Potential Drug–Drug Interactions in Medical Records of Patients With Atherosclerosis

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ABSTRACT

Background: Atherosclerosis is a cardiovascular disease that often requires combination pharmacotherapy, which may result in potential drug–drug interactions (pDDIs). Identifying pDDIs is important to support safe and effective medication use. This study aimed to evaluate potential drug–drug interactions based on the medical records of patients with atherosclerosis. **Methods:** This descriptive retrospective study used a purposive sampling technique. Medical records of patients with atherosclerosis who met the inclusion criteria were reviewed. Potential drug–drug interactions were identified using Medscape, Drugs.com, and verified with *Stockley's Drug Interactions*, 12th edition. **Results:** Among 71 patients, 14 (19.72%) had at least one potential drug–drug interaction. A total of 14 potential interaction pairs were identified, with the aspirin–ramipril combination being the most frequent, accounting for 8 of the 14 interaction pairs (57.14%). **Conclusion:** Potential drug–drug interactions were identified among hospitalized patients with atherosclerosis, with aspirin–ramipril being the most frequent interaction. Although the identified interactions were potential rather than clinically confirmed events, the findings highlight the importance of medication review and appropriate therapy monitoring to support patient safety.

Keywords: atherosclerosis; potential drug–drug interactions; medical records; drug-related problems; retrospective study

INTRODUCTION

Atherosclerosis is a cardiovascular disease characterized by the formation of plaques within the arterial wall due to the accumulation of lipids, cholesterol, and other substances, resulting in arterial narrowing and impaired blood flow (1). It is one of the leading causes of coronary artery disease and stroke, contributing substantially to global morbidity and mortality (2). The management of patients with atherosclerosis generally requires combination therapy, including antiplatelet agents, antihypertensive drugs, lipid-lowering agents, and other supportive medications (3). The concurrent use of multiple medications may increase the risk of Drug-Related Problems (DRPs), particularly drug interactions that can affect the effectiveness and safety of pharmacotherapy (4).

Drug interactions are defined as changes in the effects of a drug caused by the concomitant use of another drug, which may result in either beneficial or harmful outcomes (5). The risk of drug interactions is higher among patients receiving polypharmacy, especially those with cardiovascular diseases who often require multiple medications for long-term treatment (6). Unrecognized drug interactions may reduce therapeutic efficacy, increase drug toxicity, and worsen patients' clinical conditions. Previous studies have reported a high prevalence of potential drug interactions among patients with coronary artery disease receiving combination pharmacotherapy (4).

The evaluation of potential drug interactions can be performed through retrospective analysis of patients' medical records using reliable drug interaction references such as Medscape, Drugs.com, and Stockley's Drug Interactions. This evaluation plays an important role in preventing adverse outcomes associated with pharmacotherapy. Islamiyah et al. (2020) reported that polypharmacy among patients attending a cardiac clinic was associated with a high prevalence of potential drug interactions, highlighting the need for routine therapeutic monitoring to improve medication safety (7). Other studies have also demonstrated that the concomitant use of

antihypertensive agents and other cardiovascular medications may result in drug interactions with moderate to major severity (8).

In line with recent research developments, numerous studies have highlighted that evaluating potential drug interactions remains an important concern in patients with cardiovascular diseases because of the widespread use of combination therapy and the increasing prevalence of polypharmacy. Most published studies have focused on patients with coronary artery disease, hypertension, heart failure, or mixed cardiovascular populations, with the majority of identified interactions classified as moderate in severity and requiring clinical monitoring. These findings emphasize that early identification of potential drug interactions is essential for improving patient safety and optimizing therapeutic outcomes (9).

Nevertheless, studies specifically evaluating potential drug interactions among patients with atherosclerosis remain limited. Most previous investigations have combined various cardiovascular diagnoses into a single study population, making it difficult to characterize the specific patterns of potential drug interactions in patients with atherosclerosis. Furthermore, limited evidence is available regarding the evaluation of interaction severity, underlying mechanisms, and clinical monitoring recommendations in this patient population. These limitations indicate the need for further studies that provide a more comprehensive assessment of potential drug interactions among patients with atherosclerosis.

Based on these considerations, the novelty of the present study lies in evaluating potential drug–drug interactions among patients with atherosclerosis using retrospective medical record data and multiple established drug interaction references. The study describes the identified potential interaction pairs, their mechanisms, and their potential clinical implications to provide a comprehensive overview of potential drug–drug interactions in this patient population. The findings are expected to support pharmacists in medication review, therapeutic monitoring, prevention of Drug-Related Problems (DRPs), and improvement of medication safety. Therefore, this study aimed to evaluate potential drug–drug interactions based on the medical records of patients with atherosclerosis to provide evidence for safer and more effective pharmacotherapy in clinical practice.

METHODS

This study employed a descriptive retrospective design using medical records of patients diagnosed with atherosclerosis. The study was conducted in the inpatient department of Dr. Moewardi Regional General Hospital, Surakarta, over a three-month period to identify and evaluate potential drug–drug interactions associated with prescribed pharmacotherapy. The study population consisted of all hospitalized patients diagnosed with atherosclerosis at Dr. Moewardi Regional General Hospital, Surakarta. Samples were selected using purposive sampling. Medical records meeting the predefined inclusion criteria were consecutively included until the study period was completed. A total of 71 medical records fulfilled the eligibility criteria and were included in the analysis.

The inclusion criteria were patients aged >40 years who were diagnosed with atherosclerosis and hospitalized at Dr. Moewardi Regional General Hospital, Surakarta, with complete medical records containing patient identification number, diagnosis, age, body weight, prescribed medications, dosage, route of administration, dosing schedule, and length of hospital stay. Secondary data were obtained from patients' medical records. The collected data included demographic characteristics (age and sex), diagnosis, comorbidities, length of hospital stay, and all medications prescribed during hospitalization. These data were used to describe the characteristics of the study population and to identify potential drug–drug interactions.

Data were collected through a structured review of eligible medical records using a standardized data collection form. Potential drug–drug interactions were screened using the Medscape Drug Interaction Checker and Drugs.com Drug Interaction Checker and subsequently verified using Stockley's Drug Interactions, 12th edition, as the primary reference. When discrepancies occurred between the electronic databases, the information provided in *Stockley's Drug Interactions* was used as the final reference. The unit of analysis was the type of potential drug–drug interaction identified among the prescribed medications. The frequency of each interaction was calculated based on the number of patients in whom the potential interaction occurred. The collected data were edited, coded, tabulated, and analyzed descriptively. Frequencies and percentages were calculated to describe patient characteristics and the identified potential drug–drug interaction pairs. The findings are presented in tables and descriptive narratives to facilitate data interpretation.

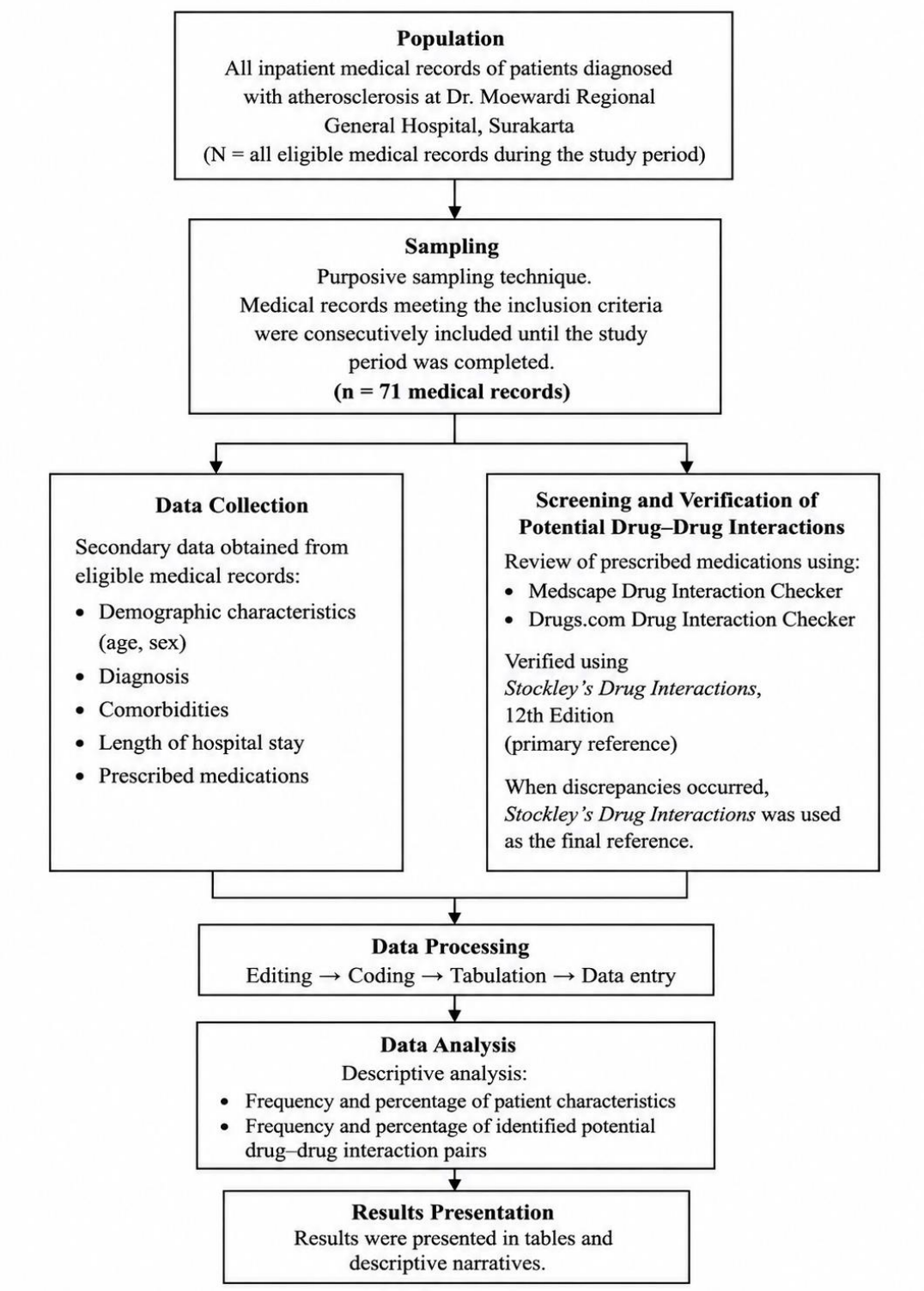

Figure 1. Research Stages Flowchart

RESULTS

Patient Characteristics

A total of 71 medical records of patients with atherosclerosis that met the inclusion criteria were included in this study. Patient characteristics comprised sex and age. These characteristics are presented to provide an overview of the study population prior to the identification of potential drug–drug interactions.

Table 1. Sex Distribution of Patients

No.	Patient Characteristics	Number of Patients (n)	Percentage (%)
1	Male	57	80.28
2	Female	14	19.72
	Total	**71**	**100**

Table 2. Age Sex Distribution of Patients

No.	Age Group	Number of Patients (n)	Percentage (%)
1	Early adulthood (35–45 years)	3	4.22
2	Late adulthood (46–55 years)	9	12.68
3	Elderly (56–65 years)	41	57.75
4	Older elderly (>65 years)	18	25.35
	Total	**71**	**100**

Comorbidities

Patients with atherosclerosis frequently presented with one or more comorbid conditions that may influence pharmacological treatment and increase the complexity of medication management. The distribution of comorbidities among the study population is presented in Table 3.

Table 3. Distribution of Atherosclerosis Patients According to Comorbidities

No.	Comorbidity	Number of Cases (n)	Percentage (%)
1	Hypertension	23	25.57
2	Diabetes Mellitus	22	24.45
3	Heart Failure	19	21.11
4	Angina Pectoris	6	6.67
5	Hyperuricemia	4	4.44
6	Chronic Obstructive Pulmonary Disease (COPD)	3	3.33
7	Pneumonia	3	3.33
8	Renal Failure	3	3.33
9	Hypoglycemia	1	1.11
10	Cirrhosis	1	1.11
11	Nephrolithiasis	1	1.11
12	Dyspepsia	1	1.11
13	Left Lung Tumor	1	1.11
14	Asthma	1	1.11
15	Acute Pulmonary Edema	1	1.11
	Total	**90**	**100**

Drug Utilization Profile

The prescribed medications for patients with atherosclerosis were analyzed according to therapeutic class, pharmacological class, and individual drug prescribed during hospitalization. This analysis provides an overview of the pharmacological treatment received by the patients and serves as the basis for identifying potential drug–drug interactions. The distribution of prescribed medications is presented in Table 4.

Table 4. Drug Utilization Profile Among Patients With Atherosclerosis

No.	Therapeutic Class	Pharmacological Class	Drug	Frequency (n)	Percentage (%)
1	Antihypertensive	ARB	Candesartan	12	5.80
			Diovan	11	5.31
			Cordarone	3	1.45

No.	Therapeutic Class	Pharmacological Class	Drug	Frequency (n)	Percentage (%)
		ACEI	Captopril	6	2.90
			Ramipril	12	5.80
		CCB	Amlodipine	9	4.34
		Beta-blocker	Propranolol	4	1.93
			Concor	4	1.93
2	Antiplatelet	-	Aspilet	39	18.84
			Miniaspi	6	2.90
			Thrombo Aspilet	2	0.97
			Clopidogrel	41	19.80
			Platogrix	1	0.49
3	Anticoagulant	-	Warfarin	1	0.49
			Tranexamic acid	3	1.45
			Kalnex	1	0.49
			Simarc	5	2.41
4	Antihyperlipidemic	Statin	Simvastatin	36	17.39
			Atorvastatin	11	5.31
		Total		**207**	**100**

Prevalence of Potential Drug–Drug Interactions

Potential drug–drug interactions were identified by reviewing all prescribed medications using Medscape Drug Interaction Checker and Drugs.com Drug Interaction Checker, with verification based on *Stockley's Drug Interactions*, 12th edition. Among the 71 hospitalized patients included in the study, 14 patients (19.72%) had at least one identified potential drug–drug interaction, whereas 57 patients (80.28%) had no identified potential drug–drug interactions. The prevalence of potential drug–drug interactions among hospitalized patients with atherosclerosis is presented in Table 5.

Table 5. Prevalence of potential drug–drug interactions among hospitalized patients with atherosclerosis

Category	Number of Patients (n)	Percentage (%)
Patients with at least one potential drug–drug interaction	14	19,72
Patients without potential drug–drug interactions	57	80,28
Total	**71**	**100**

Type of Potential Drug–Drug Interactions

Among the 14 patients with identified potential drug–drug interactions, five distinct types of potential drug–drug interactions were identified. The frequency of each interaction type was calculated based on the number of patients in whom the interaction was identified. The identified potential drug–drug interactions, their frequencies, percentages, interaction mechanisms, severity classifications, and recommended monitoring are presented in Table 6.

Table 6. Types and frequency of potential drug–drug interactions identified among patients with atherosclerosis

No.	Potential Drug–Drug Interaction	Interaction Mechanism	Severity	Recommended Monitoring	Number of Patients (n)	Percentage (%)
1	Aspirin × Ramipril	Pharmacodynamic	Moderate–Major	Monitor renal function, serum creatinine, blood pressure	8	57.14

No.	Potential Drug–Drug Interaction	Interaction Mechanism	Severity	Recommended Monitoring	Number of Patients (n)	Percentage (%)
2	Aspirin × Captopril	Pharmacodynamic	Moderate	Monitor blood pressure and renal function	3	21.43
3	Simvastatin × Amlodipine	Pharmacokinetic	Moderate	Monitor muscle symptoms and creatine kinase if indicated	1	7.14
4	Azithromycin × Warfarin	Pharmacokinetic	Moderate	Monitor INR and signs of bleeding	1	7.14
5	Furosemide × Digoxin	Pharmacodynamic	Moderate	Monitor serum potassium and signs of digoxin toxicity	1	7.14
Total					**14**	**100**

DISCUSSION

In the present study, male patients accounted for the majority of hospitalized patients with atherosclerosis (80.28%), whereas female patients represented only 19.72%. This finding is consistent with the epidemiology of atherosclerotic cardiovascular disease, in which men generally develop atherosclerosis earlier than women because of differences in sex hormones, endothelial function, lipid metabolism, and inflammatory responses. Premenopausal women are relatively protected by the vasoprotective effects of estrogen, whereas this protective effect declines after menopause, resulting in a progressive increase in cardiovascular risk (10). Furthermore, sex-related differences in plaque characteristics and vascular remodeling contribute to the higher prevalence and earlier clinical manifestation of atherosclerosis in men compared with women (11).

Patients aged 56–65 years constituted the largest age group (57.75%), followed by those aged >65 years (25.35%). This finding reflects the progressive nature of atherosclerosis, which develops over decades as a result of cumulative exposure to cardiovascular risk factors, endothelial dysfunction, chronic inflammation, oxidative stress, and vascular aging. Increasing age is recognized as one of the strongest non-modifiable risk factors for atherosclerotic cardiovascular disease because age-related vascular remodeling promotes arterial stiffness and progressive plaque formation, thereby increasing the likelihood of hospitalization in older adults (12).

Hypertension was the most common comorbidity among patients with atherosclerosis (25.57%), followed by diabetes mellitus (24.45%) and heart failure (21.11%). These findings are consistent with the pathophysiology of atherosclerotic cardiovascular disease, in which hypertension accelerates endothelial injury and plaque progression, while diabetes promotes chronic inflammation, oxidative stress, and vascular dysfunction, thereby increasing the burden of atherosclerosis (13). Hypertension and diabetes frequently coexist in patients with atherosclerosis and substantially increase the risk of adverse cardiovascular outcomes, including the development of heart failure, emphasizing the need for comprehensive cardiovascular risk management (14). The high proportion of heart failure observed in this study is also clinically relevant because multimorbidity is common among hospitalized cardiovascular patients, and the presence of multiple comorbid conditions is associated with poorer prognosis, greater therapeutic complexity, and increased medication use (15). The coexistence of multiple comorbidities frequently necessitates combination pharmacotherapy, thereby increasing the likelihood of potential drug–drug interactions in hospitalized patients (16).

The pharmacological management of patients with atherosclerosis in this study primarily consisted of antiplatelet agents, antihypertensive drugs, and lipid-lowering agents, reflecting current evidence-based strategies for reducing recurrent cardiovascular events and slowing the progression of atherosclerotic disease. Antiplatelet agents were the most frequently prescribed medications, with clopidogrel and aspirin accounting for the largest proportion of prescriptions, consistent with current recommendations that emphasize antiplatelet therapy as a cornerstone of secondary prevention in patients with established atherosclerotic cardiovascular disease (17). Antihypertensive agents, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and β-blockers, were also widely prescribed because blood pressure control is essential for reducing endothelial injury, limiting atherosclerotic plaque progression, and preventing subsequent cardiovascular complications (18). Statins represented the predominant lipid-lowering

therapy, which is in accordance with contemporary clinical evidence identifying statins as the first-line treatment for lowering low-density lipoprotein cholesterol (LDL-C), stabilizing atherosclerotic plaques, and reducing major adverse cardiovascular events in patients with atherosclerotic cardiovascular disease (19). The concurrent use of multiple cardiovascular medications observed in this study reflects the complexity of managing patients with atherosclerosis and may increase the likelihood of potential drug–drug interactions, highlighting the importance of medication review and therapeutic monitoring during hospitalization (20).

In the present study, 14 of 71 hospitalized patients (19.72%) had at least one identified potential drug–drug interaction (pDDI). This prevalence was considerably lower than that reported in previous studies involving hospitalized patients with cardiovascular diseases, in which the prevalence of pDDIs ranged from approximately 42% to over 90%, depending on the study population, prescribing patterns, interaction screening database, and criteria used to define clinically relevant interactions (21). The relatively lower prevalence observed in the present study may be explained by differences in patient characteristics, disease severity, medication regimens, and prescribing practices. In particular, polypharmacy remains one of the strongest predictors of potential drug–drug interactions among hospitalized patients (22). Recent observational studies have also shown that the prevalence of potential drug–drug interactions among hospitalized patients remains high and is influenced by patient characteristics, polypharmacy, comorbidities, and prescribing practices. These findings emphasize the importance of routine medication review and the use of validated drug interaction screening tools to improve medication safety during hospitalization (23). Therefore, the findings of this study should be interpreted as describing the prevalence of potential drug–drug interactions identified through screening of prescribed medications rather than clinically confirmed drug interaction events.

In the present study, the aspirin–ramipril combination was the most frequently identified potential drug–drug interaction, occurring in 8 of the 14 patients (57.14%) with identified potential drug–drug interactions. This predominance is expected because aspirin is widely prescribed as an antiplatelet agent for secondary prevention of atherosclerotic cardiovascular disease, whereas ramipril is commonly used to control hypertension and reduce cardiovascular risk in patients with concomitant cardiovascular disorders. The frequent concomitant use of these agents consequently increases the likelihood of identifying this potential interaction (24). The interaction is pharmacodynamic in nature, as aspirin inhibits cyclooxygenase-mediated prostaglandin synthesis, whereas ramipril exerts part of its therapeutic effect through prostaglandin- and bradykinin-mediated vasodilation. Consequently, concomitant use may attenuate the antihypertensive effect of ramipril and reduce renal perfusion, particularly in susceptible patients such as older adults or those with impaired renal function. Current evidence indicates that the clinical significance of this interaction depends on aspirin dosage and patient-specific risk factors. Low-dose aspirin, which is commonly prescribed for cardiovascular prevention, is generally not considered a contraindication to ACE inhibitor therapy; however, regular monitoring of blood pressure and renal function is recommended, especially during prolonged treatment or in patients with chronic kidney disease, heart failure, or dehydration (25). Therefore, the present findings should be interpreted as potential drug–drug interactions identified through medication screening rather than clinically confirmed interaction events, and further clinical assessment is required to determine their actual impact on patient outcomes.

In addition to aspirin–ramipril, the aspirin–captopril combination was identified in 3 of the 14 patients (21.43%) with potential drug–drug interactions, making it the second most frequent interaction observed in this study. Similar findings have been reported in studies evaluating potential drug–drug interactions using multiple interaction databases, including *Stockley's Drug Interactions*, in which combinations of aspirin with ACE inhibitors were consistently classified as clinically relevant interactions requiring close monitoring rather than routine avoidance (26). This interaction is pharmacodynamic in nature because aspirin may inhibit cyclooxygenase-mediated prostaglandin synthesis, thereby attenuating the vasodilatory and antihypertensive effects of captopril, particularly in patients with impaired renal function, heart failure, or volume depletion (27). Nevertheless, available evidence suggests that low-dose aspirin (<300 mg/day), which is commonly prescribed for secondary cardiovascular prevention, has minimal influence on the antihypertensive efficacy of captopril, whereas higher aspirin doses are more likely to reduce the therapeutic response of ACE inhibitors (28). These findings emphasize the need for individualized clinical monitoring when aspirin and captopril are prescribed concomitantly.

Another potential drug–drug interaction identified in this study was the simvastatin–amlodipine combination, which was observed in 1 of the 14 patients (7.14%) with potential drug–drug interactions. Although this interaction was infrequent, it remains clinically relevant because simvastatin and amlodipine are commonly co-prescribed in patients with atherosclerotic cardiovascular disease to manage dyslipidemia and hypertension. Previous studies evaluating potential drug–drug interactions have also identified this combination as a clinically significant interaction requiring dose consideration and appropriate monitoring (29). This interaction is pharmacokinetic in nature because simvastatin is extensively metabolized by CYP3A4, whereas amlodipine may inhibit CYP3A4-mediated metabolism, resulting in increased simvastatin plasma concentrations and an increased risk of statin-

associated muscle toxicity, including myopathy and, in rare cases, rhabdomyolysis (30). Current clinical guidelines recommend that the daily dose of simvastatin should not exceed 20 mg when co-administered with amlodipine, and patients should be monitored for signs and symptoms of statin-associated muscle toxicity (31,32).

Another less common potential drug–drug interaction identified in this study was the azithromycin–warfarin combination, which occurred in 1 of the 14 patients (7.14%) with potential drug–drug interactions. Although infrequent, this interaction is clinically relevant because azithromycin may enhance the anticoagulant effect of warfarin, thereby increasing the risk of bleeding in susceptible patients (29). The proposed mechanism is thought to involve disruption of intestinal vitamin K-producing flora, leading to reduced vitamin K availability, together with possible alterations in warfarin metabolism. These mechanisms may enhance the anticoagulant effect of warfarin and increase the international normalized ratio (INR) during concomitant therapy (33). Current clinical guidelines recommend routine INR monitoring and careful clinical assessment for bleeding complications when warfarin is prescribed concomitantly with interacting medications, particularly in older adults and those receiving long-term anticoagulant therapy (34). Consequently, careful INR monitoring is advisable whenever these agents are administered together.

Although the furosemide–digoxin combination was identified in only 1 of the 14 patients (7.14%) with potential drug–drug interactions, this interaction is clinically important because furosemide-induced hypokalemia may increase myocardial sensitivity to digoxin, thereby increasing the risk of digoxin toxicity (35). Current evidence recommends careful monitoring of serum potassium levels, renal function, and clinical signs of digoxin toxicity in patients receiving concomitant digoxin and loop diuretic therapy, particularly in older adults and those with heart failure, to reduce the risk of digoxin toxicity (36). Accordingly, electrolyte and renal function monitoring should be considered in patients receiving this drug combination.

Overall, the five identified potential drug–drug interactions differed in both frequency and potential clinical significance. The aspirin–ramipril combination was the most frequently observed, accounting for 57.14% of all identified potential drug–drug interactions. This predominance is likely attributable to the routine concomitant use of antiplatelet agents and ACE inhibitors in patients with atherosclerotic cardiovascular disease. In contrast, the azithromycin–warfarin and furosemide–digoxin combinations were identified in only one patient each (7.14%); however, these interactions may carry greater clinical significance because of their potential to increase the risk of bleeding and digoxin toxicity, respectively, if not appropriately monitored. Likewise, the simvastatin–amlodipine combination may increase the risk of statin-associated muscle toxicity through a pharmacokinetic interaction, whereas the aspirin–captopril combination may attenuate the antihypertensive effect of ACE inhibitors. These findings suggest that the frequency of a potential drug–drug interaction does not necessarily correspond to its potential clinical significance, highlighting the importance of individualized medication review and appropriate monitoring based on the characteristics of each drug combination.

This study has several limitations. First, its retrospective design relied on the completeness and accuracy of medical record documentation, which may have limited the availability of relevant clinical information. Second, the study was conducted at a single tertiary hospital, which may limit the generalizability of the findings to other healthcare settings. Third, only 14 of the 71 patients had identified potential drug–drug interactions, resulting in a relatively small number of interaction cases for analysis. Finally, this study identified potential drug–drug interactions through medication screening using validated drug interaction references and did not evaluate clinical outcomes or independently verify the occurrence of adverse drug reactions. Therefore, the identified interactions should be interpreted as potential rather than clinically confirmed events.

CONCLUSION

Potential drug–drug interactions were identified in 19.72% of hospitalized patients with atherosclerosis, with five distinct potential drug–drug interaction types detected. The aspirin–ramipril combination was the most frequently identified potential drug–drug interaction. Although the identified interactions represent potential rather than clinically confirmed events, these findings highlight the importance of systematic medication review and appropriate monitoring, particularly in patients receiving multiple cardiovascular medications. The findings of this study may provide supporting evidence for pharmacists and other healthcare professionals to identify potential drug–drug interactions and prioritize medication review and monitoring to promote safer pharmacotherapy in hospitalized patients with atherosclerosis.

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