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The effects of proton pump inhibitors on the development of post-stenting major adverse cardiovascular events in patients with acute coronary syndrome

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Abstract

Proton pump inhibitors (PPIs) are recommended for the prevention of gastrointestinal bleeding in acute coronary syndrome (ACS) patients who receive dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) but have been associated with an increased risk of major adverse cardiovascular events (MACE) in these patients. We aimed to investigate the relationship between serum asymmetric dimethylarginine (ADMA) and copeptin levels and MACE in those who started on imminent DAPT and PPI therapy after PCI. 90 patients with ACS were included in this prospective observational study and divided into three groups lansoprazole (n=30), rabeprazole (n=31), and pantoprazole (n=29). The serum ADMA and copeptin levels were examined at the time of diagnosis, at the end of 1st and 6th month. MACE was defined as mortality, recurrent AMI (acute myocardial infarction), and CST (coronary stent thrombosis) development after PCI. MACE developed in two patients in the first month and eight patients (8.9%) after six months of follow-up. At six months, CST was seen in only two patients (2.2%). At the first-month evaluation, while a significant increase was observed in serum ADMA levels at the time of admission ($p<0.001$), the copeptin levels decreased significantly in all patients ($p<0.001$). In the 6th month, the serum ADMA and copeptin levels significantly increased compared to the time of admission and 1st-month evaluation in all groups ($p<0.001$). PPIs might significantly influence serum ADMA and copeptin levels in patients undergoing coronary stenting due to ACS. Nevertheless, we did not notice clinical extrapolation of the potential effects.

Keywords: Proton pump inhibitor, dual antiplatelet therapy, ADMA, copeptin, adverse cardiovascular events

Introduction

Dual antiplatelet treatment (DAPT) with acetylsalicylic acid and a P2Y12 inhibitor improves cardiovascular outcomes in acute coronary syndromes (ACS) patients. It is recommended by international guidelines for one year following initial hospitalization. Because of the increased risk of DAPT-related gastrointestinal bleeding, the American College of Cardiology/ American Heart Association and the European Society of Cardiology recommend prophylactic proton pump inhibitor (PPI) use in patients routinely administered DAPT after coronary stenting [1,2]. However, even patients without a history of cardiovascular disease using PPI monotherapy have been shown to have a higher risk of cardiovascular risks [3]. Concomitant use of clopidogrel with PPIs has been shown to be associated with a significantly higher incidence of major adverse cardiovascular events (MACE) such as coronary stent thrombosis (CST) and acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI) [4]. The interference of PPIs with clopidogrel activation from its pro-drug form, and PPI-induced increase in serum asymmetric dimethylarginine (ADMA), an endogenous

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inhibitor of nitric oxide synthesis, are the main potential mechanisms of PPI-associated increase in the MACE [5,6]. Nevertheless, the effect of different PPIs on ADMA levels in patients with high cardiovascular risk using DAPT is unclear. Copeptin is another molecule that acts as a prognostic marker in AMI patients after successful PCI [7,8]. To our knowledge, no study has investigated the relationship between PPIs and plasma copeptin levels in patients with ACS.

We aimed to determine the occurrence of MACE as mortality, recurrent AMI, and CST in patients with ACS who started on imminent DAPT and PPI therapy in the present study. The secondary endpoint was to determine any change in serum ADMA and copeptin levels in the study cohort during the follow-up period of these patients to reveal any relationship between these parameters with PPI use and the occurrence of MACE after PCI.

Material and Methods

Study Population

This prospective observational study enrolled patients diagnosed with ACS in the Zonguldak Bulent Ecevit University hospital cardiology clinics between March 1, 2018, and May 31, 2018. Coronary stenting was performed on patients diagnosed with ACS at the operators' discretion. All the study subjects started on one of the three PPI agents with oral DAPT [aspirin and one of the other antiplatelet medications (clopidogrel, prasugrel, or ticagrelor)] for the first time. Based on the PPI type, the patients were split into three groups. They received lansoprazole, rabeprazole, and pantoprazole (n=30, 31, and 29, respectively).

Patients diagnosed with malignancy, chronic liver disease, chronic kidney disease, stable coronary artery disease other than ACS, systemic autoimmune diseases, sepsis, ACS patients under single antiplatelet therapy, and insufficient file data were excluded. Patients who were currently on PPIs or pregnant were not enrolled as well. The demographic data such as gender, age, comorbidities, body mass index (BMI), smoking, and alcohol habits were recorded. Routine blood tests, ADMA, copeptin, troponin, and mass CK-MB, were documented at admission, at the 1st and 6th months.

The non-interventional clinical research ethics committee at Zonguldak Bulent Ecevit University approved the study. (Protocol No. 2018/05; date of approval, 28.02.2018) The study's ethical guidelines align with the Helsinki Declaration of 1964.

Serum Copeptin and ADMA Levels Measurement

After successful PCI, blood samples were taken in serum-separating tubes from 90 patients. All samples were centrifuged for 10 minutes at room temperature (20–25°C) and were stored at −80°C until analyzed. ADMA and copeptin levels were measured by a microplate reader (Poweam Medical Systems Co. Ltd. China). ng/ml was used for serum ADMA levels, and pg/ml was used for copeptin levels as units of measurement.

Study Endpoints

The primary goal was to identify the emergence of MACE, defined as death, recurrent AMI, and CST while receiving DAPT and PPI treatment following PCI. The secondary objective examined changes in ADMA and copeptin levels in the study population with and without the occurrence of new cardiovascular events in relation to the PPI preparation.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS 21.0 (Armonk, NY, USA). The mean, standard deviation (SD), or median with interquartile range (IQR) for continuous variables was used. The Chi-Square test was used to determine the statistical correlations between categorical data. For regularly distributed data, two independent group t-tests were used to compare groups; for non-normally distributed variables, the Mann-Whitney U test was utilized. The association between non-normally distributed dependent variables was examined using the Wilcoxon Signed-Rank test technique. Consecutive numerical dependent variable measurements were analyzed using the Freidman test, and pairwise comparisons were made at significant levels to identify which groups differed. $P<0.05$ was used to define statistical significance.

Results

Our study comprised 90 patients with ACS and DAPT who were starting PPI for the first time. The gender split among all patients was 22.2% female (20) and 77.8% male (70). Age was 58.3 + 12.7 years on average. The majority of the patients (80%) were overweight or obese, with a mean BMI of 28±13.9. Hypertension (50%), diabetes mellitus (24.4%), and hyperlipidemia (22.2%) were the concomitant disorders that were most frequently present. Nearly 63% of the study participants had smoked in the past (Table 1).

Table 1. Demographic characteristics of the patients

Gender	
Male, n (%)	70 (77.8%)
Female, n (%)	20 (22.2%)
Age, years [Mean (±SD)]	58.3 (±12.7)
BMI (kg/m²) [Mean (±SD)]	28.1 (±3.9)
Normal (18.5- 24.9), n (%)	18 (20%)
Overweight (25-29.9), n (%)	48 (53.3%)
Obese (30-39.9), n (%)	24 (26.7%)
Comorbidities	
Hypertension, n (%)	45 (50%)
Diabetes Mellitus, n (%)	22 (24.4%)
Hyperlipidemia, n (%)	20 (22.2%)
Other, n (%)	15 (16.6%)
Alcohol	
Yes, n (%)	34 (37.8%)
No, n (%)	56 (62.2%)
Cigarette	
Yes, n (%)	57 (63.3%)
No, n (%)	33 (36.7%)
Blood Pressure (mmHg)	
Systolic [Mean (±SD)]	121.6±17.9
Diastolic [Mean (±SD)]	74.5±11.6

BMI: Body Mass Index

In the first month of evaluation, a significant increase was observed in serum ADMA levels compared to serum ADMA

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levels time of admission in all three groups (p<0.001). It was determined that only lansoprazole increased the serum ADMA level statistically significantly compared to the PPI preparation type (p=0.04). Compared to the admission and first-month evaluation, the serum ADMA levels in all three groups significantly rose at the end of the sixth month (p 0.001). (Table 2). When evaluated separately, serum ADMA levels in all PPI groups increased significantly after six months compared to serum ADMA levels at the 1st-month and the time of admission (p<0.001).

The serum copeptin levels were found to decrease in the 1st month of treatment in all PPI groups (p<0.001) (Table 2). However, the decrease was significant only in the pantoprazole group (p<0.001); no substantial change in serum copeptin levels during the first month of treatment was observed in other PPI groups. Nevertheless, serum copeptin levels increased significantly in the 6th month compared to those at admission and the 1st-month measurement in all three groups (p<0.001). (Table 2) When evaluated separately, it was observed that serum copeptin levels in the lansoprazole and pantoprazole groups increased significantly at six months compared with the first month and the time of admission (p<0.001), while in the rabeprazole group, the copeptin levels increased significantly at the 6th month compared to the 1st month (p=0.020).

Table 2. Change in serum ADMA and copeptin levels according to PPIs overtime after ACS

	Admission	1st Month	6th Month	p-value
ADMA Levels (Mean±SD)				
Lansoprazole (n=30)	30.1±11.4	77.1±24.6	138.5±48.8	<0.001
Pantoprazole (n=29)	43.6±13.1	64.9±22.1	138.0±49.1	<0.001
Rabeprazole (n=31)	27.3±10.9	61.4±20.3	138.5±50.3	<0.001
Copeptin Levels (Mean±SD)				
Lansoprazole (n=30)	47.9±12.4	40.4±17.5	66.1±27.1	<0.001
Pantoprazole (n=29)	48.5±14.5	37.6±13.6	64.1±22.4	<0.001
Rabeprazole (n=31)	50.3±15.1	43.9±13.5	62.1±25.7	0.020

ADMA: Asymmetric Dimethylarginine. PPI: Proton Pump Inhibitor, ACS: Acute Coronary Syndrome
p<0.05 is considered statistically significant

One patient in the rabeprazole group died unexpectedly at the end of the first month, and one in the pantoprazole group experienced an ST-elevated myocardial infarction. At the end of 6 months, MACE developed in 8 patients (8.9%) in all groups, including 1 ACS, 1 CST, one death occurred in the rabeprazole group, one death, 3 ACS occurred in the pantoprazole group, and one patient had CST in the lansoprazole group. According to our study, CST developed in 2 out of 90 (2.2%) (Table 3).

Table 3. Distribution of major adverse cardiovascular events development at the end of the 6th month according to PPIs

MACE	Lansoprazole		Pantoprazole		Rabeprazole		Total	
	N	%	n	%	n	%	n	%
Recurrent AMI	-	-	3	10.3	1	3.2	4	4.4
CST	1	3.3	-	-	1	3.2	2	2.2
Mortality	-	-	1	3.4	1	3.2	2	2.2
None	29	96.7	25	86.2	28	90.3	82	91.1
Total	30	100	29	100	31	100	90	100

MACE: Major Adverse Cardiovascular Events, PPI: Proton Pump Inhibitor, CST: Coronary Stent Thrombosis, AMI: Acute Myocardial Infarction

Discussion

Though there is an ongoing debate, several observational studies showed that PPIs significantly increased the risk of all-cause mortality, cardiovascular mortality, AMI, and stroke with a slight reduction of the risk of GI bleeding [9]. The theoretical background of these observations lies in 2 important mechanisms; the first one is that PPIs inhibit the liver-specific CYP2CA19 enzyme, which clopidogrel needs this enzyme group to be converted to metabolically activated forms. The second one is that PPIs inhibit dimethylarginine dimethylaminohydrolase enzyme and cause serum ADMA levels to increase dramatically [5].

ADMA inhibits or attenuates the vasoprotective effects of endothelial nitric oxide synthase; thus, increased serum ADMA levels have been associated with atherosclerosis and endothelial dysfunction [5,6]. The accumulation of ADMA due to PPI-induced inhibition of dimethylarginine dimethylaminohydrolase has also been linked to an elevated risk of cardiovascular disease in vitro and in vivo experiments [10,11]. A prospective crossover pilot research was conducted on 21 patients (11 healthy and 10 with preexisting cardiovascular disease) to determine ADMA levels with PPI use in humans. The PPI group had higher ADMA levels, especially prominent among those with cardiovascular disease [12].

Another important cardiovascular regulatory molecule is copeptin, which plays a vital role in cardiovascular stability in AMI patients. In the case of ACS, after the beginning of symptoms, copeptin is secreted quickly. And within days, the serum level gradually decreases and reaches a plateau stage. Several reports have demonstrated elevated copeptin levels at admission to the hospital, with the highest concentration occurring within the first four hours after the onset of chest pain [7,13]. The following studies have demonstrated the relationship between copeptin and the severity of left ventricular dysfunction and remodeling after acute infarction [14,15]. PPIs may also affect serum copeptin levels, contributing to PPI-induced risks for cardiovascular adverse events.

Our results, in line with the relevant literature, indicated that serum ADMA levels increased significantly within six months of follow-up in all PPI groups. Although the increase in serum ADMA levels was much more prominent in the lansoprazole group in the first month, only one patient developed CST and had additional cardiovascular problems in this group of patients. The plasma copeptin level was high at the first admission in all PPI groups due to ACS. We noticed decreasing plasma copeptin levels within the first month of onset of therapy, and its lowest rank was gradually detected at the end of the 1st month. Then remodeling started, and the plasma copeptin level increased again during the left ventricular remodeling process. We observed a significant increase in plasma copeptin levels at six months in all 3 PPI arms, which is a finding that theoretically might be associated with a higher risk of ACS in patients using PPIs.

Consequently, our study did not show the clinical extrapolation

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of the theoretical risks of increased serum ADMA and copeptin levels in our patients or the theoretical interaction of PPIs with the CYP2C19 enzyme system. Only eight of the 90 patients in our cohort had MACE at the end of six months, which was within the predicted range for MACE after coronary stenting [16].

While the guidelines recommend choosing the appropriate PPI with weaker CYP2C19 inhibitors, such as pantoprazole, instead of more potent CYP2C19 inhibitors, such as omeprazole [17], in our investigation, the pantoprazole group showed signs of MACE (1 fatality and 3 ACS). MACE was developed in 3 patients in the rabeprazole group (1 ACS, one stent thrombosis, and one death), and one patient had CST in the lansoprazole group. Cardiogenic shock and death occurred in 2 patients (1.2% 2 out of 90), and CST developed in 2 (2.2%) of 90 patients. Thus, the present study's post-stenting mortality and adverse cardiovascular events were similar to the literature data of patients treated with DAPT agents without PPI co-administration. For example, after PCI, MACE has been reported as 8.9% of the patients receiving DAPT combined with PPIs and 9.8% receiving DAPT without PPIs. This report also revealed that cardiogenic death occurred in 2.6% of patients receiving DAPT combined with PPI treatment and 3.2% using DAPT alone ($p>0.05$). The rate of recurrent AMI was not different in DAPT plus PPI groups and DAPT without PPI groups (6.6% vs. 7.1%, respectively, $p>0.05$). All-cause death occurred in 2.6% of patients in DAPT with the PPIs combination group and 3.2% of patients using only DAPT, which was not statistically different ($p>0.05$) [16]. Furthermore, we found none of our patients developed GI bleeding under DAPT and PPI combined administration. This finding was consistent with the results of many randomized controlled trials indicating that PPIs moderately reduced the risk of gastrointestinal bleeding [9,18].

As far as we are aware, there is no study in the literature that examined ADMA and copeptin levels simultaneously in ACS patients who started DAPT and PPI. Therefore, this study will contribute to the literature.

The major limiting factor of our study was that the number of patients enrolled was relatively small. The effects of other drugs, such as statins, were not evaluated, and possible additional drug-drug interactions are among the other limitations of our study.

Conclusion

When PPIs were given to DAPT patients with coronary intervention for ACS, we noticed that ADMA and copeptin levels significantly changed. This finding was detected in all study subjects independent of the PPI type. Nevertheless, the rate of MACE in our study group was not higher than the expected rates reported in similar cohorts of patients in the relevant literature. Because of their effects on ADMA and copeptin levels, PPIs added to DAPT may theoretically have the potential to increase adverse cardiovascular events; however, we did not observe any clinical extrapolation of these possible effects in the research group. Furthermore, we believe that PPI co-administration to DAPT is important to attenuate the potential risks of DAPT for gastrointestinal bleeding in patients with ACS.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The non-interventional clinical research ethics committee at Zonguldak Bulent Ecevit University approved the study (Protocol No. 2018/05; date of approval, 28.02.2018).

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