomes.

Conclusions

Our study revealed significant burden of DDIs-related ADRs in CVD admissions to the cardiology service of our hospital. Generally, about one in ten patients hospitalized with CVD might have a DDI contributing to the hospitalisation. Given the high prevalence of CVD, DDI-related harm might be significant burden worldwide. Electronic databases can be easily applied in predicting and preventing DDIs, but further improvements have been advocated to increase the quality and acceptance rates of DDI alerts. Identification of patients with high cumulative DDI-adverse event risk might ease the recognition of DDI-related harm and improve the use of

electronic databases in clinical practice.

TRANSPARENCY

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Table 1. Drug-drug interactions risk rating scale according to the LexiInteract database

Risk Rating	Action	Description
A	No Interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Modify regimen	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity - aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Table 2. Demographic and clinical characteristics of the study population

	ADR attributed to DDI		
	Yes (N=34)	**No (N=317)**	**p value**
	number of patients (%)	number of patients (%)	
Gender, female	11 (32.35)	157 (49.53)	0.211
Age, years			
mean ± S.D., total range	72.18 ± 11.05, 49-89	69.80 ± 9.98, 29-88	0.194
≥65	24 (70.59)	230 (72.56)	0.807
Number of drugs			
median [IQR], total range	8 [6-9.25], 5-15	6 [4-7], 1-14	<0.001
≥5	34 (100)	208 (65.62)	<0.001
≥10	8 (23.53)	23 (7.26)	0.005
Charlson comorbidity index			
median [IQR], total range	3 [2-4.25], 0-6	3 [2-4], 0-8	0.346
mean ± S.D.	3.21 ± 1.59	2.97 ± 1.63	0.425
Length of stay, days			
mean ± S.D., total range	10.65 ± 9.59, 2-54	9.40 ± 5.73, 1-42	0.266
Clinical diagnosis			
heart failure	17 (50)	130 (41.01)	0.313
angina pectoris	7 (20.59)	101 (31.86)	0.176
hypertension	18 (52.94)	218 (68.77)	0.062
arrhythmia	20 (58.82)	148 (46.69)	0.178
myocardial infarction in anamnesis	3 (8.82)	39 (12.30)	0.552
cerebral infarction in anamnesis	3 (8.82)	17 (5.36)	0.427
diabetes mellitus	10 (29.41)	90 (28.39)	0.900
respiratory disease	5 (14.71)	25 (7.89)	0.192
endocrine disease, excluding diabetes	2 (5.88)	16 (5.05)	0.834
gastrointestinal disease	3 (8.82)	18 (5.68)	0.442
renal disease	1 (2.94)	24 (7.57)	0.492
liver disease	0	10 (3.15)	0.607
Clinical parameters at admission			
mean ± S.D.			
heart rate	88.53 ± 27.7	88.9 ± 23.9	0.749
systolic blood pressure	132.06 ± 19.07	140.28 ± 24.23	0.057
diastolic blood pressure	77.79 ± 14.57	84.43 ± 13.79	0.008
Reason for admission			
heart failure	18 (52.94)	127 (40.06)	0.160
arrhythmia	7 (20.59)	56 (17.67)	0.692
hypertension	1 (2.94)	45 (14.20)	0.065
angina pectoris	0	40 (12.62)	0.021

ADR – adverse drug reaction; DDI – drug-drug interaction; S.D. – standard deviation; IQR – interquartile range; risk rating C - Monitor therapy; risk rating D - Consider therapy modification; risk rating X - Avoid combination

Table 3. Drug classes implicated in adverse drug-drug interactions

Drug class	Frequency (%)
Cardiovascular system	**46 (41.07)**
ACE inhibitors	10 (8.93)
Aldosterone antagonists	8 (7.14)
Antiarrhythmics, class III	6 (5.36)
Digitalis glycosides	5 (4.46)
Antiarrhythmics, class Ic	3 (2.68)
Alpha and beta blocking agents	3 (2.68)
HMG CoA reductase inhibitors	3 (2.68)
High-ceiling diuretics, sulfonamides	2 (1.79)
Peripheral vasodilatators, purine derivatives	2 (1.79)
Calcium channel blockers, dihydropyridine derivatives	2 (1.79)
Organic nitrates	1 (0.89)
Beta blocking agents, selective	1 (0.89)
Respiratory system	**27 (24.11)**
Selective beta-2-adrenoreceptor agonists	15 (13.39)
Xanthines	8 (7.14)
Anticholinergics, inhalations	4 (3.57)
Blood and blood forming organs	**17 (15.18)**
Platelet aggregation inhibitors excl. Heparin	9 (8.04)
Vitamin K antagonists	8 (7.14)
Nervous system	**14 (12.50)**
Barbiturates and derivatives	3 (2.68)
Antipsychotics	3 (2.68)
Analgesics and antipyretics, pyrazolones	2 (1.79)
Benzodiazepine derivatives	2 (1.79)
Antiepileptics, carboxamide derivatives	1 (0.89)
Anti-Parkinson drugs, dopa and dopa derivatives	1 (0.89)
Selective serotonin reuptake inhibitors	1 (0.89)
Other antidepressants	1 (0.89)
Antiinfectives for systemic use	**4 (3.57)**
Macrolides	4 (3.57)
Musculo-skeletal system	**3 (2.68)**
Antigout preparations, preparations inhibiting uric acid production	3 (2.68)
Genito urinary system and sex hormones	**1 (0.89)**
Drugs used in benign prostatic hypertrophy, alpha-adrenoreceptor antagonists	1 (0.89)
Total	**112 (100%)**

Table 4. Adverse drug reactions attributed to drug-drug interactions identified at the hospital admission

Adverse drug reactions DDIs	Patient management	Mechanism	Risk Rating, Severity, Reliability	Number of DDIs
Heart rate / rhythm (23) tachycardia, irregular heart rhythm				
aminophylline + amiodarone	monitor for toxic effects of theophylline derivatives	PK (metabolism)	C, Moderate, Fair	1
aminophylline + propafenone		PK (metabolism CYP1A2)	C, Moderate, Fair	1
aminophylline + fenoterol	monitor for increased effects of sympathomimetics (eg,	PD	C, Moderate, Fair	4
aminophylline + salbutamol	blood pressure, heart rate)	PD	C, Moderate, Fair	1
aminophylline + salmeterol		PD	C, Moderate, Fair	1
clarithromycin + digoxin	monitor for increased serum concentrations and toxic effects of cardiac glycosides	PK (P-gp, metabolism CYP3A) / PD	C, Moderate, Excellent	1
digoxin + erythromycin		PK (P-gp, metabolism CYP3A) / PD	C, Moderate, Excellent	1
erythromycin + salmeterol	monitor closely for adverse cardiovascular effects of salmeterol (e.g., increased heart rate, prolonged QT interval)	PK (metabolism CYP3A4)	C, Moderate, Fair	1
erythromycin + propafenone	monitor for QTc interval prolongation and ventricular arrhythmias. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are at greater risk	PK (P-gp, metabolism CYP3A4) / PD	C, Moderate, Fair	1
fenoterol + salbutamol	monitor for increased effects of sympathomimetics (eg,	PD	C, Moderate, Fair	1
fenoterol + salmeterol	blood pressure, heart rate)	PD	C, Moderate, Fair	2
fluphenazine + chlorpromazine	monitor for additive anticholinergic effects; monitor for additive CNS-depressant effects	PD	C, Moderate, Good	1
ipratropium + tiotropium	avoid concurrent use of ipratropium with any other drugs that have anticholinergic properties. If such combinations can not be avoided, monitor patients closely for evidence of anticholinergic-related toxicities (e.g., urinary retention, constipation, tachycardia, dry mouth)	PD	X, Major, Fair	2

phenobarbitone + propafenone	monitor for decreased propafenone effects/therapeutic failure	PK (metabolism CYP3A4)	C, Moderate, Fair	1
salmeterol + verapamil	monitor closely for adverse cardiovascular effects of salmeterol (e.g., increased heart rate, prolonged QT interval)	PK (metabolism CYP3A4)	C, Moderate, Fair	1
bradycardia				
amiodarone + carvedilol	monitor for increased signs and symptoms of bradycardia with beta-blockers; atenolol interact in the smaller degree with amiodarone	PK (metabolism CYP2D6) / PD	C, Moderate, Fair	1
carvediol + digoxin	monitor for bradycardia or heart block, as well as potential increases in digoxin concentration	PK (P-gp) / PD	C, Moderate, Excelent	1
digoxin + spironolactone	monitor closely for signs or symptoms of digoxin toxicity. Additional monitoring of digoxin concentrations may also be warranted, but spironolactone and its metabolites may interfere with many different commerical digoxin assays	PK (unknown)	C, Moderate, Fair	1
Bleeding (10)				
aspirin + vitamin K antagonist	monitor for increased signs and symptoms of bleeding	PD	D, Major, Excellent	3
aspirin + clopidogrel		PD	C, Moderate, Fair	2
amiodarone + vitamin K antagonist		PK (metabolism) / PD indirect	D, Major, Good	2
clopidogrel + vitamin K antagonist		PD	C, Moderate, Fair	2
simvastatin + warfarin	monitor for increased effects of oral anticoagulants if an HMG-CoA reductase inhibitor is initiated/dose increased. Dosage adjustments of the anticoagulant may be needed	PK (metabolism)	C, Moderate, Good	1
Blood pressure (10)				
hypertension				
amlodipine + carbamazepine	consider alternatives to dihydropyridine calcium channel blockers. Monitor for reduced therapeutic effects of the calcium channel blocker. Dose adjustment may be needed	PK (metabolism CYP3A)	D, Major, Fair	1
amlodipine + phenobarbitone	consider an alternative in order to avoid therapeutic	PK (metabolism CYP3A4)	D, Major, Fair	1
isosorbidemononitrate + phenobarbitone	failure of the substrate (amlodipine, isosorbidemononitrate)	PK (metabolism CYP3A4)	D, Major, Fair	1
enalapril + metamizole	special caution is needed in chronic heart failure patients, to avoid the potential negative consequences of concomitant	PD	C, Moderate, Excellent	1

	NSAID therapy (fluid accumulation/edema). Monitor for decreased therapeutic effects of ACE inhibitor			
hypotension				
benserazide/levodopa + furosemide	increased risk for symptomatic postural hypotension. Advise patients to minimize the risk of dizziness or falls	PD	C, Moderate, Fair	1
bromazepam + clonazepam	monitor for additive CNS-depressant effects. Such effects may include, but are not limited to, ataxia, confusion, drowsiness, respiratory depression, and weakness	PD	C, Moderate, Good	1
carvediol + fluoxetine	consider an alternative to avoid toxicity of the carvedilol. Some combinations are specifically contraindicated by manufacturers. Please review applicable package inserts	PK (metabolism CYP2D6)	D, Moderate, Fair	1
enalapril + pentoxifyline	monitor blood pressure closely and advise patients of the possibility for enhanced blood pressure lowering	PD	C, Moderate, Fair	1
furosemide + pentoxifylline		PD	C, Moderate, Fair	1
metoprolol + tamsulosin	monitor closely for additive hypotensive effects	PD	C, Moderate, Fair	1
Hyperkalemia (6)				
enalapril + spironolactone	monitor for increased incidence of hyperkalemia	PD	C, Major, Good	2
fosinopril + spironolactone		PD	C, Major, Good	3
metamizole + spironolactone	monitor blood pressure and potassium concentrations closely	PD	C, Major, Fair	1
Low red blood cells count (3)				
allopurinol + captopril	if allopurinol must be used in an ACE inhibitor patient, monitor for evidence of hypersensitivity reactions	unknown	D, Major, Fair	1
allopurinol + fosinopril		unknown	D, Major, Fair	1
allopurinol + lisinopril		unknown	D, Major, Fair	1
Elevated liver enzymes (AST and ALT) (2)				
amiodarone + simvastatin	consider using pravastatin; limit the simvastatin dose to 20 mg daily and monitor for evidence of simvastatin toxicities (eg, myalgia, liver function test elevations, rhabdomyolysis)	PK (metabolism CYP3A4)	D, Major, Good	2
Epigastric pain (1)				
digoxin+spironolactone	monitor closely for signs or symptoms of digoxin toxicity. Additional monitoring of digoxin concentrations may also be warranted, but	PK (unknown)	C, Moderate, Fair	1

	spironolactone and its metabolites may interfere with many different commerical digoxin assays			
Hyperthermia (1)				
clozapine + venlafaxine	monitor patients extra closely for evidence of serotonin toxicity (e.g., mental status changes, autonomic instability, and neuromuscular hyperactivity) or neuroleptic malignant syndrome (e.g., hyperthermia, muscle rigidity, autonomic dysfunction)	PD	C, Moderate, Fair	1

PK – pharmacokinetic; PD - pharmacodynamic; risk rating C - Monitor therapy; risk rating D - Consider therapy modification; risk rating X - Avoid combination; AST - aspartate aminotransferase; ALT - alanine aminotransferase

Table 5. Factors associated with adverse drug-drug interactions

Patients characteristics	**crude OR (95% CI)**	**p value**	**[a]adjusted OR (95%CI)**	**p value**
Gender, male	1.59 (0.77-3.27)	0.214	1.21 (0.56-2.61)	0.634
Age ≥65 years	0.91 (0.42-1.97)	0.807	0.57 (0.24-1.34)	0.195
Number of drugs	1.42 (1.23-1.63)	<0.001	-	
Charlson comorbidity index	1.09 (0.88-1.35)	0.424	0.76 (0.58-1.00)	0.052
Clinical diagnosis				
Heart failure	1.44 (0.71-2.92)	0.315	0.84 (0.39-1.82)	0.653
Angina pectoris	0.55 (0.23-1.32)	0.181	0.36 (0.14-0.91)	0.030
Diabetes mellitus	1.05 (0.48-2.29)	0.900	0.63 (0.27-1.47)	0.284
Hypertension	0.51 (0.25-1.04)	0.065	0.46 (0.21-0.99)	0.047
Arrhythmia	1.63 (0.80-3.34)	0.181	1.63 (0.76-3.49)	0.205
Respiratory disease	2.01 (0.72-5.66)	0.184	1.02 (0.32-3.28)	0.978
Reason for admission				
Heart failure	1.66 (0.81-3.37)	0.164	1.00 (0.46-2.18)	0.993
Arrhythmia	1.19 (0.49-2.88)	0.692	2.10 (0.81-5.46)	0.128
Hypertension	0.18 (0.02-1.36)	0.096	0.30 (0.04-2.28)	0.243
Potential DDIs characteristics				
risk rating				
X	7.57 (1.62-35.39)	0.010	2.35 (0.41-13.43)	0.338
D	6.13 (2.89-12.98)	<0.001	2.92 (1.24-6.89)	0.015
C	-			
number of C >2	9.17 (2.75-30.59)	<0.001	3.43 (0.90-13.15)	0.072
severity				
major	3.92 (1.86-8.29)	<0.001	2.69 (1.20-6.02)	0.017
moderate	2.14 (1.04-4.39)	0.038	1.32 (0.62-2.83)	0.476
reliability				
excellent	1.98 (0.64-6.17)	0.239	1.31 (0.40-4.31)	0.656
good	1.79 (0.83-3.84)	0.139	1.19 (0.53-2.71)	0.673
fair	3.46 (1.68-7.11)	0.001	2.82 (1.28-6.23)	0.010
mechanism				
PK/PD	4.66 (2.24-9.69)	<0.001	3.37 (1.13-10.06)	0.030
PK	4.03 (1.46-11.12)	0.007	2.43 (1.10-5.40)	0.028
PD	3.36 (1.62-6.97)	0.001	2.34 (1.09-5.04)	0.030
present additional risk factor	0.67 (0.08-5.68)	0.711	1.02 (0.09-11.12)	0.987

OR – odds ratio; CI – confidence interval; a – odds ratio adjusted for number of drugs; risk rating C - Monitor therapy; risk rating D - Consider therapy modification; risk rating X - Avoid combination; PK – pharmacokinetic; PD – pharmacodynamic; PK/PD – pharmacokinetic/pharmacodynamic

Table 6. Calculation of DDI-AE probability score based on LexiInteract monograph items

	DDI-AE probability scores	
Item	**DDI-AE 1 Points**	**DDI-AE 2 Points**
Presence of X class pDDI	2	2
Presence of D class pDDI	3	3
Presence of more than 2 C class pDDIs	3	3
Severity major	3	3
Severity moderate	1	1
Mechanism PK/PD	3	3
Mechanism PK	2	2
Mechanism PD	2	2
Number of drugs	-	multiplied by 1.4

pDDI – potential drug-drug interaction; risk rating C - Monitor therapy; risk rating D - Consider therapy modification; risk rating X - Avoid combination; PK – pharmacokinetic; PD – pharmacodynamic; PK/PD – pharmacokinetic/pharmacodynamics

Table 7. Predictive value of DDI-AE probability score

	DDI-AE probability scores			
ADR caused by DDI (clinical panel + DIPS by Horn et al.)	**DDI-AE 1**		**DDI-AE 2**	
ROC analysis				
AUC (95% CI)	0.800 (0.744-0.856)		0.811 (0.750-0.872)	
p value	<0.001		<0.001	
	cut-off value		**cut-off value**	
	≥ 7 points	**≥ 8 points**	**≥ 16 points**	**≥ 20 points**
Sensitivity	76.5%	64.7%	73.5%	61.8%
Specificity	77.9%	80.4%	66.9%	83.6%

DIPS – Drug Interaction Probability Scale; CI – confidence interval