Proton pump inhibitors in patients treated with aspirin and clopidogrel after acute coronary syndrome [105]

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ABSTRACT

Introduction: Clopidogrel is an antiplatelet agent converted to its active metabolite by cytochrome P-450 isoenzymes. Numerous drugs are known to inhibit P-450 isoenzymes, including proton pump inhibitors (PPIs), which are often associated with aspirin and clopidogrel to prevent adverse gastrointestinal effects. In vitro studies first showed that PPIs reduced the antiplatelet effect of clopidogrel, while recent clinical studies have raised concerns that the addition of a PPI to clopidogrel in acute coronary syndrome (ACS) patients could actually increase the risk of recurrent cardiovascular events.

Objective: The aim of this study was to evaluate whether the prescription of a PPI conferred a worse prognosis in patients discharged with aspirin and clopidogrel treatment after ACS.

Methods: A total of 876 patients admitted with ACS and discharged with aspirin and clopidogrel, with a planned duration of at least six months, from January 2004 to March 2008, were reviewed. Patients were classified in two groups according to whether or not a PPI was prescribed at discharge. The PPIs considered were those mainly metabolized by cytochrome P-450 2C19. We excluded patients with insufficient information available on either prescription or clinical records that could allow

Inibidores da bomba de protões em doentes tratados com aspirina e clopidogrel após síndrome coronária aguda

RESUMO

Introdução: O clopidogrel é um potente antiplaquetário que necessita de metabolização prévia pelo citocromo (cit) P450. Vários fármacos são conhecidos por inibir o cit P450, nomeadamente os inibidores da bomba de protões (IBPs). Estes são frequentemente associados à dupla anti-agregação plaquetária para prevenção de distúrbios pépticos. Estudos *in vitro* foram os primeiros a demonstrar inibição da actividade antiplaquetária do clopidogrel pelos IBPs, enquanto estudos clínicos recentes levantaram fortes suspeitas quanto à ocorrência de eventos clínicos adversos associados ao uso de IBP com o clopidogrel.

Objectivo: Determinar se a prescrição de um IBP com dupla anti-agregação se associava a pior prognóstico após síndrome coronária aguda (SCA).

População e métodos: Foram analisados 876 doentes consecutivamente admitidos por SCA de Janeiro 2004 a Março 2008, e que tiveram alta medicados com dupla anti-agregação plaquetária, com uma duração prevista de seis meses. Foram considerados apenas os IBP principalmente metabolizados pelo cit P-450 2C19 e os doentes com

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us to clearly confirm or exclude exposure to a PPI. Primary end points were six-month all-cause mortality and the composite of death, myocardial infarction and unstable angina at six months.
Results: Of the 802 patients considered for further analysis, 274 (34.2%) individuals were medicated with a PPI in addition to dual antiplatelet therapy. Patients taking PPIs were older, more often had renal insufficiency and less often had a history of coronary revascularization and smoking. They more often presented with Killip class >I and lower hemoglobin concentration on admission. There were no significant differences between the two groups in terms of medical treatment (during hospital stay and at discharge) or invasive procedures. By multivariate analysis, independent and positive predictors of PPI prescription were older age and lower hemoglobin concentration on admission. Patients taking PPIs had a slightly higher prevalence of six-month mortality (6.5% vs. 3.9%) and of the composite end point (12.9% vs. 9.2%), although without statistical significance. By multivariate analysis including potential confounding variables, the prescription of a PPI on top of aspirin and clopidogrel was still not associated with a worse prognosis.
Conclusions: In the present study, PPI prescription in addition to aspirin and clopidogrel after ACS was not associated with a worse six-month prognosis.

Key words
Acute coronary syndrome; Proton pump inhibitor; Antiplatelet therapy; Clopidogrel; Prognosis

informação suficiente disponível nos registos clínicos e/ou de prescrição. Os doentes foram classificados em dois grupos de acordo com a prescrição de IBP à data da alta. Os eventos estudados foram a morte por qualquer causa aos seis meses e o evento composto de morte, enfarte e angor instável aos seis meses.
Resultados: Dos 802 doentes incluídos, 274 (34,2%) foram medicados com IBP. Os doentes medicados com IBP (doentes IBP+) eram mais idosos, apresentavam com maior frequência insuficiência renal mas com menor frequência história tabágica e de revascularização prévia. Os doentes IBP+ apresentaram-se mais frequentemente em classe Killip superior a um e com concentração mais baixa de hemoglobina na admissão. Não se verificaram diferenças significativas entre os dois grupos quanto à prescrição médica (durante o internamento ou após alta) ou ao uso de estratégia invasiva. Após análise multivariada, os preditores independentes e positivos de prescrição de IBP foram a idade mais avançada e a concentração mais baixa de hemoglobina na admissão. Os doentes medicados com IBP apresentaram maior mortalidade aos seis meses (6,5% *versus* 3,9%) e maior prevalência do evento composto aos seis meses (12,9% vs 9,2%), sem no entanto atingir significância estatística. Após análise multivariada, com ajuste para os principais preditores de eventos clínicos adversos aos seis meses, o uso de IBP continuou a não apresentar associação com pior prognóstico aos seis meses.
Conclusão: Na população estudada, o uso de IBP com dupla anti-agregação plaquetária, após SCA, não se associou a pior prognóstico aos seis meses.

Palavras-chave:
Síndrome coronária aguda; Inibidor da bomba de protões; Terapêutica antiplaquetária; Clopidogrel; Prognóstico

INTRODUCTION

Clopidogrel is a potent antiplatelet agent that acts through inhibition of the platelet P2Y12 adenosine diphosphate receptor. In recen years, treatment with clopidogrel in addition to aspirin has been proven to reduce cardiovascular events after coronary stenting and following the whole spectrum of acute coronary syndrome (ACS) [1-3].

Clopidogrel is a prodrug converted to its active metabolite by cytochrome P-450 isoenzymes, mainly cytochrome P-450 2C19 (CYP2C19) [4, 5]. Numerous drugs are known to inhibit cytochrome isoenzymes, including proton pump inhibitors (PPIs). PPIs are frequently prescribed in combination with antiplatelet therapy, and particularly dual antiplatelet therapy, in order to prevent adverse gastrointestinal events.

Mechanistic studies, such as the OCLA study, first suggested that PPIs reduced the antiplatelet effect of clopidogrel, raising questions about the clinical significance of this PPI-clopidogrel interaction [6-8]. Recent clinical studies have also raised concerns that the addition of a PPI to clopidogrel in ACS patients increases the risk of recurrent cardiovascular events [9-11]. On the other hand, a preliminary report from the CREDO trial and a recently published study based on analysis of data from the TRITON-TIMI 38 trial found no association between the addition of a PPI to clopidogrel and an increased risk of adverse cardiovascular events [12, 13]. Moreover, the results of the COGENT trial, recently presented by Bhatt et al. at the 21st Annual Transcatheter Cardiovascular Therapeutics Conference (TCT, San Francisco, 2009), also showed no association between PPI use (in addition to clopidogrel) and a worse prognosis [14]. COGENT is the only randomized trial testing clopidogrel plus placebo versus clopidogrel plus omeprazole, in patients taking aspirin and clopidogrel. However, this study was stopped prematurely (because of financial issues) and did not randomize the predicted number of patients. Consequently, the results may be viewed by some as underpowered.

Considering these conflicting reports, there is still some uncertainty about the clinical significance of the PPI-clopidogrel interaction.

The aims of our study were to evaluate the prescription of a PPI in addition to aspirin and clopidogrel in ACS patients, to compare the baseline characteristics and therapeutic strategies of patients medicated or not with a PPI, and finally to determine whether the addition of a PPI to dual antiplatelet therapy was associated with a worse outcome.

METHODS

Patients

A total of 876 patients admitted to our coronary care unit with ACS and discharged with aspirin and clopidogrel, with a planned duration of at least six months, from January 2004 to March 2008, were reviewed. ACS diagnosis was based on symptoms suggestive of ischemia associated with electrocardiographic changes (transient or persistent ST-segment elevation, ST-segment depression, or T-wave inversion) and/or elevated levels of myocardial damage biomarkers. Patients were classified in two groups according to whether or not a PPI was associated with aspirin and clopidogrel at discharge. Demographic, clinical, laboratory, echocardiographic and angiographic data were collected. Echocardiographic data refer to the first exam performed during hospital stay; left ventricular dysfunction was defined as an ejection fraction of less than 50%. Angiographic data are from coronary angiography performed during hospital stay. Although this was a retrospective cohort study, all clinical and laboratory data were collected prospectively and recorded in a computerized database, in accordance with our department's protocol for patients admitted to the coronary care unit with ACS.

Proton pump inhibitor use

Treatment with a PPI was at the discretion of the treating physician. Prescription and clinical records were used to define exposure to PPI during the follow-up period. We first searched for patients prescribed a PPI at discharge and then tried to identify those medicated only after discharge (but only during the follow-up period). We excluded patients with insufficient information available on either prescription or clinical records that could allow us to clearly confirm or

exclude exposure to a PPI after discharge. The PPIs considered were those mainly metabolized by CYP2C19, namely omeprazole, lansoprazole and rabeprazole. Although pantoprazole can be metabolized by CYP2C19, it preferentially uses other routes and consequently was not considered in our analysis [15]. The available data did not allow us to determine the duration of PPI use or its exact temporal relation to clinical events.

Follow-up and outcomes

The primary end points were six-month all-cause mortality and the composite of death, myocardial infarction and unstable angina at six months. Follow-up was by telephone interview and by review of hospital medical records. At six months, mortality follow-up was complete in 97% of patients, while follow-up for the composite end point was possible in 92%.

Statistical analysis

The chi-square test was used to compare categorical variables, expressed as percentages. Continuous variables, expressed as means ± standard deviation, were compared using the Student's t test for those with a normal distribution, or the Mann-Whitney test otherwise. As already stated, the available data did not allow us to determine the duration of PPI use or its exact temporal relation to clinical events. Therefore, a time-varying analysis could not be performed. In order to avoid significant bias in the outcome analysis, when considering the composite end point we decided that patients with myocardial infarction or unstable angina occurring before the first identified PPI prescription (during six-month follow-up) would be excluded from the study. Excluding these patients could represent a limitation of the study; however, their inclusion in the PPI group would mean an even greater bias as the adverse event would be erroneously attributed to PPI use. Kaplan-Meier analysis was used to illustrate six-month cumulative mortality and composite end point for patients according to PPI use. The log-rank test was used to test the equality of the survivor function between the two groups. Multivariate stepwise logistic regression analysis was used to identify variables independently associated with PPI use, as well as to determine whether PPI use was independently associated with a worse six-month prognosis. The model for six-month overall mortality included age (per 1 year increase), male gender, hemoglobin concentration on admission (per 1 g/dl increment), creatinine on admission (above or below 1.5 g/dl), systolic arterial pressure on admission (per 1 mmHg increase), history of myocardial infarction (MI), Killip class >I on admission, ST-elevation MI, left ventricular systolic dysfunction and invasive strategy. The model for the occurrence of the composite event at six months included age (per 1 year increase), male gender, diabetes mellitus, creatinine on admission (above or below 1.5 g/dl), hemoglobin concentration on admission (per 1 g/dl increment), previous myocardial infarction (MI), previous angina pectoris, previous coronary revascularization, Killip class >I on admission, left ventricular systolic dysfunction and invasive strategy. All p values were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Of the 876 patients analyzed, 27 prescribed pantoprazole and 47 with no available information were excluded. Of the remaining 802 patients, 274 (34.2%) were prescribed one of the PPIs considered and 528 were not prescribed any PPI during the six-month follow-up. As previously stated, we compared the latter two groups. Of patients medicated with a PPI, the drug was prescribed at discharge in 223 patients and during the follow-up period in 51 of them. None of the 51 patients medicated after discharge had any adverse cardiovascular event before the first PPI prescription. Therefore, it was not necessary to exclude any patient from the analysis.

Baseline characteristics and in-hospital management

Baseline characteristics of the patients are shown in Table I.

Patients prescribed PPIs were older and more often had renal insufficiency but were less likely to have a history of smoking and previous coronary revascularization (surgical or percutaneous). No differences were seen regarding other cardiovascular risk factors and history.

Table I - Baseline characteristics of acute coronary syndrome patients according to PPI use

	PPI use (n=274)	No PPI use (n=528)	p
Age (years) ± SD	65±13	61±13	<0.0001
Male	73.7%	76.7%	0.39
CV risk factors			
Diabetes	25.5%	27.1%	0.67%
Hypertension	67.5%	61.4%	0.89%
Hypercholesterolemia	48.5%	49.6%	0.82%
Smoking history	34.7%	43%	0.02
Previous renal insufficiency (GFR <60 ml/min)	28.7%	16.4%	<0.0001
CV history			
Previous MI	20.1%	20.1%	1.00
Previous angina	14.6%	15.9%	0.68
Previous revascularization	7.3%	12.7%	0.02
Previous stroke	8.4%	4.9%	0.06
STEMI	35%	35%	1.00
At admission			
Heart rate (bpm) ± SD	76±19	75±17	0.64
SAP (mmHg) ± SD	138±27	140±26	0.25
Killip class >I	22.4%	14.7%	0.250
Hemoglobin concentration on admission	13.6±1.7	14.1±1.7	< 0.0001

PPI: proton pump inhibitor; SD: standard deviation; CV: cardiovascular; GFR: glomerular filtration rate; MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; SAP: systolic arterial pressure.

Patients did not differ regarding the type of presentation of ACS (with or without ST elevation). On admission, patients prescribed PPIs more frequently presented with Killip class >I and with lower hemoglobin concentration.

Treatment strategies, together with echocardiographic and angiographic data, and outcomes are shown in Table II.

There were no differences in medical treatment between the two groups, either during hospital stay or at discharge. There were also no differences regarding invasive strategy, severity of coronary anatomy or percutaneous coronary revascularization.

As PPI prescription was at the discretion of the treating physician, we sought to determine independent predictors of PPI prescription through multivariate stepwise logistic regression analysis. Variables considered in the model were those that showed a statistical association with PPI use on univariate analysis: age (above or below 60 years), hemoglobin concentration on admission (per 1 g/dl increment), creatinine on admission (above or below 1.5 g/dl), Killip class >I on admission, previous coronary revascularization and smoking history. Independent and positive predictors of PPI use were older age and lower hemoglobin concentration on admission (*Table III*).

Clinical outcomes

On univariate analysis, patients prescribed PPIs had a trend for higher six-month mortality as well as higher prevalence of the composite end point at six months (see *Figures 1 and 2* for Kaplan-Meier curves), although these results did not reach statistical significance. In order to account for potential confounding factors, we sought to determine independent predictors of adverse outcome by multivariate logistic regression analysis. The models included PPI use together with all other covariates associated with six-month adverse events. As shown in Table IV, PPI use was still not associated with a worse six-month prognosis. The trend initially observed was largely explained by differences in baseline characteristics between the two groups. Importantly, when considering adverse events, we found that 96.2% of patients taking PPIs and 97.1% of those not taking PPIs were compliant for dual antiplatelet therapy at the time of the recurrent cardiovascular event.

Table II. Treatment, echocardiographic and angiographic data, and outcomes according to PPI use

	PPI use (n=274)	No PPI use (n=528)	p
Reperfusion therapy*	63.2%	62.3%	1.00
In-hospital medical therapy			
LMWH	96%	95.6%	0.87
GP IIb/IIIa receptor blockers	6.6%	8%	0.57
ACE inhibitor	94.5%	92.6%	0.37
Beta-blocker	90.5%	93.3%	0.16
Statin	99.6%	99.4%	1.00
LVEF <50%	56.8%	55.5%	0.76
Invasive strategy	85.4%	86.9%	0.59
Coronary disease**			
Left main or three-vessel disease	17.9%	17.6%	0.92
Left main, three or two-vessel disease with LAD involvement	41%	37.7%	0.29
PCI	70.4%	63.6%	0.08
Discharge medical therapy			
ACE inhibitor	92%	89.5%	0.31
Beta-blocker	89.1%	92%	0.19
Statin	99.3%	98.7%	0..73
All-cause mortality	6.5%	3.9%	0.11
Composite end point	12.9%	9.2%	0.16

* Only in patients admitted with ST-elevation myocardial infarction; ** only in patients who underwent coronary angiography

PPI: proton pump inhibitor; LMWH: low molecular weight heparin; GP: glycoprotein; ACE: angiotensin-converting enzyme; LVEF: left ventricular ejection fraction; LAD: left anterior descending artery; PCI: percutaneous coronary intervention.

Table III. Independent predictors of PPI use

	OR*	95% CI	p
Age (above or below 60 years)	1.9	1.2-3.00	0.006
Hemoglobin concentration (per 1 g/dl increment)	0.81	0.71-0.91	<0.0001

*Adjusted for age (above or below 60 years), hemoglobin concentration on admission (per 1 g/dl increment), creatinine on admission (above or below 1.5 g/dl), Killip class >I on admission, previous coronary revascularization, smoking history.

Given the importance of dual antiplatelet therapy in the context of percutaneous coronary intervention with stenting, we decided to analyze the effect of PPI use in this patient group (n=512). Patients taking PPIs were older and more often had renal insufficiency and hypertension. On admission, they presented more frequently with Killip class >I and with lower hemoglobin concentration. No differences were seen regarding other baseline characteristics and in-hospital management. On univariate analysis, patients taking PPIs had a higher prevalence of the composite end point at six months (7.7% vs. 2.9%; p=0.03). However, on multivariate logistic regression analysis with adjustment for age (per 1 year increase), creatinine on admission (above or below 1.5 g/dl), hemoglobin concentration on admission (per 1 g/dl increment), Killip class >I on admission and left ventricular systolic dysfunction, PPI use was, once again, not shown to be an independent predictor of worse prognosis (*Table V*). It should be pointed out that the number of patients considered was significantly lower than in the main population, reducing the statistical power of the analysis.

DISCUSSION

In this retrospective analysis of 802 patients treated with dual antiplatelet therapy (aspirin and clopidogrel), we found no association

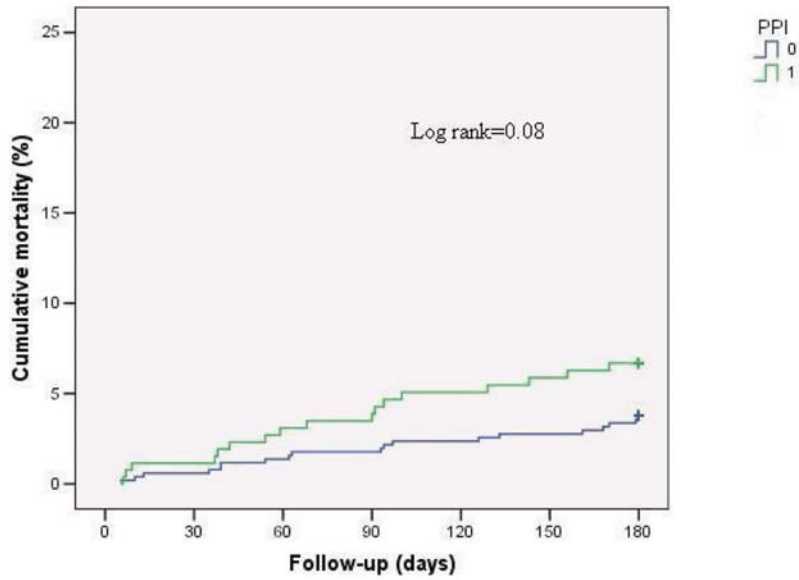

Figure 1. Kaplan-Meier curve for six-month overall mortality according to PPI use

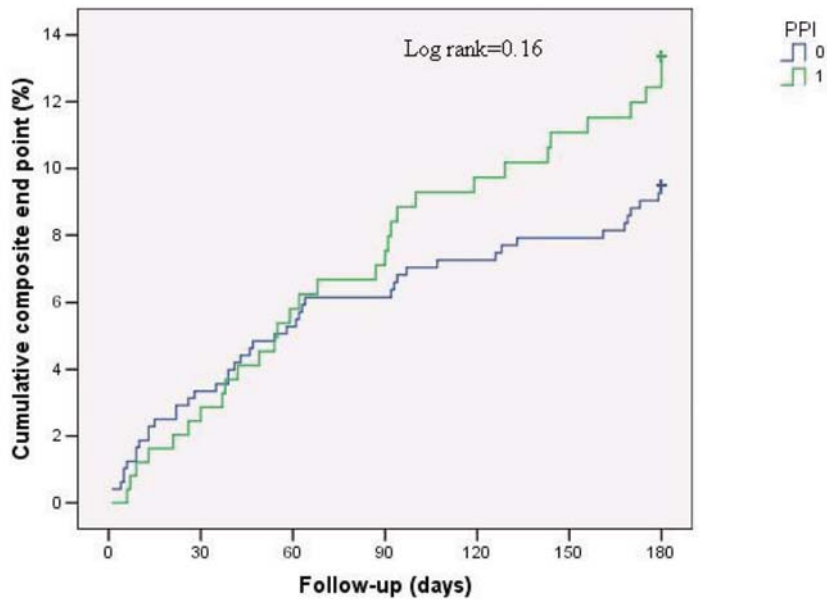

Figure 2. Kaplan-Meier curve for composite end point at six months according to PPI use

between PPI use and worse six-month prognosis in univariate as well as in multivariate analysis. Our results are therefore in agreement with those of O'Donoghue et al. (based on analysis of the TRITON-TIMI 38 data) and Bhatt et al. [13, 14].

An interesting observation regarding our data concerns the proportion of patients medicated with PPIs. About 34% of our patients were prescribed a PPI (n=274). This result is in agreement with those of both Juurlink et al. and

Table IV. Independent predictors of adverse outcome

Six-month all-cause mortality			
	OR*	95% CI	p
PPI use	1.04	0.49-2.18	0.91
Age (per 1 year increment)	1.08	1.03-1.13	<0.0001
Hemoglobin concentration (per 1 g/dl increment)	0.75	0.6-0.93	0.008
SAP (per 1 mmHg increment)	1.02	1.01-1.03	0.019
Killip class >I on admission	2.47	1.14-5.29	0.02
Composite end point at six months			
	OR**	95% CI	p
PPI use	1.1	0.64-1.9	0.71
Age (per 1 year increment)	1.07	1.03-1.08	<0.0001
Hemoglobin concentration (per 1 g/dl increment)	0.79	0.67-0.93	0.003
Previous coronary revascularization	2.87	1.41-5.81	<0.0001
Left ventricular systolic dysfunction	3.44	1.8-6.54	0.003

PPI: proton pump inhibitor; SAP: systolic arterial pressure

* Adjusted for age (per 1 year increase), male gender, hemoglobin concentration on admission (per 1 g/dl increment), creatinine on admission (above or below 1.5 g/dl), systolic arterial pressure on admission (per 1 mmHg increase), previous myocardial infarction (MI), Killip class >I on admission, ST-elevation MI, left ventricular systolic dysfunction and invasive strategy.
** Adjusted for age (per 1 year increase), male gender, diabetes, creatinine on admission (above or below 1.5 g/dl), hemoglobin concentration on admission (per 1 g/dl increment), previous myocardial infarction (MI), previous angina, previous coronary revascularization, Killip class >I on admission, left ventricular systolic dysfunction and invasive strategy.

Table V. Independent predictors of adverse outcome – composite end point at six months (patients undergoing percutaneous coronary intervention)

	OR*	95% CI	p
PPI use	2.09	0.79-5.48	0.13
Age (per 1 year increment)	1.07	1.02-1.11	0.003
Left ventricular (systolic dysfunction	5.02	1.42-17.74	0.01

PPI: proton pump inhibitor
* Adjusted for age (per 1 year increase), hemoglobin concentration on admission (per 1 g/dl increment), creatinine on admission (above or below 1.5 g/dl), Killip class >I on admission and left ventricular systolic dysfunction.

O'Donoghue et al. but contrasts with the 63.9% of patients taking a PPI in the study conducted by Ho et al.[8, 9, 13].

In our study, patients prescribed PPIs presented some differences compared to those not prescribed PPIs. Patients taking PPIs were older, more often had renal insufficiency and less often had a history of smoking and previous coronary revascularization (surgical or percutaneous). They also more frequently presented with Killip class >I and with lower hemoglobin concentration on admission. No differences were seen regarding the other baseline characteristics and in-hospital management, including medical treatment, invasive procedures and echocardiographic and angiographic data. Interestingly, and by chance, since PPI use was not randomized, the differences between patients taking PPIs and those not taking PPIs were not as pronounced as those reported by other authors [9-11]. This could have reduced confounding in the outcome analysis.

One important issue when investigating potential interactions between PPIs and clopidogrel is the concomitant use of aspirin. We decided to evaluate patients strictly on dual antiplatelet therapy for two main reasons. First, in day-to-day practice, clopidogrel is essentially prescribed on top of aspirin (in the context of dual antiplatelet therapy), monotherapy being mainly reserved for the few patients unable to take aspirin, because of hypersensitivity or major gastrointestinal intolerance. Second, we intended to reduce the potential confounding of lack of aspirin when analyzing the PPI-clopidogrel interaction. As pointed out above, when considering adverse events in our population, 96.2% of the patients taking PPIs and 97.1% of those not taking PPIs were compliant for dual antiplatelet therapy at the time of the adverse cardiovascular event. These results did not favor potential confounding by non-compliance to either antiplatelet drug. Inadequate information on concurrent aspirin use was one of the limita-

tions of some previously released observational data and was rapidly identified as a likely explanation for the higher event rate in patients using PPIs [9].

Another important issue in the evaluation of a potential clinically significant PPI-clopidogrel interaction is compliance with antiplatelet therapy. Patients' compliance is much better in the setting of randomized controlled trials, which makes the results from TRITON-TIMI 38 and COGENT more reliable regarding this issue. Although our study was observational, the majority of patients analyzed were followed after discharge in our department, and the importance of compliance with antiplatelet therapy was systematically transmitted to all of them.

The results of studies so far are conflicting. However, the harmful effects described by the first observational studies can no longer be taken as fact.

As most experts have pointed out, the only way to definitely establish the clinical significance of the PPI-clopidogrel interaction would be a randomized trial. Such a trial, COGENT, was under way until recently. It was intended to randomize 5000 patients to clopidogrel plus placebo versus clopidogrel plus omeprazole; patients were to be treated with clopidogrel for at least twelve months. Unfortunately, the trial was stopped prematurely by the sponsor due to financial issues, after 3627 patients had been enrolled. Nonetheless, the results were recently released by Bhatt et al. at the 21st Annual TCT Conference (2009) [14]. No association between PPI use (in addition to clopidogrel) and worse prognosis was found, while fewer bleeding complications were reported in the omeprazole group. However, as stated, the COGENT trial did not randomize the predicted number of patients, and consequently the results may be viewed by some as underpowered.

It should be remembered that this is not the first time that attenuation of clopidogrel's effect demonstrated *ex vivo* has failed to translate into clinical significance, namely worse outcomes. In mechanistic studies, atorvastatin was shown to attenuate clopidogrel's platelet inhibitory effect[16]. However, subsequent clinical studies, based on analysis of randomized trials, did not report an association with worse clinical outcomes [17, 18]. This, as well as the present study with PPIs, is a reminder that *ex-vivo* studies, such as platelet assays, and observational data are not equivalent to randomized controlled trials.

LIMITATIONS

There are several limitations to be considered in the interpretation of our study. First, this was a retrospective observational and non-randomized study conducted at a single hospital, and as such, both identified and unidentified confounders may have influenced the outcomes. For instance, we could not assess CYP2C19 polymorphisms, the concomitant prescription of other drugs metabolized by CYP2C19, or the existence of gastrointestinal pathology that could have influenced both PPI treatment and outcomes. Second, the number of patients studied was limited, particularly compared with other studies evaluating the same issue [9-14]. Third, PPI use was determined through the consultation of prescription and clinical records that could be incomplete. Finally, as previously stated, the duration of PPI use and its exact temporal relation to clinical events could not be determined from the available data, and consequently, a time-varying analysis could not be performed.

CONCLUSIONS

In our study, PPI use among ACS patients treated with dual antiplatelet therapy (aspirin and clopidogrel) was not associated with a worse six-month prognosis. Our results back up those recently presented by O'Donoghue et al. and Bhatt et al. [13, 14].

Although some uncertainty may remain, the evidence gathered so far favors the lack of a clinically significant detrimental effect of the combination of a PPI with clopidogrel and aspirin, as all the data derived from randomized trials showed no significant association between PPI use and worse outcomes [12-14].

One interesting way to approach this issue would be a randomized controlled trial combining both platelet assays and clinical results. In this way, the potential inhibition of clopidogrel's antiplatelet effect by PPI could be matched

with the occurrence (or otherwise) of clinical events.

Furthermore, and despite some uncertainty that may remain, recently presented results raise the question whether the statements released by the European Medicines Agency and the Food and Drug Administration were too premature and perhaps too strong, soon after the publication of the very first observational studies[19, 20].

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