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The prevalence and preventability of potentially relevant drug-drug interactions in patients admitted for cardiovascular diseases: A cross-sectional study

Milena Kovačević[1] | Sandra Vezmar Kovačević[1] | Branislava Miljković[1] | Slavica Radovanović[2] | Predrag Stevanović[2]

[1]Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia

[2]Faculty of Medicine, University Clinical Hospital Center Bežanijska Kosa, University of Belgrade, Belgrade, Serbia

Correspondence
Milena Kovačević, Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia.
Email: milenak@pharmacy.bg.ac.rs

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Summary

Aim: The aim was to describe the type and prevalence of potentially relevant drug-drug interactions (pDDIs) in a population of patients admitted for cardiovascular diseases (CVD), and management strategies for reducing the occurrence of pDDIs.

Methods: A retrospective cross-sectional study was performed on Cardiology ward of University Clinical Hospital Center in Belgrade, Serbia. A total of 527 patients, with more than one prescription during hospital stay, were enrolled in this study. Data were obtained from medical records. LexiInteract was used as the screening tool.

Results: At least one potentially relevant pDDI was identified in 83.9% of patients. Occurrence was significantly more prevalent in patients with higher number of drugs, multimorbidity, longer length of stay, arrhythmia, heart failure, infectious and respiratory disease. About 13% of pDDIs exposures were accompanied with concurrent renal or liver disease, as an additional risk for DDI manifestation. Among CVD, patients with a history of myocardial infarction possessed the highest additional risk. The most common potential clinical outcome was the effect on cardiovascular system 48.5%, renal function and/or potassium 22.3%, bleeding 9.5%, impaired glucose control 6.8% and digoxin toxicity 4.6%. Main management strategies to avoid X or D class included using paracetamol instead of NSAID or alternative NSAID (38%), alternative antibiotic or antifungal (20.4%), H_2 receptor antagonist instead of PPI (8.3%), avoiding therapeutic duplication (7.3%), and alternative HMG-CoA reductase inhibitor (7%). Heart rate, blood pressure, electrolytes/potassium and blood glucose could have been employed in monitoring for potential consequence of 72.2% C class pDDIs.

Conclusions: Use of drug interaction screening tools can be beneficial risk mitigation strategy for potentially relevant pDDIs in CVD patients. DDI screening software could be linked to the patient's laboratory results or clinical data regarding renal or liver function, as an approach to reinforce DDIs alert quality.

1 | INTRODUCTION

Cardiovascular diseases (CVD) have a significant share in the disease burden on societies worldwide.[1] They are attributed a high morbidity and mortality rate, and significant economic burden derived from medical costs and working incapacity.[2-4] Prescribed drugs significantly improve health and therapy outcomes, reducing the risk of future cardiovascular events. However, increasing

rate of multimorbidity and drug use leads to therapy becoming more complex and challenging.[5] There is evidence of rising rates of negative outcomes through drug-related problems (DRPs) - drug-drug interactions (DDIs) and adverse drug events (ADEs), in both outpatient and inpatient settings.[6,7] DDI is defined as the alteration in a drug effect caused by concomitant administration of another drug. The mechanisms of DDIs could be broadly categorised as pharmacokinetic (drug concentration is altered on its site of action) and pharmacodynamic (the response is modified without changes in the pharmacokinetics of the affected drug).[8] The outcome can be harmful if the DDI causes an increase in the toxicity of the drug, but sometimes underexposure to the drug and decreased efficacy can be harmful as well.[9] As a result, DDIs are associated with increased length of stay and cost of hospitalisation.[10,11] Other DDIs can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics to achieve the optimal synergistic antihypertensive effect.[9] One review estimates that DDIs cause 17% of all preventable ADEs in hospitalised patients and that approximately 1% of patients will experience an ADE during hospitalisation due to a DDI.[12] Meaningfully higher DDI rates were found in geriatrics settings, compared to internal medicine, both in the USA and Europe. Moreover, studies with applied patient monitoring methodology showed higher DDIs frequency among identified ADEs, compared to spontaneous reporting.[12] Nonetheless, DDIs contribute with a significant proportion to ADEs, as the number of patients involved is high.[13] A potential DDI (pDDI) is defined as the co-prescription of two drugs known to interact, and a manifestation could occur in the exposed patient.[8,14] Due to patients variability, the epidemiology data shows that the prevalence of pDDIs is consistently higher than that of actual DDIs.[13] Contemporary standards for health systems quality put the focus in research and clinical practice on recognising and implementing actions to prevent harm, that is, on preventable ADEs.[15] Established strategy to minimise the risks associated with potentially harmful drug combinations is to reduce exposure to concurrent drug administration.[16] Hence, pDDIs are identified as the predictable and preventable cause of ADEs in the literature.[17] Studies have found rates of pDDIs ranging from about 15% to 66% in hospital settings.[12,18,19] Detailed data on pDDIs characteristics in patients admitted for CVD are lacking. One study investigated iatrogenic adverse events in the coronary care unit, assessing procedures, treatment, and diagnosis-related issues, in total.[20] Other studies conducted on the cardiology ward, reported DDI and drug-food interactions frequency altogether or assessed only DDIs in the heart failure patients.[21,22] The potential of using supporting electronic systems to manage pDDIs in CVD patients was not assessed. In this regard, the aim of the study was to describe the type and prevalence of potentially relevant pDDIs in CVD patients, and to assess the concurrent exposure to additional risk factors such as renal or liver disease, which may further affect drug exposure and therapy outcomes. In addition, management strategies for reducing the occurrence of potentially relevant pDDIs were provided.

What's known

- There is evidence of rising rates of negative outcomes through drug-drug interactions (DDIs) and adverse drug events (ADEs).
- Potential DDIs (pDDIs) are identified as predictable and preventable cause of ADEs.
- Studies have found rates of pDDIs ranging from 15% to 66% in hospital settings.

What's new

- Prevalence of potentially relevant pDDIs in inpatients with cardiovascular diseases was higher than expected (about 84%), with anticipated clinical outcome on the cardiovascular system, renal function and/or potassium, bleeding, glucose control and digoxin toxicity.
- About 13% of pDDIs exposures were accompanied with concurrent renal or liver disease, as an additional risk for DDI manifestation.
- Management strategies to avoid pDDIs or to monitor for potential consequences of pDDIs in patients with cardiovascular disease were proposed.

2 | METHODOLOGY

2.1 | Data collection and study setting

A retrospective observational study was carried out on Cardiology ward of University Clinical Hospital Center Bežanijska Kosa, Belgrade, Serbia. Medical charts were obtained for a total of 651 patients consecutively hospitalised in the period from June 2012 to February 2013. Multiple patient's admissions during the study period were excluded, keeping the data only for the first admission. Other inclusion criteria included hospital stay of at least 24 hours and more than one prescription during the stay. The Ethics committee of the University Clinical Hospital Center approved this study. Data were obtained from paper medical charts and discharge letters, providing the information on patient's sociodemographic characteristics, medical history, the reason for hospitalisation and the therapy charts. Charlson comorbidity index was calculated for every patient through chart review version.[23] Screening for pDDIs was performed using LexiInteract database (Lexi-Comp, Inc., Hudson, Ohio).[24] LexiInteract showed high sensitivity (87%-100%) and specificity (80%-90%) according to the studies which have evaluated the performance of the DDI screening software.[25-27] The 24 hour interval between administrating two drugs was used for assessing pDDI prevalence. According to the LexiInteract database pDDIs of classes A (no interaction) and B (no action needed) are of academic, but not a relevant clinical concern. pDDIs of classes X (avoid combination), D (consider therapy modification) and C (monitor therapy), are considered clinically relevant,

as they require healthcare professionals attention and assessment of benefit/risk ratio for an individual patient. The pDDI characteristics were extracted from the monograph, including information on reliability rating, which indicates the quantity and nature of documentation for interaction. In addition, the interacting monograph was used to define the potential clinical outcome and to make recommendations for improving management of the identified potentially relevant pDDIs.

2.2 | Statistical analysis

Statistical analysis was performed with PASW 18.0 (SPSS Inc., Chicago, IL, USA). All possible drug pairs were created for all patients and drugs used during hospitalisation. The number of pDDIs of X, D, C, B and A category was recorded for every patient. A single C class pDDI is attributed a lower risk, compared to X and D. As this class showed almost ubiquitous presence in our study, with many patients having several identified C interactions, the expected risk of potential clinical outcome is substantially higher. For that purpose, the occurrence of X, D, and more than two C pDDIs was considered as potentially relevant risk (binary code 1). Nonparametric tests were used for the analysis. The crude prevalence ratio was calculated as the probability of pDDIs occurrence in the patients with a particular characteristic relative to the probability in patients without that characteristic. The association between patient characteristics and pDDIs occurrence was assessed by Chi-square or Fisher's exact test for independence. Wilcoxon signed-rank and McNemar's test were used to evaluate the difference in the prevalence and the number of pDDIs after considering management recommendations. Continuous descriptive variables in the text and tables were expressed by mean ± SD, with range, whereas categorical data and prevalence were presented as number (percentage), N (%). For all of the tests, a $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study population

A total of 527 patients were included in this study. The study population consisted of slightly more males (55.4%), and about 70% elderly (≥ 65 years). The mean number of drugs per patient was 7.7; moreover, about 30% of patients were prescribed 10 or more drugs. Hypertension, arrhythmia and heart failure were the most prevalent diagnoses, and more than one forth of patients had diabetes mellitus. The most frequently prescribed drugs were affecting the cardiovascular system (53.8%), blood and blood forming organs (14.7%), and alimentary tract and metabolism (14.3%). Descriptive demographic and clinical data are presented in Table 1.

TABLE 1 Patient's demographic and clinical data

Characteristics	N (%, n = 527) or Mean ± SD (range)
Gender, male	292 (55.4)
Age (y)	69.7 ± 10.8 (21-90)
≥ 65	368 (69.8%)
Length of stay (d)	9.9 ± 6.1 (0-54)
CCI (score)	3 ± 1.7 (0-9)
Number of drugs	7.7 ± 3.6 (2-25)
1-3	63 (12)
4-6	145 (27.5)
7-9	164 (31.1)
≥ 10	155 (29.4)
Reason for hospitalisation	
Heart failure	210 (39.9)
Arrhythmia	97 (18.4)
Hypertension	94 (17.8)
Angina pectoris	65 (12.3)
Dyspnoea	24 (4.6)
Cardiomyopathy	18 (3.4)
Myocardial infarction	11 (2.1)
Thrombosis	10 (1.9)
Primary discharge diagnosis	
Hypertension	322 (61.1)
Arrhythmia	255 (48.4)
Heart failure	235 (44.6)
Angina pectoris	155 (29.4)
Diabetes mellitus	142 (26.9)
Myocardial infarction	56 (10.6)
Respiratory disease	46 (8.7)
Dyslipidaemia	42 (8)
Disease of blood and blood forming organs	35 (6.6)
Renal disease	35 (6.6)
Gastrointenstinal system disease	34 (6.5)
Liver disease	26 (4.9)
Infectious disease	23 (4.4)
Endocrine disease, excluding diabetes	21 (4)
Mental disease	14 (2.7)
Neurodegenerative diseases	5 (0.9)

CCI, Charlson comorbidity index

3.2 | Prevalence and characteristics of pDDIs

The most of the identified pDDIs were of moderate severity (91%), whereas major were less represented (8.6%). Reliability rating was determined as good in 57.8% of pDDIs, followed by fair 34.3%, excellent 5.7% and poor in 2.3%. Pharmacodynamic pDDIs were the most common, with 79.8% share, and pharmacokinetic and pharmacokinetic/pharmacodynamic were almost equally distributed (10.8 and 8.6%, respectively). Metabolism was involved in 50.2% of pharmacokinetic pDDIs, renal excretion in 12.5%, and the absorption process in 3%. Table 2 shows the main drug pairs involved in identified pDDIs.

TABLE 2 The most common drug pairs involved in pDDIs

Risk rating	Drug pairs	No. of pDDIs	Summary	Type/mechanism
X	amiodarone + ciprofloxacin	6	enhanced QTc-prolonging effect (highest and moderate risk agents coadministration)	PD
	haloperidol + potassium chloride	4	enhanced ulcerogenic effect of potassium chloride (applies to its solid oral dosage forms)	PD
	fenoterol/ipratropium + potassium chloride	3		
	amiodarone + propafenone	4	altered cardiac conduction and repolarisation	PK/PD metabolism inhibition via CYP1A2
	fenoterol/ipratropium + carvedilol	3	diminished bronchodilatatory effect due to nonselective beta blockers	PD
D	amiodarone + warfarin	37	increased serum concentration of vitamin K antagonists and anticoagulant effect	PK metabolism inhibition via CYP2C9
	amiodarone + acenocoumarol	25		
	potassium chloride + spironolactone	49	enhanced hyperkalemic effect of potassium-sparing diuretics	PD
	diclofenac + furosemide	33	diminished diuretic effect of loop diuretics; enhanced nephrotoxic effect of NSAIDs	PD
	clopidogrel + pantoprazol	26	decreased serum concentration of the active metabolite(s) of clopidogrel	PK metabolism inhibition via CYP2C19
C	hypotensive agents + hypotensive agents	2052	enhanced hypotensive and adverse/toxic effect of hypotensive agents	PD
	ACE inhibitors + loop diuretics	275	enhanced hypotensive and nephrotoxic effect of ACE inhibitors	PD
	ACE inhibitors + potassium-sparing diuretics	204	enhanced hyperkalemic effect	PD
	ACE inhibitors + heparin (low molecular weight)	163		
	anticoagulants + anticoagulants or antiplatelets	175	enhanced anticoagulant effect	PD
	hypoglycaemic agents + loop diuretics	91	diminished therapeutic effect of antidiabetic agents	PD

ACE, angiotensin converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs; PK, pharmacokinetic; PD, pharmacodynamic; PK/PD, pharmacokinetic/pharmacodynamic.

Almost ubiquitous prevalence was determined for C class, with 494 patients exposed to at least one pDDI (93.7%). Furthermore, a total of 442 patients (83.9%) had exposure to potentially relevant pDDIs. The X class interactions had the least observed prevalence 5.7%. More than 40% of patients were exposed to two types of pDDIs, mostly concurrent X and C exposure. Table 3 shows calculated prevalence and crude prevalence ratios (PR) for potentially relevant pDDIs exposure, according to patients demographic and clinical characteristics. X class was significantly more prevalent in patients with the number of drugs 7-9 and ≥ 10 (PR 3.07 and 8.13, respectively), with arrhythmia (PR 4.27), infectious (PR 4.38) or respiratory disease (PR 3.18). The prevalence of exposure to D class was increased in patients with a longer length of stay (more than 7 days), a higher number of drugs, heart failure and a history of myocardial infarction. In heart failure and post-myocardial infarction patients, a significant difference ($P < .05$) in D prevalence was found between groups with and without polypharmacy, which means that number of drugs was the confounder. The number of drugs showed significant association with C class exposure, with PR ranging from 5.76 to 7.88 in different strata. Besides that, C class was more prevalent in elderly and patients with heart failure. Multimorbidity (Charlson comorbidity index > 3) was significantly associated with D and C class exposure, resulting in 38% and 22% increase in prevalence, respectively.

Renal and/or liver disease was present in average 12.9% of exposures to potentially relevant pDDIs, range 0 - 28.2%. In the group of CVD, patients with the history of myocardial infarction possessed the highest additional risk. Impaired function of elimination organs, as an independent patient risk factor for ADEs, may further affect drug exposure and increase the possibility of potential clinical outcome; for example, statin toxicity.

The most common potential clinical outcome was cardiovascular 48.5%, related to effects on heart rate, rhythm or blood pressure. The second most common was the effect on renal function and/or potassium 22.3%, followed by bleeding 9.5%, impaired glucose

TABLE 3 The prevalence and crude prevalence ratios (PR) of potentially relevant pDDIs, according to patients demographic and clinical characteristics

Risk rating	X class		D class		C class > 2		
	Prevalence (%)	Crude prevalence ratio (95% CI)	Prevalence (%)	Crude prevalence ratio (95% CI)	Prevalence (%)	Crude prevalence ratio (95% CI)	% of pDDIs exposures associated with renal and/or liver disease
Age ≥ 65	6.3	1.42 (0.62-3.24)	47.6	1.01 (0.83-1.23)	84.2	1.14 (1.03-1.26)*	11
Gender, male	5.1	0.80 (0.40-1.61)	47.6	1.01 (0.84-1.21)**	81.8	1.05 (0.96-1.14)**	13.6
Length of stay > 7 d	7.2	1.97 (0.89-4.34)	56.7	1.64 (1.33-2.02)**	83.7	1.08 (0.99-1.17)	12.1
CCI > 3	4.6	0.74 (0.34-1.62)	58.1	1.38 (1.15-1.64)*	92.5	1.22 (1.14-1.32)**	20.4
No. of drugs 1-3	1.6	reference	3.2	reference	12.7	reference	18.2
No. of drugs 4-6	0.7	0.43 (0.03-6.84)**	26.9	8.47 (2.11-34.01)**	73.1	5.76 (2.99-11.08)**	7.5
No. of drugs 7-9	4.9	3.07 (0.39-24.08)**	51.8	16.33 (4.14-64.36)**	97	7.63 (3.99-14.60)**	11.1
No. of drugs ≥ 10	12.9	8.13 (1.11-59.29)**	80	25.20 (6.43-98.78)**	100	7.88 (4.12-15.05)**	13.4
Cardiovascular diseases							
Angina pectoris	5.2	0.87 (0.40-1.92)	45.2[a]	0.93 (0.76-1.14)	89	1.14 (1.06-1.23)*	10.7
Arrhythmia	9.4	4.27 (1.77-10.27)**	49.4	1.08 (0.91-1.30)	85.1	1.10 (1.01-1.19)*	9.3
Heart failure	5.1	0.83 (0.41-1.68)	57.9[a]	1.48 (1.24-1.77)**	96.6	1.40 (1.29-1.52)**	11.7
Hypertension	5.3	0.83 (0.41-1.68)	46.3	0.94 (0.78-1.13)	85.1	1.13 (1.06-1.21)*	13.2
Myocardial infarction in anamnesis	1.8	0.29 (0.04-2.09)	57.1[a]	1.23 (0.96-1.58)**	85.7	1.06 (0.95-1.19)**	16.1
Comorbidities							
Diabetes	4.9	0.83 (0.36-1.88)	51.4[a]	1.12 (0.92-1.36)	85.2	1.07 (0.98-1.16)**	19.4
Disease of blood and blood forming organs	2.9	0.48 (0.07-3.45)	37.1[a]	0.77 (0.50-1.20)	71.4	0.87 (0.70-1.08)**	28.2
Dyslipidemia	2.4	0.39 (0.06-2.85)	42.9[a]	0.90 (0.62-1.29)	81[a]	1 (0.86-1.16)	20.8
Endocrine disease, excluding diabetes	4.8	0.83 (0.12-5.81)	42.9	0.90 (0.54-1.49)	76.2	0.94 (0.73-1.19)[c]	0
Gastrointestinal disease	0	-	50[a]	1.06 (0.75-1.50)	73.5[a]	0.90 (0.73-1.11)**	26.2
Infectious disease	21.7	4.38 (1.85-10.40)*	47.8	1.01 (0.65-1.56)	65.2[a]	0.80 (0.59-1.08)*	3.2
Mental disease	0	-	64.3	1.37 (0.92-2.04)	78.6	0.97 (0.73-1.27)**	5
Neurodegenerative disease	0	-	60	1.27 (0.62-2.61)	60	0.74 (0.36-1.51)**	0
Respiratory disease	15.2	3.18 (1.44-7.01)*	43.5	0.91 (0.65-1.28)	93.5[a]	1.17 (1.07-1.28)*	11.4

CCI, Charlson comorbidity index

[a]prevalence associated with polypharmacy ($P < .05$); Chi-square or Fisher's exact test for independence significant at *$P < .05$ or **$P < .001$

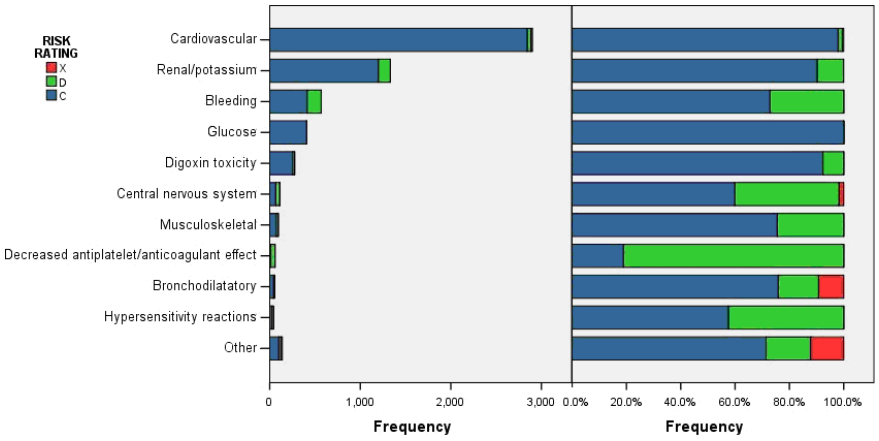

FIGURE 1 Frequency of potential clinical outcomes resulting from pDDIs (left) with relative contributions of X, D and C class (right)

control 6.8% and digoxin toxicity 4.6%. Figure 1 shows frequency of potential clinical outcomes resulting from pDDIs, with relative contributions of X, D, and C class on the right side, showing the possibility of applying different management strategies to reduce the occurrence of potential clinical outcomes. Category "Other" comprised clinical outcomes that could not be easily assigned to one main category. Anticholinergic, salmeterol-related, and toxicities emerging from NSAIDs pharmacological duplication were expected from the X interactions. On the other hand, almost equal frequencies were expected for drug toxicity and decreased drug efficacy regarding D class. Increased exposure to methylprednisolone and selective serotonin reuptake inhibitors were expected, as well as the NSAIDs duplication consequences. In contrast, pDDIs at the absorption level could lead to systemic underexposure to quinolone antibiotics and levothyroxine.

3.3 | Management strategies of potentially relevant pDDIs

LexiInteract monographs of C class state that the benefits of the concurrent use of two medications usually outweigh the risks, and rather an appropriate monitoring plan should be implemented. As previously discussed relevance for C pDDIs in the methodology section, management strategies to avoid pDDIs listed in Table 4 were applied to C class as well, to calculate the total number of the relevant pDDIs that could have been potentially prevented by using a certain surveillance system. Table 4 summarizes recommendations for improving the management of the identified pDDIs, giving the assessment of the preventability of potentially relevant pDDIs. Management strategies were categorised in 14 recommendations, based on drug pharmacokinetic or pharmacodynamic properties, or were related to the drug administration process. Recommendations to avoid X and D occurrence in 81% of pDDIs included: using paracetamol instead of NSAID or alternative NSAID (38%), alternative antibiotic or antifungal, mostly regarding QTc-prolonging potential (20.4%), H_2 receptor antagonist instead of PPI (8.3%), avoiding therapeutic duplication (7.3%), and alternative HMG-CoA reductase inhibitor (7%). Most of the suggestions for management of C class referred to closely patient monitoring of hemodynamic status or laboratory results: heart rate, blood pressure, electrolytes/potassium and blood glucose. These clinical or laboratory parameters could have been employed in monitoring for potential consequence of 72.2% C class pDDIs.

4 | DISCUSSION

DDIs are the most frequently detected DRPs in hospitalised patients.[28,29] None of the drug interactions screening tools is currently incorporated in secondary or tertiary institutions of the Serbian health system. This is the first study conducted to assess the prevalence and characteristics of pDDIs in a population of inpatients admitted for CVD. The study revealed the high total prevalence of pDDIs of 94.7%, which is somewhat higher compared to inpatient settings in other countries (19.3%-87.2%).[5,10,18,28,30-32] The main reason for observed discrepancies in results was probably the use of different DDI data bases, differences in prescribing patterns between countries and patient population included in this study.

The number of drugs prescribed was among the characteristics most strongly associated with the occurrence of pDDIs and ADRs in many studies.[7,22,31,33] In our study PR for exposure to potentially relevant pDDIs in patients with higher number of drugs ranged from 3.07 up to 25.20, compared to 1-3 drugs as a reference category. The highest PR values were calculated for D class exposure. In line with these findings, the prevalence of potentially relevant pDDIs in patients with a specific clinical characteristic were further tested regarding present polypharmacy. X class was significantly more prevalent in patients with arrhythmia, infectious and respiratory disease, irrespective of number of drugs, which gives important and precise directions for future research in CVD therapy outcomes. Furthermore, exposure to D and more than two C class pDDIs were more common in patients with heart failure and multimorbidity, although D occurrence in heart failure patients was associated with polypharmacy. These results are consistent with the prior research, as ACE inhibitors, digoxin, furosemide and spironolactone were broadly identified as predictors for DDIs and ADRs.[31,32,34-36] These commonly used drugs for heart failure are usually prescribed in combinations, thus increasing the number of drugs in therapy. Findings on the co-therapy involved in pDDIs, such as ciprofloxacin, macrolide antibiotics, and beta-agonists, are in close agreement with other

TABLE 4 Management recommendations and the assessment of the potentially relevant pDDIs preventability

	No. of pDDIs			
Management strategy	**X**	**D**	**C**	**C > 2**
Alternative cardiovascular drug within the same pharmacological group (beta blocker, calcium channel blocker, ACE inhibitor, AT_2 receptor antagonist)[a]		9	67	
Cardioselective beta blocker	5	8	71	
Alternative HMG-CoA reductase inhibitor		22	6	
Alternative antibiotic/antifungal	12	52	74	
Alternative PPI		6	56	
H_2 receptor antagonist instead of PPI		26	32	
PPI instead of H_2 receptor antagonist			51	
Paracetamol instead of NSAIDs/alternative NSAID		86/33	280	
Revised use of metoclopramide	2	8	4	
Avoiding therapeutic duplication/avoiding ACE inhibitor and AT_2 receptor antagonist coadministration	1	7/15	8	
Changes in the route of administration	12	1		
Drug administration with an acidic beverage		1		
Separate dosing time		4	12	
Flushing infusion lines between administrations		3		
Monitoring				
Electrolytes and heart rate			1920	
Blood pressure and heart rate			1000	
Electrolytes/potassium			472	
Blood glucose			259	
Potential preventability rate				
Initial number of pDDIs, N	42	494	5055	
Revised number of pDDIs, N	10*	213*	4394*	
Initial prevalence of pDDIs, No. of patients (%)	30 (5.7)	250 (47.4)	494 (93.7)	428 (81.2)
Revised prevalence of pDDIs, No. of patients (%)	8 (1.5)*	165 (31.3)*	491 (93.2)	416 (78.9)*

[a]based on pharmacokinetic properties

*McNemar's or Wilcoxon signed-rank test significant at $P < .001$

ACE, angiotensin converting enzyme; AT_2, angiotensin II receptor type 2; HMG-CoA - 3-hydroxy-3-methyl-glutaryl-coenzyme A; H_2, histamine *H2*-receptor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

studies.[32,34] Results regarding the association of age with pDDIs are inconsistent. Some studies showed higher odds of exposure to a pDDI in older patients,[10,31] but the association did not remain significant after adjusting for polypharmacy and other factors.[7,10]

Medicines used in CVD, antiinfectives, anticancer, antidiabetics and anti-inflammatory/analgesics were identified as the main classes involved in hospitalisation resulting from ADRs, ADEs, and DRPs.[37] Also, Dequito et al found that drugs for blood and blood forming organs and cardiovascular drugs were more frequently prescribed in patients with actual ADRs, than with potential ADEs.[29] It could be concluded that these drugs rather led to the manifestation of ADEs in the studied population. Therefore, the likelihood for pDDIs manifestation is our study population is increased, because of the fairly prescription of these drugs. Potential clinical outcomes on cardiovascular system, renal function and/or potassium level, bleeding and digoxin toxicity were dominantly expected in our study.

Some studies estimated that only relatively small number of all identified pDDIs resulted in an adverse event (0.1%-5.6%),[12,32] whereas others revealed that 22%-26% of ADEs prompting hospitalisation were due to DDIs.[38] Our study population consisted mostly of elderly patients, which are more susceptible to DDIs, due to age-related alterations in pharmacokinetics and pharmacodynamics.[39] The study unveiled notable proportion of potentially relevant pDDIs exposures with concurrent presence of renal and/or liver disease. In addition, some authors noted that CVD increased ADEs risk, through heart failure influence on drug elimination by altering renal and hepatic perfusion.[40] It is also stated that the prevalence of actual DDIs could be underestimated since the link between ADEs and underlying DDI was probably under-recognised as symptoms frequently may be attributed to underlying diseases.[18]

Based on the LexiInteract monographs data, 14 different management recommendations were proposed in our study, which

were based on the pharmacokinetic or pharmacodynamic drug characteristics or were realted to the drug administration process. The preventability rate was assessed for identified pDDIs to evaluate the possibility of using electronic systems as the risk mitigation strategy. Regarding the management of X and D pDDIs which are assigned a high risk and require therapy modifications, five recommendations advised in total of 81% of cases were: using paracetamol instead of NSAID or alternative NSAID (38%), alternative antibiotic or antifungal (20.4%), H_2 receptor antagonist instead of PPI (8.3%), avoiding therapeutic duplication (7.3%), and alternative HMG-CoA reductase inhibitor (7%). Recommendations regarding monitoring for potential consequences of pDDIs included: electrolytes and heart rate (in 1920 pDDIs), blood pressure and heart rate (1000), electrolytes/potassium (472) and blood glucose (259), which could be frequently and feasibly assessed during the hospital stay. Healthcare professionals are encouraged to seek to identify DRPs, using data bases and software to screen for pDDIs. There is rising evidence that clinical-pharmacist interventions, alone or combined with the electronic alerting system, may reduce clinically significant DDIs.[41,42] Extra caution is needed in patients with decreased renal or liver function, in which a higher risk of adverse clinical outcome could be expected. DDI screening electronic system should be linked to CVD patients laboratory results, especially potassium and glucose. In addition, drug pharmacokinetic properties regarding the dominant way of elimination should be considered in pDDIs alerting systems, and linked to the data on patients' renal or liver function, as these patients intrinsic characteristics could further influence the risk/benefit ratio of concomitant drug use.

Due to the retrospective design, our study has several limitations. It was performed as the cross-sectional study, obtaining the data on the total therapy used during the hospital stay. The temporal association or timing of drug introduction and potential clinical outcome is not known. For a better understanding of the DDI impact on CVD therapy outcomes and burden, a prospective design would be necessary. A close follow-up after discharge with more detailed patient information and laboratory parameters is required. A multi-centred study would diminish possible differences in prescribing patterns and would ascertain better generalisability of the data. Other limitations are closely related to the drug interaction screening software, as it checks each drug pair for pDDI and the influence of an additional drug to the DDI manifestation and consequence is not considered. The common potential clinical outcome expected from pDDIs in our study involves cardiovascular system, which could imply more difficult detection of DDIs in patients with CVD in future research, as the DDI manifestation may be attributed to CVD.

5 | CONCLUSION

This study has revealed the high prevalence of potentially relevant pDDIs in inpatients admitted for CVD. The exposure was significantly increased in patients with higher number of drugs, multimorbidity, and longer length of stay. The presence of arrhythmia and heart failure, as well as infectious and respiratory disease, was associated with increased prevalence of pDDIs. In average, about 13% of pDDIs exposures were accompanied with concurrent renal or liver disease, as an additional risk for DDI manifestation. The most common potential clinical outcome was the effect on cardiovascular system 48.5%, the effect on renal function and/or potassium 22.3%, followed by bleeding 9.5%, impaired glucose control 6.8% and digoxin toxicity 4.6%. Use of drug interaction screening tools can be beneficial risk mitigation strategy for potentially relevant pDDIs in CVD patients. DDI screening software could be linked to patients' laboratory results or clinical data regarding renal or liver function, as an approach to reinforce DDIs clinical significance and alert quality.

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AUTHOR CONTRIBUTIONS

All authors contributed to this work. Radovanović S. and Stevanović P. were responsible for study conception and acquisition of patient data. Kovačević M. entered and analysed the data, and was responsible for writing this paper. Vezmar Kovačević S. and Miljković B. contributed in the statistical analysis, interpreting and discussing the results, and writing the paper as well. All authors were responsible for revising this work critically for important intellectual content. All authors are accountable for all aspects of this work.

DISCLOSURES

No potential conflicts of interest relevant to this article were reported.

ORCID

Milena Kovačević http://orcid.org/0000-0003-2957-7965

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