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Original research paper

Prevalence and factors associated with potential clinically significant drug-drug interactions in patients with cardiovascular diseases at hospital admission

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity globally. It is estimated that 17.9 million people died from CVDs in 2019, which represents 32 % of all deaths worldwide. Cardiovascular drugs are the most common medical intervention for the prevention of cardiovascular events. CV medications have many benefits however their application is often complicated by multimorbidity and polypharmacy. Drug-drug interactions (DDIs) can lead to adverse drug events, hospitalizations, prolonged hospital stays, increased healthcare costs, and increased risk of mortality. Hospital admission provides an opportunity for pharmacotherapy analysis and for identifying DDIs which can jeopardize medication safety. The aim of this study is to determine the type and prevalence of potential clinically significant DDIs in patients with CVD and to examine factors associated with exposure to DDIs. A prospective study was conducted at the Dubrava University Hospital at the Clinic of Cardiology during a 6-month period (September 2023 – February 2024). Demographic, clinical and pharmacotherapy data were collected for each patient. The first prescribed pharmacotherapy was analyzed. The research was approved by the Hospital's Ethics Committee and each patient involved in the study signed an informed consent. Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., USA) was used for DDI analysis. Poisson regression was used for regression analysis for determining risk factors associated with exposure to DDIs. Total of 151 patients admitted to Cardiology ward were included in the research, and the average age was 67 years. Patients had an average of 9 medications in their therapy and 8 diagnoses. Overall, 1268 potential clinically significant DDIs were determined, of which the most frequently determined interactions were grade C (90.9 %), then grade D (8.6 %) and grade X (0.6 %). CV medications were involved in 88 % DDIs. The most common interventions regarding identified DDIs included exclusion one of the drugs, dose adjustment, increased monitoring of signs of bleeding, cardiac disorders, hypoglycemia, CNS depression and rhabdomyolysis, blood pressure, markers of renal function and electrolyte status. Factors associated with the prevalence of potential clinically significant DDIs were decreased renal function, recent hospitalization, total

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number of comorbidities and polypharmacy. Specific comorbidities associated with DDIs were arrhythmia, heart failure, diabetes mellitus and disease of the respiratory system. A high prevalence of DDIs of CV medications in all categories of clinical significance was determined. Managing medication safety in specific patient groups with CVDs can represent a greater challenge regarding DDIs. Certain medical conditions, such as arrhythmia, heart failure, diabetes, and diseases of the respiratory system, multimorbidity, polypharmacy, impaired renal function and recent hospitalization are identified in this research as additional factors associated with DDIs occurrence in patients with CVDs at hospital admission. Hospital admission is one of the crucial points for managing medication safety. Clinical pharmacists should regularly analyze DDIs in prescribed pharmacotherapy which enhances medication safety and also contributes to the quality of provided health care.

Keywords: clinical pharmacist, cardiovascular disease, drug-drug interactions, hospital admission

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity. It is estimated that 4.2 million people died from CVDs in 2019 in Europe, which represents 42.5 % of all deaths (1). CVDs are particularly associated with older age. In the European Union, 21.3 % of the population is 65 and older (2). It has been established that more than 70 % of the elderly develop CVD by the age of 70, and that 50 % of patients with CVD develop an additional disease (3, 4).

Cardiovascular (CV) medications are the most common medical intervention for the prevention and treatment of cardiovascular diseases (5). CV medications have many benefits however their use is often complicated by multimorbidity and polypharmacy (6, 7). The literature suggests that cardiovascular drugs should be considered high-risk drugs due to a number of potential complications if their use is not optimized (8, 9). The meta-analysis found that the classes most frequently related to hospital admissions in the elderly were beta-blockers (1.8–66.7 %), oral anticoagulants (3.3–55.6 %), digoxin (1.6–18.8 %), angiotensin-converting enzyme inhibitors (ACEIs) (5.5–23.4 %), and calcium channel blockers (1.0–8.3 %) (10). The World Health Organization has identified medication safety as one of the global priorities (11). Certain national lists of health priorities incorporated medication safety as one of the main goals (12–15).

Polypharmacy is usually highly present in patients with CVDs due to the complexity of CV diagnoses and multimorbidity. Polypharmacy complicates the management of treatment and increases the likelihood of pharmacotherapy-related problems. Pharmacotherapy--related problems lead to increased healthcare utilization, higher treatment costs, and elevated morbidity and mortality rates (16–21). Pharmacotherapy-related problems include drug-drug interactions (DDIs), adverse drug reactions (ADRs), dosage issues, especially in renal and liver impairment, potentially inappropriate medications, therapy duplication, and others. DDIs can interfere with drug effectiveness, and cause ADRs or intoxication. The published data indicates that up to 30 % of ADRs are linked to DDIs (22). Furthermore, up to 26 % of all hospital admissions related to ADRs are caused by DDIs (23, 24).

To increase medication safety, clinical pharmacists should regularly review prescribed pharmacotherapy (22). Hospital admission provides an opportunity for pharmacotherapy analysis and for identifying DDIs that can jeopardize medication safety (25). Persisting DDIs can complicate the course of treatment and generate prescribing cascades. The aim of the study was to identify potential clinically significant DDIs in patients with CVDs that can affect medication safety and factors associated with DDIs occurrence.

EXPERIMENTAL

Study design and setting

A prospective study was conducted at the Dubrava University Hospital at the Clinic of Cardiology during a 6-month period (September 2023 – February 2024). Patients were included in the research consecutively. Dubrava University Hospital is a tertiary care health institution with 600 beds, whose emergency medical service covers a population of about 350,000 inhabitants. The Clinic of Cardiology consists of five departments (Department of Intensive Cardiac Care, Department of Arrhythmias, Department of Vascular Diseases and Cardiac Valves, Department of Cardiomyopathies, Heart Failure and Transplant Cardiology and Department of Advanced Heart Failure and Post-coronary Care), a day clinic, two diagnostic-therapeutic departments (Diagnostic and therapeutic department for electrostimulation and heart electrophysiology and Diagnostic and therapeutic department for invasive and interventional cardiology) and one diagnostic department (Diagnostic department for echocardiography, imaging of the heart).

Data collection

Demographic, clinical, and pharmacotherapy data were collected for patients aged 18 years or older who were hospitalized at the Clinic of Cardiology. Patients were excluded if they were not able to answer the questions needed to complete the structured interview, did not have a caregiver who could be interviewed in case the patient was unable to participate in the interview, or were unable or unwilling to give their consent. The clinical pharmacist conducted a structured interview with the patient to obtain demographic and clinical data. The medical documentation was reviewed. Patients' diagnoses were classified according to the International Classification of Diseases (ICD-10). Recent hospitalization is defined as hospitalization over a period of one year. Recent hospitalization and history of adverse drug reactions were determined based on patient interviews, the Hospital information system, and other available patient medical documentation. Data on renal function parameters were taken from the first laboratory findings made in the hospital after the admission of patients, according to the point of data analysis. Data on medications were obtained by analyzing the first prescribed pharmacotherapy list upon admission. The research was approved by the Hospital's Ethics Committee (Number 2023/3108-01) and each patient involved in the study signed an informed consent.

Data analysis

Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA) was used for DDIs processing. Lexicomp categorizes interactions based on their clinical significance

into five categories: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination). Categories C, D, and X are considered clinically significant and were included in the analysis. Lexicomp showed high sensitivity (87–100 %) and specificity (80–90 %) (26). An expert panel of clinical pharmacists reviewed all identified drug interactions and agreed on the clinical importance of the required level of monitoring and interventions. The recommendations were forwarded to the physician.

Statistical analysis

Analyses were performed using R Core Team, 2022 (27). Standard descriptive statistics were used to analyze patient characteristics and collected data. To analyze the relationship between the criterion variables negative-binomial regression was used, *i.e.* a variant of Poison's regression with an additional dispersion parameter. The analysis shows parameters for individual variables and parameters for the logistic model.

RESULTS AND DISCUSSION

A total of 151 patients were included in this research. Demographic and clinical data of patients are presented in Table I. The proportion of male patients was higher (59.6 %) and the average age of the patients was 68 years ranging from 22 to 91 years. The mean number of medications per patient was 9 with 45 % of patients having 10 or more medications. Patients had an average of 8 diagnoses. Among 151 patients, impaired renal function (eGFR < 60 mL/min/1.73 m^2) was present in 38.4 % of patients. Category C of ATC classification of drugs were the most frequently prescribed drugs and diuretics were the most extensively used therapeutic subgroup in this class (23.8 %).

Table I. Patient's demographic and clinical data

Characteristic	Study sample (*N* = 151)
Age, years, median (IQR)	68 (61–76)
Gender, male, *N* (%)	90 (59.6)
BMI (kg m^{-2}), median (IQR)	28.4 (25.3–31.6)
Serum creatinine (μmol L^{-1}), median (IQR)	91 (72–113.5)
eGFR per CKD EPI (mL/min/1.73m^2), median (IQR)	68.2 (51.2–87.7)
eGFR stage (KDIGO classification), *N* (%)	
G1 Normal or high	33 (21.9)
G2 Mildly decreased	60 (39.7)
G3a Mildly to moderate decreased	32 (21.2)
G3b Moderately to severely decreased	18 (11.9)
G4 Severely decreased	6 (4.0)
G5 Kidney failure	2 (1.3)

Type of admission, *N* (%)	
Emergency	38 (25.2)
Elective	113 (74.8)
Recent hospitalization, *N* (%)	72 (48)
Residence, *N* (%)	
Living alone	25 (19.1)
Living with family/caregiver	105 (80.2)
Nursing home	1 (0.8)
History of adverse drug reactions, *N* (%)	32 (22.9)
Total number of diagnoses	1191
Mean number of diagnoses, median (IQR)	8 (5–11)
Mean number of medications (first prescribed therapy upon hospital admission), median (IQR)	9 (7.5–11.5)
< 5 medications	13 (8.6 %)
5–9 medications	70 (46.4 %)
≥ 10 medications	68 (45.0 %)
Total number of prescribed drugs	1411
The most common drug classes (ATC groups)	
A Alimentary tract and metabolism	297 (21.0 %)
B Blood and blood forming organs	153 (10.8 %)
C Cardiovascular system	694 (49.2 %)
C01: Cardiac therapy	73 (10.5 %)
C02: Antihypertensive drugs	23 (3.3 %)
C03: Diuretic drugs	165 (23.8 %)
C07: Beta blocking agents	105 (15.1 %)
C08: Calcium channel blockers	64 (9.2 %)
C09: Agents acting on the renin-angiotensin system	139 (20.0 %)
C10: Lipid modifying agents	125 (18.0 %)
N Nervous system	108 (7.7 %)
R Respiratory system	54 (3.8 %)

The most frequent diagnoses are demonstrated in Table II. The most common diagnoses were diseases of the circulatory system (group I), factors influencing health status and contact with health services (group Z), and endocrine, nutritional, and metabolic diseases (group E). Within diseases of the circulatory system, the largest number of patients had cardiac arrhythmia (37.7 %), followed by heart failure (35.1 %) and atherosclerotic heart disease (26.5 %). Essential (primary) hypertension, dyslipidemia, and diabetes mellitus were the most common comorbidities.

Table II. Patients' diagnoses according to the ICD-10

Diagnoses (ICD 10)	*N* (%)
A00-B99 Certain infectious and parasitic diseases	4 (0.3)
C00-D49 Neoplasms	14 (1.2)
D50-D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	16 (1.3)
E00-E89 Endocrine, nutritional, and metabolic diseases	196 (16.5)
F01-F99 Mental, Behavioral, and Neurodevelopmental disorders	9 (0.8)
G00-G99 Diseases of the nervous system	6 (0.5)
H00-H59 Diseases of the eye and adnexa	1 (0.1)
H60-H95 Diseases of the ear and mastoid process	2 (0.2)
I00-I99 Diseases of the circulatory system	522 (43.8)
J00-J99 Diseases of the respiratory system	40 (3.4)
K00-K95 Diseases of the digestive system	36 (3.0)
L00-L99 Diseases of the skin and subcutaneous tissue	8 (0.7)
M00-M99 Diseases of the musculoskeletal system and connective tissue	23 (1.9)
N00-N99 Diseases of the genitourinary system	48 (4.0)
R00-R99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	13 (1.1)
S00-T88 Injury, poisoning and certain other consequences of external causes	4 (0.3)
Z00-Z99 Factors influencing health status and contact with health services	249 (20.9)
Total number of diagnoses	1191

ICD-10 – International Classification of Diseases

Overall, 139 patients with CVD (92.1 %) had at least one potential clinically significant DDI. The rate of clinically significant DDIs was 8.4 per patient (Table III). A total of 1268 potential clinically significant DDIs were identified. Clinically significant categories of DDIs are represented by the following shares: category C (90.9 %), category D (8.6 %), and category X (0.6 %). CV medications were involved in potentially significant DDIs in 88.1 %.

The most frequent potential clinically significant DDIs of category C and the possible consequences of the detected DDIs are presented in Table IV. The most frequent DDI was between indapamide and perindopril, observed in 23.8 % of patients. The most common potential consequences of C interactions are hypotension, nephrotoxicity, hypoglycemia, and hyperkalemia. Furosemide was the most frequently implicated drug that required monitoring with 47 different drug pairs involved in category C interactions. Furosemide was present in 28.2 % of DDIs of category C.

The most frequent potential clinically significant DDIs of category D and potential results are presented in Table V. The most common potential consequences of D interactions

Table III. The frequencies of potential clinically significant DDIs in patients with CVD

N = 151	Total	DDIs classification		
		C	D	X
Mean number of DDIs per patient (min-max)	8.4 (0–36)	7.6 (0–33)	0.7 (0–5)	0.05 (0–1)
Total number of DDIs	1268	1152	109	7
Total number of DDIs involving CV medications	1117	1045	67	5
Total number of DDIs involving CVmedications/ Total number of DDIs	88.1	90.7	61.5	71.4

Table IV. The most frequent potential clinically significant DDIs of category C and potential consequences (N ≥ 15)

DDI	Incidence (*N*)	Potential consequences
Indapamide + perindopril	36	Increased risk of hypotension and nephrotoxicity.
Bisoprolol + furosemide	34	Loop diuretics can enhance the hypotensive effect of antihypertensive drugs.
Eplerenone + furosemide	33	Loop diuretics can enhance the hypotensive effect of antihypertensive drugs.
Furosemide + perindopril	23	Increased risk of hypotension and nephrotoxicity.
Bisoprolol + empagliflozin	22	Beta-blockers can increase the risk of hypoglycemia.
Furosemide + valsartan	20	Increased risk of hypotension and nephrotoxicity.
Bisoprolol + metformin	19	Beta-blockers can increase the risk of hypoglycemia.
Empagliflozin + furosemide	19	Empagliflozin can enhance the hypotensive effect of loop diuretics.
Eplerenone + perindopril	17	Increased risk of hyperkalemia.
Eplerenone + valsartan	17	Increased risk of hyperkalemia.
Metformin + perindopril	16	Perindopril may enhance the adverse/toxic effect of metformin.
Amlodipine + furosemide	15	Loop diuretics can enhance the hypotensive effect of antihypertensive drugs.
Dapagliflozin + furosemide	15	Dapagliflozin can enhance the hypotensive effect of loop diuretics.

Table V. The most frequent DDIs of category D and potential consequences

DDI	Incidence (n)	Potential consequences
Eplerenone + potassium	7	Eplerenone can enhance the hyperkalemic effect of potassium supplements.
Acetylsalicylic acid + ticagrelor	5	Increased risk of bleeding.
Bisoprolol + moxonidine	5	Alpha-2 agonists can enhance the AV-blocking effect of beta-blockers. Sinus node dysfunction may also be exacerbated. Beta-blockers can enhance the rebound hypertensive effect of alpha-2 agonists.
Moxonidine + nebivolol	5	Alpha-2 agonists can enhance the AV-blocking effect of beta-blockers. Sinus node dysfunction may also be exacerbated. Beta-blockers can enhance the rebound hypertensive effect of alpha-2 agonists.
Tramadol + zolpidem	5	Central nervous system depression.
Amiodarone + warfarin	4	Increased anticoagulant effect of warfarin, increased risk of bleeding.
Acetylsalicylic acid + ibuprofen	3	Increased risk of bleeding.
Acetylsalicylic acid + rivaroxaban	3	Increased risk of bleeding.
Alprazolam + tramadol	3	Central nervous system depression.
Cyclosporine + mycophenolate	3	Cyclosporine can decrease the concentration of mycophenolic acid's active metabolite in serum.
Empagliflozin + insulin regular	3	Increased risk of hypoglycemia.
Clopidogrel + rivaroxaban	3	Increased risk of bleeding.
Alprazolam + zolpidem	2	Central nervous system depression.
Cyclosporine + fluvastatin	2	Cyclosporine may increase the serum concentration of fluvastatin.
Dapagliflozin + insulin glargine	2	Increased risk of hypoglycemia.
Dulaglutide + insulin glargine	2	Increased risk of hypoglycemia.
Empagliflozin + gliclazide	2	Increased risk of hypoglycemia.
Empagliflozin + insulin glargine	2	Increased risk of hypoglycemia.
Gliclazide + vildagliptin	2	Increased risk of hypoglycemia.

Table VI. The identified potential clinically significant DDIs of category X and their potential consequences

DDI	Incidence (*N*)	Potential consequences
Esomeprazole + clopidogrel	2	Esomeprazole can reduce the effectiveness of clopidogrel.
Bilastine + ranolazine	1	P-glycoprotein (P-gp/ABCB1) inhibitors can increase the concentration of bilastine in the serum.
Doxazosin + urapidil	1	Alpha-1 blockers can enhance the antihypertensive effect of other alpha-1 blockers.
Formoterol + salmeterol	1	Long-acting beta-2 agonists can increase the harmful/toxic effects of other long-acting beta-2 agonists.
Potassium supplement + spironolactone	1	Increased risk of hyperkalemia.
Quetiapine + sulpiride	1	Antipsychotics can potentiate the harmful/toxic effects of sulpiride.

are increased risk of bleeding, hypoglycemia, cardiac arrhythmia, and central nervous system depression. In total, six drug pairs that should be avoided were identified. The list of identified X interactions and potential consequences is presented in Table VI.

The association between patients' characteristics and DDIs is presented in Table VII. The degree of impairment of renal function, recent hospitalization, total number of comorbidities, and the number of medications greater than 5 were associated with the occurrence of DDIs of categories C and D. Considering patients' diagnoses, increased prevalence of DDIs was found in patients with arrhythmia, heart failure, diabetes, and diseases of the respiratory system.

Along with the univariate analyses the multivariate negative binomial regression analyses were conducted to allow for the examination of unique predictive contributions of individual predictors in their context. The results are shown in Table VIII.

The results of the multivariate show the difference between the models for C and D categories where there were no significant predictors in the model for D interactions. This can be a potential artifact of the ratio for the number of predictors and the patients in the context of the dependent variable with a lower number of occurrences per patient. In future analysis, it would be recommended to include a larger sample size to verify these results. Regarding the results for the C interaction model, there were several key results. While some of the significant univariate predictors were dropped from the model, history of ADRs, acute coronary syndrome and dyslipidemia became significant predictors, indicating a suppression effect where the odds ratios for the remaining predictors become larger in the multivariate model than in their respective univariate models. Length of stay in the hospital, arrhythmia, polypharmacy, and excessive polypharmacy remain significant predictors in the multivariate model.

Polypharmacy and multimorbidity are important factors for DDI occurrence (28). More than 40 % of the total population have at least one chronic condition and multimorbidity is present in 25 % of the population (29). Polypharmacy (use of 5 or more drugs) was

Table VII. The direct (univariate) association between patients' characteristics and DDIs of categories C and D

Variable	Category C	Category D
	Odds ratio (95%CI)	Odds ratio (95%CI)
Gender	1.112 (0.824, 1.500)	0.999 (0.591, 1.688)
Age	1.011 (0.999, 1.024)	1.013 (0.991, 1.035)
BMI (kg m^{-2})	1.020 (0.988, 1.053)	1.049 (0.992, 1.109)
Creatinine	1.003 (0.998, 1.008)	1.003 (0.998, 1.008)
eGFR stage	1.266 (1.121, 1.431)***	1.205 (0.973, 1.492)
Length of stay in the hospital	1.025 (0.996, 1.054)	0.964 (0.903, 1.030)
Type of admission	1.000 (0.712, 1.404)	1.593 (0.846, 3.001)
Recent hospitalization	1.633 (1.230, 2.169)***	1.797 (1.082, 2.985)*
History of ADR	1.028 (0.711, 1.485)	0.698 (0.363, 1.342)
Total number of comorbidities	1.104 (1.065, 1.145)***	1.111 (1.042, 1.185)**
Arterial hypertension	1.446 (0.930, 2.250)	1.696 (0.724, 3.975)
Arrhythmia	1.615 [1.207, 2.162)**	1.074 (0.633, 1.823)
Heart failure	1.448 (1.072, 1.956)*	0.950 (0.553, 1.633)
Acute coronary syndrome	1.265 (0.879, 1.819)	1.532 (0.840, 2.794)
Heart transplantation	1.099 (0.592, 2.039)	1.771 (0.679, 4.622)
Atherosclerosis	1.152 (0.827, 1.605)	1.368 (0.782, 2.396)
Diabetes mellitus	1.618 (1.215, 2.155)**	1.862 (1.126, 3.079)*
Dyslipidemia	0.862 (0.636, 1.167)	0.940 (0.553, 1.599)
Diseases of the respiratory system (J0-J99)	1.446 (1.010, 2.069)*	1.139 (0.605, 2.142)
Blood diseases (D50-D89)	1.104 (0.676, 1.800)	1.018 (0.432, 2.399)
Endocrine, nutritional and metabolic diseases (diabetes mellitus and dyslipidemia excluded)	1.344 (0.957, 1.887)	1.055 (0.572, 1.945)
5–9 drugs	0.434 (0.331, 0.567)***	0.229 (0.131, 0.401)***
≥10 drugs	3.133 [2.484, 3.950)***	6.171 (3.628, 10.496)***

CI, confidence interval

determined in more than 90 % of patients with CVD. Excessive polypharmacy, concomitant use of ten or more different drugs, was determined in 45 % of patients.

The study revealed the high prevalence of potential clinically significant DDIs in patients with CVDs in first prescribed pharmacotherapy upon hospital admission. More than 90 % of patients had at least one potential clinically significant DDI and CV medications were involved in 88 % DDIs. In our study CV drugs were represented in a high percentage in all categories of DDIs. Research emphasizes the importance of including CV medications in the list of high-risk medications that require special caution and monitoring

Table VIII. The negative binomial regression analysis between patients' characteristics and DDIs of categories C and D

Variable	Category C	Category D
	Odds ratio (95%CI)	Odds ratio (95%CI)
Gender	0.527 (0.120, 2.318)	0.000 (0.000, Inf)
Age	1.081 (0.861, 1.356)	1.142 (0.687, 1.896)
BMI (kg m^{-2})	0.989 (0.977, 1.000)	1.008 (0.980, 1.037)
Creatinine	0.994 (0.970, 1.018)	1.051 (0.994, 1.112)
eGFR stage	0.997 (0.993, 1.001)	0.999 (0.989, 1.009)
Length of stay in the hospital	1.309 (1.077, 1.590)**	1.094 (0.698, 1.715)
Type of admission	0.994 (0.974, 1.014)	0.925 (0.852, 1.005)
Recent hospitalization	0.920 (0.707, 1.198)	1.093 (0.584, 2.045)
History of ADR	1.314 (1.049, 1.647)*	1.216 (0.736, 2.009)
Total number of comorbidities	1.059 (0.840, 1.335)	0.751 (0.425, 1.328)
Arterial hypertension	0.985 (0.946, 1.026)	1.023 (0.931, 1.124)
Arrhythmia	1.369 (1.004, 1.867)*	1.203 (0.553, 2.620)
Heart failure	1.082 (0.851, 1.377)	0.759 (0.434, 1.326)
Acute coronary syndrome	1.378 (1.055, 1.801)*	1.070 (0.563, 2.034)
Heart transplantation	0.861 (0.659, 1.125)	0.968 (0.556, 1.686)
Atherosclerosis	1.140 (0.734, 1.769)	1.616 (0.675, 3.867)
Diabetes mellitus	0.964 (0.765, 1.215)	1.174 (0.717, 1.922)
Dyslipidemia	1.504 (1.212, 1.866)***	1.158 (0.722, 1.857)
Diseases of the respiratory system (J0-J99)	0.984 (0.789, 1.226)	0.737 (0.448, 1.213)
Blood Diseases (D50-D89)	1.152 (0.878, 1.511)	0.845 (0.470, 1.519)
Endocrine, nutritional and metabolic diseases (diabetes mellitus and dyslipidemia excluded)	0.884 (0.593, 1.319)	1.031 (0.362, 2.936)
5–9 drugs	1.678 (1.286, 2.190)***	0.733 (0.390, 1.379)
≥ 10 drugs	7.867 (3.050, 20.291)***	6.724857e+16 (0.000, Inf)
Cragg-Uhler pseudo R^2	0.65	0.44
McFadden pseudo R^2	0.17	0.22

CI, confidence interval

(9, 15). CV medications are associated with life-threatening events, admission to intensive care units, and prolonged hospital stays (9). Therefore, we must seek to maximize medication safety. Considering the high prevalence of CV drugs in all categories of clinically significant DDIs in our research, the additional risk of CV drug harm represents drug-drug interference.

CV diseases are associated with older age. Older age and impaired renal function can increase drug exposure and the risk of actual drug interactions (30, 31). Several physiological changes are associated with aging that can affect the pharmacokinetics and pharmacodynamics of the drug. In our study, 38 % of patients had impaired renal function. Renal function deteriorates with age, and it is estimated that after the age of 40, it is lower by 10 mL/min for every 10 years (32). Medications often require dosage adjustment if renal function is below 60 mL/min/1.73 m^2, while if it is lower than 30 mL/min/1.73 m^2, the use of certain drugs can be contraindicated.

X interactions are considered drug combinations that should be avoided because the risk of concomitant use outweighs the benefit. It is important to re-evaluate the therapy and consider the exclusion of one of the drugs. Sometimes one of the representatives within the same drug group has a lower potential for interfering with other drugs and can be considered as a substitute. For example, clopidogrel in combination with esomeprazole and omeprazole is X interaction. Pantoprazole is a safer choice for gastroprotection while it has a lower possibility of influencing the effectiveness of clopidogrel. In addition, the indications for the use of PPIs should be regularly evaluated, since long-term use of PPIs is associated with several adverse effects (*e.g.* hypomagnesemia, osteoporosis, *Clostridium difficile* infection) (33).

The most frequently identified DDIs of category D carried an increased risk of bleeding related to antithrombotic agents. Clinically significant interactions with antithrombotic agents may require dose limitation of the drug according to the indication and renal function, increased monitoring of coagulation parameters, renal function, and signs of bleeding. Oral anticoagulation can represent a challenge in clinical practice and DDIs can additionally complicate the course of treatment. Groups of drugs that can contribute to bleeding risk interfering with warfarin are non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). Direct oral anticoagulants (DOACs) have a lower interaction potential compared to warfarin. However, interactions with CYP3A4 and P-gp inhibitors (*e.g.* clarithromycin, amiodarone, ciclosporin, colchicine, diltiazem, itraconazole, ketoconazole, lopinavir, ritonavir) should be considered before their application (34, 35). In case of severe bleeding, antidote therapies for DOACs, idaricuzimab and Andexanet, are available today (36, 37). Interventions that can reduce the risk of actual D interactions in patients with CVD can require dose adjustment and increased monitoring for bleeding, cardiac disorders, hypoglycemia, CNS depression, and myopathies/rhabdomyolysis.

In C interactions, antihypertensives were the most frequently involved drugs. The most common C interaction was the interaction between perindopril and indapamide. Even though antihypertensives DDIs are often targeted to achieve more efficient blood pressure control, caution and monitoring of the patient must be increased. This interaction may enhance the risk of hypotension and nephrotoxicity. The intervention is applicable to all ACEIs and sartans. A high prevalence of ACEIs in DDIs was also determined in other studies in hospital and outpatient settings (38–40). Other research emphasizes that ACEIs should be considered high-risk drugs because they can induce renal impairment, hypotension, and angioedema (9). Considering the consequences of C interactions most common interventions include increased monitoring of blood pressure, markers of renal function, electrolyte status, and signs of hypoglycemia.

In this research, factors associated with potential clinically significant DDIs were determined. Patients with certain medical conditions, such as arrhythmia, heart failure,

diabetes, and diseases of the respiratory system were more likely to have at least one DDI. The level of renal impairment, recent hospitalization in anamnesis, multimorbidity, and polypharmacy were also identified as factors associated with potential clinically significant DDIs.

Prescription of new drugs during hospitalization to treat an acute medical problem may complicate DDI issues (19). Timely identification of potential DDIs and factors associated with their occurrence can prevent actual DDIs and increase the quality of DDI management (41–43). Regular involvement of clinical pharmacists and implementation of pharmacists' interventions can enhance medication safety and contribute to the quality of provided healthcare.

Deprescription is one of the main principles of rational pharmacotherapy and it can be considered to reduce the prevalence of DDIs. Various deprescribing tools have been developed and include recommendations/options for CV medications deprescription (44–48).

Pharmacotherapy problems were determined at admission and proposed interventions were presented to the physicians. This research emphasized the high involvement of CV drugs in DDIs and the importance of admission as one of the crucial points to resolve pharmacotherapy problems. Timely resolved pharmacotherapy problems reduce the possibility of complications in achieving the desired treatment outcomes. Actual clinical outcomes associated with determined potential DDIs were not analyzed. Actual consequences of DDIs are monitored in the daily practice of clinical pharmacists and should be considered as an objective in other research in the future.

CONCLUSIONS

A high prevalence of DDIs of CV medications in all categories of clinical significance was determined. Our study revealed that DDIs represent an additional challenge for CV medication safety. Medication safety is one of the priorities of healthcare and should also include DDIs risk management. Managing medication safety in specific patient groups with CVDs can represent a greater challenge. Certain medical conditions, such as arrhythmia, heart failure, diabetes, diseases of the respiratory system, multimorbidity, polypharmacy, impaired renal function, and recent hospitalization are identified in this research as additional factors associated with DDIs occurrence in patients with CVDs at hospital admission. Hospital admission is one of the crucial points for implementing appropriate interventions for managing medication safety. Clinical pharmacists should regularly analyze DDIs in prescribed pharmacotherapy which enhances medication safety and also contributes to the quality of provided health care.

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