RESEARCH ARTICLE

Effect of omeprazole on the concentration of interleukin-6 and transforming growth factor-β1 in patients receiving dual antiplatelet therapy after percutaneous coronary intervention

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Accepted for publication July 20, 2010

ABSTRACT. ***Background.*** **Dual antiplatelet therapy (aspirin plus clopidogrel) is recommended in patients undergoing percutaneous coronary intervention (PCI). Treatment with proton pump inhibitors (PPIs) decreases bleeding rate. Alarming reports have been made that PPIs may decrease the antiplatelet activity of clopidogrel. We sought to determine whether levels of interleukin-6 (IL-6) and transforming growth factor-β1 (TGF-β1) might help distinguish individuals at risk for adverse events.** ***Methods.*** **Thirty-eight patients on aspirin and clopidogrel were enrolled and divided into two groups: group 1 [patients receiving omeprazole (n = 18)] and group 2 [patients not receiving omeprazole (n = 20)]. Patients underwent PCI and were scheduled for twelve-month clinical follow-up. The major, adverse cardiac and cerebrovascular events (MACCE) include death, re-hospitalization for acute coronary syndromes, and stroke.** ***Results.*** **Median concentrations of IL-6 were higher in group 1 at 4.7 pg/mL, in comparison with group 2, 1.65 pg/mL (p = 0.003). Median concentrations of TGF-β1 were similar in both groups (p = 0.5). Patients in group 1 had a significantly higher leukocyte count [10^3/mm^3] (median 7.5 *vs* 6.5; p = 0.04). There were no deaths during follow-up. The incidence of myocardial infarction was higher in group 1 (33.4% *vs* 5.0%; p = 0.03). MACCE at twelve months were more frequent in group 1 (55.6% *vs* 20.0%; p = 0.02). The cut-off value to predict MACCEs for IL-6 was > 3.6 pg/mL (sensitivity 64%, specificity 88%, positive predictive value 75%, negative predictive value 81%).** ***Interpretation.*** **We show here that concomitant omeprazole use is associated with an increased inflammatory reaction. Drug interactions may reduce the anti-inflammatory effect of clopidogrel. This mechanism maybe responsible for an increased risk of non-fatal, cardiovascular events, following stent placement.**

Keywords: omeprazole, clopidogrel, interleukin-6, transforming growth factor-β1

Percutaneous coronary intervention (PCI) has revolutionized the management of and outcomes in patients with coronary artery disease (CAD), with stent placement becoming an established treatment modality [1, 2]. International cardiac societies recommend dual antiplatelet therapy with aspirin and clopidogrel, in patients undergoing PCI. Aspirin, in combination with clopidogrel, has been shown to reduce recurrent, thrombotic, cardiac events in patients who have undergone stent placement. The most-feared complication of such therapy is hemorrhage. Long-term treatment with antiplatelet agents increases the rate of gastro-intestinal (GI) bleeding. Concomitant treatment with a proton pump inhibitor (PPI) decreases the bleeding rate in patients on antiplatelet therapy [3].

Clopidogrel, a thienopyridine, acts through a specific and irreversible inhibition of the adenosine diphosphate (ADP) $P2Y_{12}$ receptor, which affects both coagulation and inflammation [4, 5]. It is a prodrug that is transformed in the liver into an active metabolite by the cytochrome P450 enzyme system that includes CYP2C19 and CYP3A4. Given the crucial role of the cytochrome P450 isoenzymes (CYP2C19 and CYP3A4), drugs that inhibit these enzymes may reduce bioactivation of clopidogrel. PPIs are among competitive inhibitors of the CYP2C19 isoenzyme. Alarming reports have recently been made that PPIs may decrease the antiplatelet activity of clopidogrel due to drug-drug interactions [6] (most likely by inhibiting the formation of the active metabolite, which is responsible for the antiplatelet activity of clopidogrel), thus putting patients at risk of adverse thrombotic events [7, 8].

Interleukin-6 (IL-6), a proinflammatory cytokine, has been associated with an increased risk of future myocardial infarction [9], in-stent restenosis [10] and heart failure [11]. IL-6 plays a key role in the initiation of the inflammatory reaction. Transforming growth factor-β1

doi: 10.1684/ecn.2010.0213

(TGF-β1), mainly an anti-inflammatory cytokine, has multiple effects. It plays a crucial role in the immune response, is a mediator of the proliferation of immune cells, and influences the chemotaxis and secretion of other cytokines. It has an immunosuppressive effect and co-ordinates regenerative processes in the body [12-14].
Drug-drug interactions have been implicated in unfavorable outcomes in patients on antiplatelet and PPI therapy. In view of the multiple actions of cytokines in the inflammation and coagulation pathways, attempting to identify the role of each cytokine, therefore seems reasonable. We aimed to investigate the power of serum IL-6 and TGF-β1 concentrations to predict outcomes in a population of patients on dual antiplatelet therapy and omeprazole, who had previously undergone percutaneous coronary intervention.
We sought to determine whether serum levels of IL-6 and TGF-β1 could help distinguish individuals at risk for adverse events, who constitute a high-risk group, potentially optimizing the use of PPI during the treatment with aspirin in combination with clopidogrel after stent placement.

PATIENTS AND METHODS

Patients with a history of stent implantation who underwent coronary angiography from January 2006 to July 2008 were included in the study. Coronary angiography was performed because of the clinical presentation (worsening of anginal symptoms), and the results of exercise testing. The study population included patients from our previous study on recurrent restenosis [15]. Thirty-eight patients were enrolled and divided into two groups based on the use of clopidogrel and PPI following invasive treatment:
– group 1: patients on dual antiplatelet therapy and omeprazole (n = 18);
– group 2: patients on dual antiplatelet therapy without omeprazole (n = 20).
All patients gave their written, informed consent, and the study conforms to the Declaration of Helsinki. Exclusion criteria were: co-existing autoimmune disorders, acute infectious diseases, chronic inflammatory diseases, renal failure (creatinine serum concentration > 1.5 mg/dL), known malignant diseases, decompensated diabetes mellitus, hepatitis (including viral hepatitis, cholestatic jaundice with bilirubin concentration > 1.5 mg/dL, and/or alkaline phosphatase at least twice the upper limit of normal), severe trauma or burns during the 12 months prior to coronary angiography, ischemic or hemorrhagic stroke during the 12 months prior to coronary angiography, glucocorticoids and/or androgen therapy, psychiatric disorders, and lack of patient consent to participate.
Coronary angiography was performed using standard protocols and guidelines. Angiographic restenosis was defined using a binary approach, and the commonly used cut-off of ≥ 50% diameter stenosis.
The choice of restenosis or *de novo* lesion treatment modality (balloon angioplasty, bare-metal stent or drug-eluting stent implantation) and medical therapy was at the physicians' discretion. Aspirin was given as a once-daily dose of 75 mg. The loading dose of clopidogrel was 600mg, followed by a daily dose of 75 mg. Patients in group 1 received 20mg of omeprazole daily. No patient received GP IIb/IIIa inhibitors.
Serum concentrations of IL-6 and TGF-β1 were measured at the time of hospital discharge using commercial kit enzyme-linked immunosorbent assays (ELISA) (R&D Systems, USA) in duplicates. Measurements for each patient were made with the same kit to avoid inter-kit variability. For the IL-6 measurements, the intra-assay coefficient of variation (%CV) was 4.2%, the inter-assay coefficient of variation (%CV) was 6.4%, and the sensitivity of the ELISA assay was: < 0.7 pg/mL. For the TGF-β1 measurements, the intra-assay coefficient of variation (%CV) was 7.3%, the inter-assay coefficient of variation (%CV) was 1.8%, and the sensitivity of the ELISA assay was: < 7.0 pg/mL. Patients did not receive any of the medications mentioned in the exclusion criteria prior to the study or during follow-up.
All patients were scheduled for an elective, twelve-month clinical follow-up. We clinically monitored the patients for cardiovascular events. The major adverse cardiac and cerebrovascular events (MACCE) include death, re-hospitalization for acute coronary syndromes (ACS) (myocardial infarction, unstable angina), and stroke.

STATISTICAL ANALYSIS

Quantitative data are presented as means ± standard deviations (SD) or medians and interquartile ranges (lower and upper quartiles). Qualitative data are presented as frequencies. The Shapiro-Wilk test was used to determine whether a random sample was normally-distributed. The Mann-Whitney U-test was used to evaluate differences between the two groups. The Chi-square test with Yates' correction and Fisher's exact test were used to compare categorical variables. The Wilcoxon matched pair test was used to evaluate differences within the groups. Event-free survival at twelve months was estimated with the Kaplan-Meier method and compared with the log-rank test. The relationship between the variables studied was evaluated using the Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves were estimated for both IL-6 and TGF-β1 concentrations. The areas under the ROC curves (AUC) for IL-6 and TGF-β1 were compared using a nonparametric test. A ROC analysis was planned to identify possible cut-offs to predict MACCE. A p value of < 0.05 was considered to be significant.

RESULTS

Table 1 shows baseline and clinical characteristics. The prevalence of systemic hypertension, diabetes mellitus, hyperlipidemia and multivessel CAD was similar in both groups. The use of medications that could influence cytokine concentrations (aspirin, clopidogrel, angiotensin-converting enzyme inhibitor, statins) did not differ between the two groups. The median concentrations of IL-6 were higher in group 1 - 4.7 pg/mL (1.5-8.6) in comparison with patients in group 2 - 1.65 pg/mL (0.75-2.9)

Table 1
Patients' baseline, clinical and angiographic characteristics

	Group 1 n = 18	Group 2 n = 20	p
Age, years (mean ± SD)	62.8 ± 9.4	60.5 ± 11.8	0.5
Gender, males n (%)	15 (83.3%)	13 (65.0%)	0.3
Systemic hypertension n (%)	13 (72.2%)	14 (70.0%)	0.8
Hyperlipidemia n (%)	13 (72.2%)	15 (75.0%)	0.8
Diabetes mellitus n (%)	8 (44.4%)	6 (30.0%)	0.5
Prior myocardial infarction n (%)	13 (76.5%)	14 (70.0%)	0.6
Hospital stay, days (mean ± SD)	6.0 ± 3.1	5.4 ± 1.4	0.4
% diameter stenosis (mean ± SD)	75.3 ± 15.5	71.2 ± 19.0	0.5
Restenosis n (%)	12 (66.7%)	10 (50.0%)	0.4
De novo lesion n (%)	6 (33.3%)	10 (50.0%)	0.4
Multivessel CAD n (%)	12 (66.7%)	15 (75.0%)	0.4
Balloon angioplasty n (%)	2 (11.1%)	1 (5.0%)	0.4
Bare-metal stent n (%)	6 (33.3%)	8 (40.0%)	0.4
Drug-eluting stent n (%)	10 (55.6%)	11 (55.0%)	0.9
CAD severity n (%) - CCS 2 - CCS 3 - CCS 4	 8 (44.4%) 8 (44.4%) 2 (11.2%)	 7 (35.0%) 11 (55.0%) 2 (10.0%)	0.7
LVEF (%) (mean ± SD)	46.0 ± 12.9	42.5 ± 11.4	0.3
BMI (mean ± SD)	27.1 ± 2.6	27.5 ± 3.4	0.7
Aspirin n (%)	18 (100%)	20 (100%)	0.99
Clopidogrel n (%)	18 (100%)	20 (100%)	0.99
Beta-blockers n (%)	17 (94.4%)	20 (100%)	0.8
ACE inhibitors n (%)	15 (83.3%)	17 (85.0%)	0.9
Statins n (%)	16 (88.9%)	18 (90.0%)	0.9

(p = 0.003). The median concentrations of TGF-β1 were similar in both groups (p = 0.5) *(figure 1)*. Patients in group 1 had significantly higher leukocyte and platelet counts at discharge compared to patients in group 2 *(table 2)*. An increase in leukocyte and platelet counts at hospital discharge was observed in group 1 *(figures 2, 3)*. Leukocyte and platelet counts remained similar throughout the hospital stay in group 2 *(figures 2, 3)*. No patient was lost to follow-up. There were no deaths during the twelve-month follow-up *(table 3)*. The incidence of myocardial infarction (MI) was higher in group 1 compared to group 2 (33.4% *vs* 5.0%; p = 0.03). The prevalences of unstable angina and stroke were similar in both groups. Overall, MACCE at twelve months were more frequent in group 1 (55.6% *vs* 20.0%; p = 0.02). Twelve-month, event-free survival is depicted in *figure 4*. A substantial increase in the adverse event rate was observed in group 1, beginning from month four (starting at 100 days after hospitalization). A highly significant inverse correlation was found between IL-6 concentrations and the time of adverse events during follow-up (Spearman R = - 0.63; p < 0.001). There was no such correlation with regard to TGF-β1 (Spearman R = 0.12 p = 0.7). ROC analysis showed a high diagnostic value for IL-6 *(figure 5)*. The cut-off value to predict MACCE for IL-6 was over 3.6 pg/mL (sensitivity 64%, specificity 88%, positive predictive value 75%, negative predictive value 81%). TGF-β1 failed to provide significant results in ROC analysis [AUC 0.59 (95 % CI: 0.40-0.76); p = 0.36].

DISCUSSION

Widespread use of clopidogrel and its propensity to cause GI bleeding led the American College of Cardiology Foundation Task Force (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) to issue an expert consensus document recommending co-administration of PPI in at-risk patients receiving aspirin or clopidogrel [16]. Nevertheless, alarming reports have been made concerning the

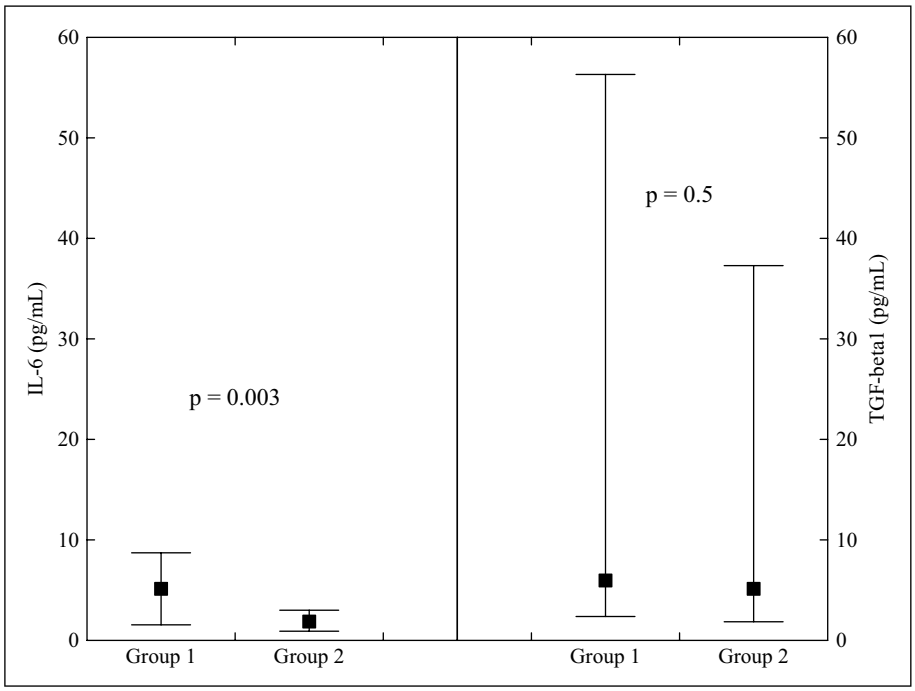

Figure 1
Median concentrations of IL-6 and TGF-β1.

Table 2
Laboratory findings on admission and at discharge [median (interquartile range)]

	On admission			At discharge		
	Group 1 n = 18	**Group 2 n = 20**	**p**	**Group 1 n = 18**	**Group 2 Nn = 20**	**p**
Leucocytes (10^3/mm^3)	6.4 (5.2-7.1)	6.3 (5.8-6.9)	0.8	7.5 (6.8-9.5)	6.5 (5.7-7.3)	0.04
Erythrocytes (10^6/mm^3)	4.5 (4.3-4.6)	4.3 (4.2-4.8)	0.7	4.5 (4.2-4.7)	4.5 (4.2-4.8)	0.8
Hemoglobin (mmol/L)	8.7 (8.0-9.2)	8.5 (8.0-9.1)	0.8	8.6 (8.1-9.0)	8.5 (8.0-9.3)	0.7
Hematocrit (%)	42 (39-46)	41 (40-45)	0.5	42 (39-45)	41 (39-45)	0.9
Platelets (10^3/mm^3)	170 (140-182)	160 (120-209)	0.5	218 (203-237)	150 (111-225)	0.03
Fasting glucose (mmol/L)	5.2 (4.8-6.3)	5.1 (4.9-6.1)	0.5	5.4 (4.6-5.9)	5.2 (4.8-6.2)	0.5
Creatinine (μmol/L)	82.0 (67.5-91.5)	77.9 (68.0-95.0)	0.6	81.1 (70.2-93.4)	80.7 (74.2-92.4)	0.9
Total cholesterol (mmol/L)	4.5 (4.1-5.2)	5.0 (4.3-5.3)	0.7			
HDL cholesterol (mmol/L)	1.3 (0.9-1.6)	1.4 (1.2-1.5)	0.5			
LDL cholesterol (mmol/L)	2.9 (2.3-3.5)	2.7 (1.9-3.4)	0.8			
Triglycerides (mmol/L)	1.2 (1.1-1.4)	1.1 (0.9-1.6)	0.8			

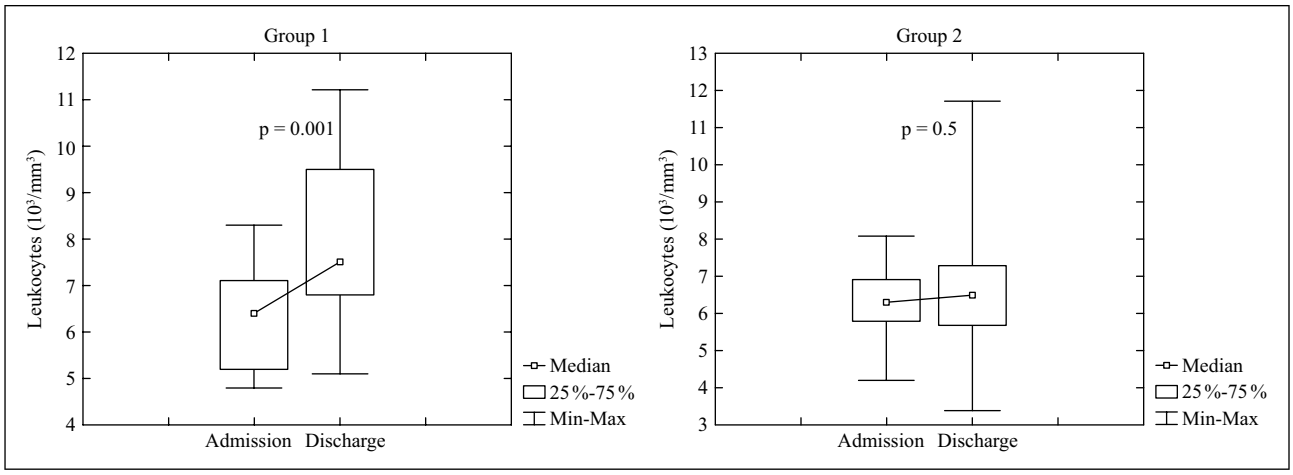

Figure 2
Changes in median leukocyte count during hospital stay in the study groups.

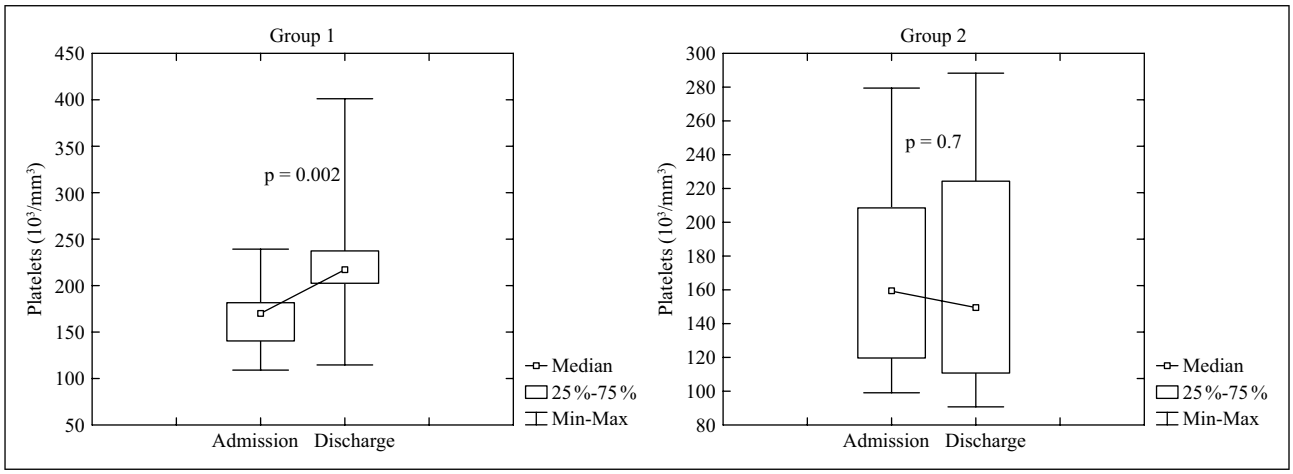

Figure 3
Changes in median platelet count during hospital stay in the study groups.

negative effects of concomitant treatment with PPI (namely omeprazole) and clopidogrel [6-8, 17]. The decrease in antiplatelet activity most likely results from a competitive inhibition at the CYP2C19 level, needed for the metabolic activation of clopidogrel.

In the present study, we examined the effect of co-administration of omeprazole with dual antiplatelet therapy (aspirin with clopidogrel) at the level of inflammatory markers, and its prognostic significance in patients with stable CAD after stent placement.

Table 3
Twelve-month follow-up

	Group 1 n =18	Group 2 n = 20	p
Death n (%)	0 (0.0%)	0 (0.0%)	0.99
MI n (%)	6 (33.4%)	1 (5.0%)	0.035
UA n (%)	2 (11.1%)	2 (10.0%)	0.8
Stroke n (%)	2 (11.1%)	1 (5.0%)	0.4
MACCE	10 (55.6%)	4 (20.0%)	0.02

MI: myocardial infarction; UA: unstable angina; MACCE: major adverse cardiac and cerebrovascular events.

We showed that patients receiving dual antiplatelet therapy plus omeprazole demonstrate an increased inflammatory state characterized by increased levels of IL-6, leukocytes and platelets. However, we found that this treatment had no effect on the concentration of TGF-β1, an anti-inflammatory cytokine.

Antonino *et al.* reported anti-inflammatory effects of clopidogrel [5]. They concluded that long-term clopidogrel therapy, in addition to lowering platelet activity, is associated with an anti-inflammatory effect (decrease in concentrations of IL-6, IL-2, tumor necrosis factor-α [TNF-α], and TNF-β). The anti-inflammatory effect of clopidogrel may also arise from the direct effects of active metabolites on the vascular wall (enhancement of nitric oxide production, which influences endothelial function, platelet function, inflammation and vasodilatory action) [18]. Moreover, it has the potential to release prostacyclin from the endothelium [19, 20]. There is some experimental evidence suggesting that IL-6 can alter cell responsiveness to clopidogrel. Yang *et al.* pretreated hepatocytes *ex vivo* with IL-6 [21]. They found that, in addition to decreased expression of carboxylesterases, IL-6 pretreatment profoundly altered the cellular responsiveness to various ester drugs, including clopidogrel.

We hypothesize that the attenuation of clopidogrel activity by PPIs may lead not only to a higher platelet reactivity [6], but may also be associated with an increased inflammatory reaction. In addition to elevated platelet activity, inflammation is another key factor associated with unfavorable outcomes and the occurrence of ischemic events [22]. In our study, we found a higher incidence of MI, although there were no deaths in either group during the twelve-month follow-up. Overall, our results suggest an increased risk of nonfatal cardiovascular events (MACCE) in patients on dual antiplatelet therapy and omeprazole. We demonstrated a high diagnostic value of IL-6 in predicting adverse events during the follow-up. Furthermore, we found a highly significant, inverse correlation between the concentration of IL-6 and the time of adverse events during the follow-up. Ho *et al.* reported similar results [7]. They found an increased risk of death and re-hospitalization for ACS during treatment with clopidogrel and PPI. In another study, Aubert *et al.* reported that the drug interaction between PPIs and clopidogrel could result in serious adverse outcomes within the first year following stent placement [17]. Juurlink *et al.* analyzed 13,636 patients who were prescribed clopidogrel following acute myocardial infarction [23]. They reported that among those patients receiving clopidogrel following acute myocardial infarction, concomitant therapy with PPIs other than pantoprazole, was associated with a loss of the beneficial effects of clopidogrel and an increased risk of reinfarction. However, Dunn *et al.* demonstrated contradictory evidence [24]. They reported that clopidogrel reduced adverse events at one year to an approximately similar degree whether or not patients were receiving a PPI. Nevertheless, PPI use was independently associated with the 28-day (HR: 1.6; 95% CI: 1.08-2.5; p = 0.022) and one-year (HR: 1.5; 95% CI: 1.1-2.1; p = 0.012) endpoints in the overall trial population.

In contrast to the reported negative omeprazole-clopidogrel drug interaction, Siller-Matula *et al.* demonstrated that the intake of pantoprazole or esomeprazole is not associated with an impaired response to clopidogrel, thus suggesting that omeprazole-clopidogrel interaction may not be a class effect [25]. It has been demonstrated in experimental studies that pantoprazole, unlike other proton pump inhibitors (omeprazole, lansoprazole, rabeprazole) exerts its highest inhibition potency toward cytochrome P450 2C9 rather than P450 2C19 [26].

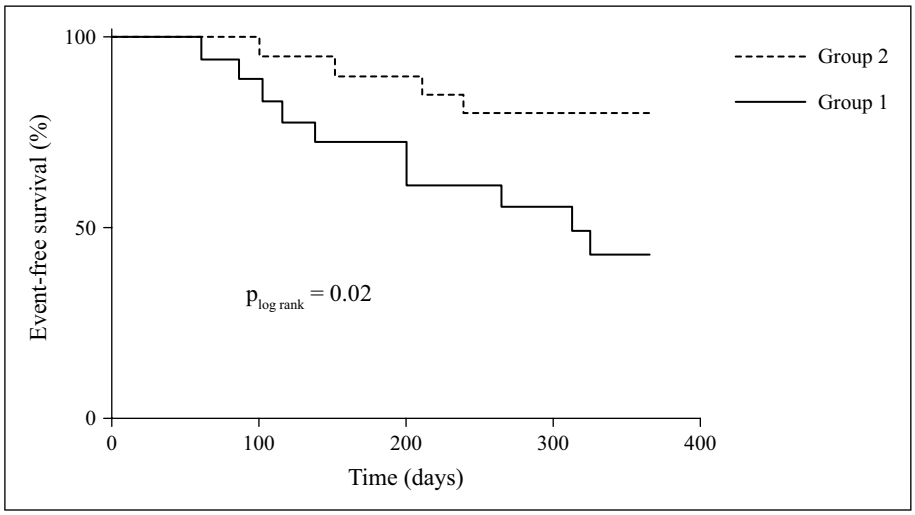

Figure 4
Event-free survival during the twelve-month follow-up.

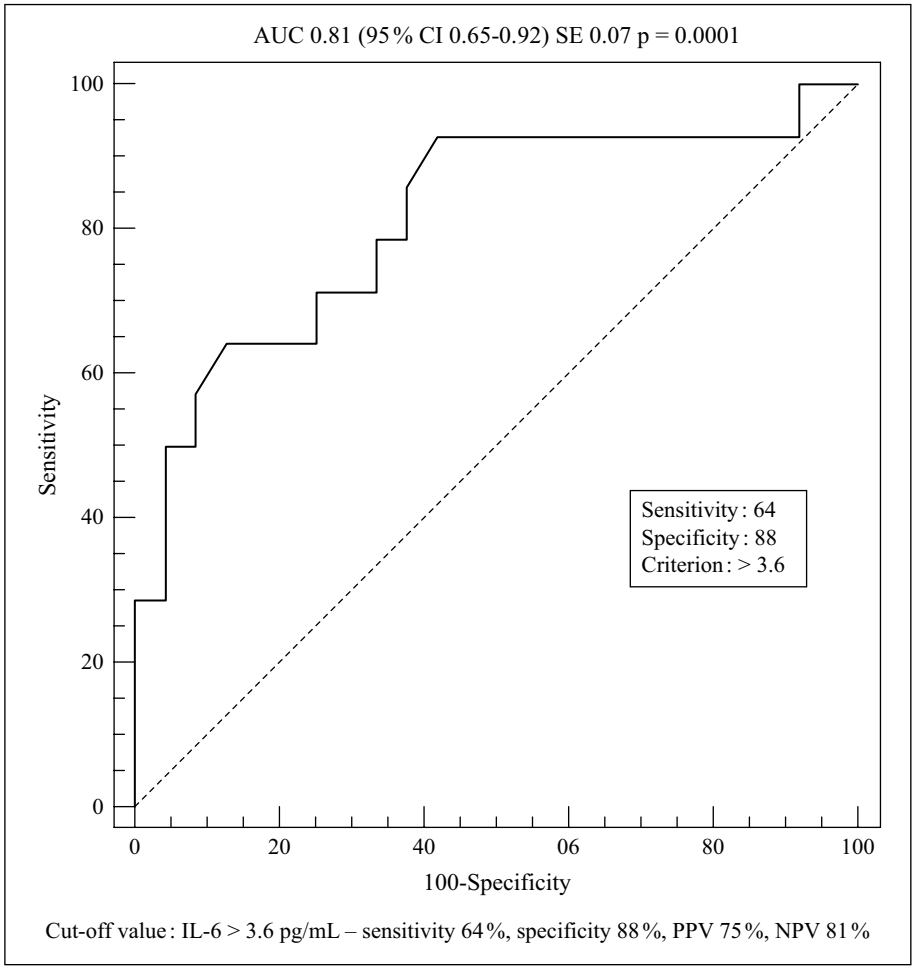

Figure 5
Diagnostic value (ROC analysis) of IL-6 concentrations to predict adverse events.
AUC: area under the curve; CI: confidence interval; SE: standard error; PPV: positive predictive value; NPV: negative predictive value.

The mechanisms underlying clopidogrel resistance remain controversial. Possible explanations include differences in resorption, genetic polymorphism of the ADP receptor [27] and drug interactions. These, in turn, attenuate the platelet response to clopidogrel (as assessed in platelet function tests). Our study offers an enhanced inflammatory reaction as another possible mechanism of action for the aforementioned drug interactions.

CONCLUSION

In conclusion, clopidogrel-omeprazole interactions may attenuate not only the antiplatelet activity of clopidogrel (as reported in the literature), but may also reduce its anti-inflammatory effect. Concomitant omeprazole use with clopidogrel is associated with an increased inflammatory reaction (characterized by increased concentrations of IL-6, leukocytes and platelets). This mechanism maybe responsible, in part, for an increased risk of non-fatal, cardiovascular events following stent placement. This, in turn, could explain one of the possible pathways for the unfavorable effects of such treatment. Concomitant omeprazole use with clopidogrel had no effect on the anti-inflammatory cytokine TGF-β1.

It is therefore our hypothesis that increased concentrations of inflammatory markers (IL-6, leukocytes), in a population of patients receiving clopidogrel and omeprazole, might be of use in identifying a subset of patients at risk for adverse events after stent placement.

It should be noted that our study has some limitations. The non-randomized study design could have led to some imprecision. A relatively small number of patients could have rendered some differences non-significant between the study groups. Further, large-scale studies are required to investigate the effects of long-term treatment with aspirin, clopidogrel and PPI on inflammation and platelet function, and their relation to clinical outcomes. We acknowledge the heterogeneity of the study group, albeit the incidence of restenosis and *de novo* lesions and treatment modalities were similar in both groups. Our results warrant further studies in an homogenous population. There is also some information suggesting that co-administration of proton pump inhibitors may decrease the oral bioavailability of aspirin, therefore reducing the aspirin cardioprotective effect [28]. The clinical significance of this interaction is yet to be determined.

Disclosure. *None of the authors has any conflict of interest or financial support to disclose.*

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