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Statins and gastroduodenal endoscopic lesions

A case–control study

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Abstract

Experimental studies showed a dose-dependent gastroprotective effect of statins on non-steroidal anti-inflammatory drug-induced endoscopic lesions, modulated by increasing endogenous nitric oxide and prostaglandin production.

We investigated the influence of chronic treatment with statins on the occurrence of endoscopic lesions in patients referred for endoscopic evaluation, adjusted for the most important etiologic and risk factors for peptic ulcer disease and its complications.

A consecutive series of 564 patients who underwent upper digestive endoscopy, stratified according to the severity of endoscopic lesions were recruited. Patients with statin therapy were included in the study group (n = 220), while patients without statins in the control group (n = 344). We correlate the influence of chronic statin therapy (at least 6 months) with factors including age up to 50 years, *Helicobacter pylori* infection, smoking and drinking habits, ulcer history, gastrotoxic drug consumption (low-dose aspirin [ASA], anticoagulants), and comorbidities.

H pylori infection was more frequent in patients with mild/severe endoscopic lesions vs. no lesions, in both groups, but the difference was not statistically significant ($P > .05$). Male gender represented a risk factor ($P < .01$) for mild/severe endoscopic lesions only in the statin group. The estimated risk for developing mild/severe endoscopic lesions with ASA intake decreased from 6.26 to 3.40 ($P < .01$) when statin therapy was associated. Patients without statins and ischemic coronary artery disease ($P < .01$; odds ratio [OR] = 2.99; 95% confidence interval (CI):1.88–4.73), heart failure ($P = .01$; OR = 2.13; 95% CI:1.36–3.34), systemic atherosclerosis ($P = .04$; OR = 2.30; 95% CI:1.44–3.67) had a statistically significant increased risk for developing mild/severe endoscopic lesions in comparison with patients in the statin group. In multivariate regression analysis models, smoking ($P < .01$; OR = 2.69; 95% CI:1.73–4.16), ASA ($P < .01$; OR = 4.54; 95% CI:2.83–7.16), and coronary artery diseases ($P = .01$; OR = 1.80; 95% CI:1.15–2.82) were independent risk factors for mild/severe endoscopic lesions, while chronic statin therapy ($P < .01$; OR = 0.31; 95% CI:0.19–0.51) was associated with a protective effect in all models.

The results of the present study support a certain protective role of chronic therapy with statins against endoscopic lesions, especially in ASA consumers or patients with cardiovascular diseases.

Abbreviations: ASA = low-dose aspirin, CI = confidence interval, HF = heart failure, NO = nitric oxide, NSAIDs = non-steroidal anti-inflammatory drugs, ORs = odds ratio, PGE2 = prostaglandin E2, PGI2 = prostaglandin I2, PPI = proton pomp inhibitors, SAT = systemic atherosclerosis.

Keywords: comorbidities, endoscopic lesions, *Helicobacter pylori*, low-dose aspirin, statin

1. Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, also known as "statins", are used to lower blood cholesterol levels and to prevent atherosclerosis, presenting beneficial effects in lowering cardiovascular risk, as well as neuroprotective properties in cerebral ischemia and stroke.[1–3]

Given that guidelines strongly recommend statin therapy in cardio- and cerebrovascular diseases and the primary and secondary prevention of myocardial infarction and stroke, statins are among the most used pharmaceutical agents in current clinical use.[2–4] The protective effect of statins is due to their properties of atherosclerotic plaque stabilization and endothelial nitric oxide (NO) synthesis.[5–7] It is believed that by reducing cholesterol levels and strengthening endothelial function, statins may also have a pro-angiogenic effect.[5,8] Due to their additional antioxidant, anti-inflammatory, and immunomodulatory positive effects, statins have been proven to: reduce the risk of fractures[9] and the incidence of dementia,[10] cataract, or cancer (colorectal, lung, prostate, and reproductive organs).[11]

It is well known that *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) are 2 of the most common causes for developing gastro-duodenal lesions,[12] complicated with upper digestive hemorrhages or perforation, which lead to increased hospitalization and mortality rates.[13]

Studies performed on experimental models (genetically pure rats) showed a dose-dependent gastroprotective effect of statins

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on NSAID- and aspirin-induced endoscopic lesions, modulated by increasing endogenous NO, prostaglandin I_2 (prostacyclin, PGI_2), and prostaglandin E_2 (dinoprostone, PGE_2) production.[14,15] Other experimental studies showed that statin use may also have a chemo-preventive potential against gastric cancer, induced probably by inhibiting the mevalonate pathway and attenuating (by reducing cellular cholesterol levels) the translocation and phosphorylation of *H pylori* cytotoxin-associated gene A (CagA).[16]

Hence, gastroprotective effects of statins in humans remain unclear, as experimental data suggests that an imbalance between toxic agents and protective mechanisms generates lesions of the gastro-duodenal layer,[14,15] and statins seem to increase the endogenous protection mechanism. The few studies that were performed in human subjects had controversial results, sustaining or declining the findings of experimental studies.[1,17–20]

We aimed to investigate the influence of chronic treatment with statins on the severity of gastro-duodenal mucosal lesions; adjusted for the most important etiologic and risk factors for ulcer and its complications (drug consumption, *H pylori* infection, comorbidities).

2. Materials and methods

2.1. Subjects

A consecutive series of 1662 patients evaluated on upper digestive endoscopies between January 2014 and December 2016 were screened for study inclusion. Gastroscopies were performed for symptoms, anemia, or to evaluate the risk of gastrointestinal bleeding. Patients using statins (atorvastatin 10–80 mg/day, simvastatin 10–80 mg/day, or rosuvastatin 10–40 mg/day) for the treatment of cardiovascular, cerebrovascular, and metabolic diseases, for a period of more than 6 months, as recommended by the guidelines, were screened for inclusion in the study group. Patients non-exposed to statin therapy were recruited for the control group.

2.2. Data collection

We collected clinical and demographical data by reviewing the medical records, performing clinical examination, and using a structured interview. Patients were considered smokers in case of an intake of more than 5 cigarettes/day, even if they quit smoking in the last 5 years. Patients consuming at least 10 units (10 mL) of pure alcohol weekly were registered as drinkers. All other patients, without smoking or drinking habits, or with amounts of toxic substances below this limit, were taken into account as non-exposed to those environmental factors. Gastrotoxic drugs were represented by: NSAIDs (diclofenac, indomethacin, ibuprofen, ketoprofen, dexketoprofenum), used as regular daily doses for more than 3 months, and long-term antiplatelet therapy (low-dose aspirin [ASA] 75–125 mg/day and clopidogrel 75 mg/day, used as cardiovascular therapy, for more than 3 months). Patients on anticoagulant therapy used acenocumarol for a therapeutic International Normalized Ratio (INR) of 2.5 to 3.5 and low-molecular-weight heparins (LMWH), also in doses adjusted for weight in cardio- and cerebrovascular therapy at least one week before the endoscopy.

Chronic medical conditions (anemia, hypertension, chronic kidney disease, atherosclerosis, diabetes mellitus, and fatty liver diseases) were considered present when the medical records of the patients stated the mentioned diagnosis based on international clinical guidelines criteria.

We investigated the interaction between statin therapy and factors such as gastrotoxic medication, *H pylori* infection, biliary reflux, smoking and drinking habits, anemia, prior ulcer disease, or other chronic comorbidities, which are mentioned as predisposing factors for peptic ulcers or upper intestinal bleeding in medical literature.[12,21–28]

Patients with acute upper hemorrhage, esophageal varices, gastric surgery, gastric or esophageal cancer, or end-stage diseases (e.g., cirrhosis, severe heart or renal failure), as well as patients with incomplete data were excluded from the study. We also excluded patients who started statin therapy earlier than 6 months or patients with intermittent consumption or non-adherence to gastrotoxic drugs (NSAIDs, antithrombotic medication). Patients who declined to sign the consent were also excluded.

A written informed consent was obtained from all included subjects and the Ethical Committee of the University of Medicine and Pharmacy of Târgu Mureş, Romania approved the study (83/22.09.2014).

2.3. Endoscopy

Endoscopic lesions were classified as erythema, submucosal hemorrhages, erosions, or ulcer. Submucosal hemorrhages were defined as hemorrhagic areas with no mucosal defect. Erosions were defined as a mucosal defect of less than 5 mm in diameter. Defects larger than 5 mm, extended into the deeper layer of the gastric or duodenal wall, were defined as ulcers. We used the Lanza classification[21,22] to assess the severity of the endoscopic lesion: score 0—normal mucosa; score 1—1 hemorrhage or erosion; score 2—2 to 10 hemorrhages or erosions; score 3—over 10 hemorrhages or erosions; score 4—more than 25 erosions, diffuse hemorrhage, or ulcer. We considered as mild or severe endoscopic lesions stages 2, 3, and 4 from the Lanza classification. Four biopsy specimens (2 from the antrum and 2 from the corpus, from the lesser and greater curvature) were taken for routine histology examination in every patient.

2.4. Histology

Biopsy specimens were fixed in 10% formalin and processed, embedded in paraffin and stained with hematoxylin-eosin, PAS-alcian blue, and Giemsa. *H pylori* infection was considered positive if the bacteria were present in at least 1 biopsy examined by usual histochemical staining. Immunohistochemical study was used if the germ was not detected in a biopsy with features supporting a high suspicion of infection (chronic active gastritis). *H pylori* infection was negative if the bacteria was absent in all biopsies. We did not include in our study patients with dysplasia or cancer, active bleeding lesions, or an incomplete set of biopsies.

2.5. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 22, Chicago, IL). Nominal variables were described as absolute and relative frequencies (%), and the association between them was analyzed using Pearson Chi-square test or Fisher Exact Test. The dependent variables were:

(1) mild/severe endoscopic gastro-duodenal lesions (0 = Lanza score 0 or 1, 1 = Lanza score 2, 3, or 4). In all models, the following independent variables were included: (1) statin: 0 = without statin, 1 = with statin;

(2) gender: males and females;
(3) age: 0 = <50 years, 1 = >50 years;
(4) smoking: 0 = no smoking, 1 = >5 cigarettes/day, including quitters during the past 5 years;
(5) *H pylori* infection: 0 = no, 1 = yes;
(6) ASA employment: 0 = no, 1 = yes;
(7) systemic atherosclerosis (SAT) residence: 0 = no, 1 = yes;
(8) coronary artery disease (CAD): 0 = no, 1 = yes.

The size effect for statistically significant associations was expressed as an odds ratio (OR) with a 95% confidence interval (CI) associated. Univariate binomial logistic regression was used to test and estimate the individual effect of the studied risk factors (such as aspirin) for developing endoscopic lesions among our study group, with a protective role of statin. The independent effect was tested using multiple binary logistic regressions. All regression models were additive models that resulted from no significance of interaction terms. Statistical significance for all tests was accomplished when the estimated significance level p was lower than .05.

3. Results

3.1. Sample characteristics

The study included 564 patients with complete set of data, divided into a study group (220 patients with chronic statin therapy) and a control group (344 patients, without statin intake). In both groups, patients were stratified based on endoscopic findings into patients with mild or severe endoscopic lesions (Lanza score 2, 3, or 4) or patients without endoscopic lesions (Lanza score 0 or 1). A homogenous repartition regarding age and gender was noticed in all study subgroups. The distribution of the known factors for gastro-duodenal lesions in the studied group based on the severity of endoscopic lesions are shown in Table 1. Age over 50 years proved to be an important risk factor for mild/severe endoscopic lesions in our study group.

In the group with statin and aspirin therapy, the difference between the percentage of patients with mild or severe endoscopic lesions and patients without endoscopic lesions was 24% (95% CI: 11.9–34.9, $P < .01$), while in the group without statin therapy and low doses of aspirin, the difference was 30.5% (95% CI: 25.4–39.5, $P < .01$).

Patients without statin treatment and co-morbidities such as ischemic CAD ($P < .01$; OR: 2.99; 95% CI: 1.88–4.73), diabetes mellitus (DM) ($P < .01$; OR: 2.17; 95% CI: 1.20–3.92), heart failure (HF) ($P < .01$; OR: 2.13; 95% CI: 1.36–3.34), SAT ($P = .04$; OR: 2.30; 95% CI: 1.44–3.67), chronic kidney disease (CKD) ($P = .01$; OR: 2.25; 95% CI: 1.39–3.66), fatty liver disease ($P = .01$; OR: 2.25; 95% CI: 1.39–3.66), and chronic obstructive pulmonary disease (COPD) ($P < .01$; OR: 2.37; 95% CI: 1.37–4.10) had a statistically significant risk for developing mild or severe endoscopic lesions in comparison with patients who had statin treatment.

3.2. Univariate binominal logistic study

We used a univariate binominal logistic regression model (Table 2) to investigate the role of the studied independent variables for mild/severe endoscopic lesion occurrence (Lanza score 2, 3, or 4), adjusted for statin consumption. For ASA or clopidogrel consumption, as well as for cardiovascular diseases (coronary artery diseases [CAD], HF, arterial hypertension, or SAT), a lower risk with statin consumption was observed (Table 2).

3.3. Multivariate regression model

We investigated the potential protective effect of chronic treatment with statins against mild/severe endoscopic gastro-

Table 1

The distribution of demographic and clinical variables in patients stratified according to the presence of endoscopic lesions.

	With statin treatment N = 220			Without statin treatment N = 344		
	Mild/severe endoscopic lesions N = 71	No endoscopic lesions N = 149	*P* value/OR[††] (CI 95%)	Mild/severe endoscopic lesions N = 127	No endoscopic lesions N = 217	*P* value/OR (CI 95%)
Age >50	71/100%	140/94%	**.04/2.13 (1.26–3.60)**	103/81%	145/66.8%	**.03/1.50 (1.37–1.65)**
Male gender	53/74.6%	62/41.6%	**.01/4.13 (2.21–7.72)**	59/46.5%	91/41.9%	.41/1.20 (0.77–1.86)
H pylori	25/35.2%	47/31.5%	.58/1.17 (0.64–2.14)	40/40.4%	59/27.2%	.39/1.23 (0.76–1.98)
ASA[‡]	59/83.1	88/59.1	**.01/3.40 (1.69–6.87)**	51/40.2	21/9.7	**.01/6.26 (3.53–11.11)**
Clopidogrel	27/38.0%	39/26.2%	.07/1.731 (0.947–3.162)	7 / 5.5%	4/1.8%	.06/3,106 (0,891–10,828)
NSAIDs	6/8.5%	21/14.1%	.23/0.56 (0.216–1.462)	18/14.2%	28/12.9%	.73/1.115 (0.589–2.108)
Anticoagulants	18/24.5%	25/16.8%	.13/1.68 (0.84–3.34)	18/14.2%	24/11.1%	.39/1.32 (0.69–2.55)
PPI	45/63.4%	113/75.8%	.05/0.55 (0.29–1.06)	61/48%	123/56.7%	.12/0.70 (0.54–1.09)
Biliary reflux	24/33.8%	61/40.9%	.31/0.73 (0.40–1.32)	47/37%	90/41%	.41/0.82 (0.52–1.30)
Anemia[§]	31/43.7%	40/26.8%	**.01/2.10 (1.16–3.82)**	57/44.9%	60/27.6%	**.01/2.13 (1.34–3.37)**
Smokers[‖]	20/28.2%	21/14.1%	**.01/2.39 (1.19–4.78)**	38/29.9%	30/13.8%	**.01/2.66 (1.54–4.57)**
Drinkers[¶]	23/32.4%	35/23.5%	.16/1.56 (0.83–2.91)	43/33.9%	51/23.5%	**.03/1.66 (1.02–2.70)**
Ulcer history[††]	41/57%	95/63%	.31/0.77 (0.43–1.38)	74/58%	129/59%	.83/0.95 (0.61–1.48)
ASA + *H pylori*	22/31%	29/19.5%	**.05/1.85 (0.97–3.54)**	15/11.8%	6/2.8%	**.01/4.71 (1.77–12.47)**

CI = confidence level: [lower limit, upper limit], NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, PPI = proton pump inhibitors.
[‡] ASA: low-dose aspirin (75–125 mg).
[§] Diagnosed by blood tests.
[‖] >5 cigarettes/day including quitters during the past 5 years.
[¶] Consumption of >10 units/week.
[#] Prior ulcer disease diagnosed by endoscopy or by radiological examination.
[††] OR was adjusted by age and sex.

Table 2

Univariable binomial logistic regression model for endoscopic lesions (Lanza score 2,3,4) occurrence adjusted for the presence of chronic statin therapy.

			95% CI				95% CI	
Variables	***P* value variable**	**OR**	**Lower**	**Upper**	***P* value statin**	**OR adjusted for statin**	**Lower**	**Upper**
ASA[‡]	<.01	4.98	3.18	7.82	<.01	0.35	0.22	0.56
Anticogulants	.10	1.48	0.92	2.38	.19	0.78	0.55	1.13
Clopidogrel	.01	1.94	1.13	3.32	.05	0.67	0.45	1.00
NSAID's	.65	0.88	0.52	1.49	.25	0.81	0.56	1.16
H pylori	.31	1.21	0.83	1.75	.24	0.80	0.56	1.15
Biliary reflux	.20	0.79	0.55	1.13	.25	0.81	0.56	1.16
Ulcer history[‖]	.48	0.88	0.62	1.25	.26	0.81	0.57	1.16
Anemia[¶]	<.01	2.12	1.47	3.05	.28	0.82	0.57	1.17
Smoking[#]	<.01	2.55	1.66	3.91	.27	0.81	0.56	1.17
Drinking[††]	.01	1.62	1.11	2.38	.26	0.81	0.57	1.16
CAD	<.01	2.61	1.75	3.91	<.01	0.53	0.35	0.79
SAT	<.01	2.11	1.45	3.05	.02	0.65	0.44	0.95
Fatty liver diseases	.04	1.46	1.01	2.12	.11	0.74	0.51	1.07
CKD	.02	1.88	1.25	2.82	.14	0.76	0.53	1.10
DM	.05	1.51	0.99	2.31	.14	0.76	0.52	1.09
HF	<.01	1.83	1.26	2.67	.03	0.65	0.44	0.96
Arterial Hypertension	<.01	2.58	1.59	4.16	.01	0.60	0.40	0.88

CAD = coronary artery disease, CKD = chronic kidney disease, CI = confidence level: [lower limit, upper limit], DM = diabetes mellitus, HF = heart failure, NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, SAT = systemic atherosclerosis.

[‡] ASA: low-dose aspirin (75–125 mg).

[‖] Prior ulcer disease diagnosed by endoscopy or by radiological examination.

[¶] Diagnosed by blood tests.

[#] >5 cigarettes/day including quitters during the past 5 years.

[††] Consumption of >10 units/week.

duodenal lesions using multivariate regression analysis, through various study models that associated the mentioned risk factors (Table 3). In all models, statins showed a protective role for gastro-duodenal lesions, while female gender was the other single protective studied variable. Age over 50 years, aspirin intake, anticoagulant therapy, CAD or atherosclerosis disease, as well as smoking were risk factors for developing mild or severe endoscopic lesions in the studied population (Table 3). *H pylori* infection was not associated in a statistically significant manner with mild or severe endoscopic lesions in our study group (Table 3).

4. Discussions

The current evidence does not enable the clarification of the association between statin therapy and gastro-duodenal mucosal lesions. Our findings support a possible gastroprotective role of statins (67% of patients without endoscopic lesions in the statin group compared to 63% in the control group), more evident after adjustment for confounding factors in patients with cardiovascular disorders and treatments.

Statins have been found to play a role in several diseases associated to bacteria,[29,30] being used even as additional therapy for the treatment of *H pylori* infection, increasing the eradication rate and ameliorating ulcer development.[30,31] Our study failed to establish a gastroprotective effect of statins against lesions associated with *H pylori* infection. Infection was more frequent in patients with mucosal lesions in both groups, but the difference did not reach the statistical significance. Selection bias from an endoscopic population, concomitant use of proton pump inhibitors (PPI), and the lack of data regarding previous eradication therapy might explain our findings.

Statins were proved to have a protective effect against NSAID-induced lesions in experimental models,[14,15] mediated by increasing NO and prostaglandin (PGI_2 and PGE_2) synthesis, and decreasing the acidity and volume of gastric secretion.[14,15,31] There were also several clinical studies that showed that statin use is associated with an increased risk for developing digestive symptoms and upper gastrointestinal hemorrhages.[18,19] At the same time, a case-control analysis performed on a Taiwanese population revealed a reduced incidence of peptic ulcer disease associated with chronic statin therapy.[5,17] Our study also suggests that statins have a protective role against ASA-induced lesions. Statins do not abate completely the gastrotoxic effect of aspirin intake, but we noticed an important reduction of the estimated risk for developing mild or severe endoscopic lesions, from 6.26 to 3.40 when statin therapy was associated. Similar results were noticed in clinical studies such as the OPUS-TIMI 16 trial, where the rate of upper gastrointestinal bleeding was reduced in patients with acute coronary syndrome who received antithrombotic therapy combined with statins.[20] A study performed on a Danish population showed a certain reduction of gastrointestinal bleeding risk in patients with ASA therapy and chronic statin consumption.[1] ASA consumption remains the most important independent risk factor for endoscopic lesions in our multivariable regression models.

As far as anticoagulants (acenocumarolum, LMWH) are concerned, in both groups the univariate analysis showed no increased risk for endoscopic lesions, despite the accepted risk of delayed healing of mucosal lesions. In the regression model, adjusted for age >50 years, *H pylori* infection, ASA, or smoking habits, anticoagulant therapy was an independent risk factor for endoscopic lesions.

The concomitant use of statins with other gastrotoxic drugs such as clopidogrel, anticoagulants, NSAIDs (other than ASA) failed to establish any gastroprotective effect. Moreover, we registered statins as being a risk factor for developing endoscopic lesions with combined antiplatelet therapy (ASA + clopidogrel)

Table 3

Multivariate regression models for mild/severe gastro-duodenal endoscopic lesions.

						95% CI for OR	
Model 1	**B**	**SE**	**Wald**	***P* value**	**OR**	**Lower**	**Upper**
Statin	0.42	0.19	4.76	.02	0.65	0.44	0.95
Gender/F[a]	0.39	0.19	4.22	.04	0.67	0.45	0.98
Age >50	0.86	0.26	10.60	.01	2.37	1.41	4.00
Smoking[b]	0.77	0.23	11.08	.01	2.17	1.37	3.44
Constant	−1.13	0.27	17.36	<.01	0.32		
						95% CI for OR	
Model 2	**B**	**SE**	**Wald**	***P* value**	**OR**	**Lower**	**Upper**
Statin	−1.11	0.23	22.10	<.01	0.32	0.20	0.52
Age >50	0.58	0.27	4.66	.03	1.79	1.05	3.05
H pylori	0.20	0.20	0.98	.32	1.22	0.82	1.81
ASA[c]	1.01	0.23	42.50	<.01	4.54	2.83	7.16
Constant	−1.37	0.24	30.43	<.01	0.25		
						95% CI for OR	
Model 3	**B**	**SE**	**Wald**	***P* value**	**OR**	**Lower**	**Upper**
Statin	0.51	0.20	6.65	.01	0.59	0.40	0.88
Age >50	0.59	0.28	4.52	.03	1.81	1.04	3.14
Smoking[b]	0.99	0.22	19.63	<.01	2.69	1.73	4.16
SAT	0.65	0.20	10.34	.01	1.92	1.29	2.85
Constant	−1.41	0.24	33.62	<.01	0.24		
						95% CI for OR	
Model 4	**B**	**SE**	**Wald**	***P* value**	**OR**	**Lower**	**Upper**
Statin	−1.14	0.24	22.45	<.01	0.31	0.19	0.51
Age >50	0.62	0.28	4.98	.02	1.86	1.07	3.23
ASA[c]	1.58	0.23	44.39	<.01	4.89	3.06	7.81
H pylori	0.14	0.20	0.49	.48	1.15	0.77	1.73
CAD	0.59	0.22	6.62	.01	1.80	1.15	2.82
Smoking[b]	1.05	0.23	20.4	<.01	2.86	1.81	4.52
Constant	−1.48	0.27	29.65	<.01	0.22		
						95% CI for OR	
Model 5	**B**	**SE**	**Wald**	***P* value**	**OR**	**Lower**	**Upper**
Statin	−1.20	0.24	24.12	<.01	0.301	0.18	0.48
Age >50	0.48	0.27	2.98	.08	1.62	0.93	2.80
H pylori	0.22	0.20	1.15	.28	1.25	0.83	1.88
ASA[c]	1.65	0.24	46.82	<.01	5.24	3.26	8.43
Anticoagulants	0.60	0.26	4.95	.02	1.82	1.07	3.08
Smoking[b]	1.06	0.23	20.61	<.01	2.88	1.82	4.55
Constant	−1.63	0.26	39.08	<.01	0.19		

CAD = coronary artery disease, CI = confidence level: [lower limit, upper limit], OR = odds ratio, SAT = systemic atherosclerosis.

[a] Female gender.

[b] >5 cigarettes/day including quitters during the past 5 years.

[c] ASA: low-dose aspirin.

(*P* = .03; OR: 2.04; 95% CI: 1.04–4.02, data not shown), but the reduced number of cases in the control group did not allow us to compare the results. Similar results were reported in a Danish population-based case–control study, where statins had no protective effect in combined gastrotoxic drug consumption.[1]

Male gender was associated with an increased risk for developing upper gastrointestinal bleeding in various studies.[1,20] In the present study, male gender represented a risk factor (*P* = .01) for mild/severe endoscopic lesions (surrogate markers for a future bleeding episode) in the statin group, but not in the control group. Our previous studies also suggest that male gender is associated with more severe endoscopic lesions in patients treated with ASA (including concomitant therapy with PPI).[23,32] The association was also shown for duodenal ulcer,[33] possibly due to the increased prevalence of *H pylori* infection in men or a possible protective effect of estrogen in duodenal lesion occurrence.[34] Other studies did not recognize gender as a risk factor for ulcers,[23,25] showing an increased risk for endoscopic lesions in female patients.[5] Our results require further investigations adjusted for other possible confounding factors.

Certain medical conditions were proved to be independent risk factors for bleeding ulcers in several case–control[23,24] and epidemiological studies.[26] For long-term aspirin users, hypertension, severe left HF, and renal failure proved to be associated with a higher risk of bleeding ulcers in a cohort study,[27] and the OPUS-TIMI 16 trial showed a high incidence of gastrointestinal bleeding in patients with hypertension, HF, and ischemic heart disease.[20] As we expected, the frequency of cardiovascular or metabolic disorders was higher in patients with statin therapy. Our results support that cardiovascular diseases (CAD, SAT, HF,

hypertension) are associated with an increased risk for endoscopic lesions, while statin treatment seems to exert a protective effect. Nevertheless, we noticed a reduced adherence to chronic statin therapy in CAD patients: 38% were not using statins for secondary prevention therapy, as guidelines recommend. For CKD or fatty liver diseases, we noticed an increased risk for endoscopic lesions, but the protective role of statins was not proved. Based on these results, we were able to assay, through several logistic regression analyses, a certain protective role of statins among patients with hypertension, ischemic heart disease, heart failure, and SAT.

Smoking and drinking habits were associated with endoscopic lesions in our population, similarly to other studies,[35,36] even when adjusting for the presence of *H pylori* infection, age up to 50 years, cardiovascular diseases, or drug consumption (aspirin or anticoagulants), without a protective effect of statins. The possible modulating role of statins in the complex pathophysiologic mechanisms of mucosal damage, combining environmental factors with specific genetic background,[37] should be further questioned in more complex studies.

The study is subject to limitations, such as the fact that it is a population-based case–control study with reduced number of patients (<1000), with a strong bias toward chronic comorbidities and lower methodological quality, compared to randomized trials. Nevertheless, an increased number of subjects would allow us to simulate in a more accurate regression model other possible independent clinical, pathological, or molecular variables. We are also aware of the fact that NSAIDs, ASA, and statins being over-the-counter drugs, it is hard to obtain accurate data regarding dosage, compliance, and treatment continuity.

One of the strengths of the study is that we revised all the cases separately, including detailed information regarding endoscopic aspects, habits, drug consumption, concomitant diseases, and personal history of the subjects. It is the first study performed in an Eastern European population, investigating the possible modulating role of statins in endoscopic mucosal lesions. The possible gastroprotective effect of statins may help practitioners to individualize the preventive strategies against gastrointestinal bleeding in patients with cardiovascular disorders and combined therapies, which frequently include gastroprotective drugs or more investigations.

Additional large, population-based, unbiased randomized trials are necessary to validate our findings, and the impact of statin use in gastrointestinal lesions promoted by other cardiovascular drugs should be furthermore investigated.

5. Conclusions

The results of the present research support a certain protective role of chronic therapy with statins against gastroduodenal endoscopic lesions, especially in ASA consumers or patients with cardiovascular diseases.

Author contributions

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