https://doi.org/10.53886/gga.e0000225_EN

ORIGINAL ARTICLE

Geriatrics, Gerontology and Aging

Drug-drug interactions in hospitalized older adults with acute coronary syndrome – a real-world study in Brazil

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Received on: July 17, 2024
Editor decisions on: Aug 29, 2024; Sept 13, 2024; Sept 24, 2024; Oct 13, 2024
Accepted on: Oct 17, 2024

Handling Editor: Márcio Galvão Oliveira

How to cite this article: Maschio-Lima TA, Godoy MF. Drug-drug interactions in hospitalized older adults with acute coronary syndrome – a real-world study in Brazil. Geriatr Gerontol Aging. 2024;18:e0000225. https://doi.org/10.53886/gga.e0000225_EN

Abstract

Objective: Our aim was to determine the frequency of drug-drug interactions in clinical practice among hospitalized older adults diagnosed with acute coronary syndrome.

Methods: This cross-sectional and descriptive study included 119 older adults with acute coronary syndrome who were admitted to a Brazilian public hospital. Potential drug-drug interactions were identified and classified using computerized databases. Adverse events were characterized according to severity, temporal relationship, causality, interactions as a determining factor, and traceability criteria.

Results: Of the total sample, 30.25% of participants had ≥1 real drug-drug interaction. A total of 53 real drug-drug interactions were identified. The median number of real drug-drug interactions was 1 (maximum 3) per patient; 5.56% of those who experienced real drug-drug interactions died and 94.44% were discharged from hospital. Of the real drug-drug interactions, 47.17% were moderate and 41.51% were serious.

Conclusions: Drug-drug interactions resulted in adverse reactions in hospitalized older adults with acute coronary syndrome in a real-world scenario in Brazil.

Keywords: older adults; acute coronary syndrome; drug-drug interactions; hospital.

INTRODUCTION

Interactions between prescribed medications, which have been amply documented in the literature, may or may not occur, requiring clinical and laboratory monitoring for detection and appropriate management.[1,2] Negative or harmful interactions result in reduced effectiveness of pharmacotherapy or adverse reactions, including deaths, increased costs, and safety risk. Thus, integrated action between pharmacists, physicians, and nurses is needed for adequate identification and management.[3,4]

Drug-drug interactions suspected of harming people can be classified as adverse events. An adverse event is any unfavorable occurrence while a medication is used, although it is not necessarily caused by the medication in question. An adverse drug reaction is any harmful and unwanted reaction that appears after normal doses of a drug are administered. Adverse events are only considered adverse reactions if causality is proven, ie, that the medication was deemed responsible for the reaction.[5,6]

Cardiovascular disease is a common life-threatening condition with high morbidity and mortality worldwide. Its most common form is coronary heart disease, with acute coronary syndrome being the most serious clinical manifestation. Acute coronary syndrome includes unstable angina and acute myocardial infarction with or without ST-segment elevation.[7]

As the population ages, the number of older adults affected by acute coronary syndrome increases. This population often has concomitant diseases and polypharmacy, and acute coronary syndrome further increases the number of prescribed medications, especially during hospitalization. This can cause pharmacotherapy-related problems, such as drug-drug interactions and adverse reactions.[8-11]

Considering that most studies only analyze potential and theoretical drug interactions in prescriptions, which may or may not occur, the aim of this study was to evaluate the real-world frequency of drug-drug interactions among hospitalized older adults diagnosed with acute coronary syndrome.

METHODS

This cross-sectional descriptive study was conducted in the cardiology unit of a large Brazilian public hospital, which is both a general and a teaching hospital (677 ward beds and 152 intensive care beds). Its cardiology unit is staffed by cardiologists and cardiology residents. By the time the study was completed, its cardiology unit still had no clinical pharmacist, although the present study was instrumental in changing this scenario.

The sample included 119 patients ≥ 60 years of age diagnosed with acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST-segment elevation) according to Brazilian guidelines who were hospitalized in the cardiology unit.[7] Participants with an inconclusive diagnosis of acute coronary syndrome (n = 21) were excluded from the study. We analyzed the medical records of each participant during the entire period of hospitalization in the clinical cardiology unit, between April and July 2020.

The Strengthening the Reporting of Observational Studies in Epidemiology recommendations were used to facilitate critical appraisal and interpretation of results. Data were collected through an adapted and validated tool according to the sample's profile (Appendix 1 – https://doi.org/10.5281/zenodo.14203674). Drug-drug interactions were identified in prescriptions using the Micromedex database, which is comprehensive and updated according to the best evidence. This database includes information on the mechanism (pharmacokinetic or pharmacodynamic), and the severity (mild: the interaction would have limited clinical effects and not require a major change in therapy; moderate: the interaction may result in an exacerbation of the patient's condition and/or require an change in therapy; serious: the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects).[12]

Adverse events were characterized according to severity, temporal relationship, causality, type of adverse drug reaction, interactions as a determining factor, and traceability criteria. The causality analysis was conducted using the Naranjo Adverse Drug Reaction Probability Scale Worksheet. This tool consists of 10 questions that are answered as Yes, No, or Unknown. Different point values (-1, 0, +1 or +2) are assigned to each answer, with total scores ranging from -4 to +13; the reaction is considered definite for scores ≥ 9 points, probable for 5-8 points, possible 1-4 points, and doubtful for ≤ 0 points.[13]

Adverse drug reactions were classified according to the Rawlins and Thompson system as Type A (dose-dependent reactions characterized by an increased drug effect that is predictable according to its pharmacological action) or Type B (unexpected dose-independent reactions that are not easily predictable pharmacologically).[14]

Hartwig's Severity Assessment Scale was used to assess the intensity of adverse drug reactions (Mild: self-limiting reactions that resolve over time without treatment; Moderate: reactions requiring treatment or increased length of hospital stay by least 1 day; Serious: life-threatening, causing permanent harm; Lethal: leading to death). The criteria for adverse reaction tracking were: digoxinemia, serum creatinine, glomerular filtration rate, serum potassium, electrocardiogram, heart rate, blood pressure, fall risk, signs and symptoms of rhabdomyolysis, creatine phosphokinase, signs and symptoms of bleeding, coagulation and platelet count, vitamin K prescription, and signs and symptoms of venous thromboembolism.

This study was approved by the research ethics committee (decision 2,274,053) in accordance with Brazilian National Health Council resolution 466/2012.

RESULTS

The sample consisted of 119 older adults diagnosed with of acute coronary syndrome who were hospitalized in a cardiology unit, 66 (55.46%) of whom were male. The median age was 70 (minimum 60, maximum 92) years. Hospitalization ranged from 2 to 25 days. The most frequent diagnosis was unstable angina (63.03%). Most patients received percutaneous transluminal coronary angioplasty (58.82%), whereas clinical treatment alone was recommended for 39.50%.

Of the total sample (n = 119), 36 (30.25%) participants had ≥ 1 (real) drug-drug interaction, 2 (5.56%) of whom died and 34 (94.44%) of whom were discharged from hospital. Table 1 provides a detailed description of participants with real drug-drug interactions. Of the 5348 potential drug-drug interactions identified by Micromedex among the analyzed prescriptions, 53 were considered real drug-drug interactions with proven clinical manifestations, in other words, real drug-drug interactions related to adverse events. The median number of proven real drug-drug interactions was 1 (minimum 1, maximum 3). Most of the real drug-drug interactions were moderate (47.17%) or serious (41.51%). Five real drug-drug interactions were classified as lethal, resulting in the deaths of 2 participants. The predominant mechanism of action of real drug-drug interactions was pharmacodynamic (n = 39; 73.58%) or pharmacokinetic (n = 14; 26.42%).

Adverse events confirmed as adverse reactions due to drug-drug interactions included psychomotor changes, bradycardia, bronchospasm, diarrhea, abdominal pain, hyperkalemia, hypokalemia, hyponatremia, postural hypotension, hemodynamic instability, nausea, nephrotoxicity, pyrosis, QT interval prolongation and arrhythmia, rhabdomyolysis, bleeding (gastrointestinal, hematoma and hematuria), and venous thromboembolism.

The drugs involved in adverse reactions due to drug-drug interactions were acetylsalicylic acid, amiodarone, atenolol, atorvastatin, bisoprolol, carvedilol, citalopram, clopidogrel, digoxin, enalapril, spironolactone, phenytoin, furosemide, heparin (low molecular weight), hydrochlorothiazide, losartan, nitroglycerin, and paracetamol.

Most adverse drug reactions were classified as Rawlins and Thompson Type A. The involved drugs included acetylsalicylic acid, amiodarone, atenolol, atorvastatin, bisoprolol, carvedilol, clopidogrel, digoxin, enalapril, furosemide, hydrochlorothiazide, heparin, losartan, nitroglycerine, phenytoin, and spironolactone. Table 2 provides a detailed description of the adverse reactions due to drug-drug interactions identified in the study.

TABLE 1. Demographic, clinical and pharmacotherapeutic characterization of older adults with real drug-drug interactions (n = 36).

Characteristics	Values
Number of older adults with real drug-drug interactions	36
Age (in years)	
Median age	73
Minimum age	62
Maximum age	92
Sex (%)	
Male	21 (58.33)
Female	15 (41.67)
Days of hospitalization in the coronary unit	
Median days of hospitalization	08
Minimum days of hospitalization	02
Maximum days of hospitalization	25
Diagnosis (%)	
Unstable angina	18 (50.00)
Acute myocardial infarction with ST elevation	12 (33.33)
Acute myocardial infarction without ST elevation	06 (16.67)
Type of treatment (%)	
Angioplasty	19 (52.78)
Only clinical	17 (47.22)
Total number of medications prescribed during hospitalization	3476
Median number of medications per prescription	13
Minimum number of medications per prescription	03
Maximum number of medications per prescription	22
Number of potential drug-drug interactions in the prescriptions	5348
Median number of potential interactions	136
Minimum potential interactions	09
Maximum potential interactions	434
Number of real drug-drug interactions	53
Median number of drug-drug interactions	01
Minimum drug-drug interactions	01
Maximum drug-drug interactions	03
Intensity of real drug-drug interactions (%)	
Mild	1 (1.89)
Moderate	25 (47.17)
Serious	22 (41.51)
Lethal	5 (9.43)
Outcome (%)	
Hospital discharge	34 (94.44)
In-hospital death	02 (5.56)

TABLE 2. Characterization of adverse reactions resulting from drug-drug interactions in older adults.

Adverse event	n	Related drug	Severity	Temporal relationship	Naranjo scale	Adverse drug reaction classification	Drug-drug interaction as a determining factor	Criterion of traceability
Psychomotor changes	1	Phenytoin	Serious	Plausible	Probable	Type A	Phenytoin X clopidogrel: increased toxicity of phenytoin due to enzymatic inhibition of cytochrome P450	Symptom monitoring
Psychomotor changes	1	Spironolactone	Serious	Plausible	Possible	Type B	Losartan X spironolactone: risk of hyperkalemia with psychomotor changes	Symptom monitoring
Bradycardia	1	Amiodarone	Moderate	Plausible	Probable	Type A	Amiodarone X atenolol: synergism, risk of cardiotoxicity with bradycardia	Electrocardiogram, heart rate monitoring
Bradycardia	1	Carvedilol	Lethal	Plausible	Possible	Type A	Carvedilol X omeprazole: increased the serum level and effect of carvedilol due to cytochrome P450 enzyme inhibition	Electrocardiogram, heart rate monitoring
Bronchospasm	1	Bisoprolol	Moderate	Plausible	Possible	Type A	Bisoprolol X salbutamol: antagonism and risk of bronchospasm	Symptom monitoring
Diarrhea	1	Digoxin	Moderate	Plausible	Definite	Type A	Digoxin X atorvastatin, carvedilol, enalapril, Spironolactone and omeprazole: increased the serum level and effect of digoxin (risk of digitalis poisoning)	Digoxinemia
Abdominal pain	1	Digoxin	Moderate	Plausible	Definite	Type A	Digoxin X atorvastatin, carvedilol, enalapril, Spironolactone and omeprazole: increased the serum level and effect of digoxin (risk of digitalis poisoning)	Digoxinemia
Hyperkalemia	4	Spironolactone	Serious	Plausible	Probable	Type A	Spironolactone X enalapril: risk of hyperkalemia	Serum potassium level
Hyperkalemia	1	Enalapril	Moderate	Plausible	Possible	Type A	Enalapril X heparin: risk of hyperkalemia	Serum potassium level
Hypokalemia	6	Furosemide	Moderate	Plausible	Possible	Type A	Furosemide X atenolol, bisoprolol, carvedilol: risk of hypokalemia	Serum potassium dosage
Hypokalemia	1	Furosemide	Lethal	Plausible	Possible	Type A	Furosemide X hydrocortisone: risk of hypokalemia	Serum potassium level
Hypokalemia	1	Furosemide	Moderate	Plausible	Possible	Type A	Furosemide X prednisone: risk of hypokalemia	Serum potassium level
Hyponatremia	1	Hydrochlorothiazide	Moderate	Plausible	Possible	Type A	Hydrochlorothiazide X citalopram: increased risk of hyponatremia	Serum sodium level
Postural hypotension	1	Nitroglycerine	Moderate	Plausible	Possible	Type A	Nitroglycerin X enalapril, fentanyl, midazolam: additive effects on blood pressure and risk of postural hypotension	Blood pressure monitoring and risk assessment
Hemodynamic instability	2	Nitroglycerine	Lethal	Plausible	Possible	Type A	Nitroglycerin X acetylsalicylic acid, enalapril, furosemide: increased the hypotensive effect of nitroglycerin	Blood pressure monitoring

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TABLE 2. Continuation.

Adverse event	n	Related drug	Severity	Temporal relationship	Naranjo scale	Adverse drug reaction classification	Drug-drug interaction as a determining factor	Criterion of traceability
Nauseas	1	Digoxin	Mild	Plausible	Definite	Type A	Digoxin X atorvastatin, carvedilol, enalapril, spironolactone and omeprazole: increased the serum level and effect of digoxin (risk of digitalis poisoning)	Digoxinemia
Nephrotoxicity	2	Enalapril	Serious	Plausible	Probable	Type A	Enalapril X spironolactone: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	2	Enalapril	Moderate	Plausible	Possible	Type A	Enalapril X hydrochlorothiazide: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	1	Enalapril	Lethal	Plausible	Possible	Type A	Enalapril X furosemide: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	1	Enalapril	Serious	Plausible	Possible	Type A	Enalapril X furosemide: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	1	Enalapril	Moderate	Plausible	Possible	Type A	Enalapril X furosemide: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	1	Furosemide	Moderate	Plausible	Possible	Type A	Furosemide X nimodipine: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	1	Losartan	Serious	Plausible	Probable	Type B	Losartan X spironolactone: risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
Nephrotoxicity	2	Losartan	Moderate	Plausible	Possible	Type A	Losartan X omeprazole: omeprazole increased the serum level of losartan due to cytochrome P450 enzyme inhibition, which increased the risk of nephrotoxicity	Measurement of serum creatinine and glomerular filtration rate
QT prolongation and arrhythmia	1	Bisoprolol	Serious	Plausible	Probable	Type A	Bisoprolol X amlodipine, furosemide increased the QT interval, while amlodipine increased the serum level of bisoprolol due to cytochrome P450 enzyme inhibition	Electrocardiography
QT prolongation and arrhythmia	1	Amiodarone	Serious	Plausible	Probable	Type A	Amiodarone X formoterol, furosemide, salbutamol: risk of QT prolongation and arrhythmias	Electrocardiography
QT prolongation and arrhythmia	2	Atenolol	Serious	Plausible	Possible	Type A	Atenolol X hydrochlorothiazide: risk of QT prolongation and arrhythmias	Electrocardiography
Pyrosis	1	Paracetamol	Moderate	Plausible	Possible	Type B	Paracetamol X metoclopramide: metoclopramide increases gastric emptying, leading to increased paracetamol absorption	Symptom monitoring

Continue...

TABLE 2. Continuation.

Adverse event	n	Related drug	Severity	Temporal relationship	Naranjo scale	Adverse drug reaction classification	Drug-drug interaction as a determining factor	Criterion of traceability
Pyrosis	1	Acetylsalicylic acid	Moderate	Plausible	Possible	Type A	Acetylsalicylic acid X metoclopramide: metoclopramide increased gastric emptying, leading to increased absorption of acetylsalicylic acid	Symptom monitoring
Rhabdomyolyses	1	Atorvastatin	Moderate	Plausible	Possible	Type A	Atorvastatin X clarithromycin: increased statin toxicity due to cytochrome P450 enzyme inhibition	Monitoring signs and symptoms of rhabdomyolysis and laboratory assessment of creatine phosphokinase
Rhabdomyolyses	1	Atorvastatin	Moderate	Plausible	Possible	Type A	Atorvastatin X diltiazem, omeprazole: increased statin toxicity due to cytochrome P450 enzyme inhibition	Monitoring signs and symptoms of rhabdomyolysis and laboratory assessment of creatine phosphokinase
Bleeding (high digestive bleeding)	1	Heparin (low molecular weight)	Serious	Plausible	Definite	Type A	Heparin X acetylsalicylic acid, clopidogrel: increased anticoagulant/antiplatelet activity and bleeding risk	Monitoring signs and symptoms of bleeding, laboratory evaluation of coagulation and platelet count, vitamin K prescription
Bleeding (hematuria)	2	Heparin (low molecular weight)	Serious	Plausible	Definite	Type A	Heparin X acetylsalicylic acid, clopidogrel: increased anticoagulant/antiplatelet activity and bleeding risk	Monitoring signs and symptoms of bleeding, laboratory evaluation of coagulation and platelet count, vitamin K prescription
Bleeding (enterorrhagia)	2	Acetylsalicylic acid	Serious	Plausible	Probable	Type B	Acetylsalicylic acid X diltiazem: increased bleeding risk	Monitoring signs and symptoms of bleeding, laboratory evaluation of coagulation and platelet count, vitamin K prescription
Local bleeding (hematoma)	1	Citalopram	Serious	Plausible	Probable	Type B	Citalopram X acetylsalicylic acid, clopidogrel and enoxaparin: citalopram reduced platelet activity and increased bleeding risk	Monitoring signs and symptoms of bleeding, laboratory evaluation of coagulation and platelet count, vitamin K prescription
Local bleeding (hematoma)	1	Heparin (low molecular weight)	Moderate	Plausible	Definite	Type A	Heparin X acetylsalicylic acid, clopidogrel: increased anticoagulant/antiplatelet activity and bleeding risk	Monitoring signs and symptoms of bleeding, laboratory evaluation of coagulation and platelet count, vitamin K prescription
Thromboembolism	2	Clopidogrel	Serious	Plausible	Probable	Type A	Clopidogrel X omeprazole/atorvastatin: omeprazole/atorvastatin inhibited activation of clopidogrel (prodrug) for cytochrome P450 enzyme inhibition. Reduced platelet aggregation and increased thrombosis risk	Monitoring signs and symptoms of thromboembolism, laboratory evaluation of coagulation and platelet count

DISCUSSION

It should be noted that some drug interactions can optimize pharmacotherapy and lead to better health outcomes. Monitoring drug-drug interactions, assessing their risks and benefits, and managing drug-drug interactions that result in adverse drug reactions are essential in clinical practice.[1-6]

Hyperkalemia is an important adverse reaction caused by drug-drug interactions, increasing the risk of cardiac arrhythmia and serious consequences, mainly in individuals with acute coronary syndrome.[15] In the present study, hyperkalemia was caused by interactions between potassium-sparing diuretics and angiotensin-converting enzyme inhibitors. This combination should be avoided in older adults, especially those with renal impairment. Frequent monitoring of the patient's serum potassium levels and glomerular filtration rate is necessary.[16]

Postural hypotension and hemodynamic instability involving nitroglycerin and other drug classes that have additive effects on blood pressure (acetylsalicylic acid, enalapril, fentanyl, furosemide, and midazolam) were also observed. Strict blood pressure monitoring is needed when nitroglycerin is associated with other classes of hypotensive drugs.[17]

Gastrointestinal bleeding, hematuria, and hematoma were observed in these drug classes. Interactions involving dual antiplatelet therapy (low-dose acetylsalicylic acid and clopidogrel) and anticoagulants (unfractionated heparin and low molecular weight heparin) led to an increased risk of bleeding. Signs of bleeding in the gums, urine, feces, in addition to skin bruises, should be frequently monitored.[18]

Modern management of acute coronary syndrome includes associations of antithrombotic drugs and invasive procedures that increase the risk of bleeding to a variable degree. Dual antiplatelet therapy reduces the risk of stent thrombosis, but continuing it for up to 1 year after percutaneous coronary intervention or myocardial infarction has the greatest benefits. However, because the risk of bleeding in dual antiplatelet therapy is proportionally related to its duration, decisions about treatment duration should be dynamic and reevaluated during the therapeutic regimen.[19,20]

In people with acute coronary syndrome, regardless of the revascularization strategy, standard dual antiplatelet therapy lasts for ≥ 12 months. Six-month therapy should be considered in patients at elevated risk of bleeding, while therapy > 12 months can be considered in tolerant people without bleeding complications.[7]

There is also evidence of increased bleeding risk due to interactions between dual antiplatelet therapy drugs and those used to treat other comorbidities (eg, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, corticosteroids, and drugs that may interfere with metabolism of antiplatelet agents). Therefore, caution is required when prescribing new medications for people with acute coronary syndrome. When bleeding occurs, the ongoing bleeding risk should be analyzed and antiplatelet agents should be reduced or temporary discontinued, being briefly restarted, whenever possible, to avoid recurrent ischemia and infarction.[21,22]

Citalopram, a selective serotonin reuptake inhibitor, was also involved in interactions in acute coronary syndrome patients. The isolated use of selective serotonin reuptake inhibitors has been associated with an increased risk of bleeding. Platelets release serotonin at sites of vascular injury but do not synthesize it; they retrieve it from blood and store it. Hence, the fact that selective serotonin reuptake inhibitors also inhibit serotonin transporters is considered to be the cause of the increased bleeding risk. There is an elevated risk of bleeding when treating concomitant disease after acute myocardial infarction in patients using acetylsalicylic acid and after acute coronary syndrome in patients using a selective serotonin reuptake inhibitor. In such cases, replacement with an antidepressant class that does not act on the serotonergic pathway is recommended.[23,24]

On the other hand, inhibition of clopidogrel activation by enzyme inhibitors (omeprazole and atorvastatin) was related to the 2 cases of thromboembolic events in this study. Clopidogrel, a prodrug, is converted into its active form through first-pass hepatic metabolism via cytochrome P450 isoenzymes (CYP3A4, CYP3A5 and CYP2C19). Antiplatelet effects may be reduced in drugs that inhibit the activity of these isoenzymes, and the risk of thromboembolic events may increase. Proton pump inhibitors, such as omeprazole, are enzyme inhibitors. To avoid this type of interaction, proton pump inhibitors with lower enzyme inhibitory activity, such as pantoprazole, are suggested.[24,25]

Both clopidogrel and some statins (eg, simvastatin, atorvastatin, and lovastatin) are metabolized via CYP3A4. However, studies of people with acute coronary syndrome found that the clinical efficacy of clopidogrel was not reduced when used concomitantly with statins.[26]

In the present study, serious adverse reactions involved interactions between drugs that can prolong the QT interval, causing arrhythmia or bradycardia (amiodarone, beta-blockers, beta-agonists, calcium channel blockers, thiazide, and loop diuretics). The probable mechanism of these interactions involves synergism or enzymatic inhibition of cytochrome P450, thus increasing the serum level of the other drug.[27]

People with acute coronary syndrome are particularly exposed to adverse reactions in the cardiovascular system due to drug-drug interactions that cause prolongation of the QT interval, arrhythmias, excessive bradycardia, and severe hypotension. Therefore, in patients receiving a combination of drugs that increases the

risk of these adverse effects, monitoring of serum electrolyte levels, blood pressure, and electrocardiography is necessary.[28]

Although the risk of myopathies is lower for atorvastatin than simvastatin, a combination of cytochrome P450 enzyme inhibitor drugs increases the serum level of atorvastatin, thus increasing the risk of myopathy. In the present study, interactions between enzyme inhibitors (clarithromycin, diltiazem, and omeprazole) resulted in rhabdomyolysis. Monitoring for signs and symptoms of rhabdomyolysis and laboratory evaluation of creatine phosphokinase is necessary, even after discharge. If creatine phosphokinase increases due to atorvastatin, the enzyme inhibitor drugs involved in the interaction should be suspended.[29]

Regarding Type A adverse drug reactions, ie, those with dose-dependent reactions according to the Rawlins and Thompson system, the dose must be adjusted to achieve the best therapeutic effectiveness while minimizing adverse reactions. Another way of managing these drugs is by monitoring the plasma concentrations. However, this method is not available for all drugs and incurs high costs to health services.[1,10,14]

Factors associated with drug-drug interactions and adverse drug reactions should be identified to prevent drug-related problems. To this end, including a clinical pharmacist in the multidisciplinary health team for pharmacotherapeutic follow-up of hospitalized patients is essential to guarantee rational and safe pharmacotherapy.[30]

The health conditions of older adults hospitalized for acute coronary syndrome should be assessed, followed by analysis of pharmacotherapy and the risk of potential drug-drug interactions. The traceability criteria must then be defined. Analysis of interactions involving medications that are potentially inappropriate for older adults and medications with a low safety margin should be prioritized due to the greater risk of adverse reactions. In conjunction with the prescriber, pharmacotherapy must be managed to prevent drug-drug interactions, thus avoiding ineffective pharmacotherapy, adverse reactions, or the worsening of adverse reactions.

The present study's limitations include incomplete information in some of the medical records, which impeded notification of adverse drug reactions. Due to methodological difficulties related to studies on drug-drug interactions, therapeutic ineffectiveness was not verified, which may have led to underestimating the frequency of interactions in the sample. The non-probabilistic sample is a further study limitation. Furthermore, the analysis of drug-drug interactions and adverse drug reactions is subject to confounding factors.

CONCLUSION

This study demonstrated that real drug-drug interactions are frequent in pharmacotherapy for hospitalized older adults with acute coronary syndrome and, in a real-world Brazilian hospital setting, were responsible for adverse drug reactions in a third of the sample.

Monitoring, identifying, and managing drug-drug interactions are essential to avoid complications arising from adverse reactions due to interactions among common drugs in the pharmacotherapy of older adults hospitalized with acute coronary syndrome. Further real-world studies on the effects of drug-drug interactions in clinical practice are recommended, particularly in hospitalized older adults, including strategies such as tool enhancement, continuing education, multidisciplinary collaboration, and monitoring protocols.

DECLARATIONS

Conflict of interest
The authors declare no conflicts of interest.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contribution
Tiago Aparecido Maschio de Lima: conceptualization, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review & editing. Moacir Fernandes de Godoy: conceptualization, methodology, supervision, validation, visualization, writing – review & editing.

Ethical approval and informed consent
This study was approved by the São José do Rio Preto Faculty of Medicine Research Ethics Committee (number 2 274 053) in accordance with National Health Council resolution 466/2012.

Data availability statement
The data underlying this research are included in the manuscript.

Reporting standards guidelines
This study was conducted and reported following the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

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