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Investigation of the Prevalence of Drug-Drug Interactions in the Cardiology Department

Jogaile Butauskaite [1,*], Austeja Zumbakyte [1], Lauryna Aukstikalne [2], Jolita Pancere [2], Skaiste Zukaitiene [1,2] and Egle Karinauske [1,2,*]

[1] Lithuanian University of Health Sciences, Medical Academy, Faculty of Medicine; austeja.zumbakyte@stud.lsmu.lt; skaiste.zukaitiene@lsmu.lt;
[2] Lithuanian University of Health Sciences, Medical Academy, Faculty of Medicine, Institute of Physiology and Pharmacology; grin.laur@gmail.com; jolita.kuseliauskyte@lsmu.lt;
* Correspondence: jogaile.butauskaite@stud.lsmu.lt (J.B.); egle.karinauske@lsmu.lt (E.K.)

Abstract: With increasing numbers of older adults worldwide, multimorbidity and polypharmacy are on the rise, highlighting the risks of harmful drug-drug interactions (DDIs) to patients. As cardiovascular agents are among the most prescribed medications, we performed an observational cross-sectional study to determine the prevalence of DDIs in a cardiology department of a secondary hospital. Patient data was obtained from medical records and screened for DDIs using the Micromedex drug interaction software. Descriptive statistics, Chi-square ($\chi 2$) test, Student's t test and Pearson's correlation test were used to analyse the results. Out of 50 participants, 45 (90%) had at least one DDI. A total of 266 DDIs were identified, with more than half classified as major. At least one major DDI was found in 78% of patients. 42% of patients were at an increased risk of bleeding due to DDIs. A statistically significant relationship was found between the detection of DDIs and both patient age ($p = 0.005$) and the number of drugs used ($p < 0.001$). Our findings pose questions about the wider prevalence and risks of drug-drug interactions among patients with cardiovascular disease.

Keywords: drug-drug interactions; drug safety; adverse drug reactions; polypharmacy

1. Introduction

Over the past century, increasing life expectancy has led to an unprecedented global rise in the number of older adults (individuals aged ≥ 65 years). By 2030, it is projected that older individuals will constitute up to 22.1% of the population in Europe and North America [1]. As a consequence of these demographic shifts, multimorbidity (the presence of two or more long-term health conditions) and polypharmacy (the regular use of five or more medications daily) are becoming increasingly common [2]. The simultaneous use of multiple medications heightens the risk of DDIs, which occur when one drug affects the efficacy or toxicity of another co-administered drug. The prevalence of DDIs among hospitalised patients ranges from 15% to 45% according to current research [3]. Certain DDIs can be beneficial and purposefully used to enhance therapeutic outcomes, others may be clinically insignificant. However, many DDIs are harmful and can lead to severe adverse drug reactions (ADRs) [4,5]. In North America and Europe, DDI-induced ADRs are estimated to account for 3-10% of all hospitalizations and are associated with longer hospital stays and higher treatment costs [6]. In Lithuania, limited studies have examined the prevalence of DDIs in medical institutions, but their findings are consistent with global statistics. A 2017 study conducted in the therapeutic departments of a tertiary hospital identified 92 potential DDIs among 121 patients [7]. Similarly, a 2019 observational study in the Psychiatry Department of a tertiary hospital found a DDI frequency of 69.7% [8]. According to the European Society of Cardiology, 65-70% of individuals aged 60-79 and 79-86% of those aged 80 and older suffer from cardiovascular diseases. Additionally, about 65% of heart failure patients have five or more comorbid chronic diseases [2]. Consequently, the elderly

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population exhibits high drug consumption for cardiovascular conditions, frequent polypharmacy, and an elevated likelihood of DDIs [2]. Given the scarcity of data on the prevalence of DDIs among hospitalised cardiology patients, this study aims to determine the prevalence of DDIs in the cardiology department of a secondary-level hospital, evaluate their clinical significance, and assess the monitoring and interventions performed in response to DDIs. The results of this study could inform the development of DDI monitoring guidelines, ultimately reducing the incidence of harmful DDIs and ensuring safe, effective, and cost-effective treatment.

2. Results

2.1. Study Population

The study included 50 patients, with 29 women (58%) and 21 men (42%). The average age of the patients was 75 years (range 49-92 years), with a standard deviation (SD) of 10.1 years, $p > 0.05$. Elderly patients (≥ 65 years) constituted the vast majority, with 43 subjects (86%) in this category. The mean number of drugs administered per patient was 8.7 (range 3-13), (SD = 2.4, $p > 0.05$). It was estimated that 92% (n = 46) of the patients in the study were exposed to polypharmacy or radical polypharmacy. Table 1 outlines the characteristics of the patients.

Table 1. Patient characteristics.

N=50		Frequency	n (%)	*p* value
BMI, kg/m2, mean (SD).	29.8 (5.0)			0.200
BMI category	Normal (18.5 to < 25)	8	16.0	
	Overweight (25 to < 30)	18	36.0	
	Class 1 Obesity (30 to < 35)	16	32.0	
	Class 2 Obesity (35 to < 40)	6	12.0	
	Class 3 Obesity (≥ 40)	2	4.0	
Creatinine clearance (Cockcroft-Gault), ml/min, mean (SD)	62.6 (29.4)			0.200
GFR category	Normal or high (≥90)	7	14.0	
	Mildly decreased (60-89)	19	38.0	
	Mildly to moderately decreased (45-59)	9	18.0	
	Moderately to severely decreased (30-44)	8	16.0	
	Severely decreased (15-29)	7	14.0	
	Kidney failure (<15)	0	0	
Hepatic function	Normal	50	100	
	Child-Pugh A	0	0	
	Child-Pugh B	0	0	
	Child-Pugh C	0	0	

2.2. Characteristics of DDIs

In total, 437 drugs were administered to the 50 patients included in the study, averaging 8.7 drugs per patient (SD = 2.4, $p > 0.05$). The minimum number of medications prescribed was 3 (n = 1), and the maximum was 13 (n = 2). A total of 266 DDIs were identified during the study. At least one DDI was found in 45 patients (90%). On average, 5.3 DDIs were identified per patient (SD = 4.0, $p > 0.05$), with a maximum of 17 DDIs in one patient (n = 1). More than half (55.3%) of all identified DDIs were classified as major, the rest were of moderate severity. No contraindicated drug combinations were recorded during the study. At least one major DDI was found in 78% of patients (n = 39).

The most frequent DDI was between perindopril and spironolactone (n = 7). The most common major DDIs in the study were between loop diuretics and NSAIDs, accounting for 12.2% of major

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DDIs (n = 18). According to Micromedex, this interaction may result in renal toxicity and a decreased diuretic effect. Moderate DDIs were most commonly observed between beta blockers and NSAIDs, comprising 13.4% of moderate DDIs (n = 16). Concomitant use of beta blockers and NSAIDs may result in an insufficient blood pressure-lowering effect of beta blockers. Other drug combinations most commonly leading to DDIs and their potential clinical outcomes are described in Table 2. It was estimated that 12.8% (n = 34) of the clinical manifestations of all identified DDIs involved an increased risk of bleeding. The most common DDIs increasing the risk of bleeding were found between NSAIDs and direct oral anticoagulants (DOACs) (n = 5), NSAIDs and platelet aggregation inhibitors (TAIs) (n = 4), low molecular weight heparins (LMWHs) and NSAIDs (n = 3), and glucocorticoids (GCs) and DOACs (n = 3). 42% (n = 21) of the study patients were at an increased risk of bleeding due to DDIs.

Table 2. The most common DDIs and possible clinical outcomes.

Interacting drug pair.	Frequency	n (%)	Possible clinical outcome	Documentation
Major DDIs				
Loop diuretics and NSAIDs	18	12.2	Reduced diuretic effectiveness Nephrotoxicity	Good
Angiotensin converting enzyme inhibitors (ACEIs) and potassium-sparing diuretics (PSD)	15	10.2	Hyperkalaemia	Good
ACEi and furosemide	10	6.8	Severe hypotension Deterioration of renal function, including renal failure	Fair
PSD and NSAIDs	10	6.8	Reduced diuretic effectiveness Hyperkalaemia Nephrotoxicity	Good
Digoxin and PSD	6	4.1	Increased digoxin exposure	Good
ACEi and aspirin	5	3.4	Reduced hyponatremic and hypotensive effects of ACE inhibitors	Fair
NSAIDs and DOACs	5	3.4	Increased risk of bleeding	Fair
Moderate DDIs				
Beta blockers and NSAIDs	16	13.4	Reduced antihypertensive effect	Good
ACEi and torsemide	15	12.6	Postural hypotension (first dose)	Good
Digoxin and loop diuretics	10	8.4	Increased risk of digoxin toxicity (nausea, vomiting, cardiac arrhythmias)	Fair
Beta blockers and digoxin	9	7.6	Increased risk of bradycardia Digoxin toxicity	Good
Beta blockers and metformin	8	6.7	Hypoglycaemia or hyperglycaemia	Good

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Angiotensin receptor blockers (ARBs) and PSD	5	4.2	Decreased symptoms of hypoglycaemia Increased risk of hyperkalaemia Increased risk of serum creatinine elevation in heart failure patients	Fair

Of the 45 patients with at least one DDI, 42 required additional monitoring, such as laboratory, clinical, and imaging tests, to track possible ADRs due to DDIs, with one third (n = 14) monitored as needed. Treatment adjustment due to DDIs was indicated for approximately half of the patients (n = 28), and performed in one patient during the study period. In the analysis of DDIs determined during the study, it was estimated that 85% of all DDIs (n = 226) required additional monitoring, which was provided in 61.1% of cases (n = 138). Treatment correction due to DDIs was required in 33.8% of cases (n = 90), and was performed in 1.1% of cases (n = 1).

To identify factors that could potentially increase the probability of DDIs, the relationship between various patient characteristics (gender, age, BMI, creatinine clearance, number of drugs used) and DDIs was evaluated. A statistically significant relationship was found between patient age and the detection of DDIs ($p = 0.005$), indicating that DDIs are recorded more frequently as patient age increases. Additionally, a statistically significant association was found between the number of drugs used and DDIs ($p < 0.001$), meaning the more drugs a patient took, the more frequent the DDIs. No significant associations were found between DDIs and gender, BMI, or creatinine clearance.

Given the wide range in the number of DDIs per patient (min = 1, max = 17), we assessed associations between the number of DDIs per patient and various characteristics (gender, age, BMI, creatinine clearance, number of medications). A strong positive correlation was found between the number of DDIs and the number of drugs used ($r = 0.691$, $p < 0.01$). Additionally, a statistically significant relationship was found between the number of DDIs per patient and the use of digoxin ($p = 0.003$).

When analysing the relationship between patient characteristics and the significance of detected DDIs, no statistically significant relationships were found. To determine factors influencing the need for additional monitoring due to DDIs, we evaluated the relationship between patient characteristics, the significance of DDIs, and the need for additional monitoring. The need for additional monitoring was statistically significantly dependent on the severity of the interaction ($\chi2 = 7.819$, $df = 1$, $p = 0.005$), with major DDIs significantly more likely to require additional monitoring compared to moderate DDIs. Additionally, DDIs identified in women required additional monitoring more often than those identified in men ($\chi2 = 6.397$, $df = 1$, $p = 0.011$). A statistically significant association was also found between the need for additional monitoring and the number of drugs used ($p = 0.021$), indicating that a higher number of drugs used increased the likelihood of requiring additional monitoring due to DDIs. No statistically significant correlations were found between the need for additional monitoring and patients' age, BMI, or creatinine clearance.

Finally, the relationship between patient characteristics, recorded DDIs, the need for additional monitoring, and the need for treatment correction was evaluated. Treatment adjustments were statistically significantly more often required for major DDIs compared to moderate DDIs ($\chi2 = 7.155$, $df = 1$, $p = 0.007$). Additionally, DDIs requiring treatment adjustments were significantly more frequent in patients with grade 3 obesity compared to other BMI categories ($\chi2 = 11.662$, $df = 4$, $p = 0.020$). For DDIs requiring additional monitoring, the need for treatment correction was statistically more frequent ($\chi2 = 5.611$, $df = 1$, $p = 0.018$).

Additionally, the need for treatment corrections was significantly dependent on the number of drugs used ($p < 0.001$). The greater the number of drugs used by the patient, the more often the need for treatment correction was identified. No statistically significant relationships were found between the need for treatment correction and the patient's sex, age, or creatinine clearance.

3. Discussion

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The prevalence of DDIs determined during the study reached 90%, confirming the hypothesis that the prevalence of DDIs in the cardiology department would exceed 50%. Similar results were described by Allabi et al. and Khaled et al., with DDI prevalences of 93% and 95% [9,10], respectively. A slightly lower prevalence of DDIs (68.1%) was found in the cardiology department at the University Hospital of Morocco [11].

The average number of drugs prescribed per patient was 8.7 (SD = 2.4, $p > 0.05$), which is lower compared to international studies where more than 10 drugs were prescribed per patient [10,12,13]. Despite the slightly lower average number of drugs used, the frequency of polypharmacy and radical polypharmacy was as high as 92%. In contrast, the Moroccan study reported an average of 5.2 drugs per patient [11].

The average number of DDIs recorded per patient was 5.3 (SD = 4.0, $p > 0.05$), with a median of 5.0. Studies in hospitals in Pakistan and Oman reported higher median DDIs of 8.5 and 9 [12,13], respectively, while other studies reported lower medians (2-4.8) [14–16].

In this study, more than half (55.3%) of all recorded DDIs were classified as major, according to the DDI categories listed in the Micromedex database. No contraindicated drug combinations were identified. The results from Oman were similar, with major DDIs accounting for 52.6% [13]. However, literature reviews found that moderate DDIs predominated in other studies [10,16–18].

The most frequently reported DDIs were between perindopril and spironolactone (n = 7). The most common serious DDIs were found between loop diuretics and NSAIDs (12.2% of serious DDIs, n = 18). Moderate DDIs were mostly observed between beta-blockers and NSAIDs (13.4% of moderate DDIs, n = 16). Other studies of a similar model did not include DDIs with non-cardiac drugs (e.g., NSAIDs), so an accurate comparison in this aspect is not possible. Additionally, not all relevant studies analysed the distribution of DDIs by drug group, creating obstacles for comparative analysis. However, some authors also identified loop diuretics [10,13] and beta-blockers [13] among the drug groups most often involved in DDIs. A significant prevalence of DDIs increasing the risk of bleeding was observed in studies, ranging from 16.4% to 20% [9,12]. In this study, the prevalence of DDIs associated with a higher risk of bleeding was slightly lower, at 12.8% of all identified DDIs. However, 42% of study patients faced an increased risk of bleeding due to the detected DDIs.

Additional treatment monitoring was required in 93.3% of patients with at least one identified DDI. All necessary additional monitoring was provided in one-third of patients (n = 14). The high prevalence of the need for additional monitoring is possible because 78% of study patients experienced at least one serious DDI. Major DDIs ($\chi2 = 7.819$, df = 1, $p = 0.005$) and DDIs identified in female patients ($\chi2 = 6.397$, df = 1, $p = 0.011$) required additional monitoring more often. The more drugs the patient used, the more often DDIs requiring additional monitoring were identified ($p = 0.021$). No further studies assessing the prevalence of the need for additional monitoring of DDIs in the Cardiology Department could be found. However, given that the majority of studies found moderate DDIs to be predominant [10,16–18], it is likely that the identified need for additional treatment monitoring would have also been greater in this study.

Treatment correction due to identified DDIs was indicated in approximately half of the patients (n = 28) but was performed in only one patient during the study period. Since this was a prospective cross-sectional study, it cannot be ruled out that treatment corrections were made after data collection. Treatment adjustments were statistically significantly more often required for major DDIs ($\chi2 = 7.155$, df = 1, $p = 0.007$) and DDIs requiring additional monitoring ($\chi2 = 5.611$, df = 1, $p = 0.018$). Treatment adjustments were also more frequently needed in patients with grade 3 obesity ($\chi2 = 11.662$, df = 4, $p = 0.020$). The higher the number of drugs used, the more often treatment adjustments were needed ($p < 0.001$). The need for treatment adjustments due to DDIs was not evaluated in other analysed studies of similar design. However, since this study found that major DDIs (requiring treatment adjustments more often) were more common than moderate DDIs, unlike in many other studies [10,16–18], it is likely that the identified need for treatment adjustments would have also been greater.

Analysing the potential risk factors for DDIs, a statistically significant relationship was found between the detection of DDIs and both patient age ($p = 0.005$) and the number of drugs used ($p <$

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0.001). Patients with polypharmacy or radical polypharmacy had statistically significantly more DDIs ($r = 0.691$, $p < 0.01$) and more major DDIs ($\chi 2 = 19.783$, $df = 2$, $p < 0.001$). This correlation between DDIs, polypharmacy, and older age is supported by studies from various countries [10,14,15,19–21]. A statistically significant relationship was also found between the number of DDIs per patient and the use of digoxin ($p = 0.003$), which is frequently involved in significant DDIs [16,18]. Appropriate additional monitoring, such as digoxin blood concentration monitoring, and appropriate dose adjustments can help reduce the risk of ADRs [18]. No statistically significant relationship between gender and the occurrence of DDIs was found. Although some studies report a higher prevalence in women [22] or men [16], most authors suggest that DDIs are not associated with the patient's gender [10,12,14,18].

Our study aligns with international research and highlights the high prevalence of DDIs in cardiology departments. To better understand the aetiology of DDIs and develop optimal monitoring and management strategies, more studies of a similar model, especially in Western Europe, should be performed. For future studies to yield more substantial results, several limitations observed in this study should be addressed.

Firstly, this study being unicentric and having a relatively modest sample size might have led to the omission of some significant factors influencing the DDI rate. Furthermore, clinical outcomes of patients related to DDIs could not be followed in this study. Therefore, future studies should include a more representative sample and analyse the prevalence of ADRs due to DDIs.

4. Materials and Methods

4.1. Design, Setting, and Population

From 2021 to 2023 "A Prospective Cross-Sectional Observational Study of the Prevalence of Problematic Pharmacotherapeutic Situations in Kaunas Hospital of the Lithuanian University of Health Sciences" was conducted. The study included 145 patients from the departments of Cardiology, Neurology, and Internal Medicine. It was approved by the Kaunas Regional Biomedical Research Ethics Committee (No. P1-BE 2-84/2021), which included permission for DDI analysis. However, data related to DDIs has not yet been published. This current study focuses on data from patients treated in the cardiology department ($n = 50$). The study included hospitalised cardiac patients aged 18 years or older who were taking at least two medications during their hospital stay and provided formal consent to participate. Patients who were receiving fewer than two medications or who refused to participate were excluded from the study.

4.2. Data Collection

Patient data was collected using paper-based and electronic medical records throughout inpatient treatment. The following data were collected during the study: patient age, gender, weight, height, lean body mass (LBM), adjusted body mass, body mass index (BMI), plasma creatinine levels, main reason for hospital admission, other illnesses, prescribed medications with indications, dosage, start and end dates (if available) of administration, information on whether medication safety and efficacy were monitored; related laboratory and instrumental test data, outcomes.

4.3. Screening and Analysis of DDIs

Micromedex interaction database was used to objectively assess the presence and severity rating of potential DDIs. Only significant DDIs were included, specifically those classified in the Micromedex database as contraindicated, major, or moderate. The most common DDIs identified in the study were analysed, and the confidence level of the data on DDIs was indicated based on information from the Micromedex database, described as follows:

- Excellent: Controlled research data clearly demonstrate the existence of DDIs.
- Good: Strong evidence suggests the existence of DDIs, but well-controlled studies are needed.
- Satisfactory: Available data are sparse, but pharmacological features lead clinicians to suspect potential DDIs, or well-described DDIs common to pharmacologically similar drugs.

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- Unknown: The confidence level of the data is not known.

The need for additional monitoring and treatment adjustments due to DDIs was assessed based on the DDI management guidelines in the Micromedex database.

To reduce data dispersion, subjects were divided into two age groups: <65 years and ≥65 years (elderly patients). Additionally, based on the number of medications used, subjects were divided into three groups: prescribed <5 drugs, 5-9 drugs (polypharmacy), and ≥10 drugs (radical polypharmacy). When potential DDIs were common to an entire drug group, the DDIs were categorised according to the involved drug groups. For DDIs specific to individual drugs within a group, the interaction was categorised by the drug name without mentioning the drug group.

4.4. Statistical Analysis

Statistical analysis was performed using SPSS v29.0.1.0 software. Descriptive statistics were applied to characterise the study data. Nominal and categorical variables were presented using frequency tables. Interval variables (such as age, creatinine clearance, BMI, and the number of drugs prescribed) underwent normality testing. Normally distributed variables were summarised using the mean and standard deviation.

To investigate the relationship between DDIs (none vs. at least one) and categorical variables such as gender, age (< 65, ≥ 65 years old), number of drugs prescribed (< 5, 5-9, ≥ 10) glomerular filtration rate (GFR) categories, and BMI categories, the Chi-squared test was utilised. For interval variables such as age, BMI, creatinine clearance, and the number of medications used daily, the relationship with DDIs (none vs. at least one) was assessed using Student's t-test for independent samples.

Pearson's correlation was performed to determine the relationship between the number of DDIs per patient and interval variables, including BMI, creatinine clearance, age, and the number of drugs prescribed. Student's t-test was also used to compare the mean number of DDIs per patient between males and females, as well as between those prescribed digoxin and those who were not.

To analyse the relationship between the significance of detected DDIs and categorical variables such as gender, age (<65, ≥65 years old), GFR categories, BMI categories, and DDI significance the Chi-squared test was used. For interval variables such as age, BMI, creatinine clearance, and the number of medications used daily, the relationship with the significance of detected DDIs (none vs. at least one) was assessed using Student's t-test for independent samples.

To determine the relationship between the necessity for additional monitoring and categorical variables such as gender, age categories, BMI categories, GFR categories, and DDI significance, the Chi-squared test was applied. For interval variables such as age, BMI, creatinine clearance, and the number of prescribed medications, the relationship with the necessity for additional monitoring was assessed using Student's t-test. The same approach was applied to determine the relationship between patient characteristics, DDI significance, the necessity for additional monitoring, and the necessity to adjust treatment.

A binomial logistic regression was initially planned to assess the influence of potential factors on the presence of at least one DDI. However, due to the exceptionally high prevalence of at least one DDI, the regression model did not fit the data and could not be validly used.

A p-value of <0.05 was considered significant.

5. Conclusions

A notably high prevalence of DDIs was observed within the cardiology department. More than half of the recorded DDIs were classified as major, with the remainder being moderate; no contraindicated drug combinations were identified. Additional monitoring for DDIs was deemed necessary for the vast majority of study patients, with complete monitoring provided in one third of cases. Treatment adjustment due to DDIs was deemed necessary for approximately half of the patients, and such adjustments were executed for one patient during the study period.

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Conflicts of Interest: The authors declare no conflicts of interest.

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