Revista O Mundo da Saúde

Factors associated with clinically relevant drug-drug interactions with statins in outpatients with coronary artery disease

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Abstract

The concomitant use of statins with other drugs is quite common and contributes to an increased risk of drug interactions that may become manifested clinically as adverse drug reactions. The objective of the study was to determine the factors associated with clinically relevant drug interactions with drug-drug statins in patients seen at the multiprofessional cardiology outpatient clinic of a university hospital. This was a cross-sectional study conducted with 148 patients. The dependent variable was whether or not there were clinically relevant drug interactions with statins according to the Scientific Statement from the American Heart Association. A logistic regression was performed to analyze the association of the occurrence of clinically relevant drug interactions with statins and independent variables. The median number of drugs used was seven (IQR=3) and the number of cardiovascular drugs was five (IQR=2), where 91.2% (n=135) had polypharmacy. The most prevalent diseases in the studied population were systemic arterial hypertension and dyslipidemia. The median number of diseases was five. The prevalence of clinically relevant drug interactions with statins was 43.2%. A positive association was identified between clinically relevant drug interactions with statins and the number of diseases (OR=4.025; CI=1.895-8.553). All potential drug interactions with simvastatin found were of clinical relevance. The most prevalent interactions were: amlodipine + simvastatin and warfarin + simvastatin. The identification of factors associated with drug interactions allows directing measures to prevent adverse events in more exposed populations, such as those with multiple comorbidities.

Keywords: Drug Interactions. Use of Medicines. Statins. Coronary Artery Disease. Cardiovascular diseases.

INTRODUCTION

Cardiovascular diseases (CVD) represent a challenge for public health, and are considered the main cause of death and hospitalizations in Brazil, creating a burden on the Brazilian health system[1]. Among CVDs, coronary artery disease (CAD) is one of the most common diseases, which is expected to be the main cause of morbidity and mortality in most developing nations by 2020[2]. CADs include stable angina, unstable angina, acute myocardial infarction (AMI), and sudden death.

One of the main modifiable risk factors for CAD is high serum cholesterol levels, especially low-density lipoprotein (LDL)[3]. To reverse this situation, national and international guidelines emphasize the importance of the prescription

DOI: 10.15343/0104-7809.202044506514

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and use of statins in reducing LDL, and consequently, for the primary and secondary prevention of cardiovascular events. The use of statins is directly associated with decreased AMI, ischemic stroke, revascularization, cardiovascular mortality, and mortality from all causes[3,4].

Statins are often used concomitantly with other drugs, which contributes to polypharmacy and the occurrence of drug-drug interactions[5]. Drug interactions can manifest clinically as adverse drug reactions (ADR) and culminate in negative clinical outcomes related to safety, such as myopathy and rhabdomyolysis[6].

To prevent such outcomes, it is necessary to identify drug-drug interactions early, especially those of clinically relevance (CR-DDI). In 2016, the American Heart Association produced a document that provides recommendations for the management of drug-drug interactions with clinically relevant statins in patients with cardiovascular diseases[6]. The realization of studies like this are extremely important since the identification of CR-DDI with statin contributes to the prevention and clinical management of these interactions and their negative outcomes.

Thus, the present study aims to determine the factors associated with clinically relevant drug-drug interactions with statins in patients with coronary artery disease treated at the multiprofessional outpatient cardiology clinic of a university hospital.

METHODOLOGY

Selection and description of participants

This was a cross-sectional study, carried out in the multiprofessional cardiology outpatient clinic of a public university hospital located in Belo Horizonte, Minas Gerais. Therefore, a convenience sample was included with 148 patients seen at the clinic from April/2018 to February/2019. Patients diagnosed with CAD, using one or more medications, including one statin; and using statins for at least 15 days, we included. As an exclusion criterion, those with verbal communication difficulties.

The data were recorded on a form developed for research purposes, which contained information on socio-demographic, clinical, and pharmacotherapeutic characteristics. Data collection included interviewing the patient and complementing the information with clinical characteristics reported in the electronic medical record. The interview was conducted before the pharmaceutical consultation by a researcher not linked to the service. In situations where the medication was administered by another person, this person was also interviewed with the patient.

Technical information

The dependent variable was defined as whether or not they have CR-DDI with statins according to the Scientific Statement from the American Heart Association. To determine the prevalence of drug interactions, they were classified according to the IBM Micromedex® Drug Interaction Checking database (electronic version)(7). Drug-drug interactions were classified according to severity, adopting the specifications of Drug-Reax®, as: contraindicated (when drugs are contraindicated for concomitant use); severe (when the interaction can bring risks to the patient's life and requires immediate medical intervention); or moderate (when the interaction may result in an exacerbation of the patient's clinical condition or demand a change in therapy). In the present investigation, the interactions defined by Drug-Reax® as mild (when the interaction may have limited clinical effects, without requiring changes in drug therapy) or unknown (when there is no definition of the degree of severity) were not included.

The dose of acetylsalicylic acid was observed for the purpose of identifying interactions involving this drug, since, for certain interactions

involving acetylsalicylic acid, the Drug-Reax® software informs in the clinical management section whether it occurs with doses used for the purpose of analgesia and antipyresis (>300 mg) or for an antiplatelet effect (70-300 mg) (7).

The study's independent variables were socio-demographic data (age, gender and education); clinical data (main diagnosis of cardiovascular diseases, chronic diseases, number of diseases); and pharmacotherapeutic drugs data (prescription drugs, polypharmacy, potential drug interactions). The elderly variable was dichotomized into yes and no, considering elderly individuals ≥ 60 years old.

The research project was approved by the Research Ethics Committee of the Federal University of Minas Gerais (COEP-MG) under number CAAE 85804818.7.0000.5149 and was developed respecting all the ethical principles contained in Resolution No. 466, of December 12, 2012, about research involving human beings. Participants who agreed to participate in the study read and signed the Informed Consent Form.

Statistical analysis

The information collected was entered into a database created in the Epi-Data® software, version 3.1 by different typists. Descriptive data analysis was performed by determining the frequencies and percentages of categorical variables. For the quantitative variables, measures of central tendency (mean and median) and dispersion measures (standard deviation - SD - and interquartile range - IQR) were performed. The variable number of diseases was dichotomized by the median.

The association between CR-DDI with statin and independent variables was performed by a univariate analysis using Pearson's chi-squared test. In the presence of at least one expected frequency less than five, Fisher's exact test was used. The independent variables that obtained a p value ≤0.20 in the univariate analysis were included in the multivariate logistic regression model. In the final model, the variables that maintained a value of p <0.05 remained. For univariate and multivariate analysis, the magnitude of the association was expressed by the odds ratio (OR) with a 95% confidence interval (CI).

The likelihood ratio test was used to compare the models. The adequacy of the final models was assessed by the Hosmer and Lemeshow test. Statistical significance was considered when p <0.05. Statistical analysis was performed using the Statistical Package for Social Sciences® (SPSS®) software, version 25.0.

RESULTS

The present study covered 148 patients, 104 (70.3%) of whom were male. The median age was 62 years and the IQR was 17. The most prevalent chronic diseases were systemic arterial hypertension (SAH) (n=107; 72.3%), dyslipidemia (n=66; 44.6%), and diabetes mellitus (n=49; 33.1%). The median number of diseases was five (IQR=3).

The median number of drugs used was 7 (IQR=3) and the number of cardiovascular drugs was five (IQR=2), where 91.2% (n=135) had polypharmacy. The frequency of patients who had potential drug interactions with statins was 85% (n=127). A more detailed description of the studied population is described in Table 1.

Table 1 – Socio-demographic, clinical and pharmacotherapeutic characteristics of the 148 patients with coronary artery disease using statins treated at the cardiology outpatient clinic of a university hospital. Source: Study data. Belo Horizonte, MG, 2019.

Sociodemographic Characteristics		
Male Gender [n, (%)]	104	(70.3)
Age in years [median (interquartile range - IQR)]	62	(17)
Schooling in years [median (interquartile range - IQR)]	4	(4)
Clinical Characteristics		
Number of diseases [median (interquartile range - IQR)]	5	(3)
Cardiovascular diagnoses		
Acute Myocardial Infarction [n, (%)]	126	(85.2)
Arrhythmia [n, (%)]	35	(23.7)
Heart failure [n, (%)]	29	(19.6)
Chronic diseases		
Systemic arterial hypertension [n, (%)]	107	(72.3)
Dyslipidemia [n, (%)]	66	(44.6)
Kidney problems [n, (%)]	26	(38.5)
Diabetes Mellitus [n, (%)]	49	(33.1)
Pharmacotherapeutic characteristics		
Polypharmacy [n, (%)]	135	(91.2)

Eight types of clinically relevant drug-drug interactions were identified with statin (Table 2), whose total absolute frequency was 75. Simvastatin was the only statin that presented CR-DDI and the interactions with the highest frequency of occurrence were with amlodipine (27) and warfarin (26).

Table 2 – Clinically relevant drug-drug interactions with statins according to the recommendations of the American Heart Association of the 148 patients with coronary artery disease using statins from a cardiology outpatient clinic of a university hospital. Source: Study data. Belo Horizonte, MG, 2019.

Drug	interactions	Potential risk	Clinical management	Absolute frequency
Statina	**Medication**			
Simvastatin	Amlodipine	Increases the plasma concentration of simvastatin and increases the risk of myopathy, including rhabdomyolysis.	Simvastatin dose limit of 20 mg.	27
	Warfarin	It may increase the risk of bleeding and rhabdomyolysis.	Monitor INR, especially when increasing or changing the dose of simvastatin.	26
	Amiodarone	It can significantly increase exposure to simvastatin and risk of myopathy or rhabdomyolysis.	Simvastatin dose limit of 20 mg.	9

to be continued...

...continuation - Table 2

Drug	interactions	Potential risk	Clinical management	Absolute frequency
	Diltiazem	It can result in increased serum concentrations of simvastatin and increased risk of myopathy or rhabdomyolysis.	Simvastatin dose limit of 10 mg.	7
	Ticagrelor	It may result in increased plasma concentrations of simvastatin.	Simvastatin dose limit of 40 mg.	2
	Colchicine	It can increase the risk of myopathy and rhabdomyolysis.	Strict monitoring of muscle toxicity.	2
	Verapamil	Increased risk of myopathy or rhabdomyolysis.	Simvastatin dose limit of 10 mg.	1
	Cyclosporine	It may result in an increased risk of myopathy and rhabdomyolysis.	Avoid concomitant use.	1

Legend: [1]INR: International Normalized Ratio.

In the univariate analysis, a statistically significant positive association was identified between the occurrence of CR-DDI with statins and the following independent variables: age greater than or equal to 60 years, number of diseases greater than five, polypharmacy, as well as having the following health diagnoses: SAH, dyslipidemia, and kidney problems. In the multivariate analysis, the number of diseases >5 showed a positive association with CR-DDI (OR=4.025, CI=1.895-8.553) (Table 3). Therefore, individuals with a number of diseases >5 are at increased risk of CR-DDI with statins.

Table 3 – Univariate and multivariate analysis of factors associated with potential drug interactions with statins classified by the American Heart Association as clinically relevant. Source: Study data. Belo Horizonte, MG, 2019.

Variable	Drug Interaction		Univariate Analysis		Multiveriate Analysis	
	Yes N (%)	No N (%)	OR (95% CI)	P value	OR (95% CI)	P value
Sociodemographic characteristics						
Elderly						
Yes	40 (62.5)	30 (47.6)	1.833 (0.904-	0.092	---	----
No	24 (37.5)	33 (52.4)	3.720)			
			1			
Clinical Characteristics						
Number of diseases						
> 5	42 (56.8)	16 (26.4)	4.025 (1.895-	0.000	4.025 (1.895-	0.000
≤ 5	32 (43.2)	47 (74.6)	8.553)		8.553)	
			1			

to be coninued...

...continuação - Table 3

Variable	Drug Interaction		Univariate Analysis		Multiveriate Analysis	
Chronic diseases						
HAS						
Yes	53 (82.8)	38 (60.3)	3.170 (1.393-	0.005	----	----
No	11 (17.2)	25 (39.7)	7.215)			
Dyslipidemia			1			
Yes	30 (46.9)	22 (34.9)	1.644 (0.805-	0.171	----	----
No	34 953.1)	41 (65.1)	3.357)			
			1			
Kidney problems						
Yes	17 (26.6)	9 (14.3)	2.170 (0.884-	0.086	---	---
No	47 (73.4)	54 (85.7)	5.325)			
			1			
Pharmacotherapeutic characteristics						
Polypharmacy						
Yes	57 (89.1)	61 (96.8)	0.267 (0.053-	0.164	---	---
No	7 (10.9)	2 (3.2)	1.339)	*		
			1			

Legend: SAH: Systemic Arterial Hypertension. 1Hosmer-Lemeshow test: 2=3.48; degrees of freedom=6; p=0.25 OR: Odds ratio; CI: confidence interval.

DISCUSSION

The study found a significant association between CR-DDI with statins and number of diseases. CVD patients tend to have multiple diseases reflecting the multimorbidity situation evidenced in a national population-based study carried out in individuals aged 50 years or older, which found an average of 2.66 comorbidities per individual, and systemic arterial hypertension and dyslipidemia were the most prevalent diseases[8]. A study carried out in the population of Florianópolis, SC detected high multimorbidity in a cardiovascular cluster (70% of the individuals in this cluster had three or more morbidities)[9].

The increase in the number of morbidities was directly associated with increasing age in the Brazilian study of multimorbidity[9]. CVDs do not exist in isolation in the elderly, and are associated with multiple comorbidities[10,11,12]. Multimorbidity leads to the administration of multiple medications, providing drug-drug interactions, which explains the association between the elderly and CR-DDI with statins, found in the univariate analysis.

Polypharmacy is beneficial in several clinical contexts[13], but even with this effectiveness, patients using multiple medications need more monitoring, due to the risks of inappropriate drug use and potential drug interactions[12]. A study carried out with adults in Scotland showed that 81% of patients with polypharmacy were exposed to potentially serious drug interactions[14].

Patients using any statin should be monitored for the occurrence of drug interactions, with greater attention to CR-DDI[6,13]. The study

detected a high prevalence of CR-DDI, which can be explained by the characteristics of patients with polypharmacy were exposed to potentially serious drug interactions[14].

Patients using any statin should be monitored for the occurrence of drug interactions, with greater attention to CR-DDI[6,13]. The study detected a high prevalence of CR-DDI, which can be explained by the characteristics of the studied hospital, as it assists patients with complex diseases and therapeutic regimes, which require the use of multiple medications. The high prevalence of CR-DDI with statins is in line with previous studies[15,16]. A study carried out with individuals treated at a community pharmacy with a mean age of 65 years, identified 62 CR-DDI and among them, 29% were with simvastatin; the main interaction found were with amlodipine + simvastatin, which corroborates with the findings of this cohort[17].

CR-DDI between simvastatin + amlodipine may increase the risk of muscle toxicity (rhabdomyolysis and myopathy) due to the elevated plasma concentrations of simvastatin when used concomitantly with amlodipine. In clinical practice, the interaction of simvastatin and amlodipine can be prevented by adjusting the dose of simvastatin to 20 mg, or by replacing simvastatin with pravastatin or atorvastatin[6].

The second most frequent CR-DDI identified in the study was between simvastatin + warfarin, which may lead to an increase in the international normalized ratio (INR) and the need to reduce the dose of warfarin[6]. Regarding the concomitant use of warfarin and simvastatin, strict control of the N should be carried out with warfarin dose adjustment whenever necessary for better patient safety[6].

The CR-DDI identified in the study were only with simvastatin, due to the greater use in the studied sample due to its easy access. It is available free of charge in Primary Health Care or via co-participation in commercial pharmacies through the Programa Aqui Tem Farmácia Popular at a reduced price[18,19,20].

Statin-based CR-DDIs are, in most cases, preventable. To develop a safe statin prescription, knowledge about the mechanisms, magnitude, and potential consequences of these interactions is necessary(6). Person-centered care demands that drug interactions are more recognized and considered in decision-making, as well as in the prescription of drugs for patients with CVD[5,21].

Therefore, the inclusion of the pharmacist in the multidisciplinary team is an important contribution to the safe use of prescribed drugs[17,22]. Interventions led by pharmacists in hospitals, homes, outpatients clinics, and community settings, mostly involving CVD drugs, have been shown to contribute to a 35% reduction in ADR in the elderly[23]. In addition, the computerization of the prescription process using a program capable of detecting CR-DDI can be a tool to support clinical decisions[24,25]. In this sense, identifying CR-DDI and its negative outcomes contributes to the implementation of measures that aim to guarantee the effectiveness and safety of the prescribed therapy. In addition, the identification of factors associated with drug interactions allows directing measures to prevent adverse events in more exposed populations, such as those with multiple comorbidities.

The present study has as limitations the retrospective data collection (it may cause bias in the analysis of drug interactions due to the possibility of incomplete data in the medical records) and the fact that the study design does not allow establishing a causal relationship. In addition, there were only drug interactions and not the negative health outcomes of the individuals studied. The sample size and the fact that the sample is of convenience is another limitation of the study, restricting the generalization of the results. On the other hand, the identification of a high frequency of CR-DDI with statins in patients with CAD brings a contribution to clinical practice that can guide actions in the investigated clinic.

CONCLUSION

The occurrence of clinically relevant drug interactions with statins in patients with coronary artery disease showed a positive association with more than five diseases. The frequency of clinically relevant drug interactions with statins was high in patients with coronary artery disease. Simvastatin was the only statin that showed clinically relevant drug interactions and the most frequent interactions were with amlodipine and warfarin.

ABREVIATIONS AND SYMBOLS

REC-MG: Research Ethics Committee of the Federal University of Minas Gerais
CAD: Coronary Artery Disease
CVD: Cardiovascular Diseases
SD: Standard Deviation
SAH: Systemic Arterial Hypertension
AMI: Acute Myocardial Infarction
CI: Confidence interval
CR-DDI: Drug interactions of clinical relevance
IQR: Interquartile range
LDL: Low density lipoprotein
OR: Odds Ratio
ADR: Adverse Drug Reaction

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Received in february 2020.
Accepted in november 2020.