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Statins and Lower Gastrointestinal Conditions: A Retrospective Cohort Study

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Abstract

Several studies have reported constipation, abdominal pain, or diarrhea as common adverse events for statins. Statins are among the most commonly prescribed medications, and the impact on the prevalence of these conditions was rarely studied as main outcomes. The aim of this study is to determine if statin therapy is associated with constipation, abdominal pain, diarrhea, or colitis. This was a retrospective cohort study using a regional military health care data from October 1, 2003, to March 1, 2012. A propensity score–matched cohort of statin users and nonusers was created based on 82 variables. The primary analysis evaluated the odds ratios of the following diagnoses: constipation, ≥3 encounters for constipation; abdominal pain, ≥3 encounters for abdominal pain; diarrhea, ≥3 encounters for diarrhea; colitis, ≥3 encounters for colitis; and endoscopy of the lower gastrointestinal tract, ≥3 endoscopies of the lower gastrointestinal tract. After propensity score matching of 6342 statin users and 6342 nonusers, there was no statistically significant difference in constipation (OR, 0.96; 95%CI, 0.87–1.05; $P = .33$), abdominal pain (OR, 0.95; 95%CI, 0.88–1.02; $P = .15$), or colitis (OR, 1.02; 95%CI, 0.91–1.14; $P = .73$). However, there was an association between statin therapy and endoscopy of the lower gastrointestinal tract (OR, 1.14; 95%CI, 1.04–1.26; $P = .002$) and decreased odds of diarrhea (OR, 0.88; 95%CI, 0.80–0.97; $P = .01$). In this retrospective cohort study, an association between statin therapy and increased likelihood of being diagnosed with lower gastrointestinal conditions could not be demonstrated, contrary to some statins package inserts.

Keywords

statins, constipation, abdominal pain, diarrhea, colonoscopy

Gastrointestinal conditions are frequent side effects of medications because of the pharmacologic effect on intestinal motility and water secretion.[1] Chronic constipation, one of the common lower gastrointestinal symptoms, has a prevalence of 14%–19% and may be associated with concurrent abdominal pain if the patient has irritable bowel syndrome.[2] Severity of symptoms correlates with loss of productivity and increased health care utilization.[3]

Statins are among the most commonly used medications, and their consumption is projected to increase because the American College of Cardiology (ACC) and American Heart Association (AHA) expanded statin therapy for primary prevention of atherosclerotic cardiovascular disease.[4] There is, however, no clear consensus in the literature on whether statins have a causal relationship with common lower gastrointestinal conditions. Several large-scale studies reported an incidence of constipation or abdominal pain in 2%–3% of statin users; however, patients in many of these studies concurrently received dietary counseling and additional lipid-lowering medications. Because of these confounding variables, it is difficult to discern if the increased incidence of constipation or abdominal pain is from statins or other simultaneous interventions.[5–7] Conversely, other randomized, controlled trials (RCTs) did not show a significant difference in constipation or abdominal pain between statin users and nonusers.[8,9] Observational studies on statin use and its association with diarrhea and colitis have also produced mixed findings. The majority of these studies are limited by study design, the presence of polypharmacy, and suboptimal definitions of statin use.[10–13] To our knowledge, there have been no large studies that directly evaluated whether statins increase the risk of lower gastrointestinal conditions.

The primary objective of this study was to examine the association of statin therapy with constipation,

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abdominal pain, diarrhea, colitis, and the use of endoscopy of the lower gastrointestinal tract in a longitudinal cohort followed within the same health care system with equal access to care. We hypothesized statin users would have increased odds of being diagnosed with constipation, abdominal pain, diarrhea, or colitis and would undergo more endoscopic procedures to evaluate these conditions.

Methods

The study methods have been previously published.[14–16] Briefly, this was a retrospective cohort study using patients enrolled in the San Antonio Military Healthcare System from October 1, 2003, to March 1, 2012, after approval from institutional review boards of relevant institutions. Clinical data were acquired using the Military Health System Management Analysis and Reporting Tool managed by TRICARE Management Activity. Extracted data included patient demographics, diagnoses, procedures, and medication prescriptions regardless of point-of-care affiliation or location. Information included both inpatient and outpatient encounter settings. The study period was divided into 2 periods: baseline period of fiscal years 2004–2005 (October 1, 2003, through September 30, 2005) and the follow-up period (October 1, 2005, through March 1, 2012).

The statin group was defined as statin-naive patients who filled a statin prescription for ≥90 days starting in the 2005 fiscal year. The nonuser group was defined as patients who were not on statin therapy during the baseline or follow-up periods.

Eligible patients were between the ages of 30 and 85 years, had 1 or more encounters during the baseline period and follow-up period, and filled at least 1 medication during the baseline period. Statin therapy was not limited to any particular statin or dose. Exclusion criteria included those who received statins for <90 days during the study period or were initiated on statins after the baseline period.[14–16]

Baseline characteristics incorporated 82 variables to create a propensity score to match statin users and nonusers and included the following: patient demographics, Charlson Comorbidity Index, predefined disease categories from the Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CSS) using the International Classification of Diseases, 9th revision-clinical modification diagnoses (ICD-9-CM) codes or their equivalency Current Procedural Terminology (CPT) codes, the number of inpatient and outpatient encounters, immunizations during the baseline period as a surrogate for patient access to care and health care utilization, and the use of particular medication classes (Table 1, Appendix).[17]

Outcomes were the following prespecified diagnosis categories of the AHRQ-CSS:

1. Constipation: ICD-9-CM codes 5640, 56400, 56401, 56402, and 56409.
2. Abdominal pain: ICD-9-CM codes 7890, 78900, 78901, 78902, 78903, 78904, 78905, 78906, 78907, 78909, 78960, 78961, 78962, 78963, 78964, 78965, 78966, 78967, and 78969.
3. Diarrhea: ICD-9-CM codes 0092, 0093, 78791, and 5645.
4. Colitis: ICD9-CM-codes 5560, 5561, 5562, 5563, 5564, 5565, 5566, 5568, 5569, 5581, 5582, 5583, 5584, 55841, 55842, 5589, 0090, 0091, and 00845.
5. Endoscopy of the lower gastrointestinal tract: ICD-9-CM codes 4523, 4525, 4824, 4521, 4523, and 4524 and their equivalent endoscopy CPT codes 45380, 45378, 45330, 45331, and 45305.

Because occasional constipation, abdominal pain, diarrhea, and colitis are of common occurrence, we included ≥3 encounters for each outcome to help differentiate between self-limited conditions and a more chronic process:

1. ≥3 encounters for constipation
2. ≥3 encounters for abdominal pain
3. ≥3 encounters for diarrhea
4. ≥3 encounters for colitis
   ≥3 endoscopies of the lower gastrointestinal tract

The primary analysis examined the outcomes mentioned above in the propensity score–matched cohort. A secondary analysis was performed using the overall cohort, which included all patients who fulfilled the inclusion and exclusion criteria:

1. We examined the odds of the predefined outcomes in the overall cohort of statin users compared with nonusers, but excluded those with baseline constipation, abdominal pain, diarrhea, or colitis.
2. We examined the odds of the predefined outcomes in the overall cohort of statin users for ≥4 years compared with nonusers to determine if duration of statin therapy made a difference in regard to the development of lower gastrointestinal conditions.
3. We examined the odds of the predefined outcomes in the overall cohort of high-intensity statin users compared with nonusers.
4. We examined the odds of the predefined outcomes in the overall cohort of high-intensity statin users compared with low- to moderate-intensity statin users to determine if there was a dose–response relationship.

Table 1. Selected Baseline Characteristics of Propensity Score–Matched Statin Users and Nonusers[a]

Variable	Nonusers, n (%) (n = 6342)	Statin Users, n (%) (n = 6342)	*P*
Age (y), mean ± SD	56 ± 12	55 ± 12	.13
Female sex	2856 (45.0)	2924 (46.1)	.23
Smoking	534 (8.4)	509 (8.0)	.44
Obesity	993 (15.7)	960 (15.1)	.43
Charlson Comorbidity Index, mean (SD)[b]	0.64 ± 1.23	0.66 ± 1.25	.29
Comorbidities[c]			
Gastritis/duodenitis	216 (3.4)	215 (3.4)	1.00
Gastrointestinal ulcers	51 (0.8)	55 (0.9)	.70
Diabetes mellitus	743 (11.7)	789 (12.4)	.21
Diabetes mellitus with complications	220 (3.5)	247 (3.9)	.22
Acute myocardial infarction	20 (0.3)	25 (0.4)	.46
Hypertension with complications	176 (2.8)	181 (2.9)	.79
Congestive heart failure	108 (1.7)	117 (1.8)	.55
Arterial thromboembolism	12 (0.2)	14 (0.2)	.85
Peripheral vascular disease	153 (2.4)	169 (2.7)	.37
Metastatic neoplasm	31 (0.5)	25 (0.4)	.43
Health care utilization			
Number of outpatient visits during baseline period, mean ± SD	31.7 ± 36.8	31.8 ± 40.6	.84
Number of inpatient admissions during baseline period, mean ± SD	0.2 ± 0.7	0.3 ± 0.8	.75
Number of encounters for immunization during baseline period, mean ± SD	0.5 ± 1.6	0.5 ± 3.7	.75
Medication, n (%)			
NSAID	3729 (58.8)	3702 (58.4)	.64
Proton pump inhibitor	2009 (31.7)	2030 (32.0)	.70
Aspirin	1835 (28.9)	1890 (29.8)	.28
Beta-blocker	1099 (17.3)	1123 (17.7)	.57
SSRI	1059 (16.7)	1067 (16.8)	.87
Calcium channel blocker	987 (15.6)	1001 (15.8)	.75
Nonstatin lipid-lowering drug	373 (5.9)	391 (6.2)	.50
Parameters not included in propensity score			
Constipation at baseline	273 (4.3)	283 (4.5)	.67
Abdominal pain at baseline	884 (13.9)	773 (12.2)	.004
Diarrhea at baseline	319 (5.0)	260 (4.1)	.01
Colitis at baseline	265 (4.2)	235 (3.7)	.19
Endoscopic procedure at baseline	1047 (16.5)	1105 (17.4)	.17

NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

[a]Complete description of baseline characteristics of the cohort was previously published.[13]

[b]Diagnosis is based on ICD-9-CM codes as identified in Deyo method for applying the Charlson comorbidity score.[14]

[c]As defined by the Agency for Healthcare Research and Quality-Clinical Classifications Software.[23]

Classification of statin intensity was based on the ACC/AHA guidelines with the modification of including simvastatin 80 mg as a high-intensity statin.[4]

Statistical analyses to compare statin users with nonusers were performed using χ^2 analysis for categorical variables and an unpaired 2-tailed *t* test for continuous variables. Odds ratios were calculated for the primary and secondary analyses. In the primary analysis, we used conditional logistic regression analysis to examine the odds ratios of outcomes. In the secondary analysis, we used separate logistic regression models for each outcome and adjusted for the propensity score. Comparisons achieving 2-tailed $P \leq .05$ were considered statistically significant. Statistical analyses were performed using commercial software (Stata, ver. 12; Stata Corp Inc, College Station, Texas; and SPSS, ver. 23; IBM, Armonk, New York).

Results

A total of 43 438 patients constituted the overall cohort, which included all patients who fulfilled the inclusion and exclusion criteria. Of those 43 438 patients, 13 626 (31.4%) were statin users, and 29 812 (68.6%) were nonusers. The mean duration of statin therapy was 2182 days. Statin users received varying types including simvastatin (74%), atorvastatin (17%), pravastatin (7%), and rosuvastatin (2%).

We matched 6324 statin users with 6342 nonusers using a propensity score. After matching, there was no statistically significant difference in baseline characteristics incorporated in propensity score matching between statin users and nonusers (Table 1).

Table 2. Outcomes in Propensity Score–Matched Cohort of Statin Users Versus Nonusers (Primary Analysis)

Outcome Variables	Nonusers, n (%) (n = 6342)	Statin Users, n (%) (n = 6342)	Odds Ratio	95%CI	*P*
Unadjusted odds ratios					
Constipation	1,086 (17.1)	1,045 (16.5)	0.96	0.87–1.05	.33
Constipation: ≥3 encounters	364 (5.7)	327 (5.2)	0.89	0.77–1.04	.15
Abdominal pain	2,123 (33.5)	2,047 (32.3)	0.95	0.88–1.02	.15
Abdominal pain: ≥3 encounters	943 (14.9)	887 (14.0)	0.93	0.84–1.03	.16
Diarrhea	1059 (16.7)	953 (15.0)	0.88	0.80–0.97	.01
Diarrhea: ≥3 encounters	391 (6.2)	299 (4.7)	0.75	0.65–0.88	≤.001
Colitis	698 (11.0)	710 (11.2)	1.02	0.91–1.14	.73
Colitis: ≥3 encounters	208 (3.3)	211 (3.3)	1.02	0.84–1.23	.88
Endoscopy lower gastrointestinal tract	949 (15.0)	1,062 (16.7)	1.14	1.04–1.26	.002
≥3 Endoscopies lower gastrointestinal tract	123 (1.9)	126 (2.0)	1.03	0.80–1.32	.85
Adjusted odds ratios for propensity score, presence of constipation, diarrhea, or abdominal pain at baseline or undergoing endoscopy, laparoscopy, or abdominal imaging at baseline					
Constipation			0.97	0.88–1.07	.54
Constipation: ≥3 encounters			0.90	0.77–1.06	.22
Abdominal pain			0.97	0.90–1.04	.38
Abdominal pain: ≥3 encounters			0.96	0.87–1.07	.46
Diarrhea			0.90	0.82–1.0	.04
Diarrhea: ≥3 encounters			0.78	0.67–0.91	.002
Colitis			1.04	0.93–1.16	.51
Colitis: ≥3 encounters			1.04	0.86–1.27	.67
Endoscopy lower gastrointestinal tract			1.17	1.06–1.29	.002
≥3 Endoscopies lower gastrointestinal tract			1.08	0.84–1.39	.57

However, statin nonusers had a higher prevalence of abdominal pain and diarrhea at baseline.

The primary analysis showed no significant difference between the 2 treatment arms using the following outcome measures: constipation, ≥3 encounters for constipation, abdominal pain, ≥3 encounters for abdominal pain, colitis, or ≥3 encounters for colitis. However, statin users had a lower odds of reporting diarrhea (odds ratio [OR], 0.88; 95% confidence interval [95%CI], 0.80–0.97; $P = .01$), lower odds of having ≥3 encounters for diarrhea (OR, 0.75; 95%CI, 0.65–0.88; $P \leq .001$). After adjusting for propensity score and the presence of lower gastrointestinal conditions at baseline, there was a significantly lower OR of diarrhea among statin users. Statin users were also more likely to have an endoscopy of the lower gastrointestinal tract during the follow-up period (OR, 1.14; 95%CI, 1.04–1.26; $P = .002$); see Table 2.

In the secondary analysis (Table 3), in the overall cohort excluding patients with baseline constipation, abdominal pain, diarrhea, or colitis, statin users compared with nonusers had increased odds of having 1 endoscopy of the lower gastrointestinal tract (OR, 1.24; 95%CI, 1.12–1.37; $P \leq .001$). Statin use for ≥4 years compared with nonuse was associated with increased odds of undergoing 1 endoscopic lower gastrointestinal tract endoscopy (OR 1.25; 95%CI 1.13–1.38; $P = .002$), but decreased odds of having ≥3 encounters for abdominal pain (OR, 0.87; 95%CI, 0.79–0.96; $P = .006$). High-intensity statin users compared with nonusers had decreased odds of ≥3 encounters for constipation (OR, 0.78; 95%CI, 0.65–0.94; $P = .008$), increased odds of abdominal pain (OR, 1.14; 95%CI, 1.04–1.25; $P = .004$), increased odds of colitis (OR, 1.18; 95%CI, 1.05–1.34; $P = .008$), and decreased odds of ≥3 endoscopies of the lower gastrointestinal tract (OR, 0.71; 95%CI, 0.53–0.94; $P = .02$). Last, when comparing low- to moderate-intensity statin users with high-intensity statin users, high-intensity statin users demonstrated higher odds of 1 encounter for abdominal pain (OR, 1.24; 95%CI, 1.10–1.39; $P \leq .001$).

Discussion

The primary analysis of the propensity score–matched cohort of 12 684 patients did not identify a statistically significant association between statin use and increased likelihood of being diagnosed with lower gastrointestinal conditions such as constipation, abdominal pain, or colitis. In fact, statin use was associated with lower odds of diarrhea. However, statin users also had a lower prevalence of diarrhea and colitis at baseline. This may suggest that clinicians avoided prescribing statins to those with these conditions at baseline, and this may have contributed to the lower likelihood of diarrhea at follow-up among statin users. In the secondary analysis, after excluding all patients with lower gastrointestinal conditions at baseline, there was no association between

Table 3. Outcomes in Statin Users Versus Nonusers (Secondary Analysis)

Outcome Measures	Nonusers, n (%) (n = 24 322)	Statin Users, n (%) (n = 10 513)	Adjusted Odds Ratio[a]	95%CI	*P*
Overall chort: excluding those with baseline constipation, abdominal pain, diarrhea, or colitis					
Constipation	2479 (10.2)	1834 (17.4)	0.95	0.86–1.04	.27
Constipation: ≥3 encounters	637 (2.6)	542 (5.2)	0.85	0.71–1.01	.07
Abdominal pain	6594 (27.1)	3160 (30.1)	0.98	0.91–1.05	.58
Abdominal pain: ≥3 encounters	2480 (10.2)	1290 (12.3)	0.95	0.86–1.06	.34
Diarrhea	2626 (10.8)	1695 (16.1)	0.96	0.87–1.05	.36
Diarrhea: >3 encounters	680 (2.8)	565 (5.4)	0.91	0.77–1.08	.27
Colitis	2276 (9.4)	1114 (10.6)	1.04	0.94–1.16	.45
Colitis: >3 encounters	450 (1.9)	320 (3.0)	1.15	0.93–1.42	.21
Endoscopy lower gastrointestinal tract	1791 (7.4)	2106 (20.0)	1.24	1.12–1.37	≤.001
≥3 Endoscopies lower gastrointestinal tract	125 (0.5)	284 (2.7)	1.13	0.84–1.53	.42
	Nonusers (n = 29 812)	Statin Users ≥ 4 years (n = 9322)	AOR[b]	95%CI	*P*
Overall cohort: statin users for ≥4 years versus nonuser					
Constipation	3780 (12.7)	2128 (22.8)	1.00	0.91–1.10	.98
Constipation: ≥3 encounters	1105 (3.7)	710 (7.6)	0.88	0.76–1.03	.11
Abdominal pain	9382 (31.5)	3267 (35.0)	0.96	0.89–1.03	.26
Abdominal pain: ≥3 encounters	3957 (13.3)	1453 (15.6)	0.87	0.79–0.96	.006
Diarrhea	3892 (13.1)	1843 (19.8)	0.94	0.85–1.03	.18
Diarrhea: >3 encounters	1095 (3.7)	684 (7.3)	0.86	0.74–1.01	.06
Colitis	3391 (11.4)	1206 (12.9)	1.05	0.94–1.17	.39
Colitis: >3 encounters	775 (2.6)	417 (4.5)	1.13	0.94–1.36	.20
Endoscopy lower gastrointestinal tract	2439 (8.2)	2229 (23.9)	1.25	1.13–1.38	.002
≥3 Endoscopies lower gastrointestinal tract	216 (0.7)	333 (3.6)	1.03	0.80–1.32	.83
	Nonusers (n = 29 812)	High-intensity Statin Users (n = 5214)	AOR[b]	95%CI	*P*
Overall cohort: high-intensity statin users versus nonusers					
Constipation	3780 (12.7)	1182 (22.7)	1.00	0.89–1.12	.97
Constipation: ≥3 encounters	1105 (3.7)	371 (7.1)	0.78	0.65–0.94	.008
Abdominal pain	9382 (31.5)	2004 (38.4)	1.14	1.04–1.25	.004
Abdominal pain: ≥3 encounters	3957 (13.3)	918 (17.6)	1.04	0.93–1.17	.50
Diarrhea	3892 (13.1)	1076 (20.6)	0.98	0.87–1.09	.68
Diarrhea: >3 encounters	1,095 (3.7)	397 (7.6)	0.85	0.72–1.02	.08
Colitis	3391 (11.4)	716 (13.7)	1.18	1.05–1.34	.008
Colitis: >3 encounters	775 (2.6)	244 (4.7)	1.18	0.95–1.47	.14
Endoscopy lower gastrointestinal tract	2439 (8.2)	1127 (21.6)	0.89	0.79–1.00	.05
≥3 Endoscopies lower gastrointestinal tract	216 (0.7)	171 (3.3)	0.71	0.53–0.94	.02
	Low to Moderate Statin (n = 8412)	High-Intensity Statin Users (n = 5214)	AOR[b]	95%CI	*P*
Overall cohort: high-intensity statin users versus low to moderate intensity statin users					
Constipation	1733 (20.6)	1182 (22.7)	1.07	0.95–1.27	.23
Constipation: ≥3 encounters	605 (7.2)	371 (7.1)	0.84	0.65–1.1	.20
Abdominal pain	2831 (33.7)	2004 (38.4)	1.24	1.10–1.39	≤.001
Abdominal pain: ≥3 encounters	1270 (15.1)	918 (17.6)	1.14	0.98–1.34	.09
Diarrhea	1553 (18.5)	1076 (20.6)	1.03	0.94–1.23	.55
Diarrhea: >3 encounters	592 (7.0)	397 (7.6)	0.95	0.82–1.09	.42
Colitis	1052 (12.5)	716 (13.7)	1.04	0.94–1.16	.43
Colitis: >3 encounters	343 (4.1)	244 (4.7)	1.06	0.89–1.26	.53
Endoscopy lower gastrointestinal tract	1825 (21.7)	1127 (21.6)	0.87	0.75–1.03	.07
≥3 Endoscopies lower gastrointestinal tract	268 (3.2)	171 (3.3)	0.68	0.45–1.02	.06

AOR, adjusted odds ratio.

[a] Adjusted for propensity score, undergoing endoscopy, laparoscopy, or abdominal imaging at baseline.

[b] Adjusted for propensity score, undergoing endoscopy, laparoscopy, or abdominal imaging at baseline, or being diagnosed with constipation, abdominal pain, or diarrhea at baseline.

Table 4. Examples of Studies That Examined Association of Statins and Lower Gastrointestinal Conditions

Study	Study Description	Results	Limitations
Studies that found an association between statin use and lower gastrointestinal conditions			
Ballantyne et al[23]	A multicenter, randomized, double-blind, parallel-dose study in 917 patients with HLD to compare the effects of high-dose atorvastatin versus high-dose simvastatin on HDL. Primary end points were related to HDL levels. Safety end points included liver enzyme abnormalities and gastrointestinal symptoms.	There was no significant difference in gastrointestinal adverse effects between atorvastatin and simvastatin. The most common drug-related gastrointestinal side effects included diarrhea (1.3% with simvastatin and 3% with atorvastatin), constipation (1.3% with simvastatin and 1.5% with atorvastatin), and nausea.	Patients were all initiated on a NCEP step 1 or equivalent diet prior to statin initiation, which is a confounding variable because dietary changes often influence gastrointestinal symptoms.
Black et al[6]	Pooled analysis that evaluated the safety profile of atorvastatin in 2502 patients from 21 completed trials and 23 ongoing trials compared with other statins (simvastatin, pravastatin, and lovastatin).	Patients received varying daily doses of atorvastatin ranging from 10 to 80 mg. Patients were treated for ≥4 weeks. The most common atorvastatin-related adverse events were constipation, flatulence, dyspepsia, and abdominal pain.	Atorvastatin doses varied greatly. The sample size was not based on a power analysis. Adverse events were reported as descriptive and did not undergo any statistical analysis.
Boccuzzi et al[5]	Safety analysis of simvastatin using controlled clinical studies and their open extensions of 2400 patients with primary HLD, with a mean follow-up period of 1 year.	Simvastatin was titrated to the maximal daily dose of 40 mg in 56% of the patients. The most frequently reported drug-related adverse events were constipation (2.5%), abdominal pain (2.2%), flatulence (2.0%), and headaches (1%).	There was no report of the prevalence of constipation or abdominal pain in the control arms of the included clinical trials.
Bonderup et al[10]	Case-control study including all patients with a diagnosis of microscopic colitis in the Danish Civil Registration System from 2005 to 2011. Data were collected prospectively by time of drug exposure and at time of microscopic colitis diagnosis; 3474 patients with collagenous colitis and 2277 patients with lymphocytic colitis. One hundred sex- and age-matched persons were randomly selected as controls. For both cases and controls, drug exposure was defined.	PPIs, NSAIDs, SSRIs, and statin use were associated with microscopic colitis, although PPIs and NSAIDs had a significantly higher OR when compared with statins or SSRIs. Statin use and collagenous colitis (AOR, 1.61; 95%CI 1.2–1.39) and lymphocytic colitis (AOR, 1.25; 95%CI, 1.13–1.38).	Retrospective study design. Drug exposure was defined as receiving 1 or more prescriptions for a particular drug within a 1-year period from the index date (not able to confirm patient was compliant with medication).
Fernández-Bañares et al[11]	Case–control study of 39 patients with collagenous colitis, 33 patients with lymphocytic colitis, 52 patients with functional chronic diarrhea, and 103 controls. Once the diagnosis was made, drug consumption history was obtained at least 2 weeks prior to the diagnosis.	Statin use was associated with lymphocytic colitis (OR, 4.6; 95%CI, 1.04–20) and functional chronic diarrhea (OR, 5.4; 95%CI, 1.2–24), but was not associated with collagenous colitis.	Confounder of higher medication use in microscopic colitis groups not accounted for in analysis. Small sample size accounts for a wide CI.
Kashliwal et al[7]	Observational cohort study to evaluate the safety profile of rosuvastatin in 11 680 patients in 2003 in England using prescription- event monitoring. Median treatment period was 9.8 months. Analysis of specific adverse events by starting dose of rosuvastatin was performed, along with a follow-up and causality assessment of significant events.	Of 11 680 patients, the most frequent reason for drug discontinuation was myalgia; however, 33 (0.28%) discontinued statin therapy because of abdominal pain.	Study had a low response rate of 40%, data are limited to general practitioners and did not include patients who were initiated on statin therapy during a hospitalization, observational study design, unable to assess patient compliance with statin therapy.

(*Continued*)

Table 4. Continued

Study	Study Description	Results	Limitations
Manocha et al[13]	Single-center retrospective case–control study of patients > 65 years old who were admitted with an acute stroke. The study included 100 patients on high-dose statins (cases) and 100 patients on low-dose statins (control) between 2008 and 2011.	Self-reported diarrhea was higher in the high-dose statin group (6%) compared with the low-dose statin group (2%), $P = .03$.	Retrospective study design; small sample size.
Oleson et al[24]	Retrospective study using patients with biopsy proven lymphocytic colitis from 24 Swedish gastroenterology clinics with corresponding clinic data from medical charts (n = 199) to determine clinical features of lymphocytic colitis and treatment outcomes.	Drug-induced lymphocytic colitis was suspected in 19 cases (10%) including 1 case of simvastatin preceding lymphocytic colitis that did not warrant statin discontinuation.	Retrospective study design, small sample size. Only 1 case was suspected to be simvastatin induced.
Zhang et al[28]	Retrospective cohort study to determine reasons for statin discontinuation in routine care settings between 2000 and 2008 in 107 835 adult patients.	Statin- related events were documented in 17.4% of patients, with 1.6% of patients reporting gastrointestinal symptoms (specific gastrointestinal symptoms were not reported).	Retrospective study design; unclear if statin discontinuation from specific adverse events was truly statin related because most patients who were rechallenged with statin therapy tolerated it long term.
Studies with mixed findings			
Beaugerie L, Pardi D.[25]	Literature review of published reports involving drug-induced microscopic colitis that was incorporated into a scoring system to determine drug causality.	Combining chronological data and causality data to create a scoring system, 21 drugs or drug classes had sufficient information to perform an analysis. Simvastatin was identified as having an intermediate likelihood of being a causative agent in the development of microscopic colitis.	Likelihood of responsibility for simvastatin was only based on 2 sources in the literature (retrospective study and a case report). There were not enough cases to distinguish between lymphocytic colitis and collagenous colitis.
Studies that found no association between statins and lower gastrointestinal conditions			
Pascua et al[12]	Prospective case–control study to evaluate the prevalence of certain medications with microscopic colitis from 2002 to 2007. Cases were identified based on biopsy-proven microscopic colitis or lymphocytic colitis (n = 26) and were matched with chronic diarrhea controls (n = 259) and "random" controls (n = 259).	This study showed no association between the use of PPIs, statins, or SSRIs with the development of microscopic colitis (AOR, 1.12; 95%CI, 0.34–3.71).	Drug exposure was defined as 1 prescription for that particular drug within the preceding year, unable to assess compliance with medical therapy.
Pedersen et al[26]	Randomized, controlled trial on 4444 patients with angina or prior myocardial infarction to determine the effect of simvastatin on morbidity and mortality. Patients were randomized to simvastatin or placebo group and were followed for a median of 5.4 years.	The overall frequency of adverse events was similar in both groups. Although the simvastatin group had 2.2% of patients report constipation, 1.6% of the placebo group also reported constipation. The study did not perform a statistical analysis to determine if there was a significant difference between the treatment and control groups.	Study end points were related to fatal and nonfatal cardiovascular events and was not powered to evaluate adverse events.

(*Continued*)

Table 4. Continued

Study	Study Description	Results	Limitations
Ridker et al[9]	RCT that enrolled 17 802 otherwise healthy patients with elevated CRP levels who were randomized to either 20 mg of rosuvastatin or placebo and were followed for the occurrence of several cardiac or vascular related events.	There was no significant difference in gastrointestinal symptoms between the statin group and the placebo group.	The study was powered to assess cardiovascular related end points and not gastrointestinal symptoms.
Shepherd et al[8]	Pooled analysis of 16 876 patients who received varying doses of rosuvastatin (33 placebo- controlled trials) to examine adverse events.	In the placebo-controlled trials, there was no significant difference in the prevalence of constipation between statin uses and nonusers.	Gastrointestinal symptom definitions may be widely varied among studies. RCTs are usually of smaller size and shorter duration; therefore, may not capture infrequent adverse events.
Verhaegh et al[27]	Retrospective case–control study of 1211 cases of microscopic colitis and 6041 controls within the British Clinical Practice Research Datalink for primary care (1992–2013). AOR calculated from conditional logistic regression.	No association of microscopic colitis with current statin use (AOR, 1.13; 95%CI, 0.94–1.36).	Retrospective design. No histological information captured in database to confirm diagnosis of microscopic colitis.
Current study			
Pearlman et al	Retrospective cohort study of 43 438 patients (13 626 statin users and 29 812 nonusers) followed longitudinally from October 2003 to March 2012 within the same health care system with similar access and benefits and no missing data. Examined odds of lower gastrointestinal symptoms in propensity score–matched cohort (6324 statin users and 6324 nonusers).	The primary analysis of the propensity score-matched cohort did not identify a statistically significant association between statin use and constipation, abdominal pain, or colitis, but did show that statin use was associated with an increased OR of undergoing 1 endoscopic evaluation of the lower gastrointestinal tract and a decreased odds ratio of diarrhea (OR, 0.88; 95%CI, 0.80–0.97) and ≥3 encounters for diarrhea (OR, 0.75; 95%CI, 0.65–0.88).	Retrospective study, unable to correlate severity of lower gastrointestinal conditions with statin use because of the use of ICD-9 codes, which do not include these descriptors.

RCT, randomized, controlled trial; HDL, high-density lipoprotein; HLD, hyperlipidemia; AOR, adjusted odds ratio; OR, odds ratio; CI, confidence interval; PPIs, proton pump inhibitors; NSAID, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; NCEP, national cholesterol education program.

statin therapy and any of the examined conditions. However, statin use was associated with greater odds of undergoing one endoscopy of the lower gastrointestinal tract. The association of statin use and endoscopic evaluation may be related to healthy-user bias; that is, people who agree to take statins are also more likely to consent to have an endoscopy of the lower gastrointestinal tract, which could have been done for screening purposes not necessarily because of a disease. The secondary analysis showed varying inconsistent associations. These inconsistencies may be a result of less than ideal adjustment for confounders using cohorts other than the propensity score–matched cohort.

One proposed mechanism for statin-induced colonic dysmotility is through the nitrous oxide pathway in which statins upregulate the expression and activity of nitrous oxide in vascular endothelial cells, which can then act on inhibitory nerves that are present throughout the colon.[18]

Package inserts and standard drug information resources such as UpToDate cite gastrointestinal conditions including constipation, abdominal pain, and diarrhea as some of the most common medication-related adverse reactions. For example, cited adverse events for rosuvastatin include constipation (3%–5%) and abdominal pain (2%), for simvastatin include abdominal pain (7%), constipation (2%–7%), and diarrhea (<1%),

and for atorvastatin include diarrhea (7%–14%) and abdominal pain (2%).[19–22] Table 4 includes a brief review of the literature that addresses statin therapy and lower gastrointestinal conditions.[5–13,23–28] In one review of 27 clinical trials, 2361 patients with primary hypercholesterolemia were treated with simvastatin (maximal daily dose achieved in 56%), with a mean follow-up of 1 year, and the most commonly reported drug-related adverse events were constipation (2.2%) and abdominal pain (2.5%). One of the limitations of this study, however, is the lack of reporting symptom prevalence in the control arm. Symptoms were reported as mild and transient and rarely required discontinuation of simvastatin (<0.3%).[5] Similarly, a postmarketing safety profile of rosuvastatin in 11 680 patients found that 33 patients (0.28%) discontinued therapy because of abdominal pain.[7] In a safety database review of 2502 patients from 21 trials, atorvastatin-related adverse events included abdominal pain (2%) and constipation (3%).[6] In an RCT comparing high-density lipoprotein changes with maximum doses of atorvastatin versus simvastatin, 1.5% and 1.3% of patients reported constipation in the atorvastatin and simvastatin groups, respectively, although there was no placebo arm for comparison.[23] A case report described a patient who had recurrent colonic dilatation and volvulus formation that ceased only after statin therapy was discontinued.[29]

In addition to abdominal pain and constipation, prior studies have also implicated statins as causative agents for the development of diarrhea and colitis.[10,11,13] However, most of these studies were of small sample size and may have had inadequate adjustment of different confounders. The atorvastatin package insert states that any dose is associated with diarrhea based on 17 placebo-controlled trials. When compared with placebo, however, only the patients who received 40 mg of atorvastatin had a higher incidence of diarrhea, whereas the remaining doses were comparable to the placebo.[30] Using an objective scoring system that involves combining chronological data and causality data to create a likelihood-of-responsibility score, simvastatin was identified as having an intermediate likelihood of being a causative agent in the development of microscopic colitis.[25] This designation was based on the presence of 1 case report of statin-associated colitis and a case–control study of 199 lymphocytic colitis patients, in which 1 case was preceded with simvastatin administration, but the patient had no symptom improvement after drug withdrawal.[24,31] A British retrospective case–control study (1211 microscopic colitis patients) and a prospective case–control study (26 microscopic colitis patients) did not find an association between microscopic colitis and statin use.[12,27] A major limitation of many of the previously mentioned studies is that they required patients to alter their diets, which may in turn cause alterations in bowel motility. In addition, some studies either lacked a placebo arm or did not explicitly report adverse events in the placebo arm. These limitations in reporting are important because of the prevalence of constipation, abdominal pain, diarrhea, and colitis in the general population.[2,32]

Our results are comparable to previously published data from RCTs containing both statin and placebo arms. Shepherd et al assessed the tolerability of statins using a pooled analysis of 16 876 patients including 33 placebo-controlled trials and showed there was no significant difference in the prevalence of constipation between statin users and nonusers.[8] Similarly, the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, which enrolled 17 802 patients, showed no difference in gastrointestinal symptoms between the statin and placebo arms.[9] Several meta-analyses and review articles could either not identify or did not mention differences in constipation or abdominal pain between statin users and nonusers.[33,34]

Our study has several limitations. We are aware of the possibility of nondifferential misclassification as a potential source of bias in our study, specifically misclassification of lower gastrointestinal conditions that may be chronic and thereby may not be documented in our captured patient encounters. In addition, by using ICD-9-CM codes, we were not able to capture disease severity. However, having ≥3 encounters for a specific diagnosis may be considered a surrogate for more severe disease. ICD-9-CM codes used were exhaustive and mutually exclusive. Using the procedural codes for endoscopy of the lower gastrointestinal tract, we were not able to determine if the endoscopies were performed to evaluate a lower intestinal condition or if it was for colon cancer–screening purposes. Hence, we cannot ascertain the cause of increased endoscopic evaluation among statin users.

Our observational data add an important layer to previously published RCTs that can be fraught with limitations. Previous RCTs were designed and powered to assess statin efficacy on a variety of cardiovascular end points and mortality, but not necessarily designed to examine uncommon adverse events. Lower gastrointestinal symptoms are subjective complaints, and there is often a discrepancy between what investigators and clinicians perceive as alteration of bowel motility compared with a patient's perception. For example, patients often report constipation because of straining, even when the stool consistency is soft and the bowel movement frequency is considered normal.[35,36] As mentioned previously, study protocols place patients on restrictive diets that could potentially alter bowel habits, cause visceral complaints, and inadvertently be classified as medication-related adverse events.

To our knowledge, our study is the largest study to examine the odds of constipation, abdominal pain, diarrhea, and colitis in statin users compared with nonusers. In addition, our cohort was followed for more than 6 years within a national health care system that captured all events regardless of location, affording a low dropout rate.

Conclusions

In conclusion, our findings suggest that long-term statin therapy had no association with constipation, abdominal pain, or colitis, rather, it may be associated with decreased odds of diarrhea.

Declaration of Conflicting Interests

None.

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