Phân tích và xây dựng danh mục tương tác thuốc tim mạch ở bệnh nhân ngoại trú tại Trung tâm Y tế Huyện Long Mỹ, Tỉnh Hậu Giang, năm 2023

TÓM TẮT

Tương tác thuốc-thuốc là các biến cố bất lợi thường xảy ra trong thực hành lâm sàng. Đáng chú ý, tỷ lệ tương tác thuốc liên quan đến thuốc tim mạch được ghi nhận cao hơn so với các loại thuốc khác. Tương tác thuốc có thể dẫn đến các hậu quả nghiêm trọng, bao gồm tăng độc tính, giảm hiệu quả điều trị, cũng như làm tăng nguy cơ nhập viện và tử vong. Mục tiêu của nghiên cứu này là đánh giá tỷ lệ, mức độ nghiêm trọng, cơ chế dược lý của tương tác của thuốc tim mạch với các thuốc khác và xây dựng danh sách các tương tác thuốc tim mạch tại bệnh nhân ngoại trú Trung tâm Y tế Long Mỹ, Hậu Giang, trong năm 2023. Chúng tôi đã tiến hành một nghiên cứu cắt ngang, hồi cứu trên tất cả các đơn thuốc liên quan đến tim mạch tại bệnh nhân ngoại trú Trung tâm Y tế Long Mỹ, Hậu Giang từ ngày 01 tháng 01 năm 2023 đến hết ngày 31 tháng 03 năm 2023. Tiêu chí đánh giá tương tác thuốc được thực hiện dựa trên ba cơ sở dữ liệu: Drugs.com (www.drugs.com/drug_interactions.html), Medscape (reference.medscape.com/drug-interactionchecker), và Micromedex (www.micromedexsolutions.com). Nghiên cứu đã xây dựng thành công danh sách gồm 23 cặp tương tác thuốc liên quan đến thuốc tim mạch có ý nghĩa lâm sàng, tạo nền tảng cho các can thiệp lâm sàng trong tương lai nhằm giảm thiểu các tương tác thuốc, đặc biệt là ngăn ngừa các trường hợp có mức độ nghiêm trọng cao.

Từ khóa: *Tương tác thuốc, thuốc tim mạch, bệnh nhân ngoại trú, Trung tâm y tế Huyện Long Mỹ.*

Assessment of cardiovascular drug-drug interactions and development of a drug-drug interactions list among outpatients at Long My Health Center, Hau Giang, in 2023

ABSTRACT

Drug-drug interactions (DDIs) are adverse events that frequently occur in clinical practice. Notably, the incidence of cardiovascular DDIs has been observed to be higher compared to other drugs. DDIs may result in severe outcomes, including increased toxicity, diminished therapeutic efficacy, and an elevated risk of hospitalization and mortality. The purpose of this research was to assess the prevalence, severity, pharmacological mechanisms of cardiovascular DDIs and develop a cardiovascular DDIs list among outpatients at Long My Health Center, Hau Giang, in 2023. We conducted a cross-sectional, retrospective study of all cardiovascular prescriptions among outpatients at Long My Health Center, Hau Giang from January 1st, 2023, to March 31st, 2023. Criteria for evaluating DDIs involve using three databases: drugs.com (www.drugs.com/drug_interactions.html), medscape (reference.medscape.com/drug-interactionchecker), and micromedex (www.micromedexsolutions.com). The study has successfully built a practical list of clinically significant cardiovascular DDIs using three databases, including 23 pairs, which will be the foundation for future clinical interventions aimed at minimizing the prevalent drug interactions, especially to prevent the occurrence of major severity.

Keywords: *Drug-drug interactions, cardiovascular medicines, outpatients, Health Center Long My, Hau Giang.*

1. INTRODUCTION

Drug-drug interactions (DDIs) refer to alterations in the concentration of medications in the bloodstream due to the concurrent presence of additional pharmaceuticals, which could potentially impact therapeutic efficacy or elevate adverse events. DDIs may result in severe outcomes, including increased toxicity, diminished therapeutic efficacy, and an elevated risk of hospitalization and mortality.[1] DDIs are events that frequently occur in clinical practice.[2] Notably, the incidence of cardiovascular DDIs has been observed to be higher compared to other drugs.[3] Indeed, clinicians frequently prescribe cardiovascular medications to the elderly, who typically have multiple comorbidities that required complex drug regimens, known as polypharmacy, which could increase the risk of DDIs.[4,5] DDIs are preventable clinical events that can be mitigated through the utilization of popular medication interaction monitoring databases, including Drug Interaction Checker, Medscape Drug Interaction Checker, and Micromedex Drug Interaction Checker. Assessment of the prevalence, mechanism, and severity of cardiovascular DDIs may inform clinical pharmacological strategies to reduce the rate of DDIs in the future.

Consequently, this study was conducted to identify cardiovascular DDIs among outpatients at Long My Health Center, Hau Giang, Vietnam and thereby develop a list of clinically relevant cardiovascular DDIs.

2. METHODS

2.1. Method

Cross-sectional, retrospective study of all cardiovascular prescriptions among outpatients from January 1st, 2023, to March 31st, 2023, satisfying the inclusion and exclusion criteria.

- Inclusion criteria: Prescriptions, including cardiovascular medication.
- Exclusion criteria:

+ The prescription only has one medication.

+ The prescription contains two drugs, of which one is a functional food or an external drug or an herbal medicinal product.

2.2. Assessment criteria

2.2.1. Drug interaction checker databases

Lookup drug interactions based on comprehensive, professional websites, including:

- Drug Interaction Checker-DI (https://www.drugs.com/drug_interactions.html),
- Medscape Drug Interaction Checker-MDI (https://reference.medscape.com/drug-interactionchecker), and

- Micromedex Drug Interaction Checker-MMDI (https://www.micromedexsolutions.com/micromedex2/librarian/).

This study recorded interactions between cardiovascular medications and other drugs.

2.2.2. Assessment criteria of clinically relevant drug interactions

According to the European Medicines Agency, a clinically relevant drug interaction is one that results in therapeutic or toxic changes that require dose adjustment or medical intervention.[6] Therefore, this study recorded interactions between cardiovascular medications and other drugs documented in the three aforementioned databases with a moderate to severe interactive severity.

2.2.3. Development a list of clinically relevant drug interactions

Identify clinically relevant drug interactions that were reported in at least two of the three above databases with a moderate to major severity or in at least one database with a major severity.

2.2.3. Data analysis

Data were analyzed using SPSS (version 16.0) software and expressed in percentage.

3. RESULTS AND DISCUSSION

During the 3-month study period, 468 prescriptions that met both inclusion and exclusion criteria were utilized for this study.

3.1. Demographic characteristics

The 468 prescriptions of the study population had nearly equal proportions of male and female participants. The mean age of included patients was 64.5 ± 12.0 years, and those aged 60 years and older accounted for the highest proportion (63.7%). There were seven types of cardiovascular diseases diagnosed among patients, of which hypertension had the highest rate (87.4%), followed by dyslipidemia (12.6%); angina pectoris and cardiomyopathy had almost the same rates (7.26% versus 6.62%); the remaining ones, such as old myocardial infarction, acute myocardial infarction and heart failure, constituted approximately 1%. This study was similar the reseach conducted by Sharma S. et al. with hypertension being the most prevalent condition. The research at Phulbari Hospital, Pokhara, Nepal, regarding cardiovascular drug interactions in outpatients revealed that over fifty percent of patients with cardiovascular disease presented with hypertension.[7] Table 1 following described patient characteristics.

3.2. Characteristics of cardiovascular medications

The average number of medications prescribed per patient was 4.76 ± 1.60 medications. A total of 256 (54.7%) of patients were prescribed five or more (known as polypharmacy). Polypharmacy is prevalent among the elderly due to the presence of multimorbidity. Notably, polypharmacy increases the risk of appearing drug interactions, which can increase the hazard of hospitalization and death if the drug interaction is contraindicated.[4,5] This study found that more than half of patients were received polypharmacy during treatment. The most frequently prescribed cardiovascular medication in this study was calcium channel blockers (60.5%), followed by angiotensin II receptor blockers-ARBs (roughly 20%); the statin and diuretic groups were approximately equivalent (around 13%); the remaining pharmaceuticals, such as angiotensin-converting enzyme inhibitors (ACEIs), organic nitrates, and β-blockers, comprised about 10%. Table 2 following showed numbers and classes of cardiovascular medications.

Table 1. Patient characteristics.

	N=468 (%)
Gender	
Females	229 (48.9)
Males	239 (51.1)
Age (years)	
≤ 40	14 (3.00)
41-60	156 (33.3)
≥ 60	298 (63.7)
Mean ± SD	64.5 ± 12.0
Types of cardiovascular diseases	
Hypertension	409 (87.4)
Dyslipidemia	59 (12.6)
Angina pectoris	34 (7.26)
Cardiomyopathy	31 (6.62)
Old myocardial infarction	8 (1.71)
Acute myocardial infarction	1 (0.21)
Heart failure	1 (0.21)

Table 2. Number and classes of cardiovascular medications.

	N=468 (%)
Number of medications	
≤ 4	212 (45.3)
≥ 5	256 (54.7)
5-7	235 (50.2)
8-10	21 (4.50)
Mean ± SD	4.76 ± 1.60
Classes of cardiovascular medications	
Calcium channel blockers (CCBs)	283 (60.5)
Angiotensin II receptor blockers (ARBs)	92 (19.6)
Statin	64 (13.7)
Diuretics	62 (13.2)
Angiotensin-converting enzyme inhibitors (ACEIs)	21 (4.49)
Organic nitrates	10 (2.14)
β-blockers	9 (1.92)

Amlodipine was the only medication that belonged to calcium channel blockers (CCBs). ARBs had two medications prescribed frequently: Telmisartan and irbesartan. Atorvastatin and rosuvastatin were anti-dyslipidemia drugs prescribed among the patients. In the diuretics, hydrochlorothiazide was documented to have the highest rate. Table 3 following indicated cardiovascular medications.

Table 3. Cardiovascular medications.

Cardiovascular medications	N=468 (%)
CCBs	**283 (60.5)**
Amlodipin	283 (60.5)
ARBs	**96 (20.5)**
Telmisartan	52 (11.1)
Irbesartan	43 (9.18)
Candesartan	1 (0.22)
Statin	**64 (13.68)**
Atorvastatin	36 (7.69)
Rosuvastatin	28 (5.99)
Diuretics	**62 (13.2)**
Hydrochlorothiazide	58 (12.4)
Furosemide	4 (0.80)
ACEIs	**21 (4.49)**
Perindopril	14 (2.99)
Enalapril	4 (0.85)
Captopril	3 (0.65)
Organic nitrates	**10 (2.14)**
Isosorbide mononitrate	10 (2.14)
β-blockers	**9 (1.92)**
Bisoprolol	5 (1.06)
Atenolol	4 (0.86)

3.3. Characteristics of DDIs

3.3.1. Prevalence of DDIs

In DI database, approximately half of prescriptions (n=468) were recorded DDIs; the number of DDIs in the MDI and MMDI was equivalent to one-thirds of prescriptions. The findings of our study regarding the prevalence of drug interactions in prescriptions were closely proportional to those of a survey conducted in Puducherry, India, which reported that 48% of prescriptions for outpatients with hypertension contained drug interactions.[8] Figure 1 illustrated the frequency of DDIs in three databases.

3.3.2. Frequency of pair of interacting drugs

The total number of drug interaction pairs in the three databases DI, MDI, and MMDI were 338, 194, and 188 pairs, respectively.

Approximately one-third of prescriptions with one pair of DDI were recorded in all three databases. In DI, there were 12.2% of prescriptions that had two pairs of DDIs per prescription; in MDI and MMDI, both were below 3%. The percentage of prescriptions with 4 or more pairs was quite low, it was below 1% across all 3 databases. Table 4 demonstrated frequency of number of drug interactions pairs.

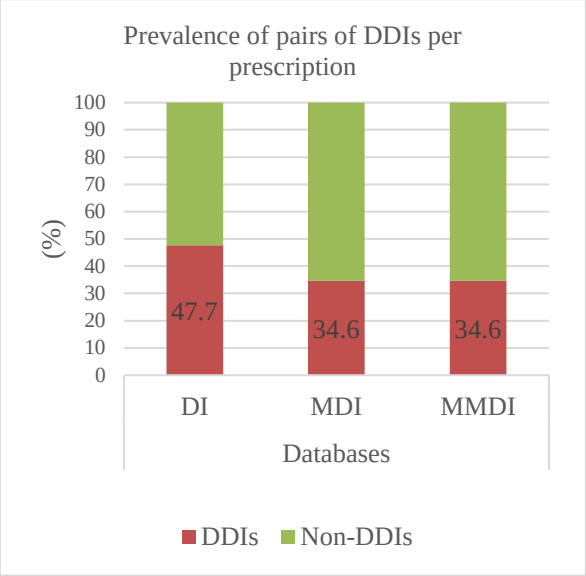

Figure 1. The prevalence of drug interaction pairs per prescription.

Table 4. The prevalence of the number of drug interaction pairs per prescription.

Number of drug interaction pairs	N=468 (%)		
	DI	MDI	MMDI
1	146 (31.2)	142(30.3)	145 (31)
2	57 (12.2)	12 (2.56)	12 (2.56)
3	12 (2.56)	4 (0.85)	3 (0.64)
4	4 (0.85)	4 (0.85)	1 (0.21)
5	2 (0.43)	-	-
6	-	-	1 (0.21)
7	-	-	-
8	2 (0.43)	-	-

3.3.3. Pharmacological mechanism of DDIs

In all 3 databases, the pharmacodynamic mechanism accounted for a higher proportion than the pharmacokinetic mechanism. In which the pharmacodynamic mechanism was higher than 83% among the pairs of interacting drugs, the pharmacokinetic mechanism was lower than 17%. A study was conducted in Ethiopia that also indicated that pharmacodynamic mechanism interactions were predominant (73.1%).[3] The drug interaction pairs based on pharmacodynamic mechanisms estimated for the majority, including: amlodipine-methocarbamol, amlodipine-methylprednisolone, amlodipine-metformin, and hydrochlorothiazide-metformin. Most of these drug interaction pairs involve antagonistic effects. Specifically, methylprednisolone increases salt and water retention and raises sympathetic receptor expression, leading to hypertension. Therefore, methylprednisolone can reduce the antihypertensive effect of amlodipine. Figure 2 showed the pharmacological mechanism of DDIs.

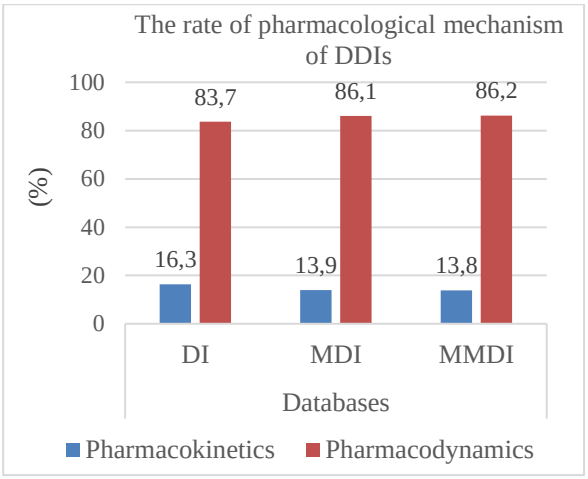

Figure 2. The rate of pharmacological mechanism of DDIs.

3.3.4. Clinically relevant DDIs

Of the 338 drug interaction pairs in DI, 324 pairs were clinically significant. There were 133 and 182 clinically relevant pairs among 194 and 188 pairs in MDI and MMDI, respectively. A study performed on cardiac patients at Ayub Teaching Hospital, Abbottabad, Pakistan, found a high incidence of clinically significant drug interactions of 84.5%.[9]

The most clinically relevant DDI was moderate interactions, accounting for 91.1% of all interactive pairs in DI. Similarly, moderate DDI constituted 68.5% and 87.7% in MDI and MMDI, respectively. Major interactions were 4.73%, 4.12%, and 9.04% in DI, MDI, MMDI, respectively. A study conducted among outpatients similarly demonstrated these results of our study.[10] Figure 3 signified the severity of clinically relevant DDIs.

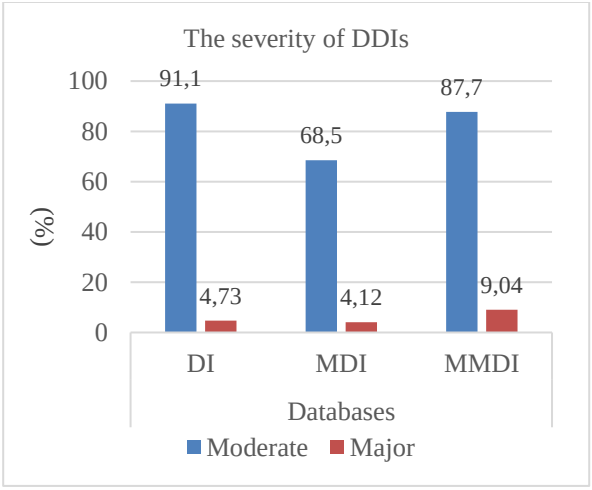

Figure 3. The frequency of clinically relevant drug interactions.

3.3.5. Pharmaceutical pairs of clinically relevant DDIs

Within the DI database, three clinically relevant drug interaction pairs, all of those were moderate in severity, were identified as having the highest prevalence among the total prescriptions analyzed (n=468), namely amlodipine-methocarbamol, amlodipine-methylprednisolone, and hydrochlorothiazide-metformin, with corresponding proportions of 12.8%, 10.5%, and 8.55%, respectively. There were 3.41% of all prescriptions with major level, including the interactions involving clopidogrel (with rosuvastatin, esomeprazole, and omeprazole), irbesartan-methocarbamol, notably the drug interaction pairs between ACEIs with ARBs. Table 5 demonstrated the most frequent clinically relevant drug interaction pairs; lookup the DI website.

For the MDI database, amlodipine-metformin was the most frequent drug interaction pair (roughly 18% of all prescriptions), with moderate in severity. Major drug interactions accounted for 1.71%, including interaction involving clopidogrel (with esomeprazole and omeprazole), celecoxib (with enalapril and captopril), and ACEIs-ARBs. Table 6 presented the details of clinically relevant DDI pairs on the MDI.

According to the MMDI website, amlodipine-metformin exhibited the highest proportion of clinically significant drug interactions, accounting for nearly 18%. A similar result was observed when this interaction was analyzed using the MDI database. Hydrochlorothiazide-metformin ranked second (8.55%). In addition, both of these interactions were classified as having moderate severity. The major drug interaction pairs with 3.63% included hydrochlorothiazide (interacting with tenoxicam, etoricoxib, and etodolac), clopidogrel (interacting with esomeprazole, omeprazole, diclofenac, and etoricoxib), rosuvastatin-antacids, and ACEIs-ARBs. Table 7 provided a comprehensive overview of clinically significant DDI pairs identified on the MMDI.

Amlodipine was the drug with the highest incidence of drug interactions across all three databases, which may be attributed to its highest frequency prescription. All identified drug interactions involving amlodipine were classified as moderate in severity. For major severity, clopidogrel-PPIs (such as omeprazole, esomeprazole), and ACEIs-ARBs pairs were consistently identified across all three databases. For clopidogrel-PPIs, these interactions have been regularly discussed among the medical experts. Mechanistically, PPIs inhibit the CYP2C19 isoform, a crucial enzyme responsible for biotransformation clopidogrel into its active metabolite, thereby potentially reducing its antiplatelet efficacy. Multiple studies have reported that the concomitant use of PPIs and clopidogrel may elevate the risk of adverse cardiovascular events.[11–13] However, the prescription of PPIs in patients receiving clopidogrel is sometimes necessary, especially for those at high risk of gastrointestinal bleeding (e.g., patients over 75 years of age, those with a history of gastrointestinal bleeding, those taking NSAIDs, and so forth). This combination has the benefit of preventing the risk of gastrointestinal bleeding but the disadvantage of increasing the adverse cardiovascular events. Therefore, the additional prescription of PPIs should be tailored, only prescribed when the patient is at high risk of gastrointestinal bleeding, and another drug in the PPI group, such as pantoprazole, should be chosen.[14] For ACEIs-ARBs, the concurrent use of both may result in increased risk of adverse events including hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure. The concomitant use of those should therefore be avoided.

3.4. Development a list of clinically relevant drug interactions

The drug interaction list was developed utilizing data from three aforementioned databases. This list serves as a foundation for clinical interventions aimed at improving outcomes related to drug interactions in the future. To ensure practicality, the study included interaction pairs that achieved a consensus of at least two-thirds of the databases with a classification of moderate or those with major severity in each database. This list provides comprehensive information on drug interaction pairs, including warn patients, clinical management strategies, levels of consensus, and severity classifications. Table 8 showed a comprehensive list of clinically relevant cardiovascular drug-drug interactions across the three databases.

Table 5. Pharmaceutical pairs of clinically relevant DDI in DI database.

Pharmaceutical pairs of clinically relevant DDI	Interactive level	Frequency	Percentage (%)
Amlodipine-methocarbamol	Moderate	60	12.8
Amlodipine-methylprednisolone	Moderate	49	10.5
Hydrochlorothiazide-metformin	Moderate	40	8.55
Amlodipine-atorvastatin	Moderate	14	2.99
Amlodipine-calcium carbonate	Moderate	14	2.99
Hydrochlorothiazide-esomeprazole	Moderate	11	2.35
Atorvastatin-esomeprazole	Moderate	10	2.14
Atorvastatin-clopidogrel	Moderate	9	1.92
Amlodipine-etodolac	Moderate	9	1.92
Perindopril-metformin	Moderate	7	1.49
Irbesartan-celecoxib	Moderate	6	1.28
Hydrochlorothiazide-methocarbamol	Moderate	5	1.07
Hydrochlorothiazide-bisoprolol	Moderate	5	1.07
Hydrochlorothiazide-lansoprazole	Moderate	5	1.07
Hydrochlorothiazide-magnesium hydroxide	Moderate	5	1.07
Rosuvastatin-Aluminum hydroxide	Moderate	5	1.07
Others [(*)]	Moderate	54	11.5
Irbesartan-methocarbamol	Major	7	1.49
Clopidogrel-rosuvastatin	Major	3	0.64
Clopidogrel-esomeprazole	Major	3	0.64
Clopidogrel-omeprazole	Major	1	0.21
Irbesartan-enalapril	Major	1	0.21
Telmisartan-perindopril	Major	1	0.21

(*) others included drug interaction pairs that had prevalence less than 1.00 percen

Table 6. Pharmaceutical pairs of clinically relevant DDI in MDI database.

Pharmaceutical pairs of clinically relevant DDIs	Interactive level	Frequency	Percentage (%)
Amlodipine-metformin	Moderate	84	17.9
Perindopril-metformin	Moderate	7	1.50
Irbesartan-celecoxib	Moderate	6	1.28
Others [(*)]	Moderate	28	5.98
Clopidogrel-esomeprazole	Major	3	0.64
Clopidogrel-omeprazole	Major	1	0.21
Irbesartan-enalapril	Major	1	0.21
Telmisartan-perindopril	Major	1	0.21
Enalapril-celecoxib	Major	1	0.21
Captopril-celecoxib	Major	1	0.21

(*) others included drug interaction pairs that had prevalence less than 1.00 percent.

Table 7. Pharmaceutical pairs of clinically relevant DDI in MMDI database.

Pharmaceutical pairs of clinically relevant DDIs	Interactive level	Frequency	Percentage (%)
Amlodipine-metformin	Moderate	84	17.95
Hydrochlorothiazide-metformin	Moderate	40	8.55
Clopidogrel-atorvastatin	Moderate	9	1.92
Perindopril-metformin	Moderate	7	1.50
Irbesartan-celecoxib	Moderate	6	1.28
Others (*)	Moderate	19	4.06
Hydrochlorothiazide-tenoxicam	Major	3	0.64
Rosuvastatin-antacid	Major	3	0.64
Clopidogrel-esomeprazole	Major	3	0.64
Clopidogrel-omeprazole	Major	1	0.21
Hydrochlorothiazide-etoricoxib	Major	2	0.43
Hydrochlorothiazide-etodolac	Major	1	0.21
Telmisartan-perindopril	Major	1	0.21
Irbesartan-enalapril	Major	1	0.21
Clopidogrel-diclofenac	Major	1	0.21
Clopidogrel-etoricoxib	Major	1	0.21

(*) others included drug interaction pairs that had prevalence less than 1.00 percent.

Table 8. A comprehensive list of clinically relevant of cardiovascular DDIs across the three databases.

Drug-drug interactions	Databases			Warnings	Clinical management
	DI	MDI	MMDI		
Clopidogrel-omeprazole/ esomeprazole	Major	Major	Major	Concurrent use of clopidogrel and omeprazole/esomeprazole may result in reduced clopidogrel's active metabolite exposure and reduced antiplatelet activity.	Consider the use of alternative medications: *Rabeprazole* (given 4 hours after clopidogrel), *lansoprazole*, *dexlansoprazole*, and *ranitidine*.
Irbesartan-enalapril Telmisartan-perindopril	Major	Major	Major	Concurrent use of ACEIs and ARBs may result in increased risk of adverse events (ie, hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	Concomitant use should generally be avoided; however, should coadministration be necessary, closely monitor blood pressure, renal function, and electrolytes.
Hydrochlorothiazide-etodolac	Moderate	Moderate	Major	Concurrent use of NSAIDs and thiazide diuretics may result in reduced diuretic	During concomitant use of NSAIDs and diuretics, monitor for signs of

				effectiveness and possible nephrotoxicity.	worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure.
Clopidogrel-diclofenac	Moderate	Moderate	Major	Concurrent use of antiplatelet agents and NSAIDS may result in an increased risk of bleeding.	Use caution and monitor the patient for signs of bleeding with concomitant use of antiplatelet agents and NSAIDs.
Rosuvastatin-aluminum hydroxide	Moderate	Moderate	Major	Concurrent use of rosuvastatin and antacids may result in reduced rosuvastatin exposure and reduced efficacy of rosuvastatin.	In patients taking antacids, administer rosuvastatin at least 2 hours after the antacid.
Captopril/enalapril-celecoxib	Moderate	Major	Moderate	Concurrent use of ACEIs/ARBs and NSAIDs may result in reduced antihypertensive effect and renal dysfunction and/or increased blood pressure.	When concomitant use is required, determine the need to monitor renal function at initiation of treatment, monitor for antihypertensive efficacy, and assess renal function periodically for signs of renal deterioration or failure, especially in patients who are elderly, during treatment initiation, in the volume-depleted, or those with preexisting renal dysfunction. Ensure that patients are adequately hydrated.
Irbesartan-celecoxib/etodolac	Moderate	Moderate	Moderate		
Enalapril/perindopril-metformin	Moderate	Moderate	Moderate	Concurrent use of ACEIs and antidiabetic agents may result in an	If concomitant use is required, conduct more frequent glucose

				increased risk of hypoglycemia.	monitoring, both during treatment and after withdrawal of an ACE inhibitor.
Atenolol-diclofenac	Moderate	Moderate	Moderate	Concurrent use of beta blocker and NSAIDs may result in reduced antihypertensive effect.	Monitor blood pressure when coadministration is required.
Irbesartan-methocarbamol	Major	Moderate	None	Concurrent use of irbesartan and methocarbamol may result in increased hypotension.	Close monitoring for development of hypotension is advised during coadministration of these agents
Clopidogrel-pantoprazole	Moderate	Moderate	None	Concurrent use of clopidogrel and pantoprazole may result in reduced clopidogrel's active metabolite exposure and reduced antiplatelet activity.	Consider the use of alternative medications: *Rabeprazole* (given 4 hours after clopidogrel), *lansoprazole*, *dexlansoprazole*, and *ranitidine*.
Bisoprolol-amlodipine	Moderate	Moderate	None	Additive reductions in heart rate, cardiac conduction, and cardiac contractility may occur when CCBs are used concomitantly with beta blockers, particularly in patients with ventricular or conduction abnormalities.	Close clinical monitoring of patient hemodynamic response and tolerance
Bisoprolol-furosemide	Moderate	Moderate	None	Diuretics and beta-blockers may increase the risk of hyperglycemia and hypertriglyceridemia in some patients.	Monitoring of serum potassium levels, blood pressure, and blood glucose is recommended during coadministration.
Hydrochlorothiazide-furosemide	Moderate	Moderate	None	The combination of a thiazide and loop diuretic may produce additive or synergistic effects on diuresis and excretion of electrolytes including sodium, potassium,	Dosages should be titrated slowly and carefully, and electrolytes, fluid status, blood pressure, and renal function should be monitored regularly.

				magnesium, and chloride.	
Hydrochlorothiazide-perindopril	Moderate	None	Moderate	Concurrent use of ACEÍ and thiazide diuretics may result in reduction of blood pressure.	Before starting ACEI therapy, decreasing or discontinuing the diuretic or increasing salt intake may minimize the risk of hypotensive effects. If these measures are not possible, reduce the ACE inhibitor starting dose.
Telmisartan-etodolac	Moderate	None	Moderate	Concurrent use of ACEIs/ARBs and NSAIDs may result in reduced antihypertensive effect and renal dysfunction and/or increased blood pressure.	When concomitant use is required, determine the need to monitor renal function at initiation of treatment, monitor for antihypertensive efficacy, and assess renal function periodically for signs of renal deterioration or failure, especially in patients who are elderly, during treatment initiation, in the volume-depleted, or those with preexisting renal dysfunction. Ensure that patients are adequately hydrated.
Clopidogrel-atorvastatin	Moderate	None	Moderate	Concurrent use of clopidogrel and CYP3A4 metabolized statins may result in decreased formation of clopidogrel active metabolites resulting in high on-treatment platelet reactivity.	If a patient develops high on-treatment platelet reactivity during treatment with clopidogrel and a statin metabolized by CYP3A4 (ie, atorvastatin, lovastatin, or simvastatin), discontinue the

					statin and substitute a statin that is not metabolized by CYP3A4 (ie, pravastatin or rosuvastatin).
Amlodipin-metformin	None	Moderate	Moderate	Concurrent use of metformin and CCBs may result in an increased risk of hyperglycemia and potential loss of glycemic control.	Observe the patients for loss of blood glucose control when such drugs are administered to a patient receiving metformin. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

4. CONCLUSION

The study has built a quietly comprehensive list of clinically significant drug interactions using three databases, which will be the foundation for future clinical interventions aimed at minimizing the prevalent drug interactions, especially to prevent the occurrence of major drug interactions. In the future, we will intervene clinically by implementing workshops and then re-evaluate the effectiveness of the intervention in subsequent studies.

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