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Original Article

Risk Factors for Potential Drug-Drug Interactions in Outpatients with Dyslipidemia

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Abstract

Background: Patients with dyslipidemia are usually multimorbid and require polypharmacy. Therefore, it is important to identify potential drug-drug interactions (pDDIs) in time to prevent their consequences. We aimed to identify and analyze risk factors contributing to their occurrence to guide health professionals.

Methods: A prospective cross-sectional study of 216 outpatients with dyslipidemia was conducted from May 2021 to April 2022 in Podgorica, the capital of Montenegro. pDDIs were identified using Medscape, Epocrates, and Drugs online interaction checkers. Multivariate regression analysis was performed to evaluate the potential predictors of interactions.

Results: pDDIs were detected in 212 (98.1%) participants, whereas pDDIs with high clinical significance were detected in 25.46%, 40.74%, and 58.8% of subjects by Drugs, Epocrates, and Medscape, respectively. Polypharmacy emerged as a risk factor for the occurrence of pDDIs in all three checkers in each category of clinical significance. The use of non-steroidal anti-inflammatory drugs and antiplatelet drugs contributes to the incidence of severe pDDIs B=1.014, 95%CI 0.681-1.346, *P*=0.000 and B=0.492, 95%CI 0.286-0.698, *P*=0.000, by Epocrates and Medscape respectively. The number of prescribers per patient was a protective factor against moderate pDDI B= -0.858, 95%CI -1.572-(-0.144), *P*=0.019 and B= -0.956, 95%CI -1.671-(-0.241), *P*=0.009, by Medscape and Epocrates, respectively, but a risk factor for the occurrence of minor pDDIs B=0.373, 95%CI 0.033-0.712 *P*=0.032 and B=0.143, 95%CI 0.042-0.244, *P*=0.006, by the same checkers.

Conclusion: Knowledge of the risk factors contributing to the occurrence of pDDIs is important for the development and implementation of strategies for their prevention, and given the high prevalence of dyslipidemia, understanding these factors seems crucial nowadays.

Keywords: Drug-drug interactions; Dyslipidemia; Interaction checker; Risk factors

Introduction

Dyslipidemia is a major risk factor contributing to the development of cardiovascular disease (CVD), which remains one of the leading causes of death worldwide (1). The number of patients with dyslipidemia is increasing every year due to the modern lifestyle (2). The drugs of choice in the treatment of dyslipidemia are statins (3). Besides statins, patients usually take additional therapies because these patients often have a variety of comorbidities (4). A greater number of drugs in therapy carries a higher risk of potential drug-drug interactions (pDDIs) (5). This is further contributed by the fact that all statins except pravastatin are substrates for isoenzymes of the CYP P40 group and interact with drugs that are inducers or inhibitors of these isoenzymes (6). Drug-drug interactions are defined as a possible interaction between two drugs that may result in a change in the therapeutic and/or toxic effect of one or both drugs (7). Depending on their clinical significance, they can be classified as those with high, moderate, and low clinical significance (8).

The prevalence of pDDIs in patients with dyslipidemia varies from 40% to 80% (9,10), whereas the prevalence of clinically significant pDDIs is 17.43% (11). However, the risk factors associated with the occurrence of pDDIs in patients with dyslipidemias have been only partially studied. Among them, only the number of medications and the presence of certain concomitant diseases have been reported as factors with significant influence (11). Thus, it is necessary to analyze in more detail which factors contribute to the occurrence of pDDIs in order to detect them in time and prevent them appropriately, especially those that are of great clinical importance and may have consequences for the patient himself, either in the form of failure to achieve a therapeutic effect or the occurrence of severe side effects (12).

Therefore, we aimed to identify and analyze risk factors contributing to the occurrence of pDDIs in patients with dyslipidemia, for each category of clinical significance.

Materials and Methods

Study design

To identify and analyze risk factors contributing to the occurrence of pDDIs in patients with dyslipidemia, a prospective cross-sectional study was conducted. The Ethics Committee of the Faculty of Medicine of the University of Montenegro approved the conduct of the study under number 2050/7.

Study population

Adult patients diagnosed with dyslipidemia who were taking at least one other medication in addition to a hypolipemic were included. The sample size was calculated based on the formula:

$$n = Z^2 x \frac{p \times q}{e^2}$$

where,
n = minimum required sample size
Z = 1.96 at 95% of Confidence Interval
p = prevalence taken as 50% for maximum sample size calculation
q = 1-p
e = margin of error, 7% (13)

The calculated sample size was 196. Taking a 10% non-response rate, the final sample size was estimated on 216 patients. Patients were recruited on a voluntary basis between May 2021 and April 2022 in primary health care facilities in Podgorica, the capital of Montenegro. Exclusion criteria for the study were incomplete medical records, patients' lack of clarity about the medications taken on the study day, use of only one medication, and patients who did not have a diagnosis code for dyslipidemia according to ICD-10 (E78) (14).

Demographic and clinical data

After signing the informed consent form, respondents completed a questionnaire in which

they were required to provide the following information: sex, age, presence of smoking and alcohol consumption, medications used in therapy, including dietary supplements, herbal medicines, etc., and information on possible drug allergies. From medical records we extracted following data regarding number of physicians who prescribe drugs, patient's personal medical history (number and type of comorbidities), and we confirmed data on medications previously reported by patients. Once the information was collected, a database was created in Microsoft Excel 2013 to enter all the data collected, including the Charlson Comorbidity Index (CCI), which was then calculated for each individual patient (15). The Interaction checker tool was used to identify pDDIs on 3 different free online platforms: Drugs.com, Epocrates, and Medscape. After entering the total therapy taken by the patient, the Interaction Checker of the Drugs.com platform determines the total number of pDDIs and classifies them according to their severity into those of high (Major), medium (Moderate) and low (Minor) clinical importance. It also explains the consequences of the interaction in question, how it occurs, and what actions are proposed (16). The other two interaction checkers work on the same principle, the only difference being the way in which the interactions are classified according to their clinical importance. Epocrates classifies them into 4 categories: Contraindicated, Avoid/Use alternative, Monitor/Modify and Caution Advised (17). Similarly, Medscape divides pDDIs into the following categories: Contraindicated, Serious/ Use alternative, Monitor Closely, and Minor (18). The results obtained from all three interaction checkers were entered into the database, after which data processing began.

Statistics

The data were processed using Excel and SPSS 26 (IBM Corp., Armonk, NY, USA). Values of categorical variables are presented as total number and percentage, whereas values of continuous variables are presented as mean ± standard deviation (range). The Shapiro-Wilk test was used to test the normality of the distribution. Spearman's or Pearson's correlation coefficient was used to assess the correlations between the potential risk factors and the observed interactions for each of the checkers and for each category of clinical significance. Standard univariate and multivariate regression analyses were performed to evaluate potential predictors of interactions based on the factors studied. P value < 0.05 was considered statistically significant.

Results

Our study involved 216 patients with a mean age of 65.03 ± 10.79 years. Both genders were almost equally represented. Detailed characteristics of the study population are shown in Table 1.

Table 1: Characteristics of the study sample

Variable	*Mean ± SD (range) or number (%)*
Gender	
Male	110 (50.93)
Female	106 (49.07)
Age (years)	65.03 ± 10.79 (30-94)
Smoking status	
Smoker	74 (34.26)
Former smoker	37 (17.13)
Non smoker	105 (48.61)
Alcohol consumption	

Yes	42 (19.44)
No	174 (80.56)
Number of prescribers for a single patient	2.53 ± 1.09 (1-6)
Number of comorbidities per patient	2.09 ± 1.10 (0-6)
Comorbidities	
Hypertension	159 (73.61)
Diabetes mellitus	61 (28.24)
Thyroid diseases	25 (11.57)
Angina pectoris	38 (17.59)
Drug allergy	15 (6.94)
Charlson Comorbidity Index	3.03 ± 1.52 (0-8)
Number of prescribed drugs per patient	7.20 ± 2.81 (2-19)
Anticoagulant therapy	21 (9.72)
Antiplatelet therapy	133 (61.57)
Antiarrhythmic drugs	15 (6.94)
Anticonvulsants	15 (6.94)
Antidepressants	12 (5.55)
Non steroidal anti-inflammatory drugs	38 (17.6)

pDDIs were detected in 212 (98.1%) participants, mostly by Drugs (2099), followed by Medscape (2042) and Epocrates (1940). Serious pDDIs were detected in 25.46%, 40.74%, and 58.8% of subjects by Drugs, Epocrates, and Medscape, respectively. Allocation of detected interactions according to mentioned interaction checkers is presented in Table 2.

Table 2: Average number of potential drug-drug interactions per patient

Type of interaction	***Mean ± SD (range)***
Medscape	
Contraindicated	0.00 ± 0.00 (0)
Serious – Use alternative	0.76 ± 0.83 (0-6)
Monitor closely	6.98 ± 6.45 (0-40)
Minor	1.72 ± 2.30 (0-15)
Total	9.45 ± 8.43 (0-49)
Epocrates	
Contraindicated	0.01 ± 0.10 (0-1)
Avoid/use alternative	0.76 ± 1.19 (0-6)
Monitor/modify therapy	7.93 ± 7.33 (0-51)
Caution advised	0.28 ± 0.68 (0-5)
Total	8.98 ± 8.25 (0-55)
Drugs	
Major	0.43 ± 0.93 (0-6)
Moderate	7.36 ± 6.65 (0-36)
Minor	1.91 ± 1.89 (0-10)
Total	9.72 ± 8.25 (0-47)

Tables 3-5 show only statistically significant results of the multivariate regression analysis, in which the risk factors for the occurrence of pDDIs are listed separately for each category of clinical significance and for each of the checkers, except for Major interactions of the Drugs checker. Indeed, none of the previously mentioned variables had a correlation greater than

0.3, so multivariate analysis was not performed. The variables that were statistically significant potential predictors of the number of major interactions in the univariate analysis were: number of prescribed drugs (B (95%CI) = 0.172 (0.134-0.211, *P*<0.001), number of prescribers (B (95%CI) = 0.238 (0.127-0.349, *P*<0.001), number of comorbidities (B (95%CI) = 0.238 (0.128-0.348, *P*<0.001), antiarrhythmics (B (95%CI) = 0.975 (0.500-1.450, *P*<0.001), antidepressants (B (95%CI) = 0.873 (0.338-1.407, *P*<0.001) and anticoagulant therapy (B (95%CI) = 0.847 (0.440-1.254, *P*<0.001).

Table 3: Significant risk factors for potential drug-drug interactions detected by Medscape

Type of interaction	***Variable***	***B***	***95% Confidence Interval for B***		***P - value***
			Lower Bound	Upper Bound	
Serious use alternative	Number of prescribed drugs	0.102	0.066	0.138	0.000
	Antiplatelet therapy	0.492	0.286	0.698	0.000
Monitor closely	Number of prescribers	-0.858	-1.572	-0.144	0.019
	Number of prescribed drugs	2.081	1.814	2.348	0.000
Minor	Number of prescribers	0.373	0.033	0.712	0.032
	Number of prescribed drugs	0.347	0.220	0.473	0.000

Table 4: Significant risk factors for potential drug-drug interactions detected by Epocrates

Type of interaction	***Variable***	***B***	***95% Confidence Interval for B***		***P - value***
			Lower Bound	Upper Bound	
Contraindicated and Avoid/use alternative	Number of prescribed drugs	0.241	0.180	0.302	0.000
	NSAID	1.014	0.681	1.346	0.000
Monitor/modify therapy	Number of prescribers	-0.956	-1.671	-0.241	0.009
	Number of prescribed drugs	2.482	2.201	2.763	0.000
Caution advised	Number of prescribers	0.143	0.042	0.244	0.006
	Number of prescribed drugs	0.055	0.016	0.093	0.006

Table 5: Significant risk factors for potential drug-drug interactions detected by Drugs

Type of interaction	*Variable*	*B*	*95% Confidence Interval for B*		*P - value*
			Lower Bound	Upper Bound	
Moderate	Number of prescribed drugs	2.164	1.935	2.394	0.000
	Number of prescribed drugs	0.371	0.305	0.437	0.000
Minor	Antiplatelet therapy	1.556	1.176	1.936	0.000

The number of medications was positively correlated with the number of pDDIs for each category of clinical significance in all three checkers. The use of NSAIDs and antiplatelet agents was positively correlated with the number of pDDIs of high clinical importance, according to Epocrates and Medscape, respectively, whereas the use of antiplatelets was positively correlated with the number of pDDIs of low clinical significance, according to Drugs. The number of prescribing physicians showed a negative correlation with the number of pDDIs of moderate significance, according to Medscape and Epocrates, whereas this variable showed a positive correlation with the number of pDDIs of low clinical significance, according to the same checkers.

Discussion

Avoiding DDIs, especially clinically significant ones, may reduce the number of outpatient visits, the number of hospitalizations, the risk of death, and the cost to the health care system. Considering that patients with chronic diseases are at higher risk of developing pDDIs (19) and that dyslipidemia is now a common disease (20), timely detection and prevention of pDDI in this patient population is extremely important.

To identify pDDIs in the group of patients with dyslipidemia, we used software from 3 different databases: Drugs, Epocrates, Medscape. Although Lexi-Interact and Micromedex were rated overall as the best tools for detecting pDDIs, Epocrates was rated as the most accurate programme. It was also ranked second in specificity and sensitivity, while Medscape was ranked third (21). Another study showed that there was no significant difference in the sensitivity of Lexi-Interact and Drugs and that the specificity of Drugs for potentially clinically significant interactions was even higher than that of Lexi-Interact (22). Unfortunately, none of these databases is ideal; each has some shortcomings and discrepancies, especially in the classification of interactions by severity. For this reason, three different databases were used to achieve greater sensitivity and accuracy of the results obtained (21).

Our results obtained with all 3 checkers show that, on average, 40% of patients were found to have at least one potentially serious DDI and that only 4 patients did not have any single pDDI. Over the past decade, the prevalence of pDDI in outpatients has increased, ranging from 16% to 91% (23). Discrepancies in the prevalence of pDDI may be attributed to differences in study population, study design, and DDI screening instruments (24). Recent studies conducted in patients with hypercholesterolemia showed that at least one pDDI was detected in 45% and 83.3% of patients, respectively (9,10), which is less compared with the results of our study in which the same was detected in 98.1% of subjects. Our results are in agreement with the studies conducted in Jordan, where the prevalence of pDDI was more than 90% (23,25), which is probably due to the high prevalence of polypharmacy among the respondents, which was also the case here, where 86.1% of the respondents were taking 5 or more medications.

Knowledge of the prevalence and predictors of clinically significant potential DDIs can help physicians and pharmacists identify patients at higher

risk for DDI-related adverse events who require more careful pharmacotherapy management to avoid adverse outcomes (26). On average, potentially serious DDIs occur in 20% of patients (11,25,27), whereas the results of our study show that their frequency is twice as high. The reason for this may be that more than half of the subjects were taking antiplatelet drugs, mainly acetylsalicylic acid, and one in six subjects was taking NSAID (Table 1), and it is well known that the combination of these drugs requires patient monitoring because of the higher risk of bleeding. A study conducted in Slovenia reported that one of the reasons for the threefold higher incidence of clinically significant DDIs in the group of patients older than 65 years compared with the general population was the more frequent use of this drug combination (28).

Understanding the risk factors that contribute to the occurrence of DDIs is critical for developing and implementing strategies for their prevention (19). Our study showed that in patients with dyslipidemia, polypharmacy, use of NSAIDs, and antiplatelet agents were risk factors for the occurrence of pDDIs. The number of prescribing physicians per patient was a protective factor against moderate pDDIs but a risk factor for the occurrence of minor pDDIs.

It is already well established that polypharmacy is a risk factor for the occurrence of DDIs (29). Patients taking five or more medications concurrently are 2.7 times more likely to experience adverse events due to a DDI (OR 2.7, 95%CI 1.9-3.1, $P<0.01$) (30). Increased medication use may be associated with the occurrence of pDDI, which is also true for the results of our study (11,19,26,31,32).

The results of our study also indicate that in patients with dyslipidemia who use a large number of drugs, special attention should be paid to those who use antiplatelet drugs and NSAIDs, in order to prevent DDIs and their unwanted consequences. Patients with dyslipidemia have an increased risk of developing atherosclerosis (1). To prevent atherothrombotic events, they receive antiplatelet agents, usually acetylsalicylic acid, for primary and secondary prevention (33). Considering that antiplatelet drugs tend to interact with other drugs due to their pharmacokinetic and pharmacodynamic properties (34), the results obtained are not surprising. Antithrombotics are the most common group of drugs with which major DDIs occur (25,26,35,36).

NSAIDs are widely used medications, especially in patients over 65 years of age with the prevalence of 96%. They are commonly prescribed for pain relief and as anti-inflammation drugs (37), but they also interact with numerous drugs, including antihypertensive and antiplatelet medications (38), which are often taken by patients with dyslipidemia as part of daily therapy along with hypolipemic medications. Because the subjects studied were patients with dyslipidemia and most of them were elderly, the influence of this factor is also predictable. Numerous studies demonstrate the influence of this group of drugs on the occurrence of severe DDIs (28,32,35,39).

The occurrence of pDDIs at the primary care level is higher because more prescribers are involved in the patient's therapy (40), whereas in inpatients, a larger number of prescribers plays a protective role in the occurrence of DDIs because there is better communication between physicians and they have better insight into the patient's overall therapy (41). The influence of the number of prescribing physicians per patient was not clear in our study, i.e., it depended on the severity of the interaction. The same influence was observed in another study (7). This phenomenon can be explained by the presence of an electronic health record system that allows physicians to view the patient's therapy. In this way, when selecting a drug to add to a patient's therapy, physicians are careful to avoid interactions that could be potentially significant for the patient, whereas potential interactions of minor significance are likely to be overlooked. Because of fatigue, excessive patient volume, and lack of time, integrating software into the electronic health information system could help physicians avoid pDDIs when prescribing therapies, minimizing potential oversights and errors, as has been done in some countries (28,42). However, the electronic system does not contain information about the medications

that patients take without a physician's prescription, often including NSAIDs, which are one of the main risk factors for the occurrence of severe DDI in this patient population. Pharmacists should play an important role here in the prevention of pDDIs, but unfortunately, in the Montenegrin healthcare system, the position of pharmacist as a control and counselling subject is not yet defined, but rather in the position of a distributor who only dispenses medications. It is known that pharmacists can make an important contribution to the detection and prevention of many problems related to therapy, including pDDIs (35,43), so it is necessary that pharmacists be more involved in the therapy of patients and accept the concept of pharmaceutical health care. The main limitation of this study is that only potential DDIs were investigated, so it is not known exactly how many of these interactions lead to an adverse event. Despite these limitations, the results of this study may provide guidance to health professionals on what factors to look for to prevent pDDIs, particularly those that may be clinically significant in patients with daily increasing dyslipidemia.

Conclusion

Patients with dyslipidemia are at increased risk for pDDIs if they are prescribed more drugs. Special attention should be paid to those taking antiplatelet agents and NSAIDs, which concomitant use increases the risk of serious adverse events. Greater involvement of health professionals may have a protective effect, and there is a need to be more vigilant in prescribing/dispensing medicines to prevent pDDIs, especially clinically significant ones, which can be supported by integrating software for their detection.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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