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The potential interaction of statins and clopidogrel in patients undergoing percutaneous coronary intervention

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ABSTRACT

Clopidogrel is widely used for patients with acute coronary syndrome. It is a pro-drug that requires bioactivation by several cytochrome P450 (CYP) enzymes, mainly CYP3A4, CYP2C9, and CYP2C19 enzymes. Lipophilic statins such as atorvastatin are used concomitantly with clopidogrel due to their beneficial effects on morbidity and mortality in the arena of cardiovascular diseases. However, lipophilic statins are eliminated by CYP3A4 and undergo the same metabolic pathway of clopidogrel. Hence, statins may compete with clopidogrel for CYP3A4 enzyme resulting in diminishing the anti-platelet effect of clopidogrel. We aimed to study the impact of concomitant statin therapy on clopidogrel efficacy in patients undergoing percutaneous coronary intervention (PCI) evaluate the clinical relevance of potential clopidogrel and statins interaction and association between use of statins and risk of future adverse cardiac events. A cross-sectional retrospective cohort study was conducted on 50 patients attending Prince Sultan Cardiac Center for follow-up after PCI. All patients discharged on clopidogrel, aspirin, and atorvastatin were later divided into two groups according to the occurrence of MACEs. Statistical analysis was performed by Statistical Package for the Social Science (SPSS; V. 21.0). This study was on adult and geriatric males (72%)and female (28%). More than half of them exhibited major adverse cardiac events (MACEs), of which 48% exhibited it after 4 to 6 months from PCI indexing followed by 1 to 3 months (34%), and the least after 7 to 9 months. A significant association arises between gender and MACEs (P=0.042). Moreover, the average age was significantly higher in patients who experience MACEs compared to others (62.7 vs. 55.4, P=0.037). Regarding comorbidities, hypertension increased in patients with MACEs (73.1%) compared to those without MACEs (45.8%). The average duration of taking clopidogrel was significantly shorter in patients with MACEs compared to those who did not (3.42 vs. 5.54 months, P<0.001). According to the findings of this study, atorvastatin affects clopidogrel efficacy in patients undergoing PCI.

1. Introduction

Coronary heart disease (CHD) is the main type of cardiovascular disease (CVD) that causes death. Therefore, it represents a major cause of the illness burden (Kleib et al., 2018). In Saudi Arabia, mortality reaches about 24.34% of the total number of death, according to data published by the WHO (Al Ahmari et al., 2017). Cigarette smoking, high blood pressure, diabetes, Mellitus, excessive dietary, fat intake, and lack of exercise have been reported as independent risk factors for CHD (Kleib et al., 2018).

Acute coronary syndrome (ACS) is a term that refers to any category of clinical signs and symptoms associated with acute myocardial ischemia. It involves unstable angina (UA), Non-ST segment elevation of myocardial infarction (NSTE-MI), and ST-segment elevation of myocardial infarction (STE-MI), all of which increase the rate of hospitalization, health care burden, and mortality. In the acute phase of ACS, intensive treatment is needed to improve prognosis (Nassr et al., 2019).

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The major causes of ACS were a breach of the coronary atherosclerotic plaque, vasospasm, resulting in platelet adhesion and secondary thrombosis. ACS patients with a specific pathological history were subjected during secondary prevention to the risk of recurrence and adverse cardiovascular events (Liu et al., 2019).

Luckily, a well understanding of the pathophysiology and mechanisms involved in ACS permit improvement in invasive interventions such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting, and secondary prevention by using drugs, such as antiplatelet therapy, angiotensin-converting enzyme blockers (ACEIs), angiotensin II receptor blockers (ARBs), and stains (Nassr et al., 2019). Currently, PCI is the key revascularization technique used in the treatment of ACS (Tang et al., 2019); due to less bleeding, simpler practice, quick procedure, more patient comfort, less, hospitalization time and lower patient and health system costs (Roghani-Dehkordi et al., 2018).

American College of Cardiology/American Heart Association, European Cardiology Society, and China Heart Society (CHS) recommendations all advocate the use of antiplatelet therapy in acute settings for ACS patients. As the major goal in the treatment of ACS is inhibiting platelet activation and consequent aggregation, Chinese diagnostic and therapeutic guidelines recommended the use of clopidogrel (Liu et al., 2019).

Despite the introduction of prasugrel, ticagrelor, and cangrelor (newer P2Y12 ADP blockers), clopidogrel remains the most commonly used drug for secondary prevention for patients with cardiovascular disease who susceptible to thrombotic and ischemic complications due to its low cost and availability (Hernandez-Suarez et al., 2018).

Clopidogrel is a prodrug that needs activation by hepatic cytochrome P450 isoenzymes such as CYP2C19, CYP3A4, and CYP2C9. These isozymes cause irreversible inhibition of the P2Y12 receptor (Burkard et al., 2012). Therefore, coadministration with drugs that metabolize by these isozymes decreases clopidogrel efficacy.

The variability in the response of clopidogrel induced inhibition of platelet accumulation is recognized, and up to 30% of patients do not obtain adequate antiplatelet effect after the first loading dose of clopidogrel (Savi et al., 2000). The hyporesponsiveness to clopidogrel can be attributed to genetic factors associated with metabolic enzymes (e.g., loss of function variant CYP2C19*2) or non-genetic factors such as age>65 years, Type 2 diabetes mellitus, decreased left ventricular function, and renal failure (Geisler et al., 2006; 2008).

Patients taking antiplatelet treatment will be most commonly administered with Proton pump inhibitors for decreasing gastrointestinal bleeding (Nagavi et al., 2016). (PPIs) are commonly used in inpatients, mostly for gastrointestinal bleeding prophylaxis. Both PPIs are metabolized by CYP2C19, at least partially. Current investigations have shown that PPIs, especially omeprazole, diminish clopidogrel efficacy; due to inhibition of CYP2C19 isozyme, which is needed for clopidogrel activation (Burkard et al., 2012).

Statins therapy is necessary for patients with ACS as they are prone to have high cholesterol levels (Chinwong et al., 2015). It decreases cholesterol level and decreases progression and rupture of the plaque by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the key enzyme responsible for cholesterol biosynthesis (Júnior et al., 2010). However, statins safety is a matter of concern because lipophilic statins (atorvastatin, simvastatin, and lovastatin) are metabolized by the same enzyme (CYP3A4) (Park et al., 2017), which involved in the activation of clopidogrel, hence possible interactions may arise between statins and clopidogrel (An et al., 2019).

Many studies have confirmed that statins, particularly those metabolized by CYP3A4, significantly diminished the antiplatelet efficacy of clopidogrel (Lau et al., 2003). However, other studies have shown that statins have no effect on clopidogrel efficacy (Saw et al., 2003). Given to inconsistency and inadequate findings of clopidogrel and statins interaction, the present study aims to determine if statins diminished clopidogrel clinical effectiveness of patients undergoing PCI.

2. Aims/objectives

2.1. General aim

To study the impact of concomitant statins therapy on clopidogrel efficacy in patients undergoing percutaneous coronary intervention.

2.2. Specific objectives

1. To evaluate the clinical relevance of potential clopidogrel and statins interaction.
2. To identify the association between concomitant use of statins and risk of future adverse cardiac events.

3. Research design and methods

3.1. Study design

A retrospective cohort study was conducted on patients who underwent PCI at Prince Sultan Cardiac Center (PSCC)/department of cardiology at King Fahad Specialist Hospital in Al Qassim, Saudi Arabia. The study involved fifty (50) participants, which were later divided into two groups according to the occurrence of MACEs after PCI.

3.2. Inclusion criteria and exclusion criteria

Patients of both gender who underwent PCI at Prince Sultan Cardiac Center and discharged on antiplatelet therapy with clopidogrel. Patients were

excluded from the study if they had: Severe cardiac dysfunction with a left ventricular ejection fraction of 30% or less, severe renal and/or hepatic failure, systemic immune system diseases, serious infections, hematologic diseases, malignant tumor, pregnancy, and lactation.

3.3. Data collection

The data was retrieved from the medical records of patients who underwent PCI at PSCC. The data collection form was designed with four sections as follows: Section one included demographics data, section two laboratory investigation, medical history, and section four concomitant medications used. Biochemical markers that indicate clopidogrel activity, such as Platelet Count and lipid profile (low-density lipoprotein, high-density lipoprotein), were analyzed.

3.4 Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Science (SPSS; V. 21.0). Counts and percentages were used to summarize categorical variables. Mean±SD was used to summarize continuous variables. Chi-square test of independence or Fisher-Exact test was used to test the association between categorical variables. Unpaired t-test was used to assess whether the mean of continuous variables was significantly different between patients that experience MACEs and patients that did not. Pearson's correlation was used to test the association between continuous variables. Hypothesis testing was performed at a 5% level of significance.

4. Results

4.1. Characteristic of study participants

The study enrolled 50 patients who underwent PCI. Out of the total number of patients, 26 experience MACEs, which represent 52% of the sample. The majority of participants (72%) were males, and the rest were females (28%). The mean age of all patients was 59.2±12.5. It increases in a group with MACEs (62.7±13.2). The average BMI for all patients was 28.5±5.43Kg/m2, which indicated that all the participants were overweight. Regarding medical history, hypertension and diabetes mellitus were higher in a group with MACEs (73.1%). Procedural characteristics revealed that STEMI was the frequent cause of PCI indication, followed by unstable angina and NSTEMI. Out of all the participants, Nearly 58% of them received one stent, and 30% had two stents (Table 1).

Results are expressed as number and percentage (%), mean±standard deviation; N: Number of patients; MACEs: Major Adverse Cardiac Events; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CAD: Coronary Artery Disease; STEMI: ST Elevated Myocardial Infarction; NSTEMI: None ST Elevated Myocardial Infarction.

Table 1: Demographic and clinical characteristic of patients (N=50)

Characteristics	Overall	Group I NO MACEs	Group II MACEs
N	50 N(%)	*24* N(%)	26 N (%)
Gender			
Male	36 (72)	21(87.5)	15 (57.7)
Female	14 (28)	3 (12.5)	11 (42.3)
Age in years	59.2 ± 12.5	55.4 ± 10.7	62.7 ± 13.2
BMI (kg/m^2)	28.5 ± 5.4	28.0 ± 5.0	28.8±5.9
Medical History/Status			
Hypertension	30 (60)	11 (45.8)	19 (73.1)
Diabetes Mellitus	32 (64)	13 (54.2)	19 (73.1)
Acute MI first *cardiovascular events*	2 (4)	1 (4.2)	1 (3.9)
Current Smoker	8 (16)	6 (25)	2 (7.7)
Previous PCI	9 (18)	5 (20.8)	4 (15.4)
Dyslipidemia	3 (6)	1 (4.2)	2 (7.7)
Family History of CAD	6 (12)	3 (12.5)	3 (11.5)
Heart failure	7 (14)	2 (8.3)	5 (19.2)
PCI Indication			
STEMI	21(42)	10 (41.7)	11 (42.3)
NSTEMI	12 (24)	5 (20.8)	7 (26.9)
Unstable Angina	15 (30)	8 (33.3)	7 (26.9)
Stable angina	2 (4)	1 (4.2)	1 (3.9)
Number of Stents			
One	29 (58)	14 (58.3)	15 (57.7)
Two	15 (30)	7 (87.5)	8 (30.8)
Three or more	6 (12)	3 (12.5)	3 (11.5)

4.2. Medications used by the study cohort

Fig. 1 showed that the most medications used by the study cohort were proton pump inhibitors (84%), followed by beta-blockers (74%)and angiotensin converting enzyme inhibitors (66%).

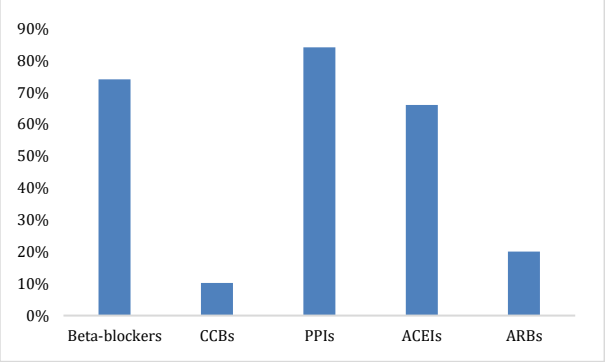

Fig. 1: Concomitant medications used by the study cohort

CCB: Calcium channel blockers; PPIs: Proton pump inhibitors; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers.

4.3. Duration of taking clopidogrel in the study cohort

Regarding the duration of taking clopidogrel, half of the study cohort (50%) have been taking

clopidogrel for 4–6 months, 34% of patients have been taking it for 1-3 months, and 16% have been taking it for 7–9 months (Fig. 2).

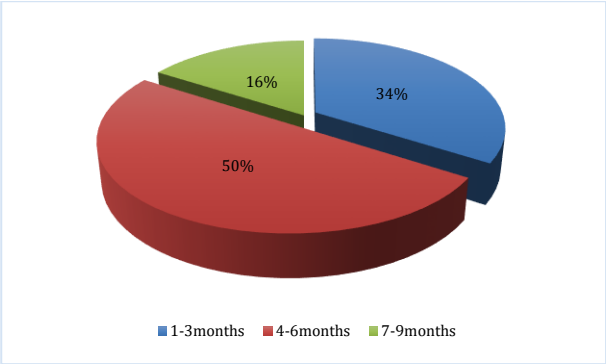

Fig. 2: Duration of taking clopidogrel

4.4. The occurrence of major adverse cardiac events after PCI indexing

Major adverse cardiac events occurred in 26 patients. Nearly (52%) half of the patients experience MACEs (46.2%) after 4 to 6 months from PCI indexing, followed by 1 to 3 months (34%). And the least (15%) after 7 to 9 months after PCI indexing Fig. 3.

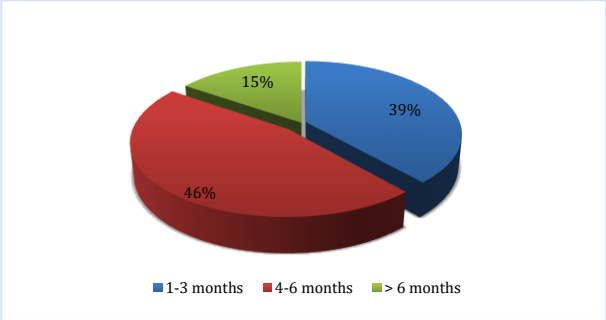

Fig. 3: Major adverse cardiac events after PCI indexing

Fig. 4 showed the distribution of major adverse cardiac events among males and females. Males patients showed higher MACEs (57.7%) in comparison with females

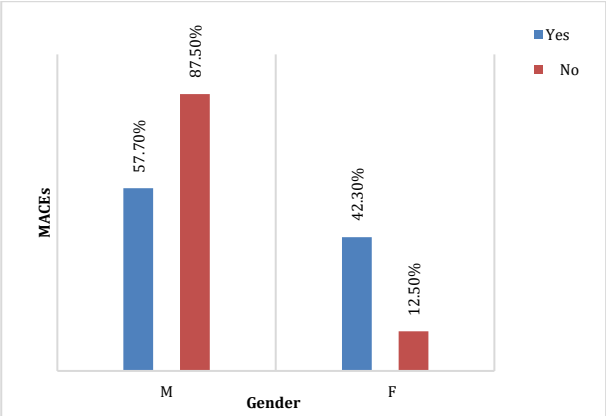

Fig. 4: Distribution of major adverse cardiac events across males and females (N=50)

4.5. Laboratory investigations

Laboratory data of patients revealed that hemoglobin, platelets, and blood urea nitrogen were in the normal range, while creatinine, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were above the normal range (Table 2).

Table 2: Patients' laboratory data (N=50)

Parameters	Mean±SD
Hemoglobin (g/dL)	14.2 (2.0)
Platelet (m3x103)	258 (61.0)
BUN (mmol/L)	5.84 (4.9)
Creatinine (µmol/L)	83.6 (41.1)
LDL (mmol/L)	11.6 (38.0)
HDL (mmol/L)	0.93 (0.23)

Results are expressed as Mean±standard deviation; BUN: Blood Urea Nitrogen; LDL: Low-Density Lipoprotein; HDL: High Density Lipoprotein

4.6. Association between MACEs and duration of taking clopidogrel

The association between MACEs and the duration of taking clopidogrel was presented in Table 3. It was noted that the average duration of taking clopidogrel was significantly shorter in patients who suffered from MACEs compared to those who did not (3.42 vs. 5.54 months, P<0.001*).*

Table 3: Correlation between MACEs and duration of taking clopidogrel

Duration	Group I NO MACEs *N=24*	Group II MACEs *N=26*	P-Value
Clopidogrel months	5.54 (1.7)	3.42 (1.6)	<0.001
Clopidogrel duration:			0.002
<3 months	3 (12.5%)	14 (53.8%)	
3–6 months	14 (58.5%)	11 (42.3%)	
>6 months	7 (29.2%)	1 (3.9%)	

Statistical analysis was performed using the Fisher-Exact test for clopidogrel duration and t-test for clopidogrel months. Results are expressed as number and percentage (%), Number of patients=50, and significance P≤0.05.

4.7. Association between MACEs and demographic, clinical characteristic of patients

The correlation of MACEs with a demographic and clinical characteristic of patients revealed a significant association between MACEs and gender (P<0.05). Moreover, the average age was significantly higher in participants that experience MACEs compared to those who did not (62.7 vs. 55.4, P<0.05).

On the other hand, none of the clinical characteristics was significantly associated with the risk of MACEs at the 5% level of significance. However, the results showed that the proportion of hypertensive patients was higher in patients with MACEs (73.1%) compared to patients without MACEs (45.8%), although the association was statistically significant at the 0.1 level (P=0.094). No

significant association was found between MACEs and procedural characteristics except that STEMI was the predominant cause of PCI indication (Table 4).

Table 4: Correlation between MACEs and demographic and clinical characteristic of patients (N=50)

Demographic and Clinical Characteristic	Group I NO MACEs	Group II MACEs	P-value
N	24	26	
Gender	N (%)	N (%)	
Male	21 (87.5)	15 (57.7)	0.042
Female	3 (12.5)	11 (42.3)	
Age in years	55.4 (10.7)	62.7 (13.2)	0.037
BMI (kg/m2)	28.0 (5.0)	28.8 (5.9)	0.611
Medical History/Status			
Hypertension	11 (45.8)	19 (73.1)	0.094
Diabetes Mellitus	13 (54.2)	19 (73.1)	0.273
Acute MI first *cardiovascular events*	1 (4.2)	1 (3.9)	1.000
Current Smoker	6 (25.0)	2 (7.7)	0.132
Previous PCI	5 (20.8)	4 (15.4)	0.721
Dyslipidemia	1 (4.2)	2 (7.7)	1.000
Family History of CAD	3 (12.5)	3 (11.5)	1.000
Heart failure	2 (8.3)	5 (19.2)	0.420
PCI Indication			
STEMI	10 (41.7)	11 (42.3)	
NSTEMI	5 (20.8)	7 (26.9)	0.965
Unstable Angina	8 (33.3)	7 (26.9)	
Stable angina	1 (4.2)	1 (3.9)	
Number of Stents			
One	14 (58.3)	15 (57.7)	
Two	7 (29.2)	8 (30.8)	1.000
Three or more	3 (12.5)	3 (11.5)	

Statistical analysis was performed using a chi-square test. Results are expressed as numbers and percentage (%), Mean±standard deviation; N: Number of patients; MACEs: Major Adverse Cardiac Events; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CAD: Coronary Artery Disease; STEMI: ST Elevated Myocardial Infarction; NSTEMI: None ST M Elevated Myocardial Infarction.

4.8. Association between MACEs and laboratory parameters

Table 5 showed that the average hemoglobin levels were significantly lower in patients that suffered from MACEs (13.5±1.77 vs. 14.9±2.02g/dl, P<0.05). None of the remaining parameters was significantly associated with the incidence of MACEs.

Table 5: Correlation between MACEs and laboratory data (N=50)

Parameters	Group I NO MACEs N (**24**) Mean ± SD	Group II MACEs N (**26**) Mean ± SD	P-value
Hemoglobin (**g/dL**)	14.9 (2.0)	13.5 (1.8)	0.010
Platelet (**m3x103**)	266 (77.5)	250 (40.5)	0.377
BUN (**mmol/L**)	6.29 (6.9)	5.43 (1.7)	0.561
Creatinine (**µmol/L**)	92.5 (55.5)	75.3 (18.1)	0.158
LDL (**mmol/L**)	23.1 (56.9)	2.48 (0.94)	0.340
HDL (**mmol/L**)	0.84 (0.24)	1.01 (0.21)	0.051

Statistical analysis was performed using an unpaired t-test. Results are expressed as Mean±SD (standard deviation); MACEs: *Major Adverse Cardiac Events*; BUN: Blood Urea Nitrogen; LDL: Low-Density Lipoprotein; HDL: High Density Lipoprotein; N: Number of patients; P≤0.05

5. Discussion

Clopidogrel has been an effective standard treatment option for patients who underwent percutaneous coronary intervention. Statins were recommended for use with clopidogrel in the latest clinical guideline for ACS conditions. It has also been speculated that significant drug-drug reactions may arise when these two drugs are administered together. On the other hand, some studies reported that no interaction occurs between them.

Statins were a well-known therapy used to lower cholesterol levels, safeguard the vascular endothelium, minimize LDL oxidation and consequently inflammation, alleviating atherosclerotic plaques, and improve blood thickness and flow (Sotiriou and Cheng, 2000).

The exact mechanism by which statins modulate platelet function is not fully understood. However, normalization of platelet hyperactivity after treatment with statins in hypercholesterolemic patients augment the hypothesis that statins have both lipid and non-lipid activity (Athyros et al., 2009).

Patients with ACS need statin therapy because they are most likely to have a high cholesterol level. Statins are lipid-lowering agents that act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, leading to decrease long-term morbidity and mortality in patients with cardiovascular disease. Lipophilic statins (lovastatin, simvastatin, and atorvastatin) were eliminated by CYP3A4, thus sharing the same metabolic pathway for clopidogrel. However, hydrophilic statins (rosuvastatin, pravastatin, and fluvastatin) are not significantly metabolized by this enzymatic pathway (Nagavi et al., 2016; Bates et al., 2011).

Little knowledge was found about whether statins can impede the metabolic activation of the prodrug, clopidogrel. This is a matter of concern as both statins and clopidogrel are concomitantly used in patients with acute coronary syndrome who underwent percutaneous coronary intervention (Beaird, 2000). Therefore, the present study was conducted on fifty patients who underwent PCI at Prince Sultan Cardiac Center in the Al Qassim region, Saudi Arabia, to evaluate the possibility of potential interaction between statins and clopidogrel.

The present study revealed that more than half (52%)of our patients who co-administered statins (atorvastatin) with clopidogrel after PCI exhibited MACEs. Nearly half of participants experience major adverse cardiac events (MACEs) after 4 to 6 months from PCI indexing, followed by 1 to 3 months (34%), and the least (15%)MACEs occur 7 to 9 months after PCI indexing. In consistent with our finding, Canadian study involved 2927 patients reported that coadministration of atorvastatin with clopidogrel

increase MACEs after PCI by 1.65-fold (Schmidt et al., 2012).

Moreover, Lau et al. (2003) stated that concomitant use of CYP3A4 metabolizing statin, atorvastatin with 300mg loading dose of clopidogrel diminished the inhibitory effect of clopidogrel on platelet aggregation. Similarly, Brophy et al. (2006) reported that patients on concomitant use of clopidogrel and atorvastatin presented an increase in risk for MI, unstable angina, repeat revascularization, cerebrovascular events, and death within 30 days, compared with those who received clopidogrel alone (Brophy et al., 2006).

In contrast, several clinical studies have failed to demonstrate adverse clinical outcomes when co-administering a CYP3A4-metabolized statin with clopidogrel (Park et al., 2017). Serebruany et al. (2004) conducted a study on three groups of patients who underwent PCI; group one is taking atorvastatin, the other group is taking other statins, and the third group does not take statins. The study showed no differences in the degree of platelet inhibition by clopidogrel among the three groups (Serebruany et al., 2004). Moreover, a prospective, randomized study by Malmström et al. (2009) reported differences between several metabolized statins related to possible interferences with the platelet inhibitory effect of clopidogrel. The study concluded that treatment with CYP3A4 metabolized statins like simvastatin or atorvastatin did not decrease the antiplatelet effect of clopidogrel maintenance treatment compared with non-CYP3A4 metabolized rosuvastatin (Malmström et al., 2009).

Regarding the personal characteristic of our participants, the majority were males (72%), and the rest were females(28%). A significant association arises between gender (P=0.042) and MACEs. Moreover, the average age was significantly higher in participants who experience MACEs compared to those who did not (62.7 vs. 55.4, P=0.037). In this context, contrasting results in the published data were found. For example, Singh et al. (2008) stated that the distribution of events across males and females was similar. However, Movahed et al. (2010) reported a greater distribution of MACEs among females than males. They attributed these differences in findings to differences in duration of follow up and years of selection.

On the other hand, none of the clinical characteristics of our participants were significantly associated with the risk of MACEs at the 5% level of significance. However, it was clear that the proportion of hypertensive patients increased in patients with MACEs (73.1%) compared to patients without MACEs(45.8%), although this association was statistically significant at the 0.1 level (P=0.094). In agreement with this finding, meta-analysis research reported that the highest rates of adverse cardiac events were among patients with hypertension comorbidity when compared to those who didn't have comorbidities (Cheung et al., 2004). Similarly, another study reported that patients with diabetes mellitus and hypertension experience a significant increase in the risk of MI, cardiovascular events (Lin et al., 2017).

Regarding the association between MACEs and the duration of taking clopidogrel, we noted that the average duration of taking clopidogrel was significantly shorter in patients who suffered from MACEs compared to those who did not (3.42 vs. 5.54 months, P<0.001). Contradictory to our result, Mukherjee et al. noted that no statistically significant differences in major adverse cardiovascular events, stroke, and myocardial infarction between those who co-administered CYP3A4 metabolized statin with clopidogrel therapy after six months of therapy (An et al., 2019).

The clinical relevance of these findings has been evaluated in several observational studies that have shown that CYP3A4-metabolised statins interfere with the clinical efficacy of clopidogrel.

6. Study limitations

Firstly, the sample size was small due to time constraints. There is no enough time to collect the data of the expected number of patients due to time constraints (Coronavirus outbreak). Secondly, some medical records were uncompleted. Thirdly, lack of a non-CYP3A4 metabolized statins treated group for comparison, as all the participants received atorvastatin, which belongs to CYP3A4 metabolized statins

7. Conclusion

The results of the present study showed that 52% of patients who discharged on clopidogrel plus atorvastatin suffered from major adverse cardiac events after percutaneous coronary intervention. Therefore, we can say that Statins in general, and atorvastatin in particular, affect the ability of clopidogrel to inhibit platelet function in patients undergoing percutaneous coronary intervention. However, future studies are strongly warranted with a larger sample size to confirm this interaction.

Compliance with ethical standards

Ethical considerations

The study was ethically approved by the Qassim Research Ethics Committee and the ethical committee of the hospital.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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