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# Clopidogrel efficacy with concomitant drug therapy in patients undergoing percutaneous coronary intervention

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ABSTRACT

Clopidogrel, as an adjunct to aspirin, has been recommended for patients undergoing percutaneous coronary intervention (PCI) to reduce adverse cardiovascular events. Clopidogrel needs activation via the cytochromes P450 enzymes. Concomitant use of clopidogrel with drugs that utilize the same enzymatic pathway may interfere with its conversion to an active form. This study aims to assess the impact of concomitant drug therapy on clopidogrel efficacy in patients undergoing PCI and to identify the association between the use of those drugs and the risk of future adverse cardiac events. A total of 126 medical records for patients followed at King Fahad Specialist Hospital, and King Saud Hospital in Qassim, Saudi Arabia, were reviewed. Patients were divided into six groups: First group clopidogrel, second to fourth group clopidogrel plus proton pump inhibitors (PPIs)/calcium channel blockers (CCBs)/statins, fifth group clopidogrel with either PPIs, CCBs, statins, and sixth group clopidogrel plus PPIs, CCBs, and statins. Descriptive statistics were performed to detect the correlation between the concomitant drug used and MACEs. Out of the total number, 58 patients had MACEs. The correlation between MACEs and medications used in the groups of clopidogrel with PPIs, statins, or combinations of PPIs with CCBs and statins, or combination of two drugs had a MACEs rate of 12% (P= 0.027), 17.2% (P= 0.0041), 19% (P= 0.0021), 43.1% (P= 0.0001) respectively in comparison to 3.45% in the clopidogrel group. Therefore, concomitant use of clopidogrel with PPIs, statins, or combinations of PPIs with CCBs and statins, or a combination of two drugs is associated with a higher risk of MACEs. This suggests that these medications may attenuate the antiplatelet effect clopidogrel. Prospective randomized studies are needed to provide firm evidence for this interaction.



## 1. Introduction

Acute coronary syndrome (ACS) is a life-threatening condition that potentially affects millions of individuals each year (Collet et al., 2014). According to American Heart Association (AHA) statistics, the number of hospital discharges with ACS in the United States in 2010 was 652,000 patients (262,000 females and 363,000 males) (Thom et al., 2006). It is characterizing by a range of myocardial ischemic situations, which includes Non-ST elevated myocardial infarction (NSTEMI), ST-elevated myocardial infarction (STEMI), or unstable angina (UA). The term non–ST-segment elevation-ACS (NSTE-ACS) includes both NSTEMI and UA (Smith et al., 2015).

The hallmark of ACS is the acute imbalance between myocardial oxygen supply and demand, which is caused by blockage of a coronary artery secondary to the formation of thrombus above atheroma plaque, which is rich with lipids that have undergone rupture or erosion. Once plaques fissured or ruptured, the content of plaque uncovered and exposed, leading to platelet activation and formation of a thrombus as well as ischemia in the corresponding myocardial area (Crea and Liuzzo, 2013; Amsterdam et al., 2014).

All patients present with ischemic symptoms should be evaluated for ACS by assessment of the patient's history, clinical presentation, and finding on physical examination, cardiac biomarkers, electrocardiogram (ECG) change, and imaging.

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However, the collection of the past medical history of patients with ACS is fundamental in assuring the desired diagnosis and treatment. Furthermore, nature of angina symptoms, previous history of coronary artery disease (CAD), age, sex of the patient, and risk factors for ACS including diabetes mellitus, hypertension, smoking, peripheral vascular disease (PVD) should be considered (Kumar and Cannon, 2009; Smith et al., 2015).

The identification and management of ACS continue to be an important public health concern. For both NSTE-ACS and STEMI, initial therapies may include oxygen if blood oxygen saturation is less than 90% or when patients have respiratory distress, intravenous opioid analgesia, and buccal or sublingual nitrates to relieve pain, anxiety, and breathlessness. To achieve relief of cardiac ischemia and to prevent the recurrence of adverse cardiac events patients should be given anti-ischemic agents include, β-blockers, calcium channel blockers (CCBs), nitrates, angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor blocker for patients who cannot tolerate ACE inhibitors), and ranolazine. Antiplatelet therapy also should be given, which includes aspirin, P2Y12 inhibitors like clopidogrel, prasugrel, and ticagrelor. Moreover, oral and parenteral anticoagulants (Kumar and Cannon, 2009; Henderson, 2014).

In addition to medical therapy, there are two management pathways for treating patients with NSTE-ACS, which include an early invasive strategy (routine invasive) and an initial conservative strategy. The early invasive strategy consists of routine coronary angiography followed by revascularization, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), as appropriate and clinically indicated. The initial conservative strategy contains initial therapeutic treatment followed by catheterization and revascularization only for patients with recurrent ischemia despite taking medical therapy (Kumar and Cannon, 2009).

Today, the management of patients with STEMI is based on two types of strategies reperfusion and revascularization by using both pharmacologic such as the fibrinolytic agent that triggers the body's own fibrinolytic system and mechanical interventions such as PCI that reduce the obstruction (Kumar and Cannon, 2009). Fibrinolytic therapy is indicated for patients with the absence of contraindications and for patients with symptom onset within the previous 12 hours (Smith et al., 2015). Reperfusion therapy should be started to all appropriate patients with symptoms before 12 hours (Kumar and Cannon, 2009). In a meta-analysis of 23 randomized clinical trials, Keeley et al. (2003) made a comparison between primary PCI and fibrinolytic therapy. They found that primary PCI was better than fibrinolytic therapy in decreasing the incidence of short and long-term adverse outcomes and death.

The PCI represents the cornerstone for the treatment of patients with ACS. It is a non-surgical technique widely used to treat narrowing and stenosis for mechanically improving myocardial perfusion in coronary artery disease. A balloon is used to dilate the coronary narrowing and implanting of a stent open the vessel. It improves the prognosis and symptoms for patients presenting with ACS, particularly STEMI (Ludman, 2018). The types of stents implanted include bare-metal stents, which used in over 90% of all PCI procedures and drug-eluting stents. This elutes an antiproliferative drug into the vessel wall for a few weeks after implantation to reduce the problem of restenosis (Serruys et al., 2009).

For patients undergoing PCI, optimal antiplatelet therapy has been recommended for secondary prevention after an ACS to diminish adverse cardiovascular events, inhibit platelet aggregation, reduce coronary stent thrombosis, and prevent future heart attacks. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is a base in the treatment of ACS after PCI (Focks et al., 2013; Nagavi et al., 2016).

Clopidogrel is a thienopyridine inactive pro-drug that need to biotransformation via the cytochromes P450 enzyme system to form active metabolites. Approximately 85% of clopidogrel undergo hydrolysis to an inactive carboxylic acid derivative by esterase, and only 15% of clopidogrel metabolized to its active 5-thiol metabolite by hepatic cytochrome P450 enzymes, mainly cytochrome CYP3A4/5 and CYP2C19, in addition to CYP2B6, CYP1A2, and CYP2C9 (Xiao et al., 2017). It irreversibly inhibits adenosine-5-diphosphate (ADP) binding to the platelet P2Y12 receptor on the cell membranes of platelet, and the subsequent ADP mediated activation of the glycoprotein GPIIb/IIIa complex, thereby preventing thrombosis and platelet activation in patients underwent PCI and stent implementation (Wang et al., 2015).

CYP activity is influenced by physical and genetic factors. Carriers of a reduced or loss-function allele of CYP2C19 show a decreased in response to clopidogrel, with 25% decrease in platelet inhibition, and 30% reduced biotransformation of clopidogrel to its active metabolite and increased cardiovascular events, MI, and stroke compared with patients with normal CYP2C19 function (Bates et al., 2011). On the other hand, medications prescribed with clopidogrel like lipid-lowering agents, glucose-lowering agents, antihypertensive drugs have been suggested as a treatment strategy to reduce cardiovascular risk may increase the risk for drug-drug interaction (Bates et al., 2011; Kwok and Loke, 2012).

Proton pump inhibitors (PPIs) are often prescribed as prophylaxis in patients taking clopidogrel to reduce gastrointestinal (GI) complications such as ulceration and related bleeding. The PPIs are pro-drugs that are activated via liver enzyme cytochrome P450 2C19, thereby decreasing the bioavailability of the enzyme, and reduce its ability to inhibit platelet activation and aggregation processes (Focks et al., 2013). However, studies have suggested that the co-administration of lansoprazole or omeprazole may reduce the

antiplatelet effect of clopidogrel, whereas this interaction was not found with omeprazole or pantoprazole (Hulot et al., 2010). Ho et al. (2009) studied 8.205 patients discharged after hospitalization for ACS and found an increased risk for rehospitalization and mortality for patients treated with clopidogrel plus PPIs compared with patients who treated with clopidogrel alone.

Patients with ACS also need statins therapy because they are most likely to have a high cholesterol level. Statins are lipid-lowering agents act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which decreases long-term morbidity and mortality in patients with cardiovascular disease. Lipophilic statins (lovastatin, simvastatin, and atorvastatin) are eliminated by CYP3A4 and undergo similar clopidogrel metabolic pathways, but hydrophilic statins (rosuvastatin, pravastatin, and fluvastatin) are not significantly metabolized by this isoenzyme (Bates et al., 2011; Nagavi et al., 2016). Therefore, lipophilic statins influence antiplatelet efficacy of clopidogrel (Bates et al., 2011).

Calcium-channel blockers (CCBs) were frequently prescribed to decrease blood pressure in hypertensive patients with manifestations of cardiovascular disease. Dihydropyridine CCBs (amlodipine, nifedipine) metabolized via CYP3A4, thereby decreasing the bioavailability of the enzyme and interfere with the conversion of clopidogrel to its active form (Peng et al., 2011). Recently, Gremmel et al. (2015) stated that CCBs reduce the efficacy of clopidogrel on ADP-induce platelet activation in patients undergoing angioplasty or stent implementation. However, the effect of CCBs on clopidogrel efficacy is still unclear (Peng et al., 2011). Consequently, in this study, we aimed to evaluate the impact of concomitant drug therapy on clopidogrel efficacy in patients undergoing percutaneous coronary intervention.

## 2. Methods

### *Study design*

A retrospective cross-sectional study was conducted in the department of cardiology at King Fahad Specialist Hospital (KFSH) and King Saud Hospital (KSH) in Qassim, Saudi Arabia, for patients undergoing PCI. The study was ethically approved by the National Committee of Bio-Ethics (NCBE).

### *Study population*

Patients followed at KFSH, and KSH, undergoing PCI and already on clopidogrel.

### *Inclusion criteria*

Patients of both genders, already on clopidogrel.

### *Exclusion criteria*

Patients were excluded from the study if they have a severe cardiac dysfunction with the left ventricular ejection fraction of 30% or less, severe renal failure with glomerular filtration rate (GFR) ≤25 mL/min/1.73m$^2$, hepatic function failure with aspartate aminotransferase (AST) and alanine transaminase (ALT) ≥80U/L, systemic immune system diseases, patients with a serious infection, hematologic diseases, malignant tumor, and pregnancy and lactation.

### *Sample size*

A total of 135 patients' medical records were reviewed in cardiology clinics at KFSH and KSH; of them, 126 patients met the inclusion criteria and included in the study (Fig. 1).

### *Study instrument*

The data was retrieved from the medical records of patients who underwent PCI at KFSH and KSH. The data collection form was designed with four sections. Section one includes demographics data, section two includes laboratory investigation, section three includes medical history, and section four includes the medications used. The data collection took place between March and April 2018.

### *Statistical analysis*

The results presented as numbers and frequencies for categorical variables and as the mean±standard deviation (SD) for continuous variables. The comparisons between groups by use of Chi-squared test for categorical variables and one-way analysis of variance (ANOVA) or unpaired Student's t-test for continuous variables. Statistical significance is defined as P value (P≤0.05). All statistical analyses were performed using statistical software SPSS version 23.

## 3. Results

### 3.1. Socio-demographic and clinical characteristic of patients

This study enrolled 126 patients who underwent PCI. They were divided into 6 groups according to medications they received after PCI as follow: Group (1) clopidogrel alone, (group II) clopidogrel plus PPI, (group III) clopidogrel plus CCBs, (group IV) clopidogrel plus statin, (group V) clopidogrel with a combination of PPIs plus CCBs or PPIs plus Statins or CCBs plus Statins, and (group VI) clopidogrel plus PPIs, CCBs, and statins.

Table 1 showed the demographic and clinical characteristics of patients in relation to the different groups. In all groups, the majority of patients were males of the highest age in group III (61.6±5.59). Regarding medical history, hypertension is more prevalent in group II, and III (80%), followed by diabetes (62%) which is more prevalent in group I. The majority of patients in all groups were having STEMI as PCI indication, and drug-eluting stents was the major type of stent used for all groups.

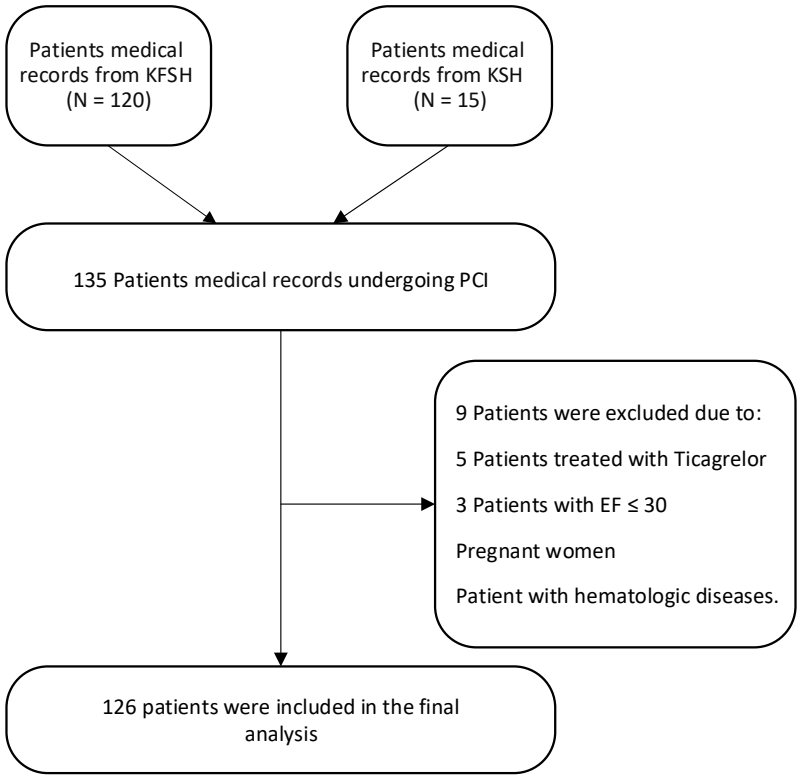



**Fig. 1:** Flowchart of the process of selections of patients' medical records

**Table 1:** Demographic and clinical characteristic of patients (N = 126)

| Characteristics | Group I | Group II | Group III | Group IV | Group V | Group VI |
|---|---|---|---|---|---|---|
| N | 16 | 10 | 5 | 23 | 57 | 15 |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Gender | | | | | | |
| Male | 12 (75) | 7 (70) | 3 (60) | 18 (78) | 47 (82) | 13 (87) |
| Female | 4 (25) | 3 (30) | 2 (40) | 5 (22) | 10 (18) | 2 (13) |
| Age in years | 60.5±10.03 | 55.4±7 | 61.6±5.59 | 59.35±11.76 | 57.39±12.66 | 56.6±10.68 |
| BMI (kg/m²) | 27.66±3.07 | 29.78±6.17 | 29.43±3.04 | 27.51±3.92 | 28.83±4.91 | 31.72±4.61 |
| Medical History/Status | | | | | | |
| Hypertension | 9 (56) | 8 (80) | 4 (80) | 13 (57) | 39 (68.4) | 9 (60) |
| Diabetes Mellitus | 10 (62) | 6 (60) | 3 (60) | 14 (61) | 35 (61.4) | 5 (33.6) |
| Acute MI first cardiovascular events | 8 (50) | 4 (40) | 2 (40) | 15 (65) | 34 (60) | 10 (67) |
| Current Smoker | 4 (25) | 6 (60) | 1 (20) | 8 (35) | 20 (35) | 4 (27) |
| Previous PCI | 5 (31) | 5 (50) | 1 (20) | 1 (4) | 11 (19) | 3 (20) |
| Dyslipidemia | 2 (12) | 4 (40) | 2 (40) | 7 (30) | 6 (10.5) | 3 (20) |
| Previous Stroke and TIA | 1 (6.25) | 1 (10) | 2 (40) | 0 | 4 (7) | 4 (26.7) |
| Peripheral-artery disease | 0 | 1 (10) | 2 (40) | 1 (4) | 3 (5) | 3 (20) |
| Family History of CAD | 1 (6.25) | 2 (20) | 0 | 1 (4) | 3 (5) | 0 |
| Previous MI | 1 (6.25) | 2 (20) | 0 | 0 | 1 (2) | 1 (7) |
| PCI Indication | | | | | | |
| STEMI | 10 (62) | 4 (40) | 2 (40) | 17 (74) | 41 (72) | 13 (87) |
| NSTEMI | 2 (12) | 2 (20) | 2 (40) | 4 (17) | 8 (14) | 1 (7) |
| Unstable Angina | 4 (25) | 4 (40) | 1 (20) | 2 (9) | 8 (14) | 1 (7) |
| Number of Stents | | | | | | |
| One | 11 (69) | 8 (80) | 4 (80) | 16 (70) | 45 (79) | 8 (53) |
| Two | 5 (31) | 1 (10) | 0 | 7 (30) | 12 (21) | 5 (33.6) |
| Three or more | 0 | 1 (10) | 1 (20) | 0 | 0 | 2 (13) |
| Type of Stents | | | | | | |
| Drug-eluting stents | 15 (93.7) | 10 (100) | 5 (100) | 22 (96) | 56 (98) | 15 (100) |
| Bare metal stents | 1 (6) | 0 | 0 | 1 (4) | 1 (2) | 0 |

Results are expressed as number and percentage (%). Group I: Clopidogrel alone; Group II: Clopidogrel+PPIs; Group III: Clopidogrel+CCBs; Group IV: Clopidogrel+Statins; Group V: Clopidogrel with either PPIs, CCBs, Statins; Group VI: Clopidogrel+PPIs+CCBs+Statins. N: Number of patients; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; TIA: Transient Ischemic Attack; CAD: Coronary Artery Disease

### 3.2. Laboratory investigations

Laboratory data of patients revealed that among the 6 groups of patients, the level of hemoglobin elevated in group IV (14.1±2.3). Also, platelet count was high in group VI (323.3±74.8) and was statistically significant from the group I (P=0.026). On the other hand, BUN and creatinine were higher in group I than in other groups. The analysis revealed that the creatinine level of patients in Group III has significant differences from those in group I (P=0.053), as shown in Table 2.

**Table 2:** Laboratory data of patients (N = 126)

| Parameters | Group I | Group II | Group III | Group IV | Group V | Group VI |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dL) | 13.0±1.9 | 12.9±2.0 | 12.0±2.9 | 14.1±2.3 | 13.9±2.1 | 13.9±2.3 |
| Platelet ($10^9$/L) | 260.5±48.0 | 278.4±68.9 | 275±45.3 | 298±73.7 | 312.9±75.0 | 323.3±74.8[a] |
| BUN (mmol/L) | 6.9±2.9 | 6.5±1.3 | 4.2±3.0 | 5.8±1.8 | 5.9±2.5 | 6.2±2.7 |
| Creatinine (µmol/L) | 92.9±45.6 | 81.4±20.1 | 67.5±12.0[a] | 84.2±24.1 | 83.4±26.1 | 83.1±28.0 |
| LDL (mmol/L) | 3.7±1.0 | 3.9±0.8 | 3.9±1.3 | 3.8±0.8 | 3.9±0.7 | 3.8±0.7 |
| HDL (mmol/L) | 0.9±0.2 | 0.9±0.3 | 1.0±0.1 | 0.9±0.2 | 0.8±0.2 | 0.8±0.2 |

Results are expressed as mean+standard deviation. Group I: Clopidogrel alone; Group II: Clopidogrel+PPI; Group III: Clopidogrel+CCBs; Group IV: Clopidogrel+Statins; Group V: Clopidogrel with either PPIs, CCBs, Statins; Group VI: Clopidogrel+PPIs+CCBs+Statins. BUN: Blood Urea Nitrogen; LDL: Low-Density Lipoprotein; HDL: High Density Lipoprotein. [a] Significant difference from group I

### 3.3. Association between MACEs and demographic and clinical characteristic of patients

Table 3 presented the correlation between MACEs versus demographic and clinical characteristics of patients. The result showed that MACEs have a significant association with diabetes mellitus and the number of stents (P=0.021 and 0.046), respectively.

**Table 3:** Correlation between MACEs and Demographic and clinical characteristic of patients

| Characteristics | MACEs | $X^2$ | P-value |
|---|---|---|---|
| N | 58 | | |
| Gender | N (%) | | |
| Male | 48 (83) | 0.756 | 0.385 |
| Female | 10 (17) | | |
| Age in years | 59.9±11.1 | 0.151 | 0.092 |
| BMI (kg/m$^2$) | 29.7±5.1 | 0.164 | 0.067 |
| Medical History/Status | | | |
| Hypertension | 42 (72) | 3.092 | 0.111 |
| Diabetes Mellitus | 40 (69) | 5.364 | **0.021** |
| Acute MI first cardiovascular events | 36 (62.1) | 1.531 | 0.385 |
| Current Smoker | 19 (32.8) | 0.009 | 0.765 |
| Previous PCI | 13 (22.4) | 0.208 | 0.649 |
| Dyslipidemia | 11 (19.0) | 0.01 | 0.983 |
| Previous Stroke and TIA | 8 (13.7) | 2.383 | 0.132 |
| Peripheral-artery disease | 5 (8.6) | 0.04 | 0.793 |
| Family History of CAD | 4 (7) | 0.368 | 0.544 |
| Previous MI | 2 (3.4) | 0.076 | 0.782 |
| PCI Indication | | | |
| STEMI | 43 (74) | 1.501 | 0.472 |
| NSTEMI | 8 (14) | | |
| Unstable Angina | 7 (12) | | |
| Number of Stents | | | |
| One | 38 (66) | 0.199 | **0.046** |
| Two | 16 (27) | | |
| Three or more | 4 (7) | | |
| Type of Stents | | | |
| Drug-eluting stents | 57 (98) | 0.199 | 0.655 |
| Bare metal stents | 1 (2) | | |

Results are expressed as number and percentage (%). MACEs: Major Adverse Cardiac Events; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; TIA: Transient Ischemic Attack; CAD: Coronary Artery Disease

### 3.4. Association between MACEs and Laboratory parameters

Regarding laboratory data, means and standard deviation were used to presents all continuous variables. The result revealed that platelet count was significant (P<0.001) correlation against MACEs, while other laboratory variables showed no significant correlation, as shown in Table 4.

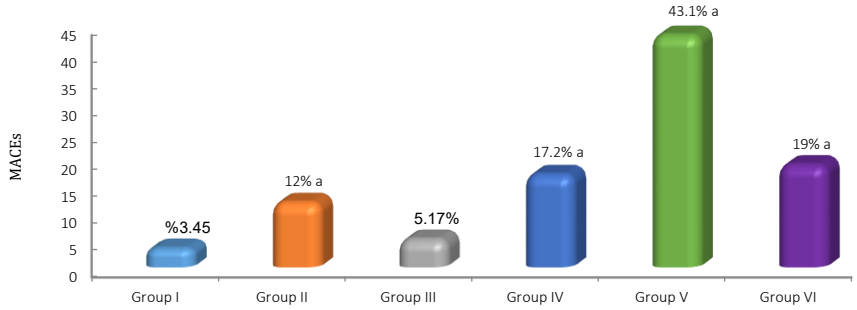
### 3.5. Distribution of MACEs among different groups of patients

Fig. 2 showed that there was a correlation between MACEs and different groups of patients. It revealed that group II (P=0.027), group IV (P=0041), group V (P=0.0001), and group VI (P=0.0021) were statistically correlated with MACEs with group I. However, group III showed no significant association (P=0.319) with MACEs.

**Table 4:** Correlation between MACEs and laboratory data (N = 58)

| Parameters | MACEs | r | P-value |
|---|---|---|---|
| Hemoglobin (g/dL) | 14.0±2.0 | 0.133 | 0.138 |
| Platelet ($10^9$/L) | 338.8±58.4 | 0.537 | **< 0.001** |
| BUN (mmol/L) | 6.1±2.0 | 0.111 | 0.215 |
| Creatinine (µmol/L) | 86.8±21.6 | 0.026 | 0.769 |
| LDL (mmol/L) | 3.9±0.7 | 0.057 | 0.523 |
| HDL (mmol/L) | 0.9±0.2 | 0.117 | 0.191 |

Results are expressed as mean±standard deviation. r: Personal correlation; MACEs: Major Adverse Cardiac Events; BUN: Blood Urea Nitrogen; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein




MACEs: Major Adverse Cardiovascular Events; Group I: Clopidogrel alone; Group II: Clopidogrel+PPIs; Group III: Clopidogrel+CCBs; Group IV: Clopidogrel+Statin; Group V: Clopidogrel with either PPIs, CCBs, Statins; Group VI: Clopidogrel +PPIs+CCBs+Statins.

**Fig. 2:** Correlation between MACEs and different groups of patients (N=58)

## 4. Discussion

Clopidogrel is a pro-drug that requires hepatic metabolism by cytochrome P-450 isoenzymes, namely CYP3A4 and CYP2C19 (Arbel et al., 2013). This study revealed that patients who were discharged on concomitant clopidogrel and PPIs, statins, or combinations of PPIs with CCBs and statins, or combination of two drugs, have a higher incidence of major adverse cardiovascular events after PCI compared to patients who were discharged on clopidogrel alone.

The CYP2C19, which metabolized PPIs, may interact with clopidogrel metabolism (Macaione et al., 2012). In this study, patients discharged on clopidogrel with PPIs after PCI returned with MACEs (P=0.027) compared with those who discharge on clopidogrel alone. The mechanism of the significant interaction with PPIs was reported by Gilard et al. (2008), who stated that omeprazole significantly decreased clopidogrel effects on platelet activity, due to competition towards CYP2C19. They found that patients on concomitant use of clopidogrel with omeprazole after PCI had the less inhibitory effect of platelet aggregation. Moreover, the study done by Juurlink et al. (2009) showed that concomitant use of clopidogrel with PPIs following acute MI is associated with a 27% higher risk of re-infarction.

In addition to that, a retrospective cohort study found that clopidogrel with PPIs was associated with a higher rate of MACEs within one year after coronary stent placement (Kreutz et al., 2010). Gupta et al. (2010), in a retrospective cohort study of 315 patients, reported that the incidence of MACE was significantly higher in patients discharged on concomitant clopidogrel with PPI therapy (MACE rate of 56% vs. 38% in patients with clopidogrel alone). On the other hand, a randomized trial found omeprazole therapy did not elevate the rates of MACEs in patients receiving concomitant therapy with clopidogrel (Bhatt et al., 2010).

Statins which metabolized by CYP3A4, such as simvastatin, atorvastatin, and lovastatin attenuate the antiplatelet effects of clopidogrel treatment due to interference with bioactivation of clopidogrel (Malmström et al., 2009). In our study, patients discharged on clopidogrel with statins after PCI exhibit MACEs (P=0.0041) compared with those who use clopidogrel alone. Several studies have attempted to address if the pharmacokinetic interaction among statins and clopidogrel is of clinical importance. Brophy et al. (2006) reported that patients on concomitant use of clopidogrel and atorvastatin had increased risk for MI, unstable angina, repeat revascularization, cerebrovascular events, and death within 30 days, compared with clopidogrel alone. Moreover, Lau et al. (2003), in a study conducted in 44 subjects, found an interaction between clopidogrel and the CYP3A4 metabolizing statin, atorvastatin. contradictory to our results, Malmström and his colleagues in a prospective, randomized study revealed that treatment with CYP3A4 metabolized statins, simvastatin or atorvastatin, did not decrease the antiplatelet effect of clopidogrel maintenance treatment compared with the rosuvastatin which metabolized by non-CYP3A4 (Malmström et al., 2009).

The CCBs and Statins are used widely in cardiology, and the chance of their co-administration with clopidogrel is very high (Urtane et al., 2013). CCBs inhibit CYP3A4, interfere with the activation of clopidogrel (Siller-Matula et al., 2008). In our study, patients discharged with CCBs after PCI showed no association with an increased incidence of MACEs (P= 0.319) compared with the use of clopidogrel alone. In agreement with our result, Ojeifo et al. (2013) study showed that the use of CCBs was not associated with increased risk of cardiovascular events in patients treated with clopidogrel (Ojeifo et al., 2013). Also, Harmsze et al. (2010), in the study, included 623 patients undergoing PCI, found that only patients with amlodipine and not with other CCBs have a poor response to clopidogrel. In a post hoc analysis of the clopidogrel for the reduction of events during observational study found no evidence that CCBs reduce clopidogrel efficacy. In contrast, a recent study about the concomitant use of CCBs, specifically verapamil and several dihydropyridines, showed that there is an alteration in the platelets' inhibitory effect of clopidogrel among patients (Good et al., 2012).

On the other hand, our study showed that patients who discharged on a combination of PPI, statin, and CCB were prone to MACEs (P=0.0021) compared with those who discharged on clopidogrel alone. Our results were in disagreement with a study

conducted in patients with ACS undergoing PCI, and the study revealed that the use of CCBs or statins was not associated with an increased risk of cardiovascular events in clopidogrel-treated patients. The results were observed when the drugs were administered alone, together, and also in combination with PPIs (Siller-Matula et al., 2008). Therefore, future studies may be needed to focus on the dose of medications and the association of adverse events in patients undergoing PCI.

## 5. Conclusion

Overall, we found that concomitant use of clopidogrel with PPIs, CYP3A4 metabolized statins, or combinations of PPIs with CCBs and statins, or combination of two drugs among patients following PCI is associated with a higher risk of MACEs compared to patients who were discharged on clopidogrel alone. Our results support the previous studies that reported co-administration of these medications might attenuate the clopidogrel's bioactivation and its beneficial antiplatelet effect to a range that might be clinically important.

In our study, the significance of interaction between clopidogrel and these medications and its impact on clinical outcomes of patients with cardiovascular disease has only been addressed retrospectively. However, large prospective randomized clinical trials are needed to rule out or prove a clinically relevant interaction between clopidogrel and these medications.

## Compliance with ethical standards

## Conflict of interest

The authors declare that they have no conflict of interest.

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