NOVEL POTENTIAL DRUG INTERACTIONS WITH BISOPROLOL IN HOSPITALIZED ACUTE CORONARY SYNDROME PATIENTS

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Objectives: *Drug-drug interactions (DDI) pose a real challenge especially in patients with complicated therapeutic regimens such as acute coronary syndrome (ACS) patients. Cardiac patients are more vulnerable to potential drug-drug interactions (pDDI). This study aimed to assess DDIs involving Bisoprolol among other drugs in ACS patients.* ***Methods:*** *This is an observational study including 128 hospitalized patients with ACS who were candidates for Bisoprolol therapy and received at least two medications. Bisoprolol peak concentration, heart rate and blood pressure of patients were assessed. Medications of patients were analyzed for potential drug interactions using Micromedex, Lexi Interact and Drugs.com databases. Assessment of actual drug interactions was also conducted.* ***Results:*** *A total of 1039 pDDIs were detected and their severity was categorized into moderate (54.95%) and major (45.04%). Regarding the actual DDIs, 4 drug interactions involving Bisoprolol were identified: Amlodipine/Bisoprolol (2.3%), Empagliflozin/Bisoprolol (10.2%), Aspirin/Bisoprolol (96.9%) and Potassium Chloride/Bisoprolol (10.2%), while 6 drug interactions involving other drugs were observed including Empagliflozin/Spironolactone (7%), Levofloxacin/Insulin (4.7%), Furosemide/Insulin (3.9%), Clopidogrel/Fondaparinux (11.7%), Aspirin/Fondaparinux (13.3%) and Aspirin/Furosemide (8.59%).* ***Conclusions:*** *This study highlighted novel drug interactions such as Amlodipine/Bisoprolol, Empagliflozin/Bisoprolol and Empagliflozin/Spironolactone interactions. The study also emphasized the possible beneficial role of these interactions in ACS patients, this warrants the need for intense monitoring of drug interactions in ACS patients for drug therapy optimization and avoidance of adverse drug reactions. This trial was registered at clinicaltrials.gov, with registration date: September 10, 2022, and registration number: NCT05536284 (https://clinicaltrials.gov/ct2/show/NCT05536284.) Retrospectively registered.*

Key words: *Drug-Drug Interactions, Acute coronary syndrome, Bisoprolol, Polypharmacy*

INTRODUCTION

Coronary artery disease as a part of cardiovascular diseases is the largest global underlying reason for both morbidity and mortality[1]. According to the World Health Organization (WHO), coronary artery disease contributed to approximately 13% of the world's total deaths in 2014[2]. The majority of patients' fatalities are associated with acute coronary syndrome (ACS)[3].

Drug–drug interaction (DDI) is among the most frequently encountered challenges in clinical practice. It has the potential to change therapeutic response of patients, lengthen their hospital stay and increase their health care costs[4]. The term "drug-drug interaction" (DDI) is defined as a compromise in drug efficacy or toxicity as a result of two or more drugs interacting with each other[5]. Whereas the definition of potential Drug-Drug Interaction (pDDI) is the co-administration of possibly interacting drugs[6].

Numerous studies reported that cardiac patients among other hospitalized patients carry a higher risk of developing DDIs[7-9]. The higher risk of DDIs may be attributed to the existence of risk factors in those patients like advanced age, polypharmacy, multimorbidity and alteration of organ functions[7-9]. Moreover, prolonged hospital stay also increases the incidence of potential drug- drug interactions (pDDIs) [10].

Following acute coronary syndrome (ACS), guidelines recommendations include the administration of dual antiplatelet therapy consisting of Aspirin and a $P2Y_{12}$ inhibitor, a beta blocker, a high intensity statin and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)[11]. Additionally, ACS patients suffer from multiple concomitant diseases such as diabetes mellitus, hypertension, history of ACS and heart failure [12]. Implementation of algorithms containing new medications such as sodium glucose cotransporter 2 (SGTL-2) inhibitors are starting to be added to Diabetic patients' regimens[13,14]. Furthermore, hospitalized ACS patients develop several in-hospital complications that require the use of antihypertensives, diuretics, anticoagulants and antibiotics [15-17]. All the previous factors further complicate patient therapy and increase the potential for drug interactions.

According to the current guidelines' recommendations, beta blocker therapy should be initiated as early as possible, unless contraindicated, and long-term therapy should be maintained[11]. Bisoprolol is one of the most prescribed beta blockers in ACS. It is a selective beta 1 receptor blocker, that reduces myocardial cells oxygen consumption through its negative inotropic and chronotropic effects[18]. Early therapy of Bisoprolol was shown to decrease ACS patients' morbidity and mortality[19,20]. Bisoprolol has an absolute bioavailability of 90% which is not altered by food intake. Its elimination half-life ranges from 10 to 11 hrs. Bisoprolol elimination involves both metabolism by cytochrome P450 (CYP) isoforms, CYP2D6 and CYP3A4/A5 [21], as well as excretion through the kidney[22].

Several studies investigated pDDIs in cardiac patients[4,23-25], however, studies reporting drug interactions with Bisoprolol are limited[26-29]. Also, most of these studies investigated potential drug interactions from a theoretical perspective lacking a practical assessment of various patients' parameters to determine the actual occurrence of the drug interaction. To the best of the authors' knowledge, this is the first clinical study to investigate drug interactions with Bisoprolol in ACS patients. Furthermore, this study also aimed to identify other common drug interactions occurring in this patient population.

PATIENTS AND METHODS

Study Design and Participants

This is an observational study, conducted at the intensive care unit and medical ward of the cardiology department of Alexandria main university hospital, Alexandria University, Egypt between September 2021 and august 2022. Ethical approval was granted from the Research and Ethics Committee of Faculty of Pharmacy, Damanhour University (Reference number 421PP34) and from Alexandria university (Reference number 0106986). Informed consent forms were signed by patients, or first relatives. Part of these patients were included in another study that discussed pharmacogenetic factors affecting Bisoprolol pharmacokinetics and pharmacodynamics. However, the current study focused on drug interactions involving Bisoprolol with other medications commonly administered in ACS patients and findings reported and discussed in this current study were not duplicated in the previous one. This trial was registered at clinicaltrials.gov with the following registration number: NCT05536284 (https://clinicaltrials.gov/ct2/show/NCT0553628 4.)

128 patients were eligible to the study as they fulfilled the specified inclusion. The inclusion criteria involved patients diagnosed with ACS which manifested as myocardial infarction with or without ST-segment elevation or unstable angina, patients aged

above 18 years old, Indicated for Bisoprolol therapy, with at least two other drugs during a period of hospital stay longer than 24 hrs [24,30.] Patients were excluded if they had contraindications to Bisoprolol therapy, had renal or hepatic impairment.

Patient Samples and Clinical Parameters

Patients' blood samples were collected at Bisoprolol peak concentration after patients reached steady state concentration. Plasma separation was achieved through centrifugation of samples at 1500 g for 10 minutes. Subsequently, Bisoprolol concentration was analyzed by high performance liquid chromatography -fluorescence detector[31].

Patients' demographics such as age, gender, and weight, in addition to, primary diagnosis, laboratory data, concomitant diseases and details of all prescribed medications during the hospital stay were collected. Moreover, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed for the participated patients.

Potential Drug Interactions Assessment

Screening of patient charts for potential drug interactions was conducted using Micromedex mobile application version 5 as well as Lexi Interact application and Drugs.com drug interaction checker. All detected potential drug interactions were then evaluated to detect the occurrence of actual drug interactions. This was conducted by assessing Bisoprolol concentration, heart rate, blood pressure and laboratory parameters in patients administered the interacting drugs combination compared to patients that didn't receive the same combination. Severity of drug interactions were assessed by Micromedex Database and the drug interaction was classified as a major interaction if it was life threatening or requiring medical intervention to minimize or prevent serious adverse drug effect while as a moderate drug interaction if it could result in exacerbation of patient's condition or require an alteration in patients' therapy[32.] Drug interactions observed in the current study and not documented on Micromedex database were reported as unclassified in severity. All potential and actual drug interactions were reviewed and assessed by three clinical pharmacists included as authors in the current study.

Statistical Analysis

Data analysis was performed using Statistical package for social sciences (SPSS) version 26. Numerical variables were reported as mean ± standard deviation (SD). Categorical variables were presented as number (percentage). Testing of normality of data distribution was performed by Kolmogorov-Smirnov test. Independent Student t-test was utilized to identify any significance between the mean values of the two study groups in normally distributed parameters and Mann Whitney test to assess any difference between the two study groups means in non-normally distributed parameters. Univariate and multivariate regression models were designed to evaluate the associated factors with the number of drug interactions per patient. The significance level considered at P≤0.05. SPSS was used to create the artwork included in this study.

RESULTS AND DISCUSSION

Results

Clinical Characteristics of The Study Population

The demographic data of participated patients revealed that the average age was 56.16±10.27. The male gender was more predominant constituting approximately 93.8%, while the female gender accounted for 6.2%. 105 (82%) patients were diagnosed with ST-segment elevation myocardial infarction. The concomitant diseases in the study population were diabetes mellitus (32%), hypertension (29.7%), history of acute coronary syndrome (21.9%), heart failure (3.1%), hypothyroidism (1.6%), Chronic obstructive pulmonary disease (3.1%), stroke (1.6%) and peptic ulcer (1.6%). The demographics and clinical characteristics of patients such as renal function tests, hepatic function tests, coagulation profile, cardiac markers, random blood glucose, hemoglobin, serum electrolytes and vital signs such as heart rate and blood pressure are reported in **Table 1.**

Drug Regimen of The Study Population

A total of 128 patients were administered Bisoprolol therapy, Bisoprolol was administered in different doses, where 37 patients were on 1.25 mg/day of Bisoprolol, 82 were on 2.5 mg/day and only 9 patients were on 5 mg/day of Bisoprolol. In order to correct Bisoprolol concentration to eliminate the

impact of dose variation, dose corrected Bisoprolol concentration was calculated according to the following equation (Bisoprolol concentration/Bisoprolol dose per day). The majority of patients were on concomitant therapy of Pantoprazole (99.2%), Aspirin (96.9%), Atorvastatin (97.7%), Ramipril (88.1%), Clopidogrel (61.7%) or Ticagrelor (35.9%) while the remainder frequency of the concomitant drug therapy are reported in **Table 2.**

. **Table 1:** Clinical characteristics of the study population (n=128).

Patients' variables	Mean ± SD or Number (%)
Patient age (years)	56.16±10.27
Gender	
Male	120(93.8%)
Female	8(6.2%)
Type of ACS	
STEMI	105(82%)
NSTEMI	23(18%)
Hospital length of stay (days)	6.88 ± 1.349
Presence of concomitant diseases	
Hypertension	38(29.7%)
Diabetes mellitus	41(32%)
Heart failure	4(3.1%)
Past ACS	28(21.9%)
Hypothyroidism	2(1.6%)
COPD	4(3.1%)
Stroke	2(1.6%)
Peptic ulcer	2(1.6%)
Renal function tests	
Serum creatinine (mg/dl)	0.99±0.21
Creatinine clearance (ml/min)	98.17±24.89
BUN (mg/dl)	16.79±5.79
Hepatic function tests	
SGPT (U/L)	51.97±24.32
SGOT (U/L)	60.44±20.40
Total bilirubin (mg/dl)	0.77±0.40
Coagulation profile	
Prothrombin time (Sec)	12.65±2.99
PTT(Sec)	37.73±16.57
INR	1.06±0.10
Cardiac markers	
Ck-mb(ng/ml)	53.51±75.86
Troponin (ng/ml)	32.12±72.14
RBS (mg/dl)	171±72.50
Serum electrolytes	
Serum sodium (mmol/L)	136.81±8.81
Serum potassium (mmol/L)	4.33±0.71
Hemoglobin (g/L)	14.30±1.82
Vital signs	
SBP (mmHg)	110.91±11.44
DBP (mmHg)	71.47±7.81
Heart rate (BPM)	82.95±9.69

ACS (acute coronary syndrome), COPD (chronic obstructive pulmonary disease), BUN (blood urea nitrogen), SGPT (serum glutamic pyruvic transaminase), SGOT (serum glutamic oxaloacetic transaminase), PTT (partial thromboplastin time), INR (international normalized ratio), CK-MB (creatine kinase), RBS (random blood glucose), SBP (systolic blood pressure) DBP (diastolic blood pressure), BPM (beats per minute).

Table 2: Drug regimen of the study population (n=128).

Number of drugs prescribed **median (range)**	**7 (5-13)**
Bisoprolol dose administered **number (%)**	
1.25 mg/day	37 (28.9%)
2.5 mg/day	82 (64.1%)
5 mg/day	9 (7%)
Bisoprolol concentration **mean ± SD**	9.25±4.08
Dose corrected Bisoprolol concentration **mean ± SD**	4.08±1.24
Concomitant therapy **number (%)**	
Aspirin	124 (96.9%)
Amiodarone	5 (3.9%)
Empagliflozin	13 (10.2%)
Insulin	44 (34.4%)
Atorvastatin	125 (97.7%)
Rosuvastatin	2 (1.6%)
Clopidogrel	79 (61.7%)
Ramipril	114 (89.1%)
Fondaparinux	18 (14.1%)
Enoxaparin	56 (43.8%)
Warfarin	15 (11.7%)
Spironolactone	37 (28.9%)
Nitrates	4 (3.1%)
Ticagrelor	46 (35.9%)
Dapagliflozin	3 (2.3%)
Levothyroxine	2 (1.6%)
Cefepime	1 (0.8%)
Ceftriaxone	2 (1.6%)
Ceftazidime	1 (0.8%)
Furosemide	12 (9.4%)
Torsemide	27 (21.1%)
Amoxicillin	1 (0.8%)
Levofloxacin	10 (7.8%)
Ampicillin	1 (0.8%)
Hydrochlorothiazide	1 (0.8%)
Hesperidin	1 (0.8%)
Colchicine	1 (0.8%)
Potassium Chloride	13 (10.2%)
Rebamipide	1 (0.8%)
Ezetimibe	1 (0.8%)
Pantoprazole	127(99.2%)
Digoxin	1 (0.8%)
Rivaroxaban	3 (2.3%)
Metronidazole	1 (0.8%)
Paracetamol	4 (3.1%)
Lactulose	2 (1.6%)
Amlodipine	3 (2.3%)
Ivabradine	2 (1.6%)
N acetyl cysteine	2 (1.6%)
Glyburide/metformin	1 (0.8%)

Potential DDIs (pDDIs) in The Study Population

A total of 1039 potential drug interactions were reported. The number of pDDIs per patient were ranked into 3 groups to 1-4 pDDIs, 5-9 pDDIs, and more than 10 pDDIs, representing 23%,55% and 26% of patients, respectively. According to the interaction severity 54.95% of pDDIs were classified as moderate while 45,04% were classified as major. In terms of avoiding drug combinations, 1.44% necessitated avoidance, while 85.56% pDDIs required only patient monitoring. **Table.3**.

Table 3: Potential DDIs (pDDIs) in the study population (n=128).

Type of prevalence	Number (%)
Severity of interactions	
Total	1039
Major	468(45.04%)
Moderate	571(54.95%)
Number of pDDIs per patient	
None	0
1-4	23(18%)
5-9	71(55.5%)
>10	34(26.6%)
Action needs to be taken	
Avoid	15(1.44%)
Monitor	889(85.56%)
Dose Adjustment	133(12.80%)
Spacing	2(0.192%)

Actual DDIs Involving Bisoprolol

Assessment of actual drug interactions with Bisoprolol was conducted. Drug interactions involved 4 precipitant medications: Amlodipine, Empagliflozin, Aspirin and potassium chloride. The administration of Amlodipine in ACS patients with Bisoprolol revealed a significantly higher Bisoprolol peak concentration (p =0.017) compared to patients not administered Amlodipine. Despite that values of SBP and DBP were lower in Amlodipine group, it did not reach statistical significance. The second precipitant medication was Empagliflozin which showed significant reduction in both of SBP (p =0.018) and heart rate (p =0.001) when co-administered with bisoprolol in comparison to ACS patients solely administered Bisoprolol therapy. The remaining two medications, Aspirin and Potassium Chloride demonstrated significant reduction in DBP (p = 0.006) and SBP (p =0.018), respectively, when co-administered with Bisoprolol in ACS patients. The severity of these 4 interactions were unclassified. However, the type of interaction was pharmacokinetic interaction with amlodipine and pharmacodynamic interaction with Empagliflozin, Aspirin and potassium chloride, drug interactions with Bisoprolol are reported in **Table.4 ,** and illustrated in **Fig.1, Fig.2, Fig.3** and **Fig.4**

Actual DDIs not Involving Bisoprolol

Six drug interactions involving drugs other than Bisoprolol were observed. All drug interactions were pharmacodynamic in nature. The combination of fondaparinux with either aspirin or clopidogrel led to a significant increase in prothrombin time and INR (p <0.05). Another interacting pair was Empagliflozin interaction with Spironolactone which was manifested as a significant decrease in SBP (p <0.01), DBP (p =0.002) and heart rate (p =0.003). Two drugs resulted in significant increase in random blood glucose when combined with Insulin which were Levofloxacin and Furosemide. Increased serum creatinine and decreased creatinine clearance were observed in patients taking the combination of Aspirin and Furosemide and the difference was found to be significant. Drug interactions involving other drugs in the current study are reported in **Table.5**.

Univariate and multivariate regression models for factors associated with potential drug interactions

A linear regression model was constructed that included all factors that may affect the number of pDDIs in each patient. Potential factors included patient age, patient gender, type of acute coronary syndrome, number of medications prescribed for each patient and hospitalization time. Each factor was analyzed with pDDIs in each patient in univariate regression analysis, then all interrelated factors were analyzed in a multivariate regression analysis and results are reported in **Table 6**. In both univariate and multivariate regression analysis the only factor that had a significant impact on the number of pDDIs in each patient was the number of medications each patient was prescribed (p<0.05).

Table 4 : Actual DDIs of Bisoprolol in the study population (n=128)

Precipitant medication	Interacting Drug Pair Bisoprolol ± (Precipitant medication)	No. of patients affected. n (%)	Affected Parameters (mean±SD)				Type of Interaction	Severity of interaction	Description of interaction
			Bisoprolol conc.	SBP	DBP	HR			
Amlodipine	**Bisoprolol** + **(Amlodipine)**	3 (2.3%)	5.77±1.41*	103.67±11.8	64.33±5.132	81.33±1.1	PK	Unclassified	Amlodipine increased Bisoprolol peak concentration
	Bisoprolol - **(without Amlodipine)**	125(97.7%)	4.04±1.22	111.08±11.42	71.64±7.79	82.99±9.8			
Empagliflozin	**Bisoprolol** + **(Empagliflozin)**	13(10.2%)	4.43±1.15	103.85±11.9*	68.46±8.006	76±7.07**	PD	Unclassified	Empagliflozin additively decreased systolic blood pressure and decreased heart rate when added to Bisoprolol
	Bisoprolol - **(without Empagliflozin)**	115(89.8%)	4.04±1.25	111.70±11.15	71.81±7.75	83.74±9.6			
Aspirin	**Bisoprolol** + **(Aspirin)**	124(96.9%)	4.08±1.25	110.61±11.2	71.19±7.78**	88±13.95	PD	Unclassified	Low dose Aspirin decreased diastolic blood pressure when combined with Bisoprolol
	Bisoprolol - **(without Aspirin)**	4(3.1%)	4.02±1.26	120±14.14	80±0	82.79±9.5			
KCL	**Bisoprolol** + **(KCL)**	13(10.2%)	4.37±1.29	103.85±10.4*	69.62±7.20	85.85±8.69	PD	Unclassified	Potassium chloride resulted in an enhanced systolic blood pressure lowering effect when combined with Bisoprolol
	Bisoprolol - **(without KCL)**	115(89.8%)	4.05±1.24	111.70±11.31	71.68±7.87	82.63±9.78			

Bisoprolol is the objective drug in the drug Interaction meaning that it's the drug whose serum concentration or effectiveness being changed while the precipitant drug is the drug whose action affects the objective drug.
Bisoprolol concentration measured in ng/ml:mg/day, SBP (systolic blood pressure) measured in mmHg, DBP (diastolic blood pressure) measured in mmHg, and HR (heart rate) measured in beats per minute. PK (pharmacokinetic) and PD (pharmacodynamic).
Results are presented as Mean± Standard deviation.
*P value<0.05 by using independent Student t Test.
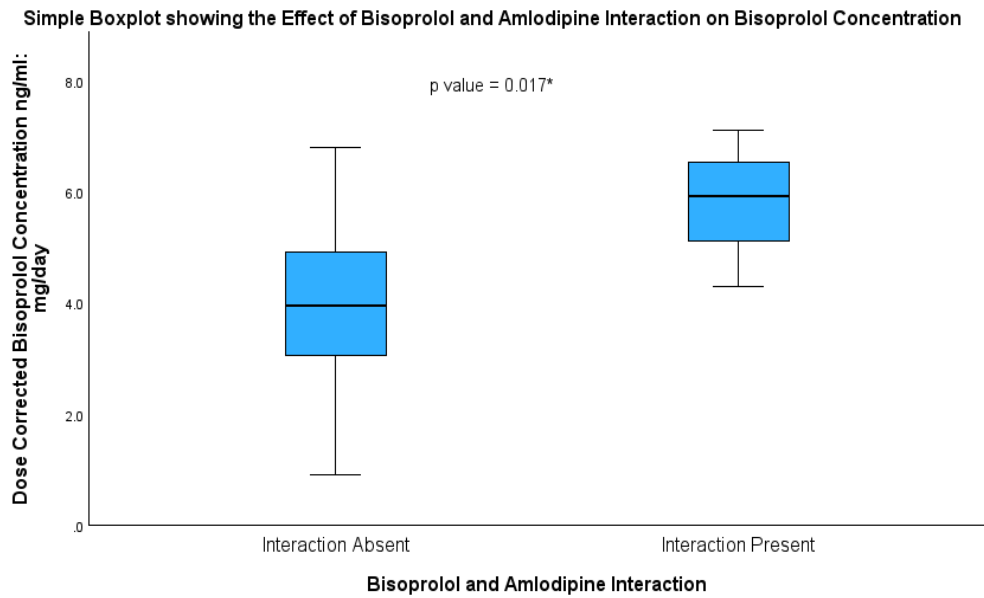**P value<0.05 By Using Mann Whitney Test.

Simple Boxplot showing the Effect of Bisoprolol and Amlodipine Interaction on Bisoprolol Concentration

Fig.1: Box Plot Showing the Effect of Bisoprolol and Amlodipine Interaction on Bisoprolol Concentration.
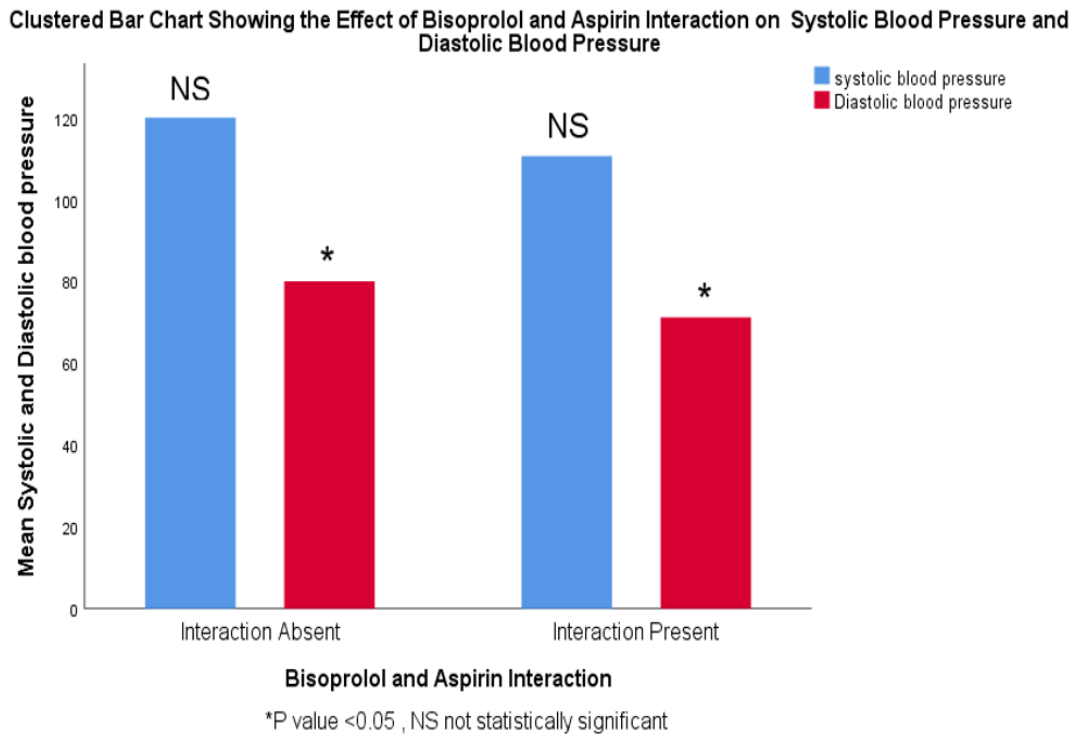

Fig.2: Clustered Bar Chart Showing the Effect of Bisoprolol and Aspirin Interaction on Systolic Blood Pressure and Diastolic Blood Pressure.
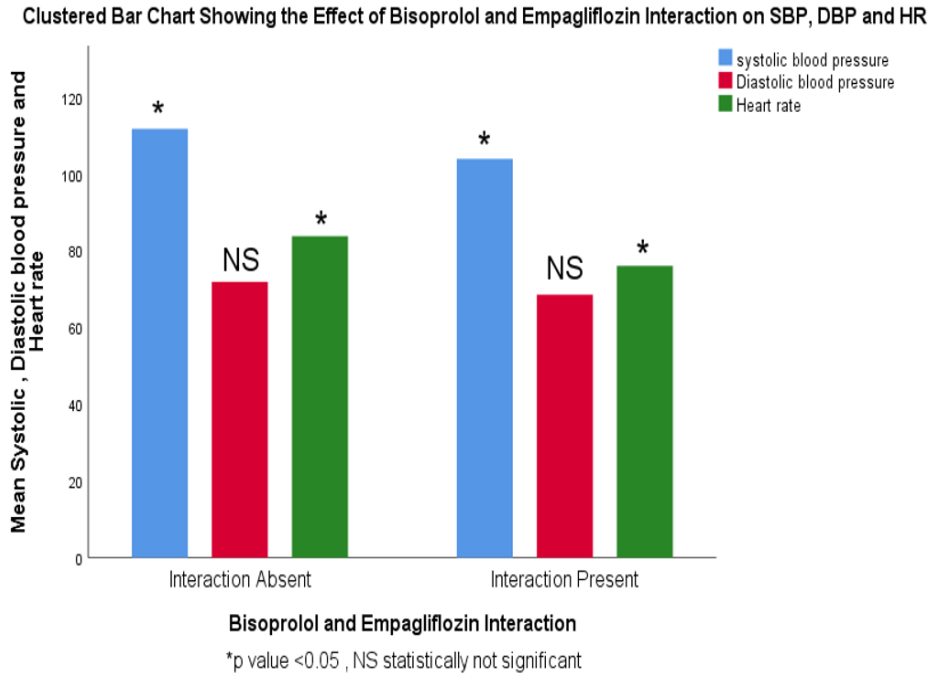
Fig.3: Clustered Bar Chart Showing the Effect of Bisoprolol and Empagliflozin Interaction on Systolic Blood Pressure, Diastolic Blood Pressure and Heart Rate.
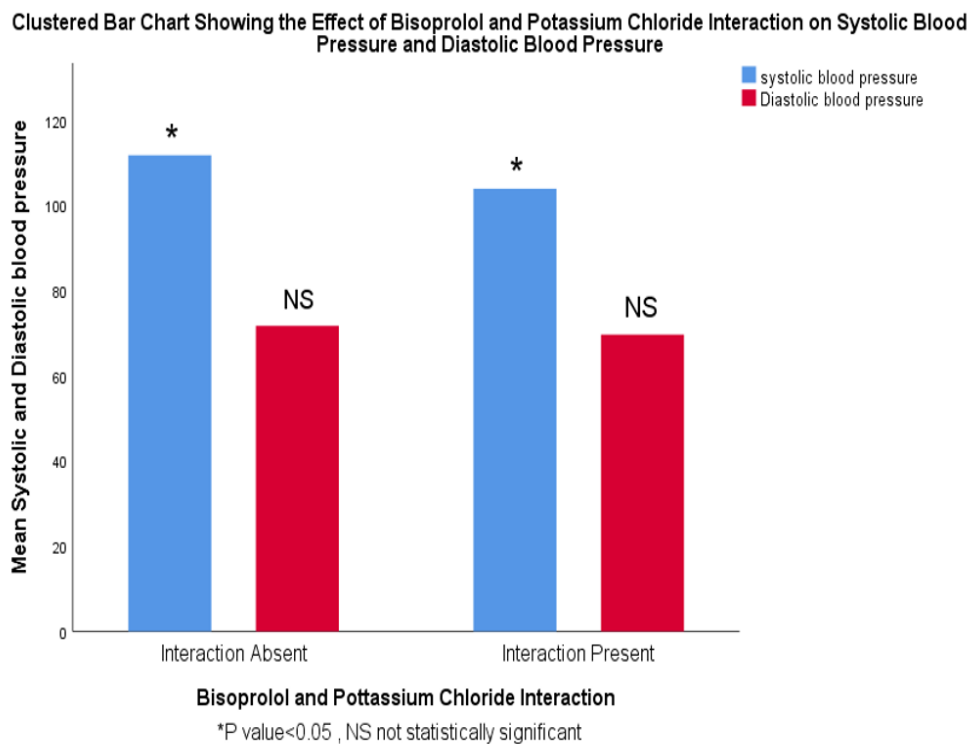

Fig.4: Clustered Bar Chart Showing the Effect of Bisoprolol and Aspirin Interaction on Systolic Blood Pressure and Diastolic Blood Pressure.

Table 5: Actual DDIs involving other drugs (n=128).

Objective medication	Interacting Drug Pair (Precipitant medication)	No. of patients affected. n (%)	Affected Parameters (mean±SD)			Type of Interaction	Severity of interaction	Description of interaction
			SBP	DBP	HR			
Spironolactone	spironolactone+ (Empagliflozin)	9(7%)	97.78±8.33**	64.44±5.27**	74.78±8.13**	PD	Unclassified	Empagliflozin works additively with spironolactone decreasing systolic and diastolic blood pressure
	Spironolactone - (without Empagliflozin)	119(93%)	111.90±11.04	72±7.72	83.57±9.55			
			PT	PTT	INR			
Fondaparinux	Fondaparinux+ (clopidogrel)	15(11.7%)	14.58±7**	39.85±20.75	1.09±0.089**	PD	Major	Fondaparinux and clopidogrel works synergistically prolonging prothrombin time and increasing INR
	Fondaparinux - (without clopidogrel)	113(88.3%)	12.39±1.86	37.44±16.03	1.05±0.10			
Fondaparinux	Fondaparinux+ (Aspirin)	17(13.3%)	14.66±6.53**	39.77±19.19	1.10±0.09**	PD	Major	Fondaparinux and Aspirin works synergistically prolonging prothrombin time and increasing INR
Fondaparinux	Fondaparinux - (without Aspirin)	111(86.7%)	12.34±1.84	37.41±16.21	1.05±0.10			
			Serum creatinine	BUN	Crcl			
furosemide	furosemide + (Aspirin)	11(8.59%)	1.11±0.2*	19.09±5.44	80.82±21.18*	PD	Major	Addition of aspirin to furosemide increases serum creatinine and affects renal function
	furosemide - (without Aspirin)	117(91.41%)	0.98±0.21	16.56±5.7	99.80±24.66			
				RBS				
Insulin	Insulin + (levofloxacin)	6(4.7%)		229.83±95.8*		PD	Major	Levofloxacin cause dysglycemia when added to insulin
	Insulin - (without levofloxacin)	122(85.3%)		168.14±70.41				
Insulin	Insulin + (furosemide)	5(3.9%)		296.20±96.8**		PD	Moderate	Furosemide is associated with hyperglycemia when combined with insulin
	Insulin - (furosemide)	123(96.1%)		165.94±67.05				

The objective drug in the drug interaction is defined by the drug whose serum concentration or effectiveness being changed while the precipitant drug is the drug whose action affects the objective drug.

SBP (systolic blood pressure) measured in mmHg, DBP (diastolic blood pressure) measured in mmHg, HR (heart rate) measured in beats per minute, PT (prothrombin time) measured in seconds , PTT (partial thromboplastin time) measured in seconds , INR (international normalized ratio) , RBS (random blood glucose) measured in mg/dl , BUN (blood urea nitrogen) measured in mg/dl , CrCl (creatinine clearance) measured in ml/min. PK (pharmacokinetic) and PD (pharmacodynamic).

Results are presented as Mean± Standard deviation.

*P value<0.05 by using independent Student t Test.

** P value<0.05 By Using Mann Whitney Test.

Table 6: Univariate and multivariate regression models for factors associated with potential drug interactions (n=128).

Parameter	Univariate linear regression			Multivariate linear regression		
	ß value	Standard error	P value	ß value	Standard error	P value
Number of prescribed drugs for each patient	2.310	0.106	<0.001[*]	2.353	0.108	<0.001*
Patient Age	-0.010	0.037	0.783	-0.022	0.017	0.178
Patient Gender	-0.792	1.549	0.610	-0.814	0.711	0.254
Patient hospital length of stay	0.444	0.277	0.111	-0.231	0.131	0.08
Type of acute coronary syndrome	1.235	0.972	0.206	0.504	0.446	0.261

*P value <0.05

Discussion

The subject of drug–drug interactions (DDIs) has gathered tremendous interest from scientific and health care organizations all over the globe[33.] Every year, a significant number of drugs are being discovered and released in the market, leading to a growing occurrence of novel drug interactions. Prevalence of pDDIs in cardiac patients was reported in previous studies to be from 21.3 % up to 91.6%[25,34-36]. Moderate pDDIs comprised a major part of drug interactions in this study, which is in accordance with existing studies' results[23,34,37].

As a member of the interdisciplinary studies, having the pharmacist can contribute substantially to decreasing drug-drug interactions. Pharmacists have a crucial role in reviewing the prescribed treatment and detecting possible interactions with the aid of drug databases, thus minimizing medication-related problems and optimizing drug therapy[5].

Regarding the results of drug interactions with Bisoprolol, pharmacodynamic interactions presented the vast majority in the present study and only one drug interaction was pharmacokinetic which was the interaction between Bisoprolol and Amlodipine as this combination resulted in an increase in Bisoprolol plasma concentration which can be explained by the fact that Amlodipine is a CYP3A4 enzyme inhibitor resulting in reduction of Bisoprolol metabolism and thus an increase in Bisoprolol plasma concentration[38] . Moreover, another study reported that calcium channel blockers not only inhibited CYP3A subfamily but also CYP2D6 [39]. Several studies reported drug interaction between Amlodipine

and other drugs such as Simvastatin, Atorvastatin and Clopidogrel due to CYP3A4 inhibition[40,41]. As far as we know, this is the first clinical study to report a pharmacokinetic drug interaction between Bisoprolol and Amlodipine.

Another intriguing drug interaction reported in this study is the combination of Empagliflozin and Bisoprolol where it resulted in a marked reduction in systolic blood pressure and heart rate while the decrease observed in diastolic blood pressure was not remarkable. Moreover, Empagliflozin not only interacted with Bisoprolol but also, it's combination with Spironolactone resulted in a considerable reduction in heart rate, systolic and diastolic blood pressure.

Several clinical studies reported a significant decline in both systolic and diastolic blood pressure caused by Empagliflozin but without a change on heart rate[42-44]. Nonetheless, a number of studies reported heart rate lowering effect of Empagliflozin and other SGLT-2 inhibitors[45,46]. The mechanism behind the heart rate decrease was speculated to be a consequence of suppression of the sympathetic nervous system via amelioration of hyperinsulinemia[47].

Empagliflozin is a selective sodium glucose cotransporter 2 inhibitor that is now being investigated as a standard treatment for type 2 diabetes mellitus. Empagliflozin reduces blood glucose via decreasing renal glucose reabsorption and, as a result, increasing glucose excretion in urine[48]. Despite that the exact mechanism of how Empagliflozin lowers blood pressure is not fully elucidated, it could be

attributed to enhanced glycemic control , weight and visceral fat reduction as a result of increased diuresis and glucosuria-associated calories loss , osmotic diuresis which leads to volume contraction, amended vascular resistance and arterial stiffness and also the reduction of uric acid levels as a consequence to disruption of uric acid transport which is induced by glycosuria[49-53]. As far as we are aware, the present study is the first to describe such drug interaction and to highlight SGTL-2 inhibitors interaction potential. Numerous studies implicated the role of elevated systolic blood pressure in increasing cardiovascular risks especially in ACS patients[54-56], this highlights that the synergistic effect of SGLT2 inhibitors (Empagliflozin) in lowering systolic blood pressure in ACS patients may in fact be beneficial for ACS patients. However, monitoring of ACS patients for abnormally low diastolic blood pressure is critical because it may be harmful to ACS patients[56,57].

Another remarkable interacting combination was observed in patients taking Aspirin and Bisoprolol as a significantly lower diastolic blood pressure was observed in these patients, The potential of Aspirin to decrease or increase blood pressure has long been in debate[58-60]. Nevertheless, many studies reported that Aspirin, especially in low dose decreases blood pressure [61,62]. Several preclinical studies reported that Aspirin is a strong antioxidant and thus decreases superoxide production in vascular tissue in normotensive and hypertensive rats[63]. Moreover, the antioxidative properties of Aspirin were reported to prevent hypertension and cardiovascular hypertrophy induced by angiotensin II in rats[64]. Furthermore, studies have demonstrated that acetylsalicylic acid (ASA) stimulates vascular endothelial cells to release nitric oxide[65,66].

Patients taking the combination of Potassium Chloride and Bisoprolol had noticeably lower systolic blood pressure. Several in vivo studies reported that Potassium Chloride lowers blood pressure[67-69]. The mechanism behind this may be due to Potassium inhibition of Sodium reabsorption, reduction in renin plasma activity, vasodilator action as a consequence of membrane Na-K ATPase activity stimulation, causing the hyperpolarization and relaxation of the vascular smooth muscle [67,69,70.]

Fondaparinux appeared to interact with two drugs, Clopidogrel and Aspirin patients taking either interacting pair had significantly higher prothrombin time and slightly but significantly higher international normalized ratio. These findings are in line with several studies that reported high incidence of drug interactions involving Aspirin, Fondaparinux and Clopidogrel in hospitalized cardiac patients[23,71]. Prolongation of prothrombin time by Aspirin has long been reported[72]. One study reported the synergistic effect of Clopidogrel when combined with anti-thrombotic agent in a mouse and dog models[73,74]. Other studies reported increased bleeding risk attributed to the use of Clopidogrel and Aspirin[75-77]. The interpretation of these interactions is based on the mechanism of action of these drugs, all of them influencing platelet aggregation and blood coagulation[78-80].

Insulin was observed to interact with two drugs, Furosemide, and Levofloxacin, both drugs caused a substantial increase in random blood glucose level in patients taking either combination. Several studies reported hyperglycemia in mice after administration of Furosemide caused by an impairment of glucose tolerance[81,82]. In clinical settings this effect was observed only in a case report that reported the development of hyperosmolar hyperglycemic state in a diabetic patient after taking Furosemide[83]. The interpretation of Furosemide induced hyperglycemia is based on glucose transport inhibition in adipose tissue and a decrease in the rate of glucose phosphorylation and glycolysis in skeletal muscle as well as inhibition of glycolytic enzymes[84]. Several studies reported the occurrence of dysglycemia and especially hyperglycemia associated with the use of Levofloxacin[85-87]. Levofloxacin's dysglycemic effects could be a result of disrupting glucose transport in cells and the function of glucose transporter 1 (GLUT1)[85,] which is a protein necessary for transporting glucose to the peripheral tissues and the central nervous system[88]. Preclinical studies also demonstrated an elevated level of epinephrine and a decrease in insulin release associated with Levofloxacin use[89,90].

Another interesting interacting drug combination was the combination of Aspirin and Furosemide where patients had slightly but significantly increased serum creatinine and significantly decreased creatinine clearance. The possible mechanisms of actions behind this observation are a decrease in renal vasodilator

effect of Furosemide by Aspirin, competition for renal excretory sites with Furosemide and inhibition of renal prostaglandin synthesis and consequently reduction of diuretic action of Furosemide[91,92]. Furthermore, a study reported that not only salicylates decrease Furosemide action but there is a decrease in salicylate excretion as well[93]. There was a case report of a woman developing renal impairment after administration of Aspirin and Furosemide[94].

Conclusion and Limitations

ACS patients included in the current study were at high risk of exposure to moderate and major potential drug interactions. Four interacting drugs with Bisoprolol has been identified, Bisoprolol/Amlodipine was the only pharmacokinetic interaction while other interactions with Bisoprolol were pharmacodynamic in nature. Another six pharmacodynamic interacting combinations were observed but not involving Bisoprolol. The number of drugs prescribed per patient was the sole major contributor to the increase in the number of pDDIs. Novel drug interactions such as Amlodipine and Bisoprolol, Empagliflozin and Bisoprolol, Empagliflozin and Spironolactone were reported. The current study also emphasized the potential beneficial role of Empagliflozin in reducing systolic blood pressure and heart rate in ACS patients. The high risk of DDIs observed among ACS patients emphasizes the role of the whole healthcare team and specifically the pharmacist in reducing the risk of DDIs. One of the limitations of this study was that results of drug interactions involving Insulin may have been reinforced by measuring confirmatory parameters such as measuring fasting and postprandial blood glucose. However, this measure was a bit difficult due to the presence of the patient in the intensive care unit. Also, this study was partially limited by the small number of patients taking the precipitant drug such as Amlodipine or Empagliflozin which warrants the need for further studies on larger number of patients.

Statements and Declarations
Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sherouk M Okda, the first draft of the manuscript was written by Sherouk M Okda,

and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

Sherouk M okda, Noha A El-Bassiouny, Ahmad Salahuddin, Sohila M. Elonsy, Ahmed El Amrawy, Amira B Kassem declare that they have no conflict of interest.

Ethical Approval

All procedures involving human participants in this present study were approved by the Research and Ethics Committee of Faculty of Pharmacy, Damanhour University (Reference number 421PP34) and from Alexandria university (Reference number 0106986) and were performed in accordance with the ethical standards of the 1964 declaration of Helsinki.

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نشرة العلوم الصيدلية

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تفاعلات دوائية محتملة جديدة مع البيزوبرولول في مرضى متلازمة الشريان التاجي الحادة في المستشفى

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تشكل التفاعلات الدوائية تحديًا حقيقيًا خاصة في المرضى الذين يعانون من أنظمة علاجية معقدة مثل مرضى متلازمة الشريان التاجي الحادة . مرضى القلب أكثر عرضة للتفاعلات الدوائية المحتملة . تهدف هذه الدراسة إلى تقييم التفاعلات الدوائية التي تتضمن البيسوبرولول والأدويــة الأخــرى لــدي مرضى متلازمة الشريان التاجي الحادة في مصر. تم إجراء هذه الدراسة في الفترة من سبتمبر ٢٠٢١ إلى أغسطس ٢٠٢٢ على مرضى متلازمة الشريان التاجي الحادة في مشتفي كلية الطب بالاسكندرية . تم ادراج المرضى الذين تم تشخيصيهم بمتلازمة الشريان التاجي الحادة ، والذين تم إعطاؤهم دوائين على الأقل، مع الإقامة في المستشفى لمدة يوم واحد على الأقل والذين تم علاجهم بعقار البيزوبرولول. تم قياس تركيز البيسوبرولول بالدم ومعدل ضربات القلب وضغط الدم لدى المرضى. تم تحليل أدويــة المرضى لمعرفة حدوث تفاعلات دوائية محتملة باستخدام قاعــدة بيانـات Micromedex , و Lexi interactو Drugs.com تم بعد ذلك تقييم جميع التفاعلات الدوائية. تمت الدراسة علــي ١٢٨ مريضــا، وكان لدى كل مريض تفاعل دوائي محتمل واحد علي الأقل . تم الكشف عن ١٠٣٩ تفاعــل دوائــي محتمل لدي المرضي، وكانت شدة التفاعلات المحتملــة متوسـطة (٥٤.٩٥٪) أو شــديدة الخطــورة (٤٥.٠٤٪). فيما يتعلق بالتفاعلات الدوائية الفعلية، تم الكشف عن ٣ تفاعلات دوائيــة جديــدة تشــمل أملوديبين/بيسوبرولول (٢.٣٪)، إمباغليفلوزين/بيسوبرولول (١٠.٢٪) وإمباجليفلوزين/سبيرونولاكتون (٧٪)، بينما لوحظت ٧ تفاعلات دوائية معروفة و مؤكدة تشمل الأسبرين/بيسـوبرولول (٩٦.٩)٪ ، كلوريد البوتاسيوم/بيسوبرولول (١٠.٢٪) ، ليفوفلوكساسين/أنسولين (٤.٧٪) ، فوروسيميد/أنسولين (٣.٩٪) ، كلوبيدوقرل/فونــــدابارينوكس (١١.٧٪) ، أســــبرين/فوندابارينوكس (١٣.٣٪) ، أسبرين/فوروسيميد (٨.٥٪) . سلطت هذه الدراسة الضوء على التفاعلات الدوائية المحتملــة الجديدة التي تشمل بيسوبرولول مع الأدوية الاخرى مما يستدعي الحاجة إلى مراقبة مكثفة للتفاعلات الدوائيــة لدى مرضى متلازمة الشريان التاجي الحادةلتحسين العلاج الدوائي وتجنب التفاعلات الدوائية الضارة.