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Research Article

The Association between Co-Administration of Omeprazole and Clopidogrel and Cardiovascular Outcomes

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Abstract

Objective: To examine whether co-administration of clopidogrel and omeprazole affects the clinical outcomes of clopidogrel treatment.

Design and Methods: A retrospective cross-sectional study of 4078 patients after a percutaneous coronary intervention and stent implantation. Seven hundred twenty-three clopidogrel-treated patients who fulfilled the inclusion criteria of the study were included: 318 treated only with clopidogrel; 405 treated with clopidogrel and omeprazole (study group). The interaction between the drugs was examined in relation to adverse clinical outcomes such as all-cause mortality, Major Adverse Cardiovascular Events (MACE) and cardiac hospitalizations during one year.

Results: No significant difference was detected between the groups regarding the primary outcomes of the study. Regression models adjusted to basic characteristics and clinical variables showed a significant association between the study group and the primary outcomes through interactions with specific covariates: "all-cause mortality" through interaction with the covariate ethnicity (not-Jewish) (OR = 43.12, 95% CI 1.19-1567.8, P = 0.04), "MACE" through interaction with the covariates gender (female) and complicated angioplasty (OR= 9.36, 95% CI 2.04-42.94, P= 0.04); and "cardiac hospitalizations" through interaction with the covariates extent of artery stenosis and hypertension (OR= 2.65, 95% CI 1.043-6.76, P = 0.04).

Conclusion: Addition of omeprazole to clopidogrel may be associated with increased incidence of negative clinical outcomes, including death and MACE. These findings underscore the need for conduction of prospective randomized controlled trials that will examine the association between addition of omeprazole to clopidogrel and the incidence of clinical outcomes.

Keywords: Acute Coronary Syndrome; Clopidogrel; Major Adverse Cardiac Events; Omeprazole; Percutaneous Coronary Intervention

Abbreviations

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Grafting; CYP-450: Cytochrome-P-450; DAPT - Dual Antiplatelet Therapy; GI: Gastrointestinal; LVEF: Left Ventricular Ejection Fraction; MACE: Major Adverse Cardiovascular Event; MI: Myocardial Infarction; NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; PPI: Proton Pump Inhibitor; STEMI: ST-Segment Elevation Myocardial Infarction

Introduction

Dual Antiplatelet Therapy (DAPT) with aspirin and P2Y12 receptor antagonists - including clopidogrel, prasugrel and ticagrelor - is a well established treatment strategy for the reduction of Major Adverse Cardiovascular Events (MACE) among patients after Acute Coronary Syndromes (ACSs), especially those who underwent a Percutaneous Coronary Intervention (PCI) and stent implantation [1-11]. Low adherence to treatment (with) or early withdrawal of P2Y12 antagonists increase the risk of MACE [12-16]. Although the newer drugs prasugrel and ticagrelor are increasingly used in patients after ACS and PCI [17-19], clopidogrel is still regarded as a useful [20] and widely used drug [17,18,21,22]. These data underscore the crucial space that clopidogrel still occupies in the treatment of post-PCI patients.

Clopidogrel is a pro-drug that must undergo metabolism by cytochrome-P-450 (CYP450) enzymes (particularly CYP 2C19) in order to become active [23-30]. Thus, decreased function of CYP 2C19 - due to genetic or environmental reasons -is expected to reduce the antiplatelet activity of clopidogrel. These include polymorphisms of the CYP 2C19 encoding gene [5,24,26,28-37], interactions with drugs that inhibit CYP 2C19 [23,30,38], and with grapefruit juice [30,39].

Proton Pump Inhibitors (PPIs) are a family of drugs used for the treatment of gastric acid-related disorders [40,41], and are among the most widely used medications in the world [42-44]. PPIs inhibit H^+/K^+-ATPase leading to potent inhibition of gastric acid secretion. Usually, they are given to patients receiving DAPT in order to decrease the

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risk of dyspepsia and Gastrointestinal (GI) bleeding [45,46]. Similar to clopidogrel, PPIs are pro-drugs that require metabolism in order to become active (particularly through CYP2C19 and CYP3A4) and thus may inhibit the conversion of clopidogrel to its active metabolite and potentially alter its efficacy [30,47,48]. Among the clinically used PPIs it seems that only omeprazole significantly inhibits CYP2C19 and thus reduces the antiplatelet activity of clopidogrel [30,49-53].

In 2006, Gilard and co-authors were the first to report that administration of omeprazole together with clopidogrel was associated with a significant increase in platelet reactivity and decreased antiplatelet activity of clopidogrel [54]. It is thought that omeprazole attenuates the antiplatelet activity of clopidogrel by competitive inhibition of CYP2C19 (mainly) and reduction of the active metabolite of clopidogrel. Subsequently, numerous studies have reported that omeprazole attenuates the antiplatelet activity of clopidogrel [30,36,37,49-52,54-59].

Based on the findings of these observational studies, several medical agencies around the world have issued in the past safety announcements warning against concomitant use of clopidogrel and PPIs (particularly omeprazole) due to a potential drug-drug interaction that may attenuate the antiplatelet activity of clopidogrel [60,61]. However, a number of other observational studies, reported contradicting findings [25,59,62-67]. Furthermore, a large scale randomized clinical trial comparing omeprazole to placebo in DAPT users (the COGENT trial) showed that co-administration of omeprazole together with clopidogrel plus aspirin significantly decreased the incidence of adverse GI events without increasing the rate of MACE [68]. Post-hoc analyses of the COGENT trial [69] in patients undergoing PCI within 14 days of randomization and patients presenting with ACS (managed with or without PCI) reported similar results.

Over the years several reviews and meta-analyses addressed the question of concomitant clopidogrel and PPI treatment arriving at inconsistent conclusions [47,48,70-73]. Therefore, the aim of the present study was to examine the interaction between clopidogrel and omeprazole in order to elucidate whether omeprazole reduces the therapeutic efficacy of clopidogrel.

Methods

Design

A retrospective analysis of patients' cohort. The design of the study is presented in Figure 1.

Study population

The study included patients who underwent a successful angioplasty with at least one stent implantation at Soroka University Medical Center hereafter, Soroka between 2005 to 2009, and were treated with clopidogrel with or without omeprazole. Exclusion Criteria: 1) Age under 18 years old; 2) low rate of adherence to pharmacotherapy – patients who purchased less than 50% of the predicted number of pills during the time of follow-up, or discontinued treatment with clopidogrel before/at three months according to pharmacy distribution recordings; 3) significant renal failure (serum creatinine > 2.0 mg/dl); 4) chronic liver disease; 5) left ventricular ejection fraction less than 25% or/and New York Heart Association functional class IV heart failure; 6) pregnancy or breast feeding during the study period; 7) oral anticoagulation treatment; 8) coexisting conditions that limited life expectancy to less than 12 months; 9) participation in other investigational trials at the time of the survey; and, 10) patients who were receiving any other drugs that inhibit or/and metabolized by CYP 2C19 (fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, escitalopram, venlafaxine, imipramine, amitriptyline, clomipramine, moclobemide, nelfinavir, nilutamide, phenytoin, phenobarbital, topiramate, diazepam, cyclophosphamide, fluconazole, chloramphenicol, ketoconazole, indomethacin and estrogen-containing oral contraceptives).

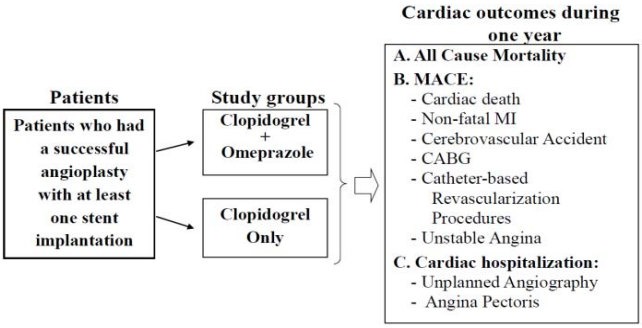

Figure 1: Study design.
CABG: Coronary Arteries Bypass Grafting; MACE: Major Adverse Cardiac Event; MI: Myocardial Infarction.

Sample size was calculated by incidence of clinical endpoint of 33% in the group of patients who were treated with clopidogrel plus omeprazole and 20% in the group who was treated only with clopidogrel, for $\alpha = 0.05$ and power $(1-\beta)$. Based on these assumptions, we calculated a sample size of 180 patients in each group. The sample size was calculated using the Power Sample Size Calculations (P.S. version 3.02) software.

Data collection

Data was collected from the hospital's computerized medical records. The data included demographic and clinical characteristics, cardiovascular risk factors and comorbidities, chronic medications, and PCI procedure data. Data collection was performed on the day of admission to the Cardiology department at which the stent implantation was performed and 12 months after admission.

Clinical endpoints

Three primary outcomes were defined: all-cause mortality; MACE; cardiac hospitalization for unplanned angiography or angina pectoris. MACE was defined as: cardiac death, non-fatal MI, cerebrovascular accident, CABG, unstable angina, and, catheter-based revascularization procedures.

Statistical analysis

Statistical analyses were completed using SPSS 18. For comparison between dependent variables (categorical variable) and independent categorical variables, we used chi-square test. For the same comparison with independent quantitative normally distributed variables, we used one-way ANOVA or group t-test, and for independent quantitative abnormally distributed variables we used Kruskal-Wallis ANOVA test or Mann-Whitney U test. For survival analysis, we used a Cox regression to evaluate the time period of adverse cardiac events in independent association between uses of

Table 1: Baseline and clinical characteristics of the study population.

		Clopidogrel Only (n=318), Number (%)	Clopidogrel + Omeprazole (n = 405), Number (%)	*P*
Age (Mean ± SD)		61.3 ± 11.7	64.2 ± 11.9	0.001
Body Mass Index (Mean ± SD)		28.07 ± 4.6	28.8 ± 4.86	0.72
Gender	Male	266 (83.6)	294 (72.6)	0.001
Ethnicity	Jew	279 (87.7)	327 (80.7)	0.036
Smoking	Yes	171 (53.8)	196 (48.4)	0.151
Alcohol Use	Yes	131 (41.2)	187 (46.2)	0.181
Respiratory Disease	Yes	22 (6.9)	54 (13.3)	0.005
Renal Disease	Yes	16 (5)	18 (4.4)	0.711
History of Stroke or Transient Ischemic Attack	Yes	13 (4.1)	24 (5.9)	0.262
Carotid or Vertebral Artery Disease	Yes	1 (0.3)	1 (0.2)	0.865
Diabetes Mellitus	Yes	92 (28.9)	146 (36)	0.04
Dyslipidemia	Yes	277 (87.1)	373 (92.1)	0.02
Hypertension	Yes	173 (54.4)	260 (64.2)	0.007
Cardiac Dysrhythmias	Yes	31 (9.7)	41 (10)	0.859
History of Heart Failure	Yes	124 (39)	151 (37)	0.657
Family History of CAD	Yes	107 (34)	115 (29)	0.134
Thrombolysis	Yes	20 (6.3)	22 (5.4)	0.631
CABG	Yes	43 (13.5)	59 (14.6)	0.679
ACS presentation	STEMI	73 (23)	71 (17.5)	0.116
	NSTEMI	60 (18.9)	74 (18.3)	0.384
	UA	62 (19.5)	95 (23.5)	0.289
	Elective	123 (38.7)	165 (40.7)	-
Stent Type	BMS	89 (28)	73 (18)	0.001
	DES	212 (66.7)	306 (75.6)	0.008
Pulmonary Edema	Yes	6 (1.9)	4 (1)	0.306
Cardiogenic Shock	Yes	0 (0)	3 (0.7)	0.124
Use of Clopidogrel Three Months Before the Index Admission	Yes	35 (11)	52 (12.8)	0.452

Abbreviations: ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; ICCU: Intensive Cardiac Care Unit; NSTEMI: Non-ST Elevation Myocardial Infarction; STEMI: ST Elevation Myocardial Infarction; UA: Unstable Angina.

omeprazole versus no omeprazole, as time varying covariates. We used binomial and multinomial logistic regression, adjusted for all variables (patient data, cardiac data, procedure data, angiographic data, and medication data) in order to assess the association between use of omeprazole, the independent variable of interest, and adverse outcomes among patients taking clopidogrel at the times of follow-up. Adjusted odds ratios and their 95% confidence intervals are presented. All tests of significance were two-tailed with the level of significance < 0.05.

Ethical aspects

The study was approved by the Institutional Ethics Committee in Soroka (authorization number 10550).

Results

Study population

A total of 4078 patients who underwent a successful angioplasty with stent implantation in Soroka during the years 2005 to 2009 were screened for inclusion in the study. Of those, 723 patients were finally included in the study out of which 318 received clopidogrel only and 405 received clopidogrel and omeprazole (Study Group) (Figure 2).

Baseline and clinical characteristics of the study population are presented in Table 1. Patients in the Study Group were significantly older than those of the clopidogrel only group (64.2 + 11.9 *vs.* 61.3 + 11.7 year, respectively, P= 0.001) and had a higher incidence of respiratory disease (13.3% *vs.* 6.9%, P=0.005), hypertension (64.2% *vs.* 54.4%, P= 0.007), diabetes mellitus (36% *vs.* 28.9%, P= 0.04) and dyslipidemia (92.1% *vs.* 87.1%, P= 0.02). On the other hand, the clopidogrel only group included more male patients than the Study Group (83.6% *vs.* 72.6%, P= 0.001). Regarding PCI procedure, more patients in the clopidogrel only group underwent a bare metal stent insertion (28% *vs.* 18%, P = 0.001) while more patients in the Study Group underwent a drug eluting stent implantation (75.6% *vs.* 66.7, P= 0.008). Table 2 shows the pharmacotherapy of the groups. As seen, more patients in the clopidogrel only group were treated with angiotensin converting enzyme inhibitors (84% *vs.* 77.8%, P = 0.037, respectively). On the other hand, more patients in the Study Group

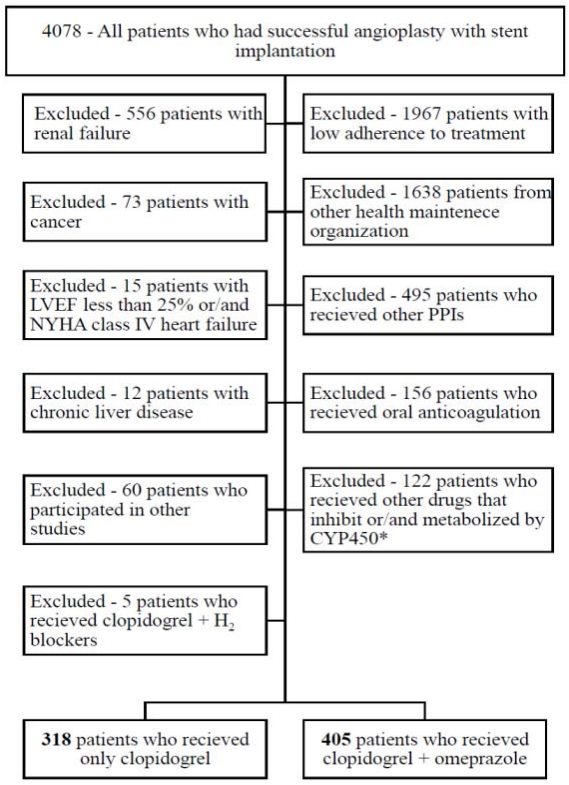

Figure 2: Screening and enrollment to the study. *Other drugs that inhibits or/and are metabolized by CYP450 (see Methods).
CYP450: Cytochrome-P450; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association; PPI: Proton Pump Inhibitor.

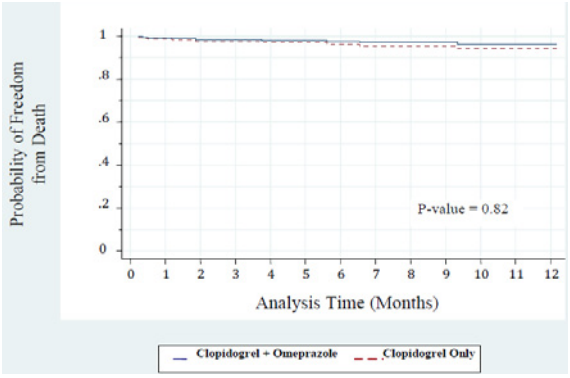

Figure 3: Cox proportional hazard regresion for all-cause mortality. The HR was adjusted to ethnicity, respiratory diseases, and diabetes mellitus.

were treated with bezafibrate (10.6% *vs.* 5.3%, P = 0.011) and polypharmacy - received at least five drugs simultaneously (97% *vs.* 92.5%, P= 0.005).

Study outcomes: Table 3 shows the results of the primary outcomes of the study. All-cause mortality did not significantly differ between the groups (P = 0.257). The occurrence of MACE (P = 0.292) and cardiac hospitalization (P = 0.249) also did not significantly differ between the groups. These results indicate that there was no significant difference between the groups regarding the primary outcomes of the study. Furthermore, there were no significant associations between subgroups (specific outcomes) or according to the stratification variables. However, it is important to mention that the sub-group analysis was limited by the small absolute numbers of specific events.

One of the major objectives of prescribing omeprazole together with antiplatelet drugs (particularly aspirin) is to reduce the risk of GI bleeding. We found that the rate of GI bleeding in the Study Group was significantly higher than that of the clopidogrel only group (9% *vs.* 2%, respectively; P = 0.001).

Furthermore, we performed a multivariate analysis to determine the association between the primary outcomes of the study and different covariates. A logistic regression adjusted to all covariates revealed that some covariates influenced the probability of each event. The covariates for each model were chosen based on their clinical importance and statistical significance (P< 0.05) in a univariate analysis and combined them with relevant interactions. We found that the association between the Study Group and "all-cause mortality" was strengthened and became significant (OR = 43.12, 95% CI 1.19-1567.8, P = 0.04) through an interaction with the covariate ethnicity "not-Jewish". Similarly, it was found that the association between the Study Group and "MACE" was strengthened and became significant (OR= 9.36, 95% CI 2.04-42.94, P = 0.004) through an interaction with the covariates gender (female) and complicated angioplasty (defined as an angioplasty that resulted in acute vessel closure, stent thrombosis, perforation, or dissection). Moreover, the association between the Study Group and "cardiac hospitalizations" was strengthened and became significant (OR= 2.65, 95% CI 1.04-6.76, P = 0.04) through an interaction with the covariates extent of

Table 2: Treatment drugs of the study population at discharge from intensive cardiac care unit.

		Clopidogrel Only (n=318), Number (%)	Clopidogrel + Omeprazole (n=405), Number (%)	*P*
ARBs	Yes	28 (8.8)	50 (12.3)	0.128
ACEIs	Yes	267 (84)	315 (77.8)	0.037
Statins	Yes	310 (97.5)	387 (95.6)	0.167
Bezafibrate	Yes	17 (5.3)	43 (10.6)	0.011
Aspirin	Yes	300 (94.3)	385 (95.1)	0.666
Beta Adrenergic Blockers	Yes	251 (78.4)	312 (77)	0.543
Calcium Channel Blockers	Yes	47 (14.8)	82 (20.2)	0.057
Diuretic Drugs	Yes	40 (12.6)	63 (15.6)	0.256
Polypharmacy*	Yes	294 (92.5)	393 (97)	0.005

* Polypharmacy - use of five drugs groups simultaneously. Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers.

Table 3: Specific clinical outcomes of the study population.

Clinical Endpoints		Clopidogrel Only (n=318), Number (%)	Clopidogrel + Omeprazole (n=405), Number (%)	*P*
All-Cause Mortality		5 (1.6)	11 (2.7)	0.257
MACE	Cardiac Death	1 (0.3)	2 (0.5)	0.672
	Non-fatal MI	0 (0)	2 (0.5)	0.197
	CVA	2 (0.6)	0 (0)	0.123
	CABG	0 (0)	1 (0.2)	0.545
	Catheter-based Revascularization	24 (7.5)	38 (9.4)	0.187
	Unstable Angina	4 (1.3)	5 (1.2)	0.61
	All	31 (9.7)	48 (12)	0.292
Cardiac Hospitalizations	Unplanned Angiography	21 (6.6)	32 (7.9)	0.248
	Angina Pectoris	0 (0)	3 (0.7)	0.163
	All	21 (6.6)	35 (8.6)	0.249
GI bleeding		6 (2)	36 (9)	0.001

CABG: Coronary Artery Bypass Grafting; CVA: Cerebrovascular Accident; MI: Myocardial Infarction; GI: Gastrointestinal.

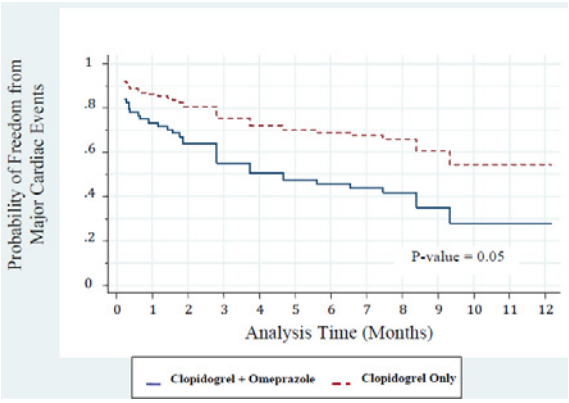

Figure 4: Cox proportional hazard regresion for major cardiac events. The HR was adjusted to ethnicity, respiratory diseases, and diabetes mellitus.

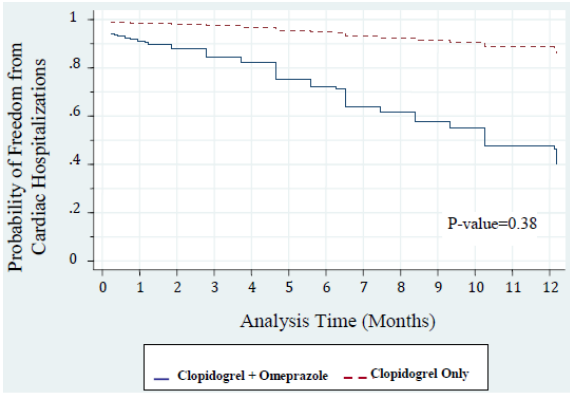

Figure 5: Cox proportional hazard regresion for cardiac hospitalizations. The HR was adjusted to ethnicity, respiratory diseases, and diabetes mellitus.

artery stenosis and hypertension.

A Cox regression analysis adjusted to ethnicity, respiratory disease and diabetes revealed that treatment with clopidogrel plus omeprazole was associated with a similar probability for a one year survival (freedom from death) as compared to treatment with clopidogrel only (adjusted HR = 0.65, P = 0.82, Figure 3). However, a Cox regression analysis adjusted to ethnicity, respiratory disease and diabetes showed that the use of clopidogrel plus omeprazole was significantly associated with an increased risk for one year MACE as compared to use of clopidogrel only (adjusted HR= 6.13, P= 0.05, Figure 4). We examined the incidence of events during the first year after PCI in the two groups of the study. It was found that in both groups MACE was more frequent at one month after PCI as compared to all subsequent time-points during the first year after PCI. Moreover, a Cox regression analysis adjusted to ethnicity, respiratory disease and diabetes revealed that treatment with clopidogrel plus omeprazole was associated with a non-significant increase in the risk for one year cardiac hospitalizations as compared to treatment with clopidogrel only (adjusted HR = 2.08, P = 0.38, Figure 5).

Discussion

The major finding of the present study is that there was a significant association between the addition of omeprazole to clopidogrel and the primary outcomes all-cause mortality, MACE, and cardiac hospitalization through interactions with specific covariates. These results are consistent with previous studies [4,14,56,58,59,74-76,23,31,36,37,49-51,55]. The increased incidence of the primary outcomes in the Study Group seems to derive from the fact that the patients of this group were sicker and probably had a poorer prognosis than those in the clopidogrel only group. As compared to the clopidogrel only group, the Study Group was significantly older, had a higher rate of patients who received a drug eluting stent, had a higher rate of co-morbidities including respiratory diseases, diabetes mellitus, hypertension and dyslipidemia (as presented by a higher percentage of patients who received bezafibrate for hypertriglyceridemia), and had a higher percentage of patients who were treated with at least five drugs (polypharmacy).

Although the rate of the primary outcomes did not differ significantly between the study groups (Table 3), a Cox regression analysis showed that the use of clopidogrel plus omeprazole was associated with an increased risk for one year MACE as compared to the use of clopidogrel only (adjusted HR= 6.13, P= 0.05, Figure 4). This result suggests that on the long-term, the addition of omeprazole to clopidogrel is associated with increased risk for MACE.

The major objective of prescribing omeprazole together with antiplatelet drugs (particularly aspirin) is to reduce the risk of GI bleeding. In the present study we found that the rate of GI bleeding in the Study Group was significantly higher than that of the clopidogrel only group (9% *vs*. 2%, respectively; P = 0.001, Table 3). The reason for this finding is not fully understood. A plausible explanation is that patients in the Study Group were given omeprazole as a preventive treatment due to a history of GI bleeding or/and high risk for GI bleeding. This is to say that omeprazole was not the leading cause for GI bleeding and that such patient may have suffered a bleeding event regardless of whether they were or were not administered with omeprazole. This is a temporal bias typical to retrospective studies in which it is difficult to determine the causative association between examined parameters. It is important to mention that treatment guidelines support the use of PPIs in patients after STEMI (and PCI) in two cases: patients with a history of GI bleeding and in patients with multiple risk factors for GI bleeding (such as advanced age, concurrent use of anticoagulants, steroids or non-steroidal anti-inflammatory drugs including high dose aspirin, and helicobacter pylori infection) [77,78]. Similar to our findings, a retrospective study from Taiwan reported that patients who were treated with clopidogrel plus a PPI had a higher incidence of recurrent hospitalization for major GI complications than those who were treated with clopidogrel only [79].

Another hypothesis of our study was that the incidence of MACE will be more frequent at one month as compared to one year after PCI. This assumption relied primarily on previous evidence [80-82] that the incidence of sub-acute thrombosis is higher in the first month post-PCI as compared to subsequent time points. Indeed, in this study the incidence of MACE was highest at one month after PCI, underscoring the need for a more extensive follow-up during this period of time, and possibly a more aggressive treatment regimen.

Regression models adjusted to all variables showed that there is a significant association between the Study Group and the primary outcome "all-cause mortality" through an interaction with ethnicity (not-Jewish). This result suggests that among Bedouin arab patients, the use of clopidogrel together with omeprazole may be associated with increased risk of death. The possible reasons for this result may include a particular genetic polymorphism and a low adherence to treatment among Bedouin patients, but also due to a high incidence of comorbidities [83-85] and low healthcare accessibility and utilization in this population [84-86]. Similarly, there was a significant association between the Study Group and the primary outcome "MACE" through an interaction with gender and complicated angioplasty. This result suggests that among female patients who had a complicated PCI, the use of clopidogrel with omeprazole may be associated with an increased risk for MACE. This finding may derive from differences in the anatomical and physiological characteristics of the coronary arteries and the cardiovascular system in general between women and men, making women more susceptible to coronary thrombotic events [87,88]. Moreover, there was a significant association between the Study Group and the primary outcome "cardiac hospitalizations" through an interaction with the covariates extent of artery stenosis and hypertension. This result suggests that among patients with hypertension and severe coronary artery stenosis the use of clopidogrel together with omeprazole may be associated with increased risk of cardiac hospitalizations. Hypertension and severe coronary stenosis are known risk factors for thrombotic cardiac events. Taken together, these three profiles may help predicting which patient may have a higher risk of adverse outcomes when given clopidogrel together with omeprazole [89-91].

Limitations

One of the limitations of the present study is that it is a retrospective cross-sectional study and, thus, has a low number of events, which decreases the statistical power of the study. Another limitation is the large number of patients who were excluded due to unknown/low adherence to pharmacotherapy, missing data, as well as other reasons. The exclusion of these patients may have biased the results. However, since adherence to pharmacotherapy is a detrimental factor in treatment success, an otherwise analysis method of the data could also influence the outcomes of the study.

Conclusion

The results of this retrospective study suggest that there were significant associations between addition of omeprazole to clopidogrel and the primary outcomes all-cause mortality, MACE and cardiac hospitalizations among patients who underwent a PCI and stent implantation. Logistic regression models revealed that these associations occurred through interactions with specific covariates. It is important to mention that recent clinical practice recommendations, the results of studies on the concomitant use of clopidogrel and PPIs, and the introduction of prasugrel and ticagrelor has affected physicians' prescribing habits. Studies report a steady decline in the prevalence of clopidogrel administration, with or without omeprazole. However, clopidogrel remains the most commonly used P2Y12 receptor antagonist among ACS inpatients, underscoring its importance in the treatment of post-PCI patients. Current treatment guidelines (which were published after the conduction of the present study) suggest that omeprazole does not reduce the therapeutic efficacy of clopidogrel and, thus, do not recommend against concomitant use of omeprazole together with clopidogrel. However, taking into account that numerous studies found that omeprazole may reduce the therapeutic efficacy of clopidogrel, further prospective, randomized, placebo-controlled, double-blind studies are necessary to elucidate the association between omeprazole and the clinical outcomes of clopidogrel treatment.

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