ORIGINAL ARTICLE

Proton pump inhibitors and statins: a possible interaction that favors low-density lipoprotein cholesterol reduction?

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Abstract
Background: Proton pump inhibitors (PPIs) might influence the metabolism of cholesterol and statins in the liver.
Aim: The impact of PPIs on low-density lipoprotein cholesterol (LDL-C) levels in statin-treated patients.
Methods: Retrospective observational study including consecutive statin-treated individuals followed for ≥3 years in a university hospital lipid clinic. Demographic characteristics as well as clinical and laboratory data were recorded at baseline and the most recent visit. High, moderate and low-intensity statin therapy was defined according to the expected LDL-C reduction (≥50%, 30-50%, and <30%, respectively). We compared the LDL-C reduction in subjects receiving statin + PPI with those on statin alone and assessed the overall effect of PPI administration on LDL-C lowering.
Results: Of 648 statin-treated subjects, 7% were also taking a PPI. There was no difference between PPI vs. non-PPI group regarding baseline characteristics and intensity of lipid-lowering therapy. Stepwise linear regression analysis showed that PPI use was significantly associated with LDL-C reduction (b =0.104, p =0.005) along with baseline LDL-C levels (b =0.482, p <0.001), treatment with ezetimibe (b =0.198, p <0.001), presence of diabetes (b =0.168, p <0.001), compliance with treatment (b =0.205, p <0.001), intensity of statin treatment (b =0.101, p =0.005) and cardiovascular risk (b =0.082, p =0.049). Subjects receiving statin + PPI had a higher LDL-C reduction by 6.4% compared with those taking a statin alone (fully adjusted p =0.005).
Conclusions: PPIs may modestly boost the statin-mediated LDL-C reduction. This effect should be confirmed by prospective clinical studies. Hippokratia 2015; 19 (4): 332-337.

Keywords: cholesterol, cytochrome, interaction, proton pump inhibitors, statin

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Introduction

Statins and proton pump inhibitors (PPIs) are among the most commonly prescribed drugs[1]. In 2013, 24.4 and 15.3 million patients in the US received lipid-lowering drugs and PPIs, respectively[1]. Statins remain the cornerstone therapy for cardiovascular (CV) disease prevention while PPIs are frequently co-administered with clopidogrel or aspirin in clinical practice in high-risk patients for gastroprotection[2,3]. PPIs have recently been associated with clinically relevant side effects as well as interactions with other drugs[2,4-8]. Moreover, it has been reported that PPIs might interfere with cholesterol metabolism[9-11]. Indeed, PPIs may increase statin action since both drugs are metabolized by the same P450 cytochromes (CYP3A4, CYP2C19)[10]. Lansoprazole may act as an agonist for liver X receptor (LXR), which is associated with cholesterol metabolism[9]. However, there are no studies on the effect of chronic PPI use on statin-mediated low-density lipoprotein cholesterol (LDL-C) reduction in clinical practice.

The present study assessed the possible effect of chronic PPI use on LDL-C reduction in statin-treated individuals in a lipid clinic.

Subjects and methods

Design and conduct

This was a retrospective (from 1999 to 2013) observational study as previously described[12,13]. Briefly, consecutive adults followed up for ≥3 years for the treatment of dyslipidemia in the Outpatient Lipid Clinic of the University Hospital of Ioannina, in Greece were included. For all study participants, a complete assessment of their lipid-lowering and concomitant treatments was obtained. The study protocol was approved by the institutional Ethics Committee of School of Medicine, University of Ioannina (No 3231, 7/5/2012).

Demographic characteristics as well as clinical and laboratory data were recorded at the baseline and most recent visit. These included age, gender, smoking status, body mass index (BMI), blood pressure (BP) readings,

liver and muscle enzymes together with history of CV risk factors and concomitant diseases. The rates of adverse events related to statin therapy were also recorded: myalgias, an increase of creatine phosphokinase (CK) >10 times the upper limit of normal values (ULN) and an increase of liver enzymes >3 times the ULN. Subjects were classified into three CV risk groups ('very high', 'high' and 'moderate') and treated for dyslipidemia according to the European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines[3]. The intensity of statin therapy was defined according to the expected LDL-C reduction (≥50, 30-50 and <30%)[14]. Patients were classified according to their compliance with treatment as 'good' and 'poor' compliers if they took ≥ and <80% of the prescribed tablets, respectively. All subjects received hypolipidemic dietary instructions during their follow-up.

Exposure status and case – control definition

For the primary analysis, exposed patients were defined as those who received, at least, a 2-year supply of PPIs up to the last visit. We included only subjects receiving PPIs as gastroprophylaxis in case of treatment with aspirin and/or clopidogrel. Active ulcer, gastritis, and gastroesophageal reflux disease (GERD) were considered as exclusion criteria. The most commonly used PPIs were omeprazole, esomeprazole, lansoprazole or pantoprazole.

After excluding those taking lipid-lowering therapy at the baseline visit, individuals on statin + PPI during follow-up were considered as case subjects, while those receiving a statin without a PPI as controls.

We investigated whether the use of PPIs together with other factors (i.e. CV risk, concomitant lipid-lowering therapy, BMI change and baseline lipid levels) contributed to the changes of LDL-C and we compared the degree of LDL-C reduction between case and control subjects. Additionally, we assessed the safety of PPI + statins combination by comparing the changes in liver or muscle enzymes and the rates of statin-associated adverse events.

Statistical analyses

Continuous variables were tested for normality by the Kolmogorov-Smirnov test, and logarithmic transformations were applied accordingly. Parametric and non-parametric data are presented as mean ± standard deviation (SD) and median [interquartile range (IQR)], respectively. The differences of continuous numeric values between the two groups are expressed as mean (95% confidence interval [CI]). For categorical values, frequency counts and percentages were applied. Chi-square tests were performed for interactions between categorical values. Pearson's and Spearman's correlation coefficients (r) were used to investigate the relationship of the changes in LDL-C with other parametric and nonparametric variables, respectively. The independent contribution of variables being significantly associated with LDL-C changes in univariate analysis was assessed with stepwise linear regression analysis. These variables were used as covariates in the multivariate analysis of covariance (MANCOVA) to assess the difference in LDL-C reduction between case and control subjects. Two-tailed significance was defined as $p < 0.05$. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) 21.0 software (SPSS IBM Corp., Armonk, New York, USA).

Results

Of 1,000 consecutive patients being assessed, 648 subjects were eligible for inclusion in the present analysis after excluding those taking lipid-lowering treatment at the baseline visit and those with active gastrointestinal disease. Of those, 607 individuals (93%) were on a statin and 41 (7%) on a statin + chronic PPI during follow-up. Mean age was 56 ± 11 years; 45% were males and the study participants were followed-up for seven years (median). Baseline demographic and clinical characteristics of study subjects are shown in Table 1. Patients taking statin + PPI were older, had higher CV risk, higher prevalence of hypertension and CV disease, higher high-density lipoprotein cholesterol (HDL-C) levels and were more likely to receive clopidogrel compared with those on statin alone (Table 1). No difference was noticed between the two groups regarding their lipid-lowering therapy and compliance with treatment (Table 1).

The changes in metabolic and safety profile of study subjects from baseline to most recent visit are shown in Table 2. No significant differences were found between the two groups regarding the changes in these parameters except for the reductions noticed in diastolic blood pressure and levels of total cholesterol (TCHOL) and LDL-C (Table 2).

No differences were found regarding statin-induced adverse events between subjects taking statin + PPI and those on statin alone. The corresponding rates for myalgias and increase of liver enzymes >3 times the ULN were 0.5% vs. 2.4% ($p = 0.231$) and 0.2% vs. 2.4% ($p = 0.123$), respectively for the two groups. Neither of the two groups exhibited increase of CK >10 times the ULN.

Correlation coefficient analyses indicated that baseline LDL-C levels ($r = 0.495$, $p < 0.001$), follow-up duration ($r = 0.133$, $p = 0.001$), treatment with aspirin ($r = 0.126$, $p = 0.001$), clopidogrel ($r = 0.098$, $p = 0.013$), ezetimibe ($r = 0.384$, $p < 0.001$), PPIs ($r = 0.121$, $p < 0.001$), along with the intensity of statin therapy ($r = 0.241$, $p < 0.001$), compliance with lipid-lowering treatment ($r = 0.161$, $p < 0.001$), diabetes ($r = 0.156$, $p < 0.001$) and CV risk ($r = 0.169$, $p < 0.001$) were significantly associated with LDL-C reduction.

Stepwise linear regression analysis taking account all the above parameters indicated that chronic PPI treatment remained an independent predictor for LDL-C reduction (beta = 0.104, $p = 0.005$) (Table 3). Specifically, a higher LDL-C reduction by 6.4% was found in individuals on statin + PPI compared with controls (95% CI: 1.9-10.9%, $p = 0.005$, after adjusting for the effect of the baseline LDL-C levels, presence of diabetes, ezetimibe use, compliance with treatment, intensity of statin treat-

Table 1 Baseline characteristics of 648 subjects enrolled retrospectively in this observational study and treatment at the most recent visit [Parametric and non-parametric values are expressed as mean ± standard deviation and median (inter-quartile range), respectively, unless percentages are shown].

		Statin alone	Statin + PPI
N		607	41
Male, %		45	39
Age, years		56 ± 11	61 ± 9*
Follow-up, years		7 (4-10)	8 (5-13)
Smoking, %		17	15
SBP, mmHg		140 (128-155)	148 (130-159)
DBP, mmHg		89 (80-95)	90 (78-92)
Glucose (fasting), mg/dL		95 (88-105)	97 (84-106)
Waist, cm		98 ± 11	99 ± 12
BMI, kg/m^2		27.5 ± 3.5	27.6 ± 3.8
TCHOL, mg/dL		265 ± 46	259 ± 43
TG, mg/dL		135 (97-190)	138 (101-169)
HDL-C, mg/dL		54 ± 14	59 ± 17*
LDL-C, mg/dL		181 ± 41	172 ± 39
eGFR, mL/min/1.73 m^2		79 ± 14	74 ± 12*
Uric acid, mg/dL		5.1 ± 1.5	4.8 ± 1.5
Hypertension, %		73	89*
Metabolic syndrome, %		55	58
Cardiovascular disease‡, %		19	39*
Diabetes, %		20	29
Chronic kidney disease, %		12	22
Cardiovascular risk¥	Moderate	12	0*
	High	42	29*
	Very high	46	71*
Treatment with antiplatelet agents, %	Aspirin	19	27
	Clopidogrel	12	24*
Antihypertensive therapy, %		71	88*
Statins (median dose, mg)	Atorvastatin, %	42 (20)	39 (30)
	Rosuvastatin, %	29 (10)	34 (15)
	Simvastatin, %	24 (40)	27 (40)
	Fluvastatin, %	4 (80)	0
	Pravastatin, %	1 (40)	0
Intensity of statin treatment†	High	29	37
	Moderate	67	61
	Low	4	2
Ezetimibe, %		19	27
Fibrates, %		3	5
Omega-3 fatty acids, %		4	2
Coleveselam, %		1	0
Compliance with lipid-lowering treatment	Good (≥80%)	94	90
	Poor (<80%)	6	10

PPI: proton pump inhibitors, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, TCHOL: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. To convert from mg/dL to mmol/L multiply by 0.02586 for TCHOL, HDL-C and LDL-C, by 0.01129 for TG and by 0.06 for glucose. ‡: Cardiovascular disease comprised of coronary heart disease, stroke, aneurysm, peripheral arterial disease and carotid stenosis ≥50%. ¥: Cardiovascular risk was classified according to European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias[3]. †: Intensity of statin treatment is based on the average expected low-density lipoprotein cholesterol reduction (≥50, 30-50 and <30%, respectively)[14]. *: p <0.05 for the comparison between subjects on statin alone and those on statin + PPI.

ment, CV risk). In sub-group analysis, this difference remained significant in individuals receiving rosuvastatin (10.8%, 95% CI: 3.3-18.4%, p =0.005, after adjusting for the same covariates). Despite not being significant, a similar trend towards a higher LDL-C reduction between case and control subjects was noticed among those taking atorvastatin (3.9%, 95% CI: -3.2-11.2%, p =0.280) and simvastatin (2.9%, 95% CI: -6.5-12.4%, p =0.535).

Table 2: Changes in metabolic profile, liver and muscle enzymes of 648 study participants from baseline to last visit [Median follow-up: 7 years; 607 on a statin alone and 41 on a statin + chronic PPI. Parametric and non-parametric values are expressed as mean ± standard deviation and median (interquartile range), respectively, unless percentages are shown].

		Baseline visit	Recent visit	P vs. baseline	Change, %
Glucose (fasting), mg/dL	Statin	95 (88-105)	97 (90-109)	<0.001	+2.1%
	Statin + PPI	97 (84-106)	96 (91-109)	0.183	-1.0%
BMI, kg/m^2	Statin	27.5 ± 3.5	28.5 ± 3.8	<0.001	+3.6%
	Statin + PPI	27.6 ± 3.8	28.3 ± 4.9	0.173	+2.5%
Uric acid, mg/dL	Statin	5.1 ± 1.5	5.3 ± 1.5	0.002	+3.9%
	Statin + PPI	4.8 ± 1.5	5.2 ± 1.5	0.142	+8.3%
SBP, mmHg	Statin	140 (128-155)	129 (120-136)	<0.001	-7.8%
	Statin + PPI	148 (130-159)	132 (121-138)	<0.001	-10.8%
DBP, mmHg	Statin	88 (80-95)	79 (73-84)	<0.001	-10.2%
	Statin + PPI	90 (78-92)	74 (70-80)*	<0.001	-17.7%‡
eGFR, mL/min/1.73 m^2	Statin	79 ± 14	74 ± 16	<0.001	-6.3%
	Statin + PPI	74 ± 12	67 ± 16	0.007	-9.4%
TCHOL, mg/dL	Statin	265 ± 46	174 ± 31	<0.001	-34.3%
	Statin + PPI	259 ± 43	162 ± 27*	<0.001	-37.5%‡
TG, md/dL	Statin	135 (97-190)	111 (85-148)	<0.001	-17.8%
	Statin + PPI	138 (101-169)	108 (93-134)	0.002	-21.7%
HDL-C, mg/dL	Statin	54 ± 14	55 ± 14	0.002	+1.9%
	Statin + PPI	59 ± 17	57 ± 15	0.568	-3.4%
LDL-C, mg/dL	Statin	181 ± 41	95 ± 25	<0.001	-47.5%
	Statin + PPI	172 ± 39	82 ± 25*	<0.001	-52.3%‡
AST, IU/L	Statin	21 (18-25)	23 (20-27)	<0.001	+9.5%
	Statin + PPI	21 (19-25)	22 (18-30)	0.260	+4.8%
ALT, IU/L	Statin	21 (17-28)	23 (18-29)	0.036	+9.5%
	Statin + PPI	20 (16-24)	19 (14-28)	0.993	-5.0%
γ-GT, IU/L	Statin	18 (13-27)	19 (14-26)	0.227	+5.5%
	Statin + PPI	17 (11-26)	17 (12-38)	0.927	0%
ALP, IU/L	Statin	71 (57-94)	58 (47-73)	<0.001	-18.3%
	Statin + PPI	80 (58-111)	59 (43-75)	<0.001	-26.2%
CK, IU/L	Statin	94 (72-130)	105 (78-155)	<0.001	+11.7%
	Statin + PPI	111 (74-143)	111 (82-179)	0.178	0%

PPI: proton pump inhibitors, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, TCHOL: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGT: gamma glutamyltranspetidase, ALP: alkaline phosphatase, CK: creatine phosphokinase, ‡: $p < 0.05$ after adjusting for baseline values. To convert from mg/dL to mmol/L multiply by 0.02586 for TCHOL, HDL-C and LDL-C, by 0.01129 for TG and by 0.06 for glucose.

Discussion

The present study suggests, for the first time to our knowledge, that treatment with PPIs may modestly increase statin-mediated LDL-C reduction without increasing the risk of liver and muscle toxicity.

It has been reported that PPIs may be involved in cholesterol metabolism[9,11]. A study investigating whether *helicobacter pylori* infection was associated with changes in serum lipid levels indicated that its eradication significantly increased HDL-C after taking amoxicillin, clarithromycin, and omeprazole[15]. Despite not being significant, a trend towards a reduction in TCHOL and LDL-C levels was noticed in that study[15]. PPIs can decrease the intra-lysosomal acidity through the inhibition of the lysosomal membrane H^+/K^+ ATPase[11]. Therefore, these drugs could inhibit the intra-lysosomal oxidation of LDL-C[11]. In addition, lansoprazole and other PPIs with structure similarities might act as LXR agonists[9]. Lansoprazole can activate endogenous LXR in a concentration-dependent manner, followed-up by transcriptional up-regulation of LXR related genes leading to the increase of their proteins[9]. These proteins are involved in cholesterol metabolism and various steps of atherosclerosis[9]. Indeed, a synthetic LXR ligand reduced LDL-C in nonhuman primates with normal lipid levels[16].

Furthermore, the possible cholesterol-lowering effect of PPIs on statin-treated individuals could be attributed to the liver metabolism of both drugs (CYP450)[10,17]. It is known that atorvastatin and simvastatin are metabolized by the cytochromes CYP3A4 and CYP2C8 while rosuvastatin is metabolized by CYP2C9 and CYP2C19[17]. PPIs also undergo similar hepatic metabolism, involving

Table 3: Stepwise multivariate linear regression analysis taking into account the use of proton pump inhibitors (PPIs) and other factors affecting the changes of lipid parameters.

Regressors	LDL-C reduction (beta/p)
Baseline LDL-C	0.482 (<0.001)
Ezetimibe	0.198 (<0.001)
Diabetes	0.168 (<0.001)
Compliance with lipid-lowering therapy	0.205 (<0.001)
PPIs	0.104 (0.005)
Intensity of statin therapy†	0.101 (0.009)
CV risk¥	0.082 (0.049)
R^2 X 100	43.2

†: Intensity of statin treatment is based on the average expected low-density lipoprotein cholesterol reduction (≥50, 30-50 and <30%, respectively)[14]. ¥: Cardiovascular risk was classified according to European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias[3]. LDL-C: low-density lipoprotein cholesterol, PPIs: proton pump inhibitors, CV: cardiovascular.

the cytochromes CYP3A4, and CYP2C19[10]. Most PPIs are weak inhibitors of CYP3A4, while omeprazole and esomeprazole are the most potent CYP2C19 inhibitors[10]. By competing with such isoforms, PPIs may reduce the metabolism of statins resulting in an increase of their LDL-C-lowering efficacy[17,18]. In a similar way, esomeprazole and omeprazole have been suggested to reduce the antiplatelet effect of clopidogrel by competing for the same cytochrome[2]. Nevertheless, PPIs have not been considered yet to interact with statins[7,8].

In our study, a high proportion of the participants taking statin + PPI were also receiving clopidogrel (Table 1). Despite the fact that few reports have demonstrated a statin-clopidogrel interaction, posthoc analyses from randomized clinical trials have not associated the co-administration of statins and clopidogrel with an increased cardiovascular risk[19]. In addition, the effect of clopidogrel on LDL-C reduction did not remain significant in our multivariate regression analysis. Thus, the use of clopidogrel may not account for the higher LDL-C reduction noticed in the subjects taking statin + PPI in our study.

Inhibitors of CYP450 are associated with skeletal muscle or liver toxicity by increasing the plasma concentrations of statins[18,20]. In this context, PPIs have been related to myopathy including polymyositis in statin-treated individuals[21-24]. Nevertheless, no differences were found regarding the changes in liver or muscle enzymes and the rates of statin-induced adverse events between cases and controls in this study.

A higher proportion of individuals taking statin + PPI were on antihypertensive therapy compared with the control group (Table 1). This may explain the greater reduction in diastolic, and systolic BP noticed in the former group (Table 2).

Study limitations

This was a retrospective observational study not specifically designed to investigate the effect of PPIs on statin-induced LDL-C lowering. Unfortunately, there were no data available on the specific PPIs used. Therefore, we were not able to assess possible differences among various PPIs. Also, the number of patients on statin + PPIs was small. Despite careful adjustment, residual confounding may still be present. Diet could account for the noticed difference in LDL-C reduction between the two groups. Indeed, individuals taking PPIs due to gastrointestinal disorders usually follow a fatless diet. In order to avoid this bias, subjects diagnosed with an active ulcer, gastritis or GERD were excluded. Adherence to a healthy diet confers to a significant CV risk reduction, even in statin-treated individuals[25,26]. Thus, individuals at very high CV risk, such as the majority of those taking PPIs in our cohort, might have followed a stricter diet leading to greater cholesterol reduction. On the other hand, a less strict diet followed by those not receiving a PPI could explain the increase in markers of metabolic syndrome and non-alcoholic fatty liver disease (i.e. glucose, BMI, uric acid and liver enzymes, as shown in Table 2) although there was no significant difference between the two groups. Unfortunately, we have no data on participant diet. Another residual factor could be the lower estimated glomerular filtration rate (eGFR) in the group of statin + PPI[27]. Nevertheless, no association between eGFR and LDL-C reduction was evident.

Conclusion

Chronic PPI use may be associated with a modest enhancement in LDL-C lowering efficacy of statins. This possible effect should be documented in prospective clinical studies.

Conflict of Interest

ME and EL have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. ME has disclosed that he is an Editorial Board member of JCPT. FB, CR, EK and MK have no conflict of interest to report.

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