



## Potential Cardiovascular Drug Interactions in Egypt: Incidence, Outcomes, Mechanism, and Management

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### Abstract

**Background/aim:** Cardiovascular diseases usually involve multiple drug co-administration giving the potential for many drug-drug interactions. Limited data is available regarding drug interactions of cardiovascular diseases in Egypt. This work studied potential drug-drug interactions of cardiovascular diseases in Egyptian patients with consideration to incidence, types, management, and prevention. **Methods:** A cross-sectional retrospective study was performed on outpatients with cardiovascular disorders in the Delta region of Egypt. About 4,100 prescriptions were analyzed for drug-drug interactions. Lexi-comp program was used as the screening tool. **Results:** The frequency of potential drug-drug interactions was 11% of which cardiovascular drugs represent 3%. Major therapeutic classes of drug interactions with the cardiovascular drugs were analgesics, antiplatelets, anticoagulants, proton pump inhibitors, anti-gout, and Ginkgo herb. The risk for category X drug interaction requiring avoiding combinations was 39% and the risk for category D drug interaction requiring modifying drug was 61%. The main mechanisms for drug interaction were pharmacokinetics "metabolic inhibitions and P-gp inhibition" and pharmacodynamics interaction and the major reported toxicity was bleeding, nephrotoxicity, irregular heartbeats, visual disturbance, and myopathy. **Conclusions:** Preventive programs are required for the increased incidence of potential cardiovascular drug interaction in Egypt. Drug monitoring, minimizing risk factors, and increasing awareness of potential drug interaction in cardiovascular diseases are recommended in clinical practice in Egypt.

**Keywords:** Cardiovascular, interactions, pharmacokinetic, incidence, Egypt.

### 1. Introduction

With the increase of patients with multiple comorbidities, pharmacotherapy has become more complex increasing the risk of drug-drug interaction (DDI) in a great manner (Burger et al., 2005). Drug-drug interactions occur when the drug effect is altered by other drug administration (Niu et al., 2019). Pharmacokinetic or pharmacodynamics mechanisms can contribute to these interactions. Pharmacokinetic interactions occur when the drugs have the ability to change absorption, distribution, metabolism, and excretion of the other drug. Also, pharmacodynamic interactions occur if drugs have agonist or antagonist activities for both therapeutic efficacy and side effects (Pedro-Botet et al., 2015). Outcomes from DDIs include severe side effects causing hospitalizations and life-threatening conditions. About 6-30% of all ADRs are attributed to DDIs (Wang et al., 2016). Furthermore, ADR is caused by DDIs representing 2.8% of yearly hospital

admission every year in USA (Carpenter et al., 2019).

Cardiovascular disorders (CVD) have been the main cause of worldwide mortality since 1980 according to The Global Burden of Disease (GBD) trial (Wessler et al., 2013). In 2019, WHO estimated that 32% of all deaths worldwide are caused by CVDs. Also, CVDs are the main reason for disease burden in Eastern Mediterranean Region (Nalamachu et al., 2014). In Egypt, potential drug interactions with the cardiovascular drug include both synthetic and herbal products. For example, Ginkgo Biloba is a common herbal product usually written in prescription to enhance cognition and attention in Alzheimer's. This herb showed potential drug interaction with factor Xa antagonist and aspirin increases the risk for bleeding. Herbs including plant products in common beverages and juices like green tea also have the potential for drug interactions (Abdelkawy et al., 2015).

According to WHO in 2018 deaths from coronary heart disorders in Egypt were 29.38% of total deaths and cardiovascular risk factors were common in university students confirming the need for preventive measures for cardiovascular disorders (Abdelkawy et al., 2016). Recent treatment guidelines of cardiovascular disorders like congestive heart failure, atrial fibrillation, myocardial infarctions, and hypertension usually involve many therapeutic regimens. These therapeutic regimens include antihypertensive drugs, antiarrhythmic drugs, cardiac glycosides and nitrates, antiplatelets, anticoagulants, and antihyperlipidemic drugs. This multiple drug administration gives the potential for significant drug interactions in clinical practice affecting both therapeutic efficacy and side effects of drugs (Shaik et al., 2016).

Potential drug interactions should be considered in the treating of patients' illnesses. They may cause potentially harmful effects to patients especially the risk-benefit ratio is not accurately estimated. However, no reports of potential drug interactions with cardiovascular drugs are found in Egypt, the incidence, and pattern of DDIs in Egypt are not well documented besides, little information is available about the strategies that have been used for their prevention. So, this study aims to identify the potential drug interactions with cardiovascular drugs for Egyptian outpatients giving insights about incidence, mechanisms, management, and preventions.

## 2. Materials and methods

### 2.1. Collection of samples

An observational retrospective study was performed on Egyptian outpatients admitted to Egyptian community pharmacies in the Delta region of Egypt. Delta region includes six Governorates "Kafrelsheikh, Gharbia, Menoufia, AlQalyubia, Dakahlia, and Damietta". Male and female patients aged  $\geq 18$  years were included in the study that was approved by the Research Ethics Committee of Kafrelsheikh University according to the Helsinki declaration. All participants gave their informed consent. Prescriptions were collected over 12 months from January 1, 2019, till January 1, 2020, to ensure that drugs commonly prescribed in a specific season are included. Cardiovascular drugs included antihypertensive drugs,

antiarrhythmic drugs, digoxin, nitrates, antiplatelets, antihyperlipidemic, and anticoagulants.

### 2.2. Lexicomp Analysis

All prescriptions that contained cardiovascular drugs were analyzed for potential drug-drug interactions using the Lexicomp® (Lexicomp, Inc., Ohio, USA) DDI database. In Lexicomp, each interaction provides a five risk rating category from A, B, C, D, and X, which reflects both the level of urgency and the actions necessary to overcome the interaction. Potential DDIs included both "D" and "X" risk ratings. These two categories require drug modification or avoiding combinations giving the ability to have clinical significance in medical practice. The individual prescription may contain more than one potential DDI. Risk factors that affect the interaction were also documented. These risk factors included obesity, smoking, and diabetes.

### 2.3. Statistical analysis

Descriptive statistics using mean  $\pm$  SD were used to calculate the incidence of a potential drug interaction. All the statistical analysis was carried out with SPSS program (SPSS, IBM corporation version 16.0) considering  $P < 0.01$  as statistically significant.

## 3. Results

Exactly 5445 prescriptions were included in the study and analyzed. Participants' demographics were presented in Table 1. As revealed from Figure 1, 599 potential DDIs were identified with an overall incidence of 11%. Only 116 potential interactions with cardiovascular were reported (2.1% of the overall prescription). About 18 interactions for every one thousand prescriptions showed category D interactions requiring drug modification. Similarly, about 3 interactions for every one thousand prescriptions showed Category X interactions requiring avoiding combination.

Table 1. Patien's demographic data.

	Incidence
Age range	"26-67 years"
Gender	Male 2300 (42.2%) Female 3145 (57.8%)
Governorate	Kafrelsheikh 1851 (34%) Gharbia 1362(25%) Menoufia 980 (18%) AlQalyubia 436 (8%) Damietta 272 (5%) Dakahlia 544 (10%)
Risk factors	Obesity 653 (12%) Diabetes 1198 (22%) Smoking 1524 (28%)

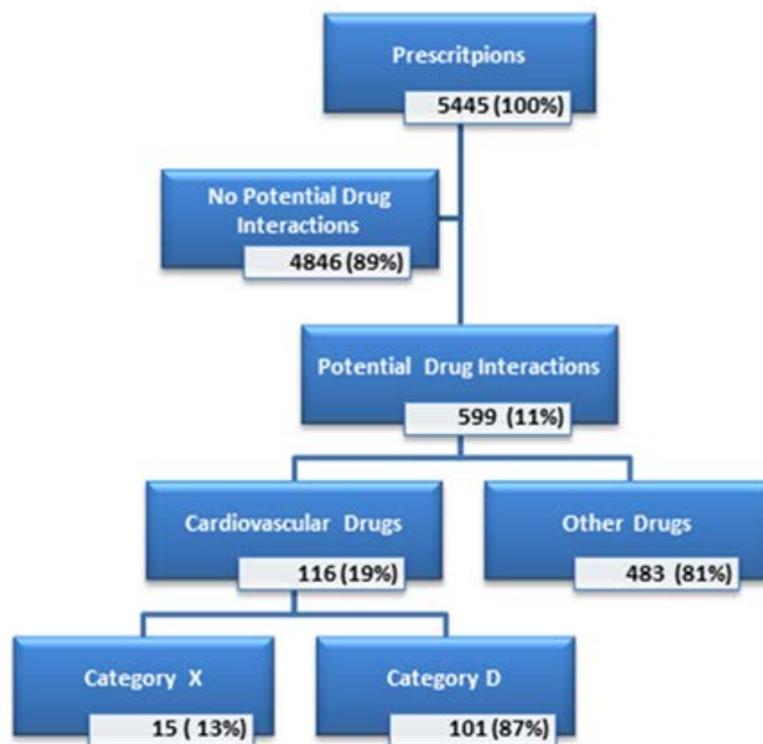


Figure 1. Incidence of potential drug interaction with cardiovascular drugs

As explored in Table 2, the outcomes from potential drug interactions varied according to drug nature. The major three reported outcomes were bleeding, severe bradycardia, and myalgia. Bleeding is the main interaction risk with both anticoagulants and antiplatelet drugs. In addition, severe bradycardia with heart block risk is the main interaction outcome with B blockers and CCBs. Myalgia is the main interaction risk from statin interactions (Elmekawy et al., 2021, Sharaf et al., 2021). Patients should be informed about symptoms and signs for expected outcomes of these interactions. Also, patients should be encouraged to contact the physician if any expected symptoms or signs appear from these interactions.

#### 4. Discussion

To understand and expect DDIs, knowledge of pharmacokinetics and pharmacodynamics is very important. The main reported interaction mechanisms include both pharmacodynamics and pharmacokinetics mechanism in the following orders “pharmacodynamics additive effects > enzyme inhibition > P glycoprotein inhibition > plasma protein displacements. Additive pharmacodynamics effects were the main mechanisms for interactions with anticoagulants, antiplatelets, and B blockers. While, enzyme inhibitions (CYP 3A4, CYP2C19, CYP2C9) were the main mechanisms for interactions with atorvastatin (Abdelkawy et al., 2020), clopidogrel, and CCBs. P glycoprotein was the main mechanism for interactions with digoxin and amiodarone. Finally, plasma protein displacement was the expected mechanism for interactions with aspirin and warfarin. The incidence of drug interactions with cardiovascular drugs

according to both cardiovascular therapeutic and pharmacological classes was shown in Figure 2 and Figure 3, respectively. The three major therapeutic classes “represent 89% of potential interaction” were antiplatelets, anticoagulants, and antihypertensive drugs 36%, 32%, and 21%, respectively. Similarly, the three major pharmacological classes “represent 60% of potential interactions” were aspirin, warfarin, loop diuretics 26%, 17%, and 16%, respectively. This confirms the importance of giving more attention to these therapeutic classes in clinical practice. These classes require continuous evaluation of drug interactions with other concurrent drugs and double-checking by a clinical pharmacist if possible. In pharmacy practice, the significant role of the pharmacist in checking prescriptions for any possible interaction with these therapeutic classes should be emphasized before prescription dispensing preventing possible medication errors and avoiding any expected harmful outcomes. In a similar way, tables 3 showed major therapeutic classes of drug interactions with cardiovascular drugs. The three major therapeutic classes “represent 68% of potential interaction” were NSAIDs, anticoagulants, and antiplatelet drugs 25%, 22%, and 21%, respectively. Consequently, these classes required more attention when prescribed cardiovascular drugs to avoid any probable drug interactions.

Tables 4 showed the top ten drug-drug interactions of cardiovascular diseases. The educational program should focus on these interactions in teaching and training courses of drug interactions in Egypt. Pearson correlation coefficient revealed that there was no significant correlation between reported risk factors “smoking, obesity, diabetes” and incidence and/or severity of drug interactions with cardiovascular diseases.

This study explored the importance of the preventive program to avoid potential medication errors in clinical practice and to avoid any hazardous effects of these interactions on Egyptian patients. Most cardiovascular patients take a large number of drugs meaning many drugs per prescription. This polypharmacy increases the likelihood of DDIs. Previous studies showed that the incidence of potential drug interactions with cardiovascular drugs correlated with the staying period at the hospital, prescribed drugs, patients' age, and sex. Also, they revealed that the elderly patients usually

over 60 years old and females have a higher rate of DDIs (Mateti et al., 2011).

Limitations of the current study involve that prescription for pediatrics and more regions from different governorates of Egypt should be included in further studies. Also, herbal products including beverages and juices should be considered in further drug interactions evaluations.

Table 2. List of potential drug interactions with cardiovascular drugs “risk rating D or X” on the Lexicomp drug interaction software program

Pharmacological Class	Drug A	Drug “B”	Outcome	MOA	Recommendation
B Blockers	Propranolol	Clonidine	Sinus node dysfunction or AV node block.	Additive PD interaction	1) Close monitoring of heart rate. 2) Avoid abrupt Withdrawal of drugs
		Ergotamine	Severe peripheral ischemia	Additive vasoconstriction.	1) Consider alternatives 2) If cannot be avoided, monitor closely.
	Bisoprolol	Tizanidine	Sinus node dysfunction or AV node block.	Additive PD interaction	1) Close monitoring of heart rate. 2) Avoid abrupt withdrawal of drugs.
CCBs	Nifedipine	Phenytoin	Loss of nifedipine action	PKcyp3A4 induction	Avoid combination
		Clarithromycin	Nifedipine toxicity	PK Enzyme inhibition	Lower Nifedipine dose on clarithromycin initiation
	Verapamil	Ivabradine	QT-prolongation, bradycardic risk	PK CYP3A4 inhibition	Avoid combination
		Rivaroxaban	risk of major bleeding	Additive PD interaction	Avoid combination
	Diltiazem	Atorvastatin	Atorvastatin toxicity (myositis, rhabdomyolysis, hepatotoxicity).	PK CYP3A4 inhibition	- Lower atorvastatin doses of - Fluvastatin, pravastatin, and rosuvastatin may be less affected by diltiazem.
Diuretic	Loop diuretics (Furosemide, torsemide, bumetanide)	NSAIDS (indomethacin, aspirin, diclofenac sod, celecoxib , tenoxicam)	Diminishing the diuretic effect and enhancing the nephrotoxic effect of NSAIDS	PD interaction.	1) Monitor closely for AKI and response. 2) Avoid in heart failure and cirrhosis. 3) Consider using other NSAID (e.g., ketoprofen, and ketorolac).
Class 1a	Quinidine	Digoxin	Digoxin toxicity	PK “PgP inhibitor” 1) Increase absorption 2) decrease elimination	Reduce digoxin dose by 25% to 50%
Class 3	Amiodarone	Digoxin	Digoxin toxicity	PK “PgP inhibition”	Reduce digoxin dose 30-50%
		Warfarin	Bleeding risk	PK enzyme inhibition	Warfarin dosage reduction of 30- 50%
Nitrates	Nitroglycerin	Sildenafil	Severe systemic Vasodilation	Additive PD interaction.	Avoid combination
Cardiac Glycosides	Digoxin	Amiodarone	Digoxin toxicity	PK “PgP inhibitor	Reduce digoxin dose 30-50%
		Quinidine	Digoxin toxicity	Multiple PK mechanisms : 1) Increase absorption 2) PK “PgP inhibitor” 3) decrease	Reduce digoxin dose by 25% to 50%

				elimination	
Anti Xa	Rivaroxaban & Apixaban	Ginkgo biloba	Bleeding risk	Additive PD interaction	Avoid combination
		Aspirin	Bleeding risk	Additive PD interaction	-Avoid combination "rivaroxaban" - Monitoring and caution "apixaban"
		Verapamil	Bleeding risk	Additive PD interaction	Avoid combination
		Ibuprofen	Bleeding risk	Additive PD	monitor for bleeding signs
Vitamin K antagonist	Warfarin	Aspirin	Bleeding risk	Additive PD interaction	Monitor bleeding risk
		Amiodarone	Bleeding risk	PK enzyme inhibition	warfarin dosage reduction of 30- 50%
		Tenoxicam	Bleeding risk	Additive PD interaction	Monitor bleeding risk
		Clopidogrel	Bleeding risk	Additive PD	monitor for bleeding signs
		Diclofenac Sodium	NSAIDS enhance warfarin effect	Additive PD	<u>Replace with Acetaminophen or Monitor</u> for bleeding.
Fenofibrate	Bleeding risk	PK (CYP2C9 inhibition, PP displacement)	Monitor INR more frequently, with close monitoring for bleeding		
Heparin	Heparin	Venlafaxine	Bleeding risk	Additive PD interaction	Heparin dose reduction
		Clopidogrel	Bleeding risk	Additive PD interaction	Heparin dose reduction
LMWH	Enoxaparin	Diclofenac sod.	Bleeding risk	Additive PD interaction	Avoid combination
		Aspirin	Bleeding risk	Additive PD interaction	Avoid combination
		Clopidogrel	Bleeding risk	Additive PD interaction	Avoid combination
P2Y12 Antagonist	Clopidogrel	PPI (Esomeprazole, Omeprazole)	Loss antiplatelet activity of clopidogrel	PK "enzyme inhibitors of prodrug"	Avoid combination Rabeprazole or pantoprazole may be lower-risk alternatives
		Anticoagulants "Heparin & Warfarin"	Bleeding risk	Additive PD interaction	Heparin dose reduction Increase monitoring for bleeding if these agents are used concomitantly.
		Evening Primrose Oil	Bleeding Risk	Additive PD	increased monitoring for adverse effects (bleeding, CNS bleeds)
Aspirin	Aspirin "low dose"	Anticoagulants	Bleeding risk	Additive PD interaction	- Avoid combinations or Monitor bleeding risk
		NSAIDS (diclofenac, Meloxicam, indomethacin, celecoxib)	-Salicylates toxicity -Bleeding risk -diminishing cardioprotective effect.	-Additive PD interaction -PK (Plasma Protein) displacement) & (reduce kidney excretion)	-Monitor for Bleeding risk -Alternative analgesics (e.g., acetaminophen) may be a safer choice.
		Ticagrelor	Enhance the antiplatelet effect of Ticagrelor.	Additive PD interaction	Avoid maintenance aspirin doses greater than 100 mg/day in patients receiving

		Gingko Biloba	Enhance the effect of Salicylates.	Additive PD interaction	ticagrelor. -Consider alternatives -Monitor for bleeding.
Statin	Atorvastatin Rosuvastatin	Colchicine	Statin toxicity	-PK enzyme inhibition PD "additive myopathy"	Monitor for signs of muscle pain and/or rhabdomyolysis.
	Atorvastatin	Diltiazem	atorvastatin toxicity	PK CYP3A4 inhibition	- lower atorvastatin doses
Fibrates	Fenofibrate	Warfarin	Bleeding risk	PK -CYP2C9 inhibition -PP displacement	Monitor INR more frequently, with close monitoring for signs and symptoms of bleeding

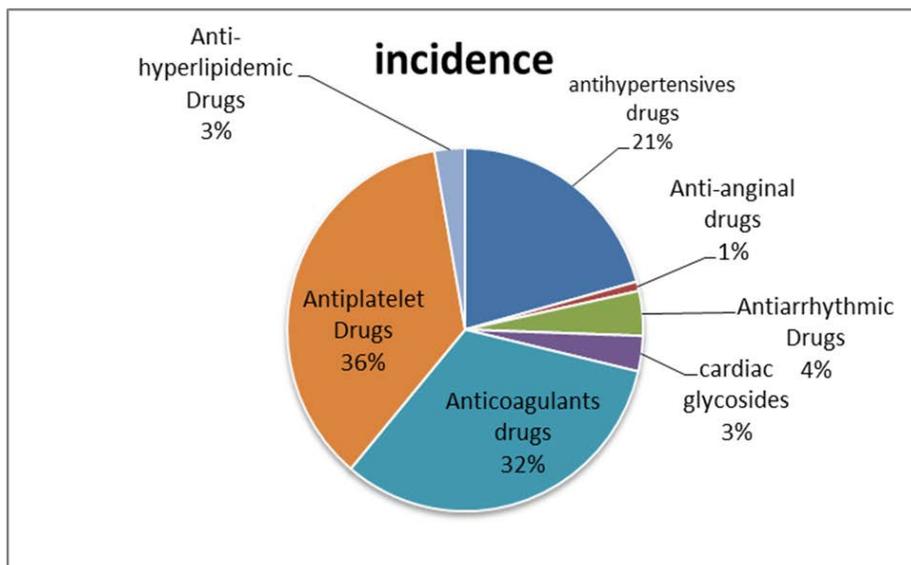


Figure 2. Cardiovascular therapeutic classes that show potential drug-drug interactions.

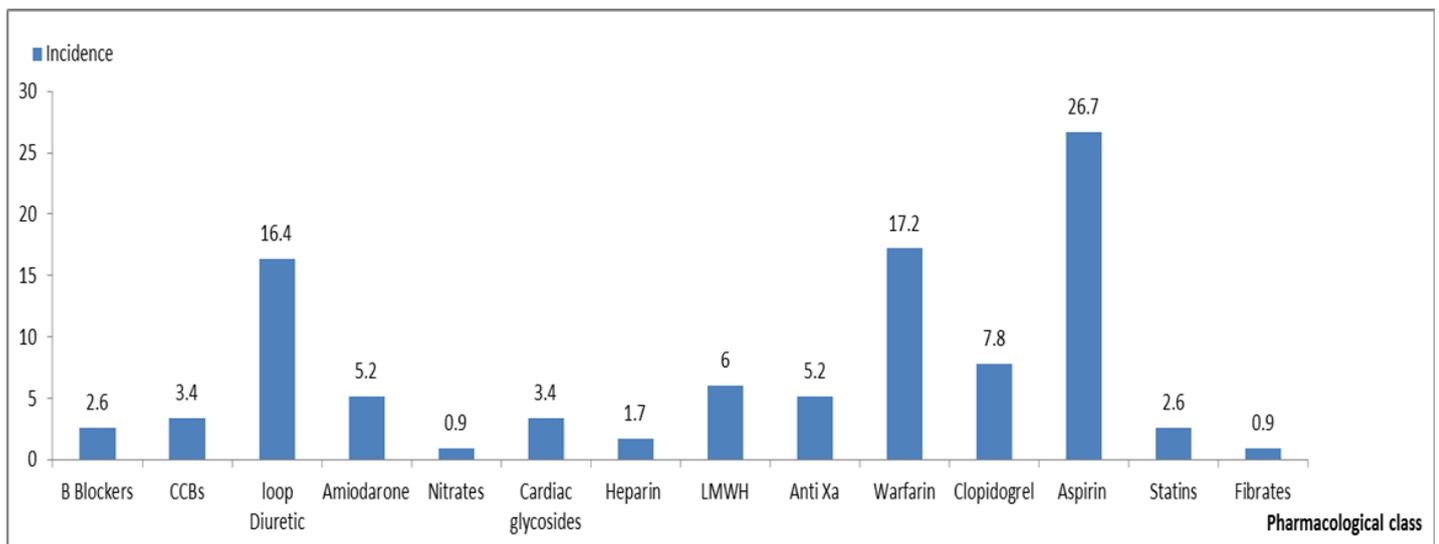


Figure 3. Cardiovascular pharmacological classes that show potential drug-drug interactions.

Tables 3: Major therapeutic classes that interact with cardiovascular drugs

Therapeutic Class	Incidence (%)
NSAIDs	25
Anticoagulants	22.4
Antiplatelets	20.7
Proton Pump Inhibitors	5.2
Antiarrhythmic "Amiodarone"	5.2
Cardiac glycosides "Digoxin"	3.4
Ginkgo Biloba	3.4
Antigout "Colchicine"	2.5

NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 4. Top 10 Drug-drug Interactions of Cardiovascular Diseases.

Drug A	Drug B	Safe alternative
Aspirin	Warfarin	acetaminophen is an acceptable alternative to aspirin (Ilya M. et al., 2015 ).
Loop diuretic	NSAIDs	Replace loop diuretics with thiazides and indapamide.
Warfarin	NSAIDs	Paracetamol and selective COX 2 inhibitors (Celecoxib) are safe alternatives (Ilya M. et al., 2015).
Clopidogrel	Proton pump inhibitors (omeprazole, esomeprazole)	Rabeprazole or Pantoprazole are safe alternatives to omeprazole (Funk-Brentano et al., 2013; Jin Choi et al., 2017 ).
Aspirin	NSAIDs	-Paracetamol and selective COX 2 are safe alternatives to NSAIDs (Krauss et al.,2020). -Clopidogrel is safe alternative to aspirin.
Amiodarone	Warfarin	-Replace amiodarone with Less interacting dronedarone. -Replace warfarin with apixaban (Flaker et al., 2014).
Amiodarone	Digoxin	Replace oral digoxin by IV digoxin.
Aspirin	Ginkgo Biloba	Stop Ginkgo Biloba before antiplatelets intake (Gardner et al., 2007; Agbabiaka et al.,2017).
Rivaroxaban	Ginkgo Biloba	Stop Ginkgo Biloba before antiplatelets intake (Gardner et al., 2007; Agbabiaka et al.,2017).
Aspirin	Ticagrelor	Replace ticagrelor with clopidogrel (Berger, 2013).

## Conclusion

Egyptian outpatients taking cardiovascular drugs are at a high risk of hazardous DDIs as revealed from the reported incidence from prescription. This emphasizes the need for the evaluation of potential DDIs during prescription writing to avoid harmful outcomes of drug interactions. In addition, giving DDI-related information to the health care team and using software programs by the dispensing pharmacist can play an essential role in minimizing the rate of DDIs. The preventive program, monitoring for interactions outcome, and increasing awareness of potential drug interaction in cardiovascular diseases are recommended in clinical practice in Egypt.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Research Ethics Committee Permission

This study was approved by the local Ethics and guides of the Faculty of Pharmacy, Kafrelsheikh University University Egypt.

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## Authors' contribution

O AbdelMaged, K Abdelaty, D Khalil, K Abdelkawy, M. Y. Abdelgaied designed and conducted the study. All authors collected and analyzed the data. The final version of the manuscript was revised and approved by K Abdelkawy and M. Y. Abdelgaied.

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