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Original Article

Statin use is associated with lower rates of stricture development in patients with Crohn's disease: a propensity score-matched study of two nationwide population databases

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Abstract

Background: Intestinal stricture affects over half of patients with Crohn's disease (CD) and has significant associated morbidity. Statins possess both anti-inflammatory and anti-fibrotic properties and may improve CD outcomes, although current data are limited. This study assessed whether statin use is associated with a reduced risk of new stricture development in CD in a diverse US population, and evaluated the role of IBD therapy in any association.

Methods: We conducted a retrospective cohort study comparing patients with CD with and without statin exposure using the EVERSANA US electronic health records database. Findings were independently validated in a second database (Merative MarketScan). Patient demographics, co-morbidities, laboratory measurements, and CD medications were assessed. The primary outcome was development of new stricture as defined by a composite endpoint of an encounter for stricture diagnosis or occurrence of a stricture-related procedure. Propensity score (PS)-matched Cox proportional hazards models were used to estimate associations.

Results: The EVERSANA cohort comprised 1210 statin recipients and 25 000 non-statin users. Over a mean follow-up of 3.8 years, PS-matched statin users had a 28% reduction in the risk of new-onset stricture (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.53-0.99, $P = .043$). The Merative cohort contained 9577 statin users and 56 918 non-statin users. Over a mean follow-up of 3.6 years, PS-matched statin use had a 29% risk reduction in new-onset stricture (HR 0.71, 95% CI 0.66-0.77, $P < .001$).

Conclusions: Statin use is independently associated with reduced progression to stricture formation in two PS-matched large and diverse cohorts of patients with CD.

Key words: Crohn's disease, intestinal stricture, statin, HMG-CoA reductase inhibitors.

1. Introduction

Crohn's disease (CD) is a chronic, immune-mediated condition of the gastrointestinal (GI) tract characterized by segmental inflammation that can affect any part of the GI tract from mouth to anus. Long-standing intestinal inflammation is associated with the development of fibrosis, excess deposition of extracellular matrix in the intestinal wall,[1] and muscular hypertrophy and hyperplasia.[2,3] More than 50% of patients with CD experience clinically significant bowel obstruction from intestinal stricture[4] and nearly half of patients with CD require bowel resection surgery within 10 years of diagnosis.[5] Postoperatively, up to 70% of patients require reoperation within 10 years of initial bowel resection surgery, with most patients undergoing resection due to stricturing CD.[6] Thus, the identification of therapies to mitigate stricture formation is of key clinical interest.

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are the most prescribed medication in the USA[7] and are used primarily for their lipid-lowering effects to reduce the risk of atherosclerotic cardiovascular disease. Prior data have demonstrated immunomodulatory, anti-inflammatory, and anti-fibrotic properties of statins, especially as related to hepatobiliary and intestinal disease.[8–13] In inflammatory bowel disease (IBD) specifically, statins have been associated with decreased rates of new-onset CD, less use of steroid therapy, and lower risk of colectomy.[14–17]

Population-based data also suggest that statin use may mitigate the risk of IBD-related surgeries such as intestinal

resections and stoma formation in CD,[18] although these data are limited by homogeneity of the studied population and limited assessment of the role of advanced IBD therapy in this association. Given the known molecular targets of statins, which include several anti-inflammatory and anti-fibrotic pathways implicated in stricturing CD, we hypothesized that statins may reduce stricture formation in CD, particularly by inhibiting extracellular matrix production by mesenchymal cells, potentially through modulation of transforming growth factor β1 (TGF-β1) signaling and the Rho pathway—a central regulator of cytoskeletal organization and fibrogenic activity.[2,8,10,19–20] This rationale, along with the substantial burden of stricturing disease and the lack of approved therapies for it, prompted us to specifically investigate whether statin use is associated with reduced risk of stricture development in two large, diverse US administrative databases of patients with newly diagnosed CD. We also specifically examined whether concomitant IBD therapy modified this association.

2. Methods

2.1. Data sources

We conducted a retrospective cohort study utilizing two widely utilized, representative, national databases in the USA (EVERSANA EHR database, and Merative database) to evaluate the association between statin use and the development of intestinal stricture in newly diagnosed CD.[21,22] The EVERSANA EHR integrated database contains electronic health records (her) data from over 120 million de-identified US patients and includes data from over 2000 outpatient health centers, over 500 hospitals, and over 30 health systems. The Merative database contains hospital, ambulatory, laboratory, and pharmaceutical claims data from over 273 million patients. We initially assessed the association of statin exposure on stricture development in CD using the EVERSANA database, and subsequently replicated the analysis in the Merative database. This second analysis was conducted to validate our findings in a larger population size as well as to evaluate additional variables not able to be investigated through the EVERSANA database, such as IBD medication therapy. While some degree of patient overlap between the two databases cannot be entirely excluded, the distinct data capture methods and the substantially larger size of the Merative database ensure that it includes a broader and complementary patient population beyond those represented in the EVERSANA database.

The EVERSANA database included patients who met the study criteria from January 2010 to January 2024 while the Merative database included patients who met the study criteria from January 2007 to December 2021, which represent the latest data available in the Merative database at the time of our analysis. We excluded patients in the Merative database for whom pharmaceutical data were not available.

2.2. Study population definition

New diagnosis of CD was defined as the first appearance in the database of an international classification of disease (ICD-9/ICD-10) code corresponding to CD in any adult subject with at least two separate encounters with ICD coding for CD. We excluded patients with prior ICD diagnoses of stricture, intestinal obstruction, fistula, intra-abdominal abscess, or if they had a Current Procedural Terminology (CPT) code for a CD-related procedure (defined below) at any time before CD diagnosis. The date of study inclusion was marked as the first subsequent outpatient visit after an ICD diagnosis of CD. This method of cohort identification has been utilized in multiple prior studies of new-onset IBD.[15,23–25] Additionally, we eliminated subjects with more than one measurement of fecal calprotectin ≥120 µg/g in the 6-month period preceding study inclusion to ensure that the first ICD code for CD truly represented a new diagnosis of IBD, rather than the first recording of a diagnostic code. All patients were required to have at least 12 months between the time of CD diagnosis and the last encounter with ICD coding of CD to allow for a latency-time window and minimize detection bias.

2.3. Intervention and control definition

We employed a new-user design restricted to patients with newly diagnosed CD, comparing the risk of stricture formation between new initiators of statin therapy and new initiators of any non-statin medication. New medication use was defined as having at least a 6-month duration prescription ordered within 6 months of study inclusion. Anatomical Therapeutic Chemical (ATC) code was used to classify medications as statin (C10AA) or non-statin. For patients in the statin-exposed group, the period between CD diagnosis and statin initiation was treated as unexposed time to prevent immortal time bias.

2.4. Study outcome definition

The primary outcome was development of new stricture, defined as a clinical visit or hospitalization for stricture (defined by the first ICD-9/10 code for intestinal obstruction) or if any of the following stricture-related procedures (defined by CPT code) occurred: small bowel resection, strictureplasty, or endoscopic intestinal dilation. This definition is similar to that of a previously published population-based study of CD progression in newly diagnosed patients.[23]

To maximize the likelihood that this stricture definition truly represented a new stricture event—rather than the first database capture of an existing stricture diagnosis at the time of CD diagnosis—we excluded patients who developed the primary outcome within 3 months of initial CD diagnosis. For patients with newly diagnosed CD who developed stricture, only those who started a medication (statin or non-statin) at least 6 months before the stricture episode were included.

2.5. Study outcome validation

The definition of new stricture was validated against manual chart review of our hospital-wide retrospective database (the Stanford Research Repository [STARR]) to ensure strong classification performance. Specifically, our definition of new stricturing disease was 87% accurate in a cohort of 200 patients randomly selected from all STARR patients with CD meeting study inclusion and exclusion criteria (Table S1).

2.6. Data collection

Demographic data including age at CD diagnosis, age at study inclusion, gender, Charlson comorbidity index,[26] and duration of study-follow up (defined as the period between date of inclusion and date of last encounter for ICD diagnosis of CD) were evaluated. The following laboratory values, identified using Logical Observation Identifiers Names and Codes (LOINC), were collected within 6 months of study inclusion: low-density

lipoprotein (LDL; highest value selected if multiple measurements were available), fecal calprotectin (highest value), C-reactive protein (CRP; highest value), albumin (lowest value), and platelets (highest value). Data on IBD medications were collected, including whether there was exposure to the following classes of IBD therapy during the study period: 5-aminosalicylate (5-ASA), anti-tumor necrosis factor (TNF), anti-integrin, anti-interleukin (IL) 12/23, anti-IL23, Janus kinase (JAK) inhibitor, or immunomodulators such as 6-mercaptopurine, methotrexate, and azathioprine. The number of IBD therapies and number of steroid courses prescribed were also analyzed. Exposure to medications commonly prescribed to patients with cardiovascular disease (aspirin, angiotensin-converting enzyme [ACE] inhibitor/angiotensin II receptor blocker [ARB], fibrate, and thiazolidiedione) was recorded. Data on duration of statin use and statin intensity were also evaluated. Statin intensity, defined by the American Heart Association,[27] classifies statins as low, moderate, or high intensity based on drug type and dosage, reflecting the expected degree of LDL reduction (eg, <30%, 30-49%, ≥50%).

2.7. Statistical analysis

High-dimensional propensity score (PS)-matching was performed in a 1:1 ratio using the nearest neighbor method with a caliper width of 0.2, consistent with established methodological standards.[28] We selected 1:1 matching rather than 1:*n* matching to prioritize comparability between treatment groups over gains in sample size or precision. Variables incorporated into PS-matching included age at study inclusion, sex, Charlson comorbidity index, fecal calprotectin, CRP, platelet count, albumin, follow-up duration, number of steroid courses, number of IBD agents, and exposure to advanced therapy.

After PS-matching, a univariate analysis was first performed comparing patients with new statin use to those with new use of any other medication. Multivariate Cox proportional hazards regression was then performed, with variables specified a priori: age at study inclusion, sex, Charlson comorbidity index, follow-up duration, statin use, and IBD medication exposure. Laboratory markers of inflammation were intended to be included a priori, but were ultimately not included due to high rates of missing data (>95%). Medications commonly used in cardiovascular disease that were statistically significant in the univariate analysis were included in the multivariate analysis.

Additional secondary pre-specified analyses were conducted examining the association of (1) the duration of statin exposure, (2) intensity of statin therapy, and (3) statin class (ie, hydrophilic vs lipophilic) with new stricture in the multivariate Cox regression. A secondary post-hoc analysis was performed comparing LDL value to the primary outcome to reduce confounding by indication. Further secondary post-hoc analyses were conducted by separating the Merative cohort into those on advanced IBD therapy (such as anti-TNF, anti-integrin, anti-IL23, anti-IL12/23) during the study and those who did not have exposure to advanced IBD therapy. The Cox regression analyses were repeated on these two subsets to further characterize the relationship between statin use, advanced IBD therapy, and stricture development.

Categorical variables were analyzed using chi-squared testing. Continuous variables were analyzed using the Mann–Whitney U test. Statistical analyses were conducted using R statistical software[29] on the Redivis platform through Stanford University.[30] A P value of <.05 was considered statistically significant.

2.8. Ethical considerations

The study was approved via an umbrella institutional review board protocol for all de-identified population database studies at Stanford University.

3. Results

3.1. Baseline demographics

In the EVERSANA cohort, 26 210 patients were included, of whom 1210 were statin recipients and 25 000 initiated other medications. After PS-matching, 1208 patients were retained in each arm, with baseline demographics generally similar between groups (Table 1). In the Merative database, 66 495 patients were included, of whom 9577 were statin recipients and 56 918 initiated other medications. Following PS-matching, 9577 patients were included per arm (Table 2). Sex and duration of study follow-up were similar between groups (Table 2). Statin-exposed patients were older at study inclusion with more co-morbidities and higher use of cardiovascular medications compared to users of any other medication (Table 2), although this effect was less pronounced than in the unmatched cohort. Differences in IBD medication use are outlined in Table 2. Notably, both groups had comparable rates of advanced IBD therapy exposure (Table 2).

3.2. Statin use is associated with lower rates of stricture formation in CD and longer time-to-stricture

In the PS-matched multivariate Cox regression analysis of the EVERSANA cohort, statin use was associated with a reduced risk of stricture formation compared with use of other medications (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.53-0.99, $P = .043$; Figure 1). Similarly, in the PS-matched multivariate Cox regression analysis of stricture formation in the Merative cohort, statin use was associated with lower risk of stricture formation compared with use of other medications (HR 0.71, 95% CI 0.66-0.77, $P \leq .001$; Table 3; Figure 2). New stricture diagnoses during follow-up were less frequent among statin users than non-users in both EVERSANA (5.5% vs 7.5%, $P = .048$) and Merative (11% vs 16%, $P < .001$). Female sex was independently associated with lower likelihood of stricture development (HR 0.86, 95% CI 0.80-0.93, $P < .001$; Table 3) while older age at study inclusion was associated with higher likelihood of stricture development (Table 3).

3.3. Statin use for 12 months or longer correlates with less CD stricture formation

In the pre-specified secondary analysis of the Merative cohort, Cox multivariate regression was repeated utilizing various durations of statin use. Compared to use of any other medication, statin use between 6 and 12 months was associated with similar hazard ratio of stricture formation (HR 0.83, 95% CI 0.67-1.0). However, statin durations of 12–24 months (HR 0.84, 95% CI 0.72-0.97) and >24 months (HR 0.67, 95% CI

Table 1. Baseline demographics for high dimensionality propensity score-matched groups in the EVERSANA cohort.

	Any other medication ($n=1208$)	Statin-exposed ($n=1208$)	Standardized mean difference (SMD)
Female, n (%)	709 (58.7%)	679 (56.2%)	0.050
Mean age, years (SD)	59.9 (11.2)	58.6 (10.8)	0.122
<18 years	0 (0%)	0 (0%)	NA
18-29 years	17 (1.4%)	7 (0.6%)	0.084
30-39 years	61 (5%)	67 (5.5%)	0.022
40-49 years	133 (11%)	172 (14.2%)	0.097
50-59 years	318 (26.3%)	383 (31.7%)	0.119
60-69 years	445 (36.8%)	389 (32.2%)	0.098
70-79 years	234 (19.4%)	190 (15.7%)	0.096
80-89 years	0 (0%)	0 (0%)	NA
≥90 years	0 (0%)	0 (0%)	NA
Race, n (%)			
White	680 (56.3%)	686 (56.8%)	0.010
Other	452 (37.4%)	452 (37.4%)	0.00
Black	65 (5.4%)	61 (5%)	0.015
Asian	11 (0.9%)	9 (0.7%)	0.018
Hispanic, n (%)	62 (5.1%)	72 (6%)	0.036
Index year (%)			
Before 2000	0 (0%)	0 (0%)	NA
2000-2004	0 (0%)	0 (0%)	NA
2005-2009	0 (0%)	0 (0%)	NA
2010-2014	255 (21.1%)	271 (22.4%)	0.032
2015-2019	482 (39.9%)	477 (39.5%)	0.008
2020+	471 (39%)	460 (38.1%)	0.019
Mean pre-index days (SD)	3964.7 (4200.4)	3533.5 (4138.8)	0.103
Mean follow-up days (SD)	1361.1 (1181)	1413.5 (1190.5)	0.044
Lost to follow-up, n (%)	0 (0%)	0 (0%)	NA
Number of encounters, n (SD)	3.1 (3.6)	3.3 (3.8)	0.038
CPT (SD)	39.4 (126.1)	49.3 (193.3)	0.061
ICD9 (SD)	7.5 (33.2)	6.5 (17.6)	0.039
ICD10 (SD)	23.4 (51.8)	22.3 (43)	0.022
Prescriptions (SD)	154.4 (708.7)	120.9 (578)	0.052
Comorbidity score (SD)	3.3 (2.9)	3.1 (2.7)	0.077
Malignancy, n (%)	169 (14.0%)	98 (8.11%)	0.188
Metastatic solid tumor, n (%)	51 (4.22%)	30 (2.48%)	0.097
Diabetes, n (%)	173 (14.3%)	328 (27.2%)	0.321
Diabetes with complications, n (%)	65 (5.38%)	101 (8.36%)	0.118
Congestive heart failure, n (%)	72 (5.96%)	85 (7.04%)	0.044
Myocardial infarction, n (%)	20 (1.66%)	71 (5.88%)	0.223
Peripheral vascular disease, n (%)	102 (8.44%)	115 (9.52%)	0.038
Chronic pulmonary disease, n (%)	296 (24.5%)	288 (23.8%)	0.015
Cardiovascular disease, n (%)	66 (5.46%)	113 (9.35%)	0.149
Dementia, n (%)	11 (0.91%)	12 (0.99%)	0.009
Hemiparaplegia, n (%)	4 (0.33%)	15 (1.24%)	0.103
Mild liver disease, n (%)	131 (10.8%)	105 (8.69%)	0.073
Severe liver disease, n (%)	21 (1.9%)	12 (0.99%)	0.076
Renal disease, n (%)	126 (10.4%)	103 (8.53%)	0.065
Peptic ulcer disease, n (%)	52 (4.3%)	43 (3.56%)	0.038
Rheumatic disease, n (%)	72 (5.96%)	73 (6.04%)	0.003
HIV, n (%)	8 (0.66%)	5 (0.41%)	0.034

Abbreviations: CPT, current procedural terminology; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; SD, standard deviation.

0.61-0.73) were both independently associated with a lower likelihood of stricture formation (Figure S1).

In the second pre-specified secondary analysis evaluating statin intensity and stricture development, low (HR 0.66, 95% CI 0.55-0.80), medium (HR 0.73, 95% CI 0.67-0.80), and high (HR 0.66, 95% CI 0.56-0.78) statin intensities were all associated with a lower likelihood of stricture development compared to use of any other medication (Figure S1). Additionally, use of high-intensity statin was not associated with less stricture development compared to use of low or medium intensities. In the third pre-specified secondary analysis, both hydrophilic (HR 0.77, 95% CI 0.67-0.87) and lipophilic (HR 0.69, 95% CI 0.63-0.76) statin classes were associated with a lower likelihood of stricture as compared to use of any other medication.

Table 2. Baseline demographics for high dimensionality propensity score-matched groups in the Merative database.

	Any other medication (n=9577)	Statin-exposed (n=9577)	Standardized mean difference (SMD)
Mean age at Crohn's diagnosis (SD) (years)	53.0 (7.96)	54.0 (7.40)	0.093
Female subjects (%)	4663 (48.7)	4661 (48.7)	<0.001
Charlson comorbidity index (mean (SD))	0.86 (1.45)	1.00 (1.46)	0.096
Malignancy (%)	664 (6.9)	443 (4.6)	0.099
Metastatic solid tumor (%)	132 (1.4)	52 (0.5)	0.086
Diabetes (%)	806 (8.4)	1916 (20.0)	0.337
Diabetes with complications (%)	160 (1.7)	498 (5.2)	0.195
Congestive heart failure (%)	205 (2.1)	305 (3.2)	0.065
Myocardial infarction (%)	53 (0.6)	298 (3.1)	0.192
Peripheral vascular disease (%)	267 (2.8)	467 (4.9)	0.109
Chronic pulmonary disease (%)	1431 (14.9)	1383 (14.4)	0.014
Cardiovascular disease (%)	295 (3.1)	552 (5.8)	0.131
Dementia (%)	12 (0.1)	15 (0.2)	0.008
Hemiparaplegia (%)	43 (0.4)	56 (0.6)	0.019
Mild liver disease (%)	713 (7.4)	714 (7.5)	<0.001
Severe liver disease (%)	74 (0.8)	17 (0.2)	0.087
Renal disease (%)	359 (3.7)	372 (3.9)	0.007
Peptic ulcer disease (%)	222 (2.3)	229 (2.4)	0.005
Rheumatic disease (%)	479 (5.0)	436 (4.6)	0.021
HIV (%)	51 (0.5)	28 (0.3)	0.037
Age at study inclusion			0.092
18-29 years	95 (1.0)	64 (0.7)	
30-39 years	541 (5.6)	413 (4.3)	
40-49 years	2042 (21.3)	1855 (19.4)	
50-59 years	4614 (48.2)	4819 (50.3)	
60-69 years	2285 (23.9)	2426 (25.3)	
70-79 years	0 (0)	0 (0)	
80+ years	0 (0)	0 (0)	
Duration of study follow-up			0.019
12-18 months (including 18 months)	1645 (17.2)	1652 (17.2)	
18-36 months (including 36 months)	3366 (35.1)	3443 (36.0)	
>36 months	4566 (47.7)	4482 (46.8)	
LDL value (mg/dL) (mean (SD))	105 (36.9)	101 (36.1)	0.086
Statin exposure duration			1.43
No statin	9577 (100.0)	0 (0)	
6-12 months (including 12 months)	0 (0)	789 (8.2)	
>12 months to 24 months (including 24 months)	0 (0)	2057 (21.5)	
>24 months	0 (0)	6731 (70.3)	
Statin class			2.49
Hydrophilic statin (%)	0 (0)	2338 (24.4)	
Lipophilic statin (%)	0 (0)	7239 (75.6)	
Cardiovascular medications			
Aspirin use (%)	160 (1.7)	413 (4.3)	0.156
Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use (%)	3193 (33.3)	5346 (55.8)	0.464
Fibrate use (%)	580 (6.1)	1099 (11.5)	0.193
Thiazolidinedione use (%)	159 (1.7)	549 (5.7)	0.217
Number of IBD therapies used			0.026
No IBD maintenance therapy used (%)	2300 (24.0)	2222 (23.2)	
One IBD therapy used (%)	4315 (45.1)	4295 (44.8)	
Two IBD therapies used (%)	1980 (20.7)	2027 (21.2)	
Three or more IBD therapies used (%)	982 (10.3)	1033 (10.8)	
IBD medications			
5-ASA exposure (%)	5419 (56.6)	5835 (60.9)	0.087
Anti-TNF exposure (%)	1692 (17.7)	1724 (18.0)	0.009
Anti-integrin exposure (%)	31 (0.3)	35 (0.4)	0.007
Anti-IL12/23 exposure (%)	148 (1.5)	217 (2.3)	0.053
Anti-IL23 exposure (%)	1 (0.0)	5 (0.1)	0.024
JAKi exposure (%)	11 (0.1)	18 (0.2)	0.019
Immunomodulator exposure (%)	3138 (32.8)	2741 (28.6)	0.088
Exposure to advanced therapy (%)	1802 (18.8)	1875 (19.6)	0.019
Number of steroid courses (mean (SD))	5.34 (11.5)	5.70 (12.5)	0.030

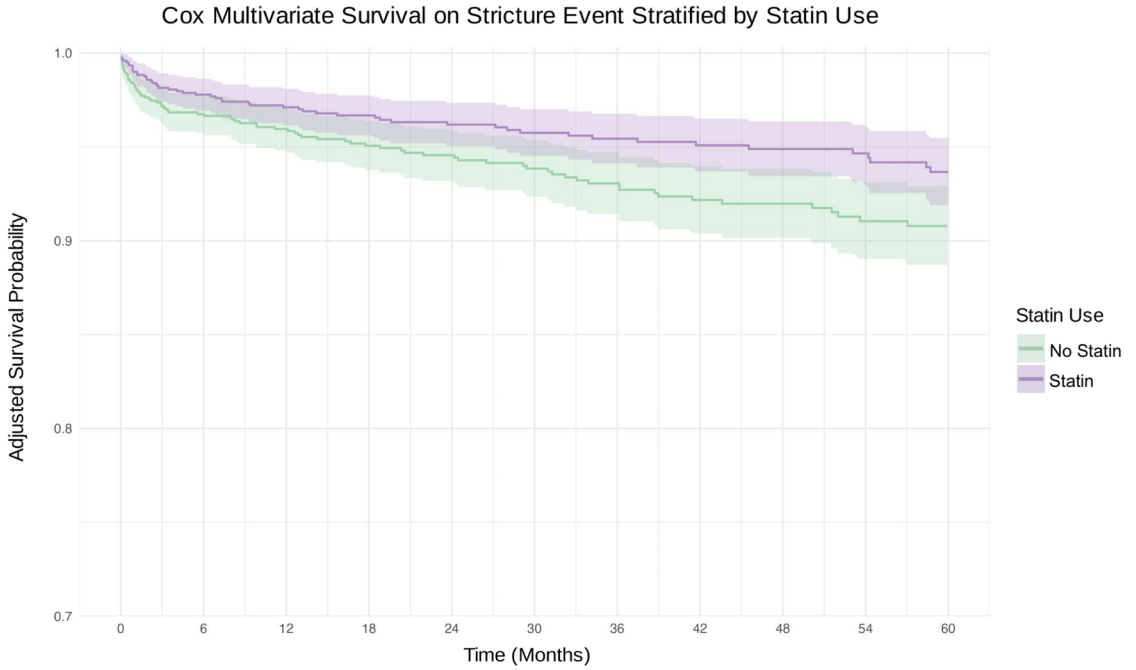

Figure 1. Cox survival curve comparing the primary outcome survival between statin recipients and statin non-recipients, in years for the propensity score-matched EVERSANA cohort.

Table 3. Propensity-matched multivariate Cox proportional hazard ratios for stricture development in the Merative cohort.

Variable	Hazard ratio	Lower confidence interval	Upper confidence interval	*P*-value
Female sex	**0.861**	**0.796**	**0.931**	**<.001**
Age 18-49 at study inclusion	1	1	1	
Age 50-59 at study inclusion	**1.22**	**1.12**	**1.34**	**<.001**
Age 60-69 at study inclusion	**1.42**	**1.26**	**1.60**	**<.001**
Charlson comorbidity index	**1.03**	**1.01**	**1.06**	**.016**
Aspirin use	1.01	0.819	1.25	.914
Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use	0.915	0.843	0.994	.034
Fibrate use	1.06	0.930	1.22	.367
Thiazolidinedione use	0.976	0.789	1.21	.827
Study follow-up duration 12-18 months (including 18 months)	**1**	**1**	**1**	
Study follow-up duration 18-36 months (including 36 months)	**0.614**	**0.523**	**0.720**	**<.001**
Study follow-up duration >36 months	**0.361**	**0.306**	**0.426**	**<.001**
Statin exposure	**0.710**	**0.655**	**0.770**	**<.001**
Number of steroid courses	**1.01**	**1.00**	**1.01**	**<.001**
Number of IBD agents (none)	**1**	**1**	**1**	
One IBD agent	**0.831**	**0.745**	**0.927**	**.001**
Two IBD agents	1.00	0.884	1.14	.946
Three IBD agents	**1.19**	**1.02**	**1.39**	**.023**
Advanced IBD therapy exposure	**1.69**	**1.52**	**1.88**	**<.001**

Bold: Statistically significant ($P < 0.05$).

3.4. LDL value does not correlate with stricture formation in CD

Given that statins are commonly used for treatment of hyperlipidemia, we evaluated if there was an association between hyperlipidemia (LDL ≥ 130 mg/dL)[31] and onset of stricture independent of statin use. When comparing statin-exposed patients with CD and hyperlipidemia to statin-exposed patients with CD without hyperlipidemia, there was no difference in *de novo* stricture ($n = 9577$, HR 0.73, 95% CI 0.16–3.4).

We also evaluated specifically if LDL levels were associated with stricture formation. The Cox multivariate regression was repeated after replacing the variable statin use with LDL value and we found that LDL value did not correlate with stricture formation (HR 1.0, 95% CI 0.98-1.0).

3.5. Statin use is associated with less stricture formation regardless of advanced IBD therapy exposure

A secondary analysis was conducted on Merative cohort subjects on advanced IBD therapy (such as anti-TNF, anti-integrin, anti-IL23, or anti-IL12/23 medication) to understand statin use

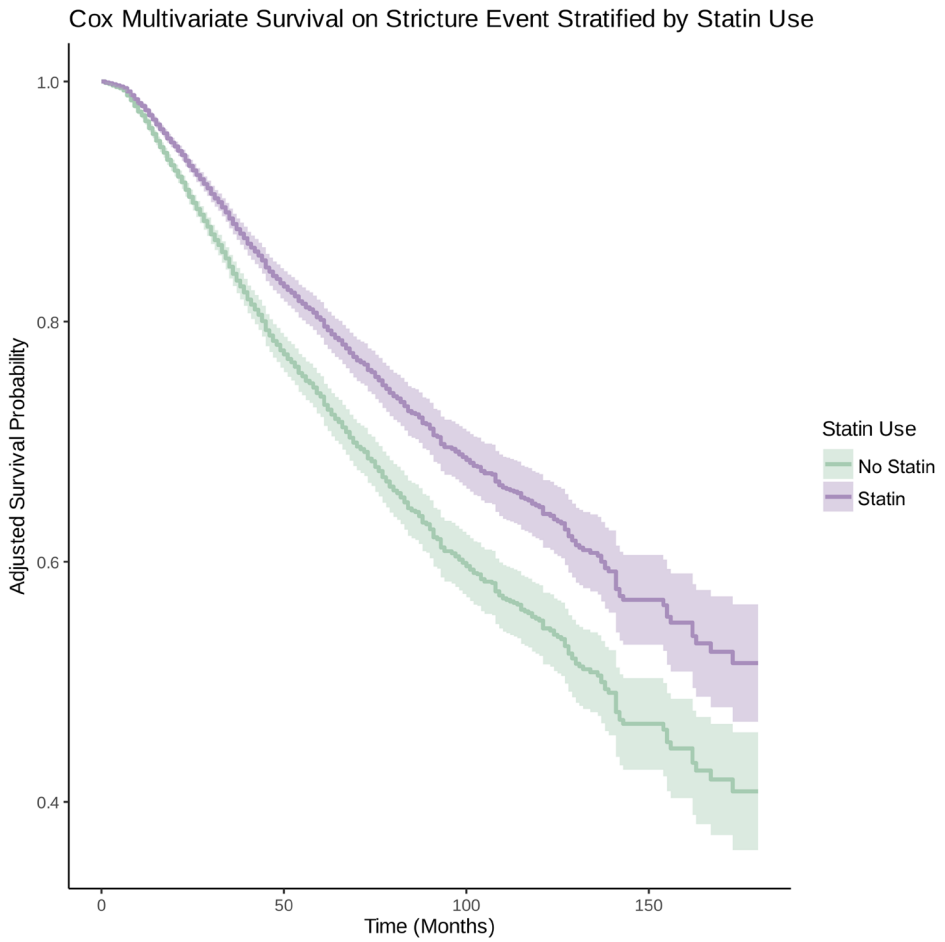

Figure 2. Covariate-adjusted Cox hazard curve on stricture development comparing statin use and use of any other medication in the propensity score-matched Merative cohort.

and stricture formation among patients on advanced therapy. After PS-matching, there were 1865 patients in each arm. Among patients on advanced therapy, stricture development remained less likely in statin recipients compared to recipients of any other medication (19% vs 26%, $P < .001$). In the multivariate Cox regression controlling for age at study inclusion, co-morbidity, follow-up duration, cardiovascular medications, and number of IBD medications, statin use was independently associated with a lower odds of stricture formation (HR 0.73, 95% CI 0.63-0.84, $P < .001$; Table S2). Compared to use of one advanced IBD therapy, use of two or three IBD agents both had similar risk of stricture development.

Finally, the subset of the Merative cohort patients who were not on advanced IBD therapy were evaluated in a separate post-hoc secondary analysis. After PS-matching, there were 7853 patients in each arm. Stricture development remained less likely in statin recipients compared to recipients of any other medication (9.5% vs 13%, $P < .001$). In the multivariate Cox regression controlling for age at study inclusion, co-morbidity, follow-up duration, cardiovascular medications, and number of IBD medications, statin use was independently associated with a lower odds of stricture formation (HR 0.72, 95% CI 0.65-0.79, $P < .001$; Table S2).

4. Discussion

Statin use was associated with lower rates of stricture formation in two diverse, US-based, PS-matched cohorts of patients with CD. This association persisted after controlling for age, duration of time studied, gender, co-morbidities, cardiovascular medication use, and IBD medication use. Statin use for at least 1 year and all levels of statin intensity were associated with a lower likelihood of stricture formation.

Statin use has previously been associated with favorable outcomes relevant to IBD. Namely, statin use has been associated with a lower risk of new-onset IBD—particularly CD—in national databases from two different countries.[15,16] Additionally, statin use was associated with a reduction in steroid use in a study of almost 12 000 patients with IBD.[14] Notably, these studies found that statin exposure at all intensities and solubilities (hydrophilic/lipophilic) were associated with favorable IBD outcomes. This is similar to our findings, although we additionally found that statin use for at least 12 months was associated with a lower risk of stricture. It may be that even low-dose statin use (regardless of solubility or intensity) for at least 1 year could be clinically favorable in patients with IBD. We noted a lower risk of stricture formation in women with CD, which is consistent with prior data demonstrating a higher risk of abdominal surgery in male patients with CD.[32]

A recent study examining statin use and disease course in IBD utilized a large Swedish healthcare registry to demonstrate a 46% lower risk of CD-related surgery in statin users compared to non-users.[18] While compelling, that analysis evaluated all IBD-related surgeries collectively, without distinguishing stricturing disease from other indications, and it matched

patients only on exposure to corticosteroids, immunomodulators, and the anti-TNF agents infliximab and adalimumab. In contrast, our study focuses specifically on surgery and non-operative management (eg, dilation) for stricturing CD, providing a more mechanistically relevant outcome for statin's potential fibrosis-modifying effects. Moreover, 86% of the CD subjects were of Nordic origin in the Swedish study, whereas our cohort represents a more demographically diverse US population. Our models additionally incorporate the full spectrum of contemporary advanced IBD therapies (including anti-integrin, anti-IL12/23, and JAK inhibitors), as well as statin intensity and duration. Our data refine and expand the current understanding of how statin use may mitigate the risk of adverse outcomes in stricturing CD, providing further clinical applicability and guidance for IBD patients using statins.

Prior data suggest multiple potential mechanisms through which statin use may modulate stricture formation in CD, particularly as it relates to intestinal fibrosis and intestinal smooth muscle hypertrophy. Statin pre-treatment prior to *in vitro* TGF-β1 exposure inhibited activation of human intestinal fibroblasts.[10] Statin use also inhibits activity of submucosal mesenchymal cells via the rho pathway in both *ex vivo* human intestinal explants and *in vitro* rat models of radiation-induced intestinal fibrosis.[8] The rho pathway is a key player in regulating the smooth muscle cell proliferation thought to underlie CD stricturing disease.[2] In addition to these potential anti-fibrotic properties, statin use is also associated with reductions in both intestinal and systemic inflammation. In a small prospective study of 10 patients with CD who were given atorvastatin for 13 weeks, there was a 34% reduction in the chemokine CXCL10, which is responsible for promoting T lymphocyte recruitment and mediating intestinal inflammation.[9] Statin use may also modulate the gut microbiome; in two distinct fecal metagenomic cohorts, statin use was associated with a lower prevalence of the dysbiotic *Bacteroides2* (Bact2) enterotype, which is also associated with higher systemic inflammation levels.[33] Statin-related modulation of the microbiome may mitigate stricture formation in CD through modulation of the Bact2 enterotype, which is more common in those with IBD compared to the general population and is associated with differences in response to anti-TNF therapy in IBD.[34,35]

Consistent with other studies, we noted a high use of 5-ASA in this study of patients with CD.[36,37] This high rate of 5-ASA use in our study population may also be due to restricting the cohort to those with newly diagnosed CD without prior complications, which could have captured a milder form of CD that otherwise has limited IBD treatment options. Additionally, we recorded any exposure to 5-ASA during the study period, however brief, so this finding may also reflect transient use early in diagnosis. Prior population-based data consistently show a high use of 5-ASA in patients with CD.[14,36,37] For example, in a study evaluating statin use and reduction of steroid utilization of nearly 12 000 patients, 87% had 5-ASA exposure while only 56% had ulcerative colitis, suggesting a high use of 5-ASA in CD.[14] Exposure to advanced therapy was associated with an increased likelihood of stricture formation in the Merative cohort, probably reflecting confounding by indication since patients with more severe disease are preferentially treated with advanced agents. Importantly, the protective association between statin use and stricture risk persisted within the subset of patients on advanced IBD therapy. These findings suggest that statin use may confer benefit even among patients with moderate-to-severe disease, although this cannot be definitively established in a population-based cohort.

There are several strengths of this study. First, we used a large, diverse, and nationally representative cohort to study statin and CD stricture formation, and were able to subsequently validate our findings and evaluate the role of all contemporaneous IBD medication therapies in a second nationally representative cohort. Second, we manually validated our definition of new stricture formation in a hospital-wide retrospective database to ensure that our definition captured true new instances of stricturing CD. Third, we controlled for many potential confounding variables through the use of high-dimensional PS matching as well as the use of a new user design to minimize biases from existing users. Finally, the decision to study patients who initiated either statin or any other medication within 6 months of diagnoses also minimized length-time bias.

Our study also has limitations. First, this study was retrospective. While utilizing methods such as PS-matching and new-user design mitigates biases introduced by retrospective data, the risk of such biases is not completely eradicated with these methods. For example, statin users were older with more cardiovascular comorbidities than non-users in our study, though to a lesser degree after PS-matching. This was probably because typical indications for statin use are uncommon in healthy patients below the age of 40. Regardless, the association between statin use and lower likelihood of new stricture remained true in the subset of patients who were diagnosed with CD before age 50 (data not shown). While most patients had missing data for laboratory values of inflammation such as fecal calprotectin, albumin, CRP, and platelets, the association between statin use and lower risk of stricture remained when the multivariate analysis was conducted with these laboratory markers of inflammation. Another limitation of the study was that we were unable to characterize CD subtype, which limited our ability to evaluate any role of specific disease location patterns.

Misclassification of new stricture diagnosis was an additional potential limitation. We took additional steps to mitigate this potential bias. First, we used multi-tier criteria for defining new stricture, which we externally validated by manual chart review in a retrospective database at our medical center. We additionally designed the study to exclude patients who developed any CD complications up to 3 months after CD diagnosis to reduce the possibility that coding of stricture represented the first capture of an existing stricture diagnosis, as opposed to a true new stricture. Together, these steps make it unlikely that misclassification alone explains our findings.

Another potential limitation of the study was confounding by statin indication. To minimize confounding, we used the Charlson comorbidity index in our high dimensionality PS-matching to match groups by common indications for statins such as myocardial infarction and cerebrovascular accident. We additionally evaluated LDL value and hyperlipidemia as confounding variables with no association found with the primary outcome. This is consistent with prior population-based data evaluating statin use and risk of new-onset IBD, which did not find confounding by dyslipidemia diagnosis in sensitivity analyses.[16]

In conclusion, we identified for the first time that statin use was associated with a nearly 30% lower risk of new stricture in CD in two diverse, US-based cohorts. While there is a biologically plausible mechanistic basis for this association,

prospective data are needed to inform whether statin use is truly protective against stricture formation in CD. These findings, if confirmed prospectively, could have immediate implications for risk stratification and secondary prevention in CD.

Author contributions

A.D.V.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual contents. C.K.: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual contents. C.W.P.: acquisition of data, analysis and interpretation of data. S.G.: acquisition of data, analysis and interpretation of data. D.D.: drafting of the manuscript. F.R.: critical revision of the manuscript for important intellectual content. S.R.S.: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, funding acquisition, study supervision. All authors approved of the final manuscript. Guarantor of the article: Sidhartha R. Sinha.

Supplementary material

Supplementary material is available at *ECCO-JCC* online.

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Conflicts of interest

No conflicts of interest exist for all authors.

Data availability

Analytic methods of the study are available upon request to authors. The data underlying this article will be shared on reasonable request to the corresponding author.

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