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A Prospective Study of Disease Pattern and Assessment of Drug Interactions with Clopidogrel Among In-Patients At A Tertiary Care Hospital

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ABSTRACT: To assess the prescribing pattern and drug- drug interactions of the clopidogrel among in-patients a tertiary care hospital. A prospective observational study conducted on 126 hospitalized patients in the inpatient departments at a tertiary care hospital (BBH) during six month. A data collection form prepared based on objectives and data required to be collected. This data collected from patients profile, medicine chart, nurse notes, daily doctor's reports of patients, lab tests and other additional information. All of this detail collected from patients who are used clopidogrel at their treatment. Data collection form is made of two parts, one of it is related to the patients' information and prescription of clopidogrel and other part is related to interactions of clopidogrel and scales to evaluate the interactions. 61.90% of these patients were male and 38.09% of these patients were female. Most of patients under clopidogrel therapy were in ages between 56 to 75 years old and with most past and present diseases of cardiovascular diseases infection diseases on their treatment chart paper. 29.36 % interactions identified with clopidogrel (37 patients), 75.67% of them classified with in male and 24.32% of them into female. Most interactions were between clopidogrel and Pantoprazole, Omeprazole and Aspirin Based on the our evaluation in this study on interaction with use of scales, 10.81% were identify as severe interactions, 54.05% were classify and identify as moderate in their interactions and 35.13% were classify as mild in their interactions. Based on their possibility of relation the effect and interactions, whereas we found that 18.91% of interactions were defined, 59.45% of interactions were probable and 21.62% of them were possible. Clopidogrel used for several indication as Heart Disease (41.26%), Myocardia Infraction (34.92%), Angina (16.66%), Coronary Artery Bypass Surgery (1.58%), Stroke (10.31%), Artery Atherosclerosis (3.96%) and other unknown condition (6.34%). According to data collected in this study and its compare to other study, clopidogrel were use in patients with ages between 56 to 75 years old more in males and with most past and present diseases of cardiovascular diseases. One of four patients had clopidogrel interactions with other drugs, where mostly found in male than females. Available data suggest that pantoprazole is the PPI most likely to have a significant interaction with clopidogrel. Pantoprazole should be used since it is the PPI least likely to interact with clopidogrel but caution should be exercised in the concomitant.

KEYWORDS: Drug Interactions, Clopidogrel, Prescribing Pattern

I. INTRODUCTION

The drug–drug interaction profile of clopidogrel in previous reports mainly focused on the combination therapy of clopidogrel with several other western medicines, including proton pump inhibitors, statins, calcium-channel blockers, insulin tropic agents, azole antifungal agents, angiotensin converting enzyme inhibitors, digoxin, fluoxetine, morphine, caffeine, ritonavir, cyclosporine, rifampicin, sibutramine, and efavirenz[11].

Abrocitinib: agents with antiplatelet properties may enhance the antiplatelet effect of abrocitinib. Do not use antiplatelet drugs with abrocitinib during the first 3 months of abrocitinib therapy. The abrocitinib prescribing information lists this combination as contraindicated. This does not apply to low dose aspirin (81 mg/day or less). It is classified as risk x and should be avoid their combination.

Acalabrutinib: May enhance the antiplatelet effect of agents with antiplatelet properties. It is classified as risk c and need to monitor therapy.

Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.): may enhance the antiplatelet effect of other agents with antiplatelet properties. It is classified as risk c and need to monitor therapy.

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Alpelisib: BCRP/ABCG2 inhibitors may increase the serum concentration of alpelisib. In Management Avoid co-administration of BCRP/ABCG2 inhibitors and alpelisib due to the potential for increased alpelisib concentrations and toxicities. If co-administration cannot be avoided, it should be monitor closely for increased alpelisib adverse reactions. It is classified as risk d and need to consider therapy modification.

Amiodarone: may decrease serum concentrations of the active metabolite(s) of clopidogrel. It is classified as risk c and needs monitor therapy.

Amodiaquine: CYP2C8 Inhibitors (Moderate) may increase the serum concentration of Amodiaquine. It is classified as Risk X and it is needed to be avoiding combination.

Anticoagulants: Agents with antiplatelet properties may enhance the anticoagulant effect of anticoagulants. It is classified as risk C and needs monitor the therapy.

Apixaban: Antiplatelet Agents (P2Y12 Inhibitors) may enhance the adverse/toxic effect of Apixaban. Specifically, the risk for bleeding may be increased. In the management, carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. It is classified as risk D and considered therapy modification.

Bupropion: CYP2B6 Inhibitors (Weak) may increase the serum concentration of bupropion and the risk classified as C, which needs the monitor of therapy.

Calcium Channel Blockers: May diminish the therapeutic effect of Clopidogrel. It is classified as risk C and needs to monitor therapy.

CYP2C19 Inducers (Strong): May increase serum concentrations of the active metabolite(s) of Clopidogrel. At Management it is better to consider alternatives to this combination when possible. If combined, monitor for increased clopidogrel effects and toxicities (eg, bleeding) if clopidogrel is combined with a strong CYP2C19 inducer. It is classified as risk D: Consider therapy modification.

CYP2C19 Inhibitors (Moderate): May decrease serum concentrations of the active metabolite(s) of Clopidogrel. It is classified as risk C and needs monitor of therapy.

CYP2C19 Inhibitors (Strong): May decrease serum concentrations of the active metabolite(s) of Clopidogrel. At management Consider alternatives to this combination whenever possible. If such a combination must be used, monitor patients closely for evidence of a diminished response to clopidogrel. It is classified risk D and considered therapy modification.

Dabigatran Etexilate: Antiplatelet Agents (P2Y12 Inhibitors) may enhance the adverse/toxic effect of Dabigatran Etexilate. Specifically, the risk of bleeding may be increased. Antiplatelet Agents (P2Y12 Inhibitors) may increase the serum concentration of Dabigatran Etexilate. Specifically, clopidogrel may increase dabigatran serum concentrations. In management carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. It is classified as risk D and considered therapy modification.

Dasabuvir: CYP2C8 Inhibitors (Moderate) may increase the serum concentration of Dasabuvir. It is classified as risk C and needs monitor therapy.

Edoxaban: Antiplatelet Agents (P2Y12 Inhibitors) may enhance the adverse/toxic effect of Edoxaban. Specifically, the risk of bleeding may be increased. In management carefully consider the anticipated risks and benefits of this combination. If combined, increased monitoring for bleeding is recommended. It is classified as risk D and do consider therapy modification.

Enoxaparin: Agents with Antiplatelet Properties may enhance the anticoagulant effect of Enoxaparin. In management discontinue antiplatelet agents prior to initiating enoxaparin whenever possible. If concomitant administration is unavoidable, monitor closely for signs and symptoms of bleeding. It is classified risk D and considers therapy modification.

Enzalutamide: CYP2C8 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Enzalutamide. CYP2C8 Inhibitors (Moderate) may increase the serum concentration of Enzalutamide. It is classified risk C and needs monitor of therapy.

Erythromycin (Systemic): May diminish the antiplatelet effect of Clopidogrel. It is classified as risk C and needs to monitor of therapy.

Esomeprazole: May diminish the antiplatelet effect of Clopidogrel. Esomeprazole may decrease serum concentrations of the active metabolite(s) of Clopidogrel. It is classified as risk X therefore it needs to avoid combination.

Fentanyl: May diminish the antiplatelet effect of Antiplatelet Agents (P2Y12 Inhibitors). Fentanyl may decrease the serum concentration of Antiplatelet Agents (P2Y12 Inhibitors). It is classified as risk C which needs monitor therapy.

Grapefruit Juice: May decrease serum concentrations of the active metabolite(s) of Clopidogrel. In management it is better to advise

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patients receiving clopidogrel to minimize consumption of grapefruit and grapefruit juice. Consumption of three 200 mL glasses of grapefruit juice a day may substantially reduce clopidogrel antiplatelet effects. It is classified as risk D and considers therapy modification.

Rivaroxaban: Antiplatelet Agents (P2Y12 Inhibitors) may enhance the adverse/toxic effect of Rivaroxaban. Specifically, the risk of bleeding may be increased. In the management carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. It is classified as risk D and Consider therapy modification.

Rosuvastatin: Clopidogrel may increase the serum concentration of Rosuvastatin and classified as risk C and needs monitor of therapy.

Salicylates: Agents with Antiplatelet properties may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. It is classified as risk C and needs monitor therapy

Pantoprazole: May decrease serum concentrations of the active metabolite(s) of Clopidogrel. In management: Due to the possible risk for impaired clopidogrel effectiveness, clinicians should carefully consider the need for proton pump inhibitor therapy in patients receiving clopidogrel. Other acid-lowering therapies do not appear to share this interaction. It is classified as risk C and monitor therapy.

Omeprazole: May diminish the antiplatelet effect of Clopidogrel. Omeprazole may decrease serum concentrations of the active metabolite(s) of Clopidogrel. It is classified as risk X and needs to be avoiding from combination.

Omega-3 Fatty Acids: May enhance the antiplatelet effect of agents with antiplatelet properties. Classified as risk C and needs to monitor therapy.

Multivitamins/Minerals (with AE, No Iron): May enhance the antiplatelet effect of agents with antiplatelet properties. Classified as risk C and monitor therapy.

Morphine (Systemic): May diminish the antiplatelet effect of Antiplatelet Agents (P2Y12 Inhibitors). Morphine (Systemic) may decrease the serum concentration of Antiplatelet Agents (P2Y12 Inhibitors). In management it is consider alternative anti-ischemic/analgesic therapies (eg, beta-blockers, nitroglycerin) in patients with acute coronary syndromes treated with a P2Y12 inhibitor when possible. The risks associated with other opioids are unknown. It is classified as risk D and considered therapy modification.

Lansoprazole: May decrease serum concentrations of the active metabolite(s) of Clopidogrel. It is classified as risk C and needs to monitor of therapy.

Heparin: Agents with antiplatelet properties may enhance the anticoagulant effect of Heparin. In the management which needs decrease the dose of heparin or agents with antiplatelet properties if co-administration is required. It is classified as risk D and Considered therapy modification.

There is a report of the mechanisms for a poor response to clopidogrel which are unclear, although genetic, metabolic, cellular, and clinical factors have been proposed. Clopidogrel is a prod-rug. It is believed that reduced generation of its active metabolite contributes to poor clopidogrel responsiveness, due to variability in intestinal absorption and the availability and/or activity of cytochrome P450 isoenzymes[14, 21]. A drug that reduces the availability of clopidogrel's active metabolite will lessen clopidogrel-induced platelet inhibition and represents a potential interaction with clopidogrel. This is important because a reduced response to clopidogrel leads to an increased risk of major adverse cardiac events such as cardiovascular death, stent thrombosis, recurrent acute coronary syndrome, and recurrent revascularization[1]. Attention has been placed on a potential interaction observed between clopidogrel and the widely used proton pump inhibitors (PPIs).[11] PPIs are commonly used for gastrointestinal bleeding prophylaxis in patients receiving antiplatelet therapy. In a 2008 American College of Cardiology/American College of Gastroenterologists/American Heart Association (AHA) Clinical Expert Consensus Document [1]. PPI therapy with aspirin and clopidogrel in patients with a history of gastrointestinal bleeding. In fact, a combined total of 100 million prescriptions are written for both PPIs and clopidogrel annually.14 However, this does not include all omeprazole use since, at some strengths, it is available over-the counter. It has been hypothesized that PPI use concurrently with clopidogrel will increase the risk of major adverse cardiac events[1].

In 2006, a study by Gillard et al. raised concerns about a possible drug-drug interaction between clopidogrel and omeprazole (a PPI) that could result in a decreased efficacy of clopidogrel when taken in combination with omeprazole [6]. Clopidogrel is a pro-drug that is metabolically activated by the cytochrome p450 2C19 (CYP2C19); omeprazole (and its enantiomer, esomeprazole) is also metabolized through the same liver enzyme. Therefore, it is biologically plausible that the PPI may interfere with clopidogrel

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metabolism and attenuate its antiplatelet effects[3]. Subsequent trials and studies were conducted to test the hypothesis, but yielded mixed results. Donoghue et al. published in September 2009 a study concluding that their trial did not support the decision to avoid concomitant use of PPIs with clopidogrel [7]. Laine et al. reached a similar conclusion in a November 2009 publication[8]. In contrast to these studies, Gillard et al. published another study in 2008, concluding that, based on 124 patients enrolled in a double-blind placebo-controlled trial; omeprazole had a significant inhibitory effect on clopidogrel, as assessed by vasodilator-stimulated phosphoprotein phosphorylation test [9, 3]. Prescribing costs in primary care have also been identified could make savings and improve efficiency Clopidogrel is included because it is a more expensive medicine than the alternative aspirin and there may be scope for cost savings. The measure used for clopidogrel is defined daily dose per 1000 cardiovascular[2]. Cardiovascular diseases (CVDs) are the major cause of death worldwide and their mortality rate is more than any other cause. About 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Out of these deaths, 85% are due to heart attack and stroke[1]. For stroke survivors, antithrombotic therapy is recommended[2, 3]. This therapy may include vitamin K antagonist therapy or antiplatelet therapy. Antiplatelet therapy can reduce the relative risk of ischemic stroke by proximately 15% [4].Four major antiplatelet agents are used to treat ischemic stroke either alone or in combination which are ticlopidine, aspirin, dipyridamole and clopidogrel. If the patient has cardio embolic strokes he is treating with vitamin K antagonist therapy but if he has non-cardio embolic strokes he will be treated with antiplatelet therapy[4, 9]. Anti-platelet drugs are one of the major drugs could be used by prescribers in many conditions, including cardiovascular diseases. The clopidogrel used with defined daily dose per cardiovascular patients and it is used by prescribers in their prescriptions in most of patients. Clopidogrel is a more expensive medicine than the alternative aspirin and there may be scope for cost savings; in some cases it is used along with other antiplatelet like aspirin to achieve better results. In this study we focus on the prescriptions of clopidogrel along with its possible drug interactions that can be finding.

Table 01- Clopidogrel Information

Trade names	Plavix, Iscover, others
Pregnancy category	B1
Routes of administration	By mouth
Bioavailability	>50%
Protein binding	94–98%
Metabolism	Liver
Onset of action	2 hours
Elimination half-life	7–8 hours (inactive metabolite)
Duration of action	5 days
Excretion	50% Kidney,46% bile duct
Formula	$C_{16}H_{16}ClNO_2S$
Pharmacologic Category	Antiplatelet Agent; Antiplatelet Agent, Thienopyridine; P2Y12 Antagonist

II. OBJECTIVE

Primary Objective:

A. To assess the prescribing pattern of the clopidogrel among in-patients a tertiary care hospital.

B. To assess drug- drug interactions with clopidogrel at a tertiary care hospital.

Secondary Objective:

A. To evaluate the severity of interactions among patients used clopidogrel.

B. To evaluate the possibility of relations between clopidogrel and its interactions In patients hospitalized.

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III. METHODOLOGY

Study Design:

It is a prospective observational study conducted in the inpatient departments at a tertiary care hospital.

Source of data and Materials:

- Inpatient prescription
- Medication chart
- Medication history chart
- Medicine strips
- Medication history interview

Inclusive Criteria:

- Pediatric patient are not taken into consideration.
- Pregnancy women
- Patients in OP department.
- Patients considered as poisoned diagnosis
-

Exclusion Criteria:

- All non-pregnancy patients hospitalized in hospital
- Patients with age of greater than 18 years old
- both genders male and female

Sample Size:

This clinical study is done on 126 hospitalized patients at BBH, which patients and their information is collected according to the needs of the study.

Tools and Books:

To do better of this study and complete it, as well as fix our vague tips in study, we used valid international studies, articles and available text books to find a process and method for our study; also there some useful software and websites like Micromedex, Medscape and other we used to get better knowledge about drug interactions disease and patients**.**

Method of collection of data:

A data collection form prepared base on objectives and data required to be collected. This data collected from patients profile, medicine chart, nurse notes, daily doctor's reports of patients, lab tests and other additional information. All of this detail collected from patients who are used clopidogrel in their treatment.

Data collection form is made of two parts, one of it is related to the patients' information and prescription of clopidogrel and other part is related to interactions of clopidogrel and scales to evaluate the interactions.

Data collection is done till the patient discharge from the hospital by any reason. During collection of data for any patient was monitor for total days in hospital to evaluate interactions of clopidogrel. When the data collected completely per patient it entered to computer software named excel which prepared based of data collection form and requests for study.

In this study we used similar articles, text books, websites, and valid software such as Micromedex and Medscape as tools to reach better result of study.

Study procedure:

All medically relevant information is noted in a predefined data collection form. Alternatively, the demographic data and the detailed history of patient regarding past, present, family, personal and drug history recorded in data collection form. The other details like the present diagnosis, reason for the present admission also noted with in duration of 6 month. Patients of both genders who are admitted into the inpatient wards in the Hospital, in age greater than 18 years are include in the study.

A professional form prepared with all of details about interactions to study about the clopidogrel interactions; for prove of the drug interactions DIPS scale have been used to see the probability. And also a differential scale used to evaluate the severity of interactions based on the Medscape and Micromedex scales.

After completion of data collection on patients, they enter to excel software and used to prepare results based on the objectives.

Statistical analysis:

Descriptive statistics were applied for calculation of mean, standard deviation, frequencies, and percentage of patient's demographic/clinical characteristics, and medication related data. The statistical package for social sciences for windows, version 22.0 was used for data analysis.

Study period:

The study and data collection carried out for a period of 6 month (24 weeks)

Study site:

The study is done in the inpatient departments of Bangalore Baptist Hospital in Bangalore, Karnataka, India.

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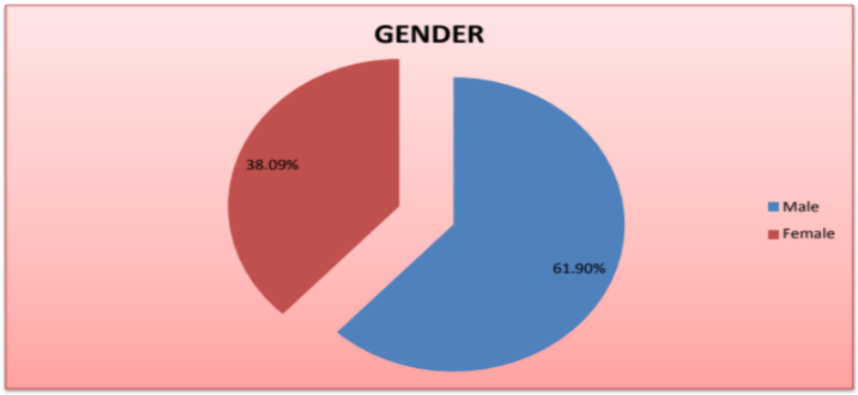
IV. OBSERVATION

This study is conducted on 126 patients at Bangalore Baptist hospital, a tertiary care hospital. 61.90% of these patients were male and 38.09% of these patients were female (table02) (figure03).

Table02: Classification of Patients Based On the Gender

GENDER	NUMBER	PERCENTAGE
Total	126	100%
Male	78	61.90%
Female	48	38.09%

Figure03: Evaluation of Patients Based On the Gender



In other hands, patients are classified into 8 groups of ages to evaluate the population of patients considered to use of clopidogrel; according to data collected on this patients, most of patients were under clopidogrel therapy were in ages between 56 to 75 years old (table 3) (figure 4)

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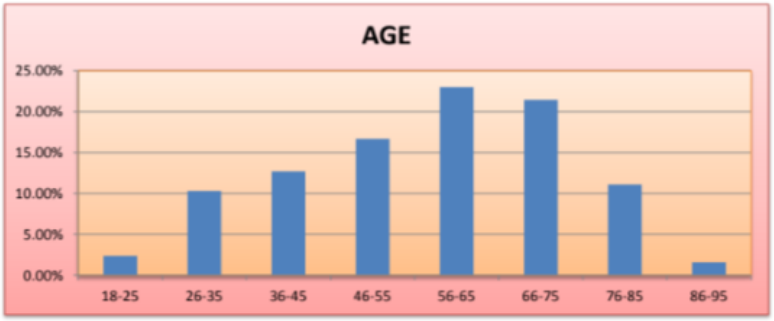
Table03: Classification of Patients Based On the Age

AGE	NUMBER	PERCENTAGE
18-25	3	2.38%
26-35	13	10.31%
36-45	16	12.69%
46-55	21	16.66%
56-65	29	23.01%
66-75	27	21.42%
76-85	14	11.1%
86-95	2	1.58%

Figure04: Evaluation of Patients Based In the Ages



Also patients are evaluated according to their past history of diseases. Therefore based on the data, 12.69% of patients had nervous system diseases, 73.80% of patients had cardiovascular diseases, 26.98% of patients had respiratory tract system diseases, 2.38% cancer, 20.63% history of surgery, 19.04% had hormonal and glands diseases, 36.50% had muscle and skin diseases, 9.52% fractures and bones conditions, 18.25% gastrointestinal system disease, 24.60% urinary tract diseases, 48.41% infection diseases and 11.1% of patients had rare and different situations which were not included in above categories (table 4) (figure 5)

Table04: Evaluation of Population History of Disease

PAST HISTORY	NUMBER	PERCENTAGE
Nervous System Diseases	16	12.69%
Cardiovascular Diseases	93	73.80%
Respiratory Tract System Diseases	34	26.98%
Cancer	3	2.38%
Surgery	26	20.63%
Hormonal And Glands Diseases	24	19.04%
Muscle And Skin Diseases	46	36.50%
Fractures And Bones Conditions	12	9.52%
Gastrointestinal System Disease	23	18.25%
Urinary Tract Diseases	31	24.60%
Infection Diseases	61	48.41%
Other Rare Situations	14	11.1%

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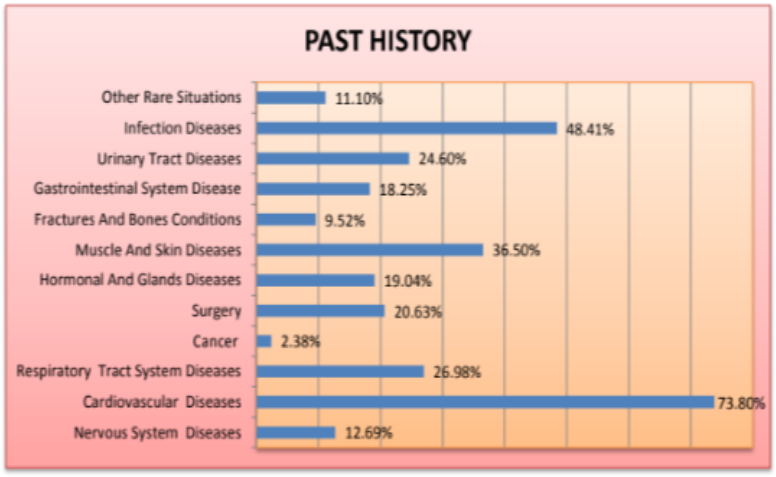
Figure05: Evaluation of Population History of Disease

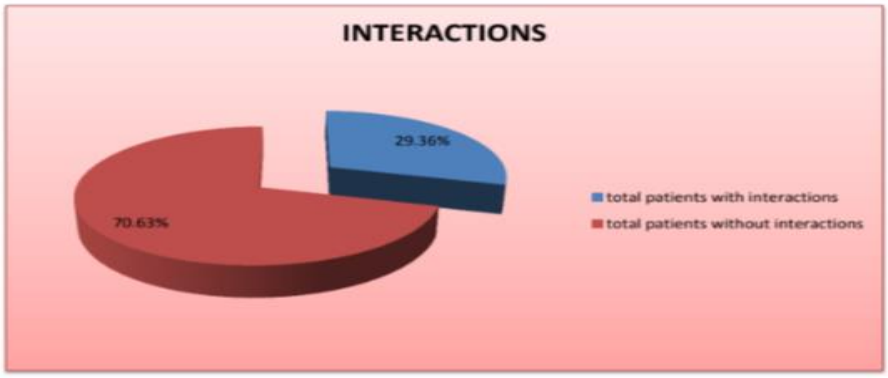


Out of 126 patients used clopidogrel, 29.36 % interactions identified with clopidogrel and other drug on their treatment and 70.63% of patients had no history of interaction with clopidogrel during their interactions (table 6) (figure 7).

Table06: Evaluation the Population of Interactions

INTERACTIONS	NUMBER	PERCENTAGE
Total Population	126	100%
Total Patients With Interactions	37	29.36%
Total Patients Without Interactions	89	70.63%

Figure07: Population of Interactions



Among 37 patients found with clopidogrel interactions, 75.67% of them classified with in male categorize and 24.32% of them into female categorize. Therefore males were the most exposed to clopidogrel; interaction on their treatment (table 7) (figure 8).

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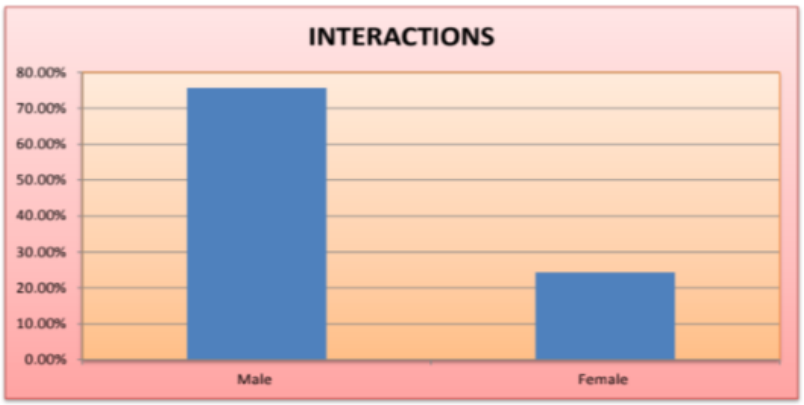
Table07: Population of Interactions Based On the Gender

INTERACTIONS	NUMBER	PERCENTAGE
Male	28	75.67%
Female	9	24.32%

Figure08: Population of Interactions Based On the Gender



Based on the data collected in these study, clopidogrel had interactions with Omeprazole (16.21%), Aspirin (16.21%), Hydrocortisone (8.1%), Pantoprazole (18.91%), Metronidazole (8.1%), Budesonide 13.51%), Heparin (2.7%), Repaglinide (2.7%), Fluconazole (2.7%), Phenytoin and Cyclosporine (2.7%) (table 8) (Figure 9).

Table08: Drugs Interactions with Clopidogrel

DRUG NAME	INTERACTION WITH	NUMBER	PERCENTAGE
CLOPIDOGREL	Omeprazole	6	16.21%
	Aspirin	6	16.21%
	Hydrocortisone	3	8.1%
	Pantoprazole	7	18.91%
	Metronidazole	3	8.1%
	Budesonide	5	13.51%
	Heparin	2	5.4%
	Repaglinide	1	2.7%
	Fluconazole	2	5.4%
	Phenytoin	1	2.7%
	Cyclosporine	1	2.7%

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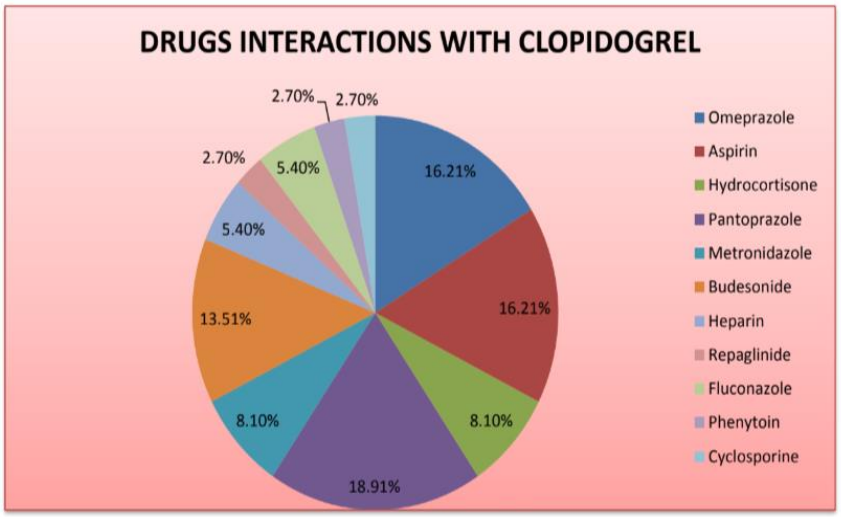
Figure09: Evaluation of Drugs Interact With Clopidogrel

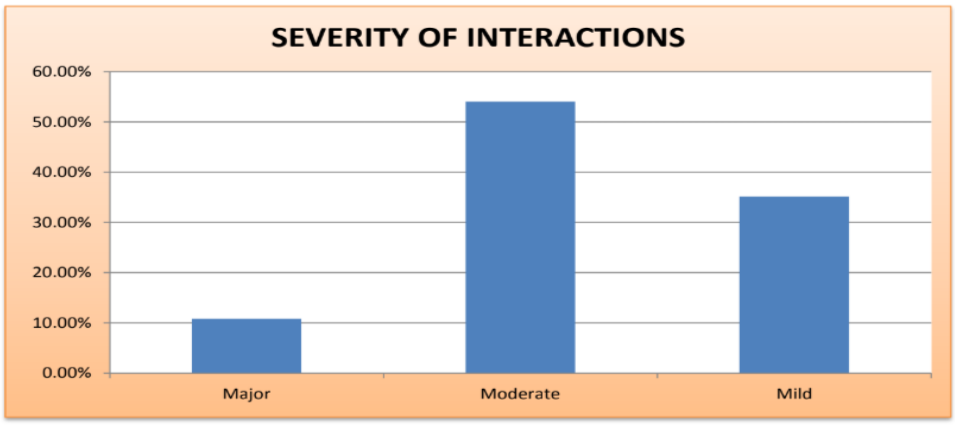


Based on the our evaluation in this study on interaction with use of scales, 10.81% were identify as severe interactions, 54.05% were classify and identify as moderate in their interactions and 35.13% were classify as mild in their interactions (table 9) (figure10).

Table09: Evaluation the Severity of Interactions

TITLES	NUMBER	PERCENTAGE
Severe	4	10.81%
Moderate	20	54.05%
Mild	13	35.13%

Figure10: Evaluation the Severity of Interactions



In other hand we evaluate interaction based on their possibility of relation the effect and interactions, whereas we found that 18.91% of interaction were defined, 59.45% of interactions were probable and 21.62% of them were possible (table10) (figure11).

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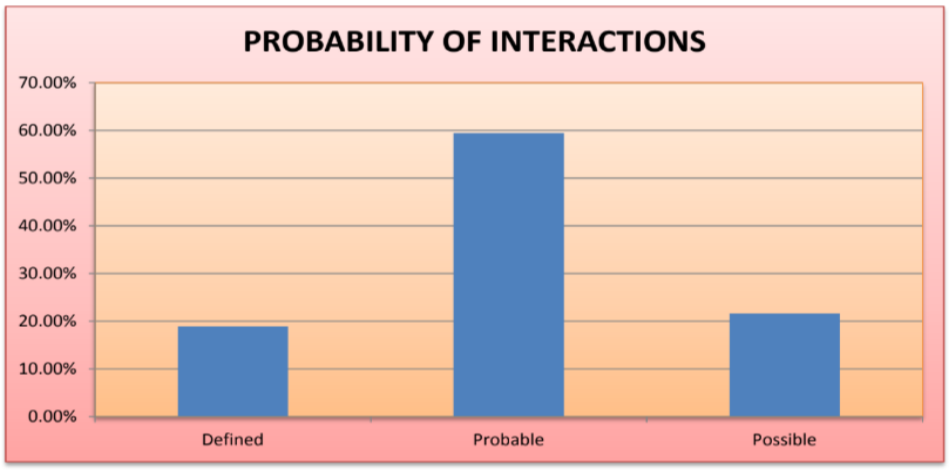
Table10: Evaluation the Probability of Interactions

TITLES	NUMBER	PERCENTAGE
Defined	7	18.91%
Probable	22	59.45%
Possible	8	21.62%

Figure11: Evaluation the Probability of Interactions



Clopidogrel used for several indication or target of actions, these indications could be named as Heart Disease (41.26%), Myocardia Infraction (34.92%), Angina (16.66%), Coronary Artery Bypass Surgery (1.58%), Stroke (10.31%), Artery Atherosclerosis (3.96%) and other unknown condition (6.34%) (Table11) (Figure12).

Table11: Classification of Indications Use for Clopidogrel

DISEASES NAME	NO / PATIENT	PERCENTAGE
Heart Disease	52	41.26%
Myocardia Infraction	44	34.92%
Angina	21	16.66%
Coronary Artery Bypass Surgery	2	1.58%
Stroke	13	10.31%
Artery Atherosclerosis	5	3.96%
other unknown	8	6.34%

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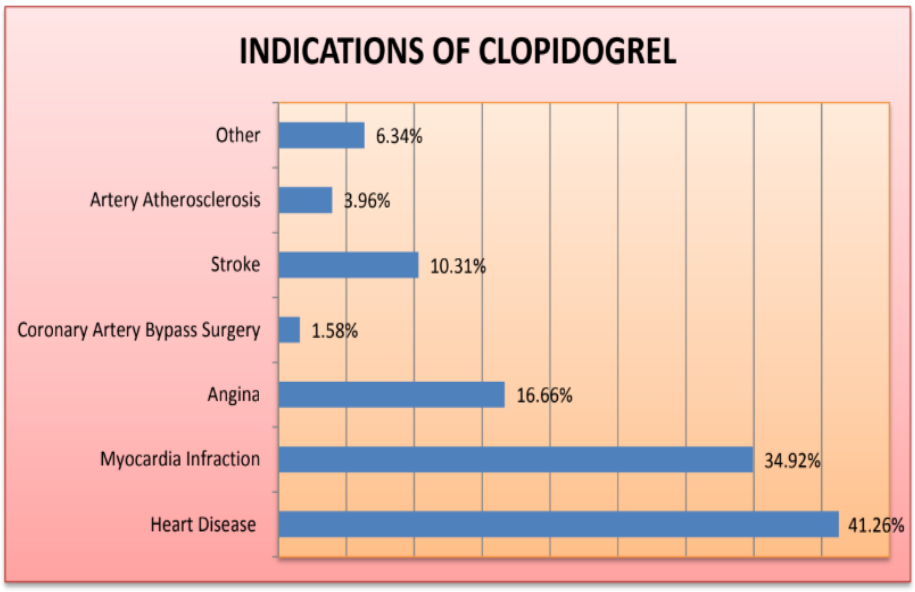
Figure 12: Classification of Indications Use for Clopidogrel



V. DISCUSSION

This study is conducted on 126 patients, 61.90% of these patients were male and 38.09% of these patients were female. Most of patients were under clopidogrel therapy were in ages between 56 to 75 years old, where in Annie Guérin and Reema Mody study the median age of patients were 65 years old and it is done only on female patients. Also in Sheng-Feng Lin study, most age of patients were around 65 years old and male population were more than females, and in Nehad J. Ahmed study the majority of the patients who received clopidogrel were in the ages between 50 to 69. Based on this data we can achieve that mostly patients are exposed top clopidogrel use by any reason are mostly in ages between 50 to 70 years old. Most past and present diseases of patients were cardiovascular diseases Infection Diseases; where in most of studies reviewed for our study cardiovascular conditions were the most popular diseases.

About interactions, 29.36 % interactions identified with clopidogrel (37 patients) 75.67% of them classified within male and 24.32% of them into female. Therefore males were more incidences to show interactions of clopidogrel; other condition like their population of disease and treatment or multiple diseases could be effective on this percentage. Most interactions were between clopidogrel and Pantoprazole, Omeprazole and Aspirin; which could be because of their high significant and helpful need on treatment charts.

Based on the our evaluation in this study on interaction with use of scales (Medscape, lexicomp, Micromedex and etc.), 10.81% were identify as severe interactions, 54.05% were

classify and identify as moderate in their interactions and 35.13% were classify as mild in their interactions. Based on their possibility of relation the effect and interactions, whereas we found that 18.91% of interactions were defined, 59.45% of interactions were probable and 21.62% of them were possible. Therefore we achieved that most of these interaction also could be affected by other situations as disease, foods, environments or drugs. Mechanisms of these interactions mostly were the increasing or decreasing of other drug among two drugs which could be because of same specific enzymes such as CYP2C19, CYP1A2, CYP2B6, CYP2C9 and CYP3A4 . Clopidogrel used for several indication as Heart Disease (41.26%), Myocardia Infraction (34.92%), Angina (16.66%), Coronary Artery Bypass Surgery (1.58%), Stroke (10.31%), Artery, Atherosclerosis (3.96%) and other unknown condition (6.34%) . where in Annie Guérin and Reema Mody study they identified Over three-quarters of patients in both groups had indications for other ischemic heart diseases (76.3% and 79.9%, respectively), and 38.5% and

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40.7%, respectively, suffered recent strokes. And in compare to P. A. KUBLER and P. I. PILLANS, Clopidogrel was predominately used for secondary prevention of ischemic heart disease (60%) and following percutaneous coronary intervention (34%). A significant proportion of patients (29%) received clopidogrel outside the prescribing guidelines.

VI. CONCLUSION

According to data collected in this study and its compare to other study, clopidogrel were use in patients with ages between 56 to 75 years old more in males and with most past and present diseases of cardiovascular diseases. One of four patients had clopidogrel interactions with other drugs, where mostly found in male than females. Available data suggest that pantoprazole is the PPI most likely to have a significant interaction with clopidogrel. Pantoprazole should be used since it is the PPI least likely to interact with clopidogrel but caution should be exercised in the concomitant. Physicians may have been more inclined to switch patients or to start prescribing clopidogrel combination therapy with a treatment that was available but in study level of it. Clopidogrel was used frequently and mainly alone without combination. It is important to prescribe it appropriately and it is the responsibility of pharmacists to check for the appropriateness of its dispensing and to check for drug-drug interactions before dispensing it.

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