

Reduced risk of Barrett's esophagus in statin users: Case-control study and meta-analysis.

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Short Title: Statins and Barrett's esophagus

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Abbreviations: aOR, adjusted odds ratio; BE, Barrett's esophagus; CI, confidence interval; COX, cyclo-oxygenase; EAC, esophageal adenocarcinoma; NSAID, non-steroidal anti-inflammatory drug; OR odds ratio

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Abstract

Background: Use of statins has been associated with a reduced incidence of esophageal adenocarcinoma in population-based studies. However there are few studies examining statin use and the development of Barrett's esophagus.

Aim: To examine the association between statin use and the presence of Barrett's esophagus in patients having their first gastroscopy.

Methods: We have performed a case-control study comparing statin use between patients with, and without, an incident diagnosis of non-dysplastic Barrett's esophagus. Male Barrett's cases (134) were compared to 268 male age-matched controls in each of two control groups (erosive gastro-esophageal reflux and dyspepsia without significant upper gastrointestinal disease). Risk factor and drug exposure were established using standardised interviews. Logistic regression was used to compare statin exposure and correct for confounding factors. We performed a meta-analysis pooling our results with 3 other case-control studies.

Results: Regular statin use was associated with a significantly lower incidence of Barrett's esophagus compared to the combined control groups (adjusted OR 0.62 (95% confidence intervals 0.37-0.93)). This effect was more marked in combined statin plus aspirin users (adjusted OR 0.43 (95% CI 0.21 – 0.89)). The inverse association between statin or statin plus aspirin use and risk of Barrett's was significantly greater with longer duration of use. Meta-analysis of pooled data (1098 Barrett's, 2085 controls) showed that statin use was significantly associated with a reduced risk of Barrett's esophagus (pooled adjusted OR 0.63 (95% CI 0.51 - 0.77))

Conclusions: Statin use is associated with a reduced incidence of a new diagnosis of Barrett's esophagus.

Introduction

There has been a dramatic increase in the incidence of esophageal adenocarcinoma (EAC) in the developed world (1,2). The reasons for the upsurge are unclear but increasing gastro-esophageal reflux and the increasing prevalence of obesity are likely to be important. (3,4). It is accepted that metaplastic transformation of the esophageal squamous mucosa to intestinal-type mucosa (Barrett's esophagus (BE)) is a premalignant phenotype, although the overall rate of progression is relatively low (probably about 1 in 300 patients per year, or less)(5-7) and this has allowed the development of surveillance and localised treatment strategies such as radio-frequency ablation as means of preventing the development of EAC (8). However overall mortality from EAC remains considerable with 5-year survival less than 25% (9).

One avenue that may offer some promise for both patients with known Barrett's esophagus and the wider population is chemoprevention. Several lines of evidence suggest that statins (HMG-CoA reductase inhibitors) and cyclo-oxygenase (COX) inhibitors (especially low-dose aspirin) may have some utility in the chemoprevention of esophageal adenocarcinoma. In experimental studies statins and COX-2 inhibitors have useful anti-cancer effects. Statins inhibit proliferation, induce apoptosis and inhibit growth factor signalling in Barrett's cell lines (10,11) and whilst COX-pathway inhibitors also have experimental anticancer effects, these are additive to those of statins (10-12). Several observational studies and two meta-analyses (13-17) have reported that statin use is associated with a lower rate of progression to cancer in patients with Barrett's esophagus and again this effect is significantly enhanced in combination with aspirin (16). In a meta-analysis, pooled adjusted odds ratios showed that statin use in the Barrett's population was associated with a 43% reduction in the risk of malignant progression (OR = 0.57 (95% CI 0.43- 0.75)) and this effect was even more pronounced in those concurrently using low-dose aspirin (OR 0.26 (95% CI 0.1-0.68))(16).

Population-based studies have also shown that statin use is associated with a reduced incidence of esophageal adenocarcinoma, a 19% reduction in EAC was reported in a meta-analysis (OR 0.81 (95% CI 0.75-0.88))(16). Subsequently a further large study using the UK General Practice Research Database reported that statin use in the general population was again associated with a reduced incidence of EAC (OR 0.58 (95% CI 0.39 – 0.87))(18).

Therefore there are intriguing data that statins, particularly in combination with aspirin or other cyclooxygenase inhibitors may prevent the development of EAC. An important question is whether statins have actions in preventing the development and establishment of BE or whether they predominantly prevent malignant progression of BE. This question is important both for our understanding of the pathogenesis of BE and EAC but also in planning chemopreventative strategies. Therefore we have performed a case-control study to examine whether statin use is associated with a reduced incidence of Barrett's esophagus.

Materials and Methods

Cases and controls

All cases and controls were recruited from patients under the care of the Gastroenterology Unit at the Norfolk and Norwich University Hospital. This is a large, public, secondary and tertiary referral hospital, serving a population of approximately 600 000. All patients gave written informed consent and the study was approved by the Norfolk Research Ethics Committee and the Norfolk and Norwich University Hospital Research Governance Committee.

Controls and cases were recruited as part of a larger project examining risk and prognostic factors for gastrointestinal diseases (14,15,19). All subjects were planned to undergo their first ever gastroscopy. All subjects were interviewed by trained interviewers immediately preceding their endoscopy as previously reported (14,15,19). The standardised interview included demographic and social details, prescribed and over-the-counter medicine use. Medication use was regarded as positive if taken at least once per week for at least 6 months prior to the interview. Aspirin and non-aspirin NSAIDS were recorded separately. When subjects had taken more than one type or dose of a drug in any class, the usage was classified according the current dose regime. Results from the interviews were cross-referenced with clinical notes and letters (19). In case of discrepancy in records of drug exposure, the patients' description was used. Diagnostic endoscopy was performed by consultant gastroenterologists (111 subjects), accredited (141 subjects) - or consultant-supervised (53 subjects) trainees or accredited nurse-endoscopists (97 subjects) with Olympus XQ240, XQ260 or XQ290 video-endoscopes.

For the study, incident Barrett's esophagus cases were included if they were having their first ever diagnostic gastroscopy during the study period and this demonstrated an endoscopic diagnosis of Barrett's esophagus with at least 3 cm of Barrett's epithelium visible and had intestinal metaplasia subsequently confirmed on histology. Two Control groups, (i) erosive

gastro-esophageal reflux (“reflux”) and (ii) dyspepsia without erosive reflux (“dyspepsia”) were included and both were sex and age matched (within 5 years), 2 controls per case in each group from those attending for diagnostic gastroscopy for any symptoms. Controls were included in the reflux group if Los Angeles grade B-D changes were seen at endoscopy. Controls in the non-reflux group were those referred for investigation of upper GI symptoms without any subsequent significant endoscopic findings. Patients with either a Barrett’s segment < 3 cm in maximal length, or lacking intestinal metaplasia on histology, or Los Angeles A endoscopic changes were excluded from the study completely, in order to keep clarity to the cases and controls. Other exclusions were: evidence of dysplasia or neoplasia or anywhere in the upper GI tract, gastroduodenal ulceration or an inability to complete the interview.

Statistical analysis

An initial minimal sample size of 127 Barrett’s cases and 254 of each of reflux-controls and non-reflux controls was planned to give 80% power to detect an odds ratio of 0.50 assuming a statin use prevalence of 35 % in controls. In this initial exploration of any potential effects of statins we planned to limit the study to males: both statin use and a new diagnosis of Barrett’s esophagus are less common in females and recruiting cohorts of suitable size (approximately 160 cases, 320 controls did not seem feasible). The exposure to statins and other medications of interest were compared against the control groups using a chi square statistic. The analyses were performed using SPSS for windows version 16.0 (IBM, Portsmouth, United Kingdom). The differences between the groups were quantified using the calculated odds ratios and 95% confidence intervals, with the significance level set at $P < 0.05$. Unconditional logistic regression was used to correct for potentially confounding

factors: age, smoking, alcohol use, body mass index, waist circumference and all prescribed and over the counter medications recorded (14,15,19).

Meta-analysis

The Pubmed, EMBASE, Cochrane Library, Web of Science and Wiley Interscience and Google Scholar databases were searched for relevant publications, published in English up to 31/3/2015 using the search terms “Barrett’s esophagus,” esophagus,” “statin,” and “Hydroxymethylglutaryl-CoA reductase inhibitor.” The reference lists of these papers were then hand searched for any additional publications. Randomised controlled studies, case-control studies and prospective cohort studies were eligible for inclusion. Meta-analysis was performed as previously described (16,20).

Results

Baseline characteristics and confounding variables

A total of 134 incident Barrett's cases and 268 erosive-reflux and 268 dyspepsia controls were recruited. All subjects were white and of North West European origin, Participation was 100% of those approached about the study. The baseline characteristics of controls and cases are listed in table 1. All groups were reasonably well matched regarding basic demographic details, with no statistically significant differences, although rates of smoking, both current and previously, and body mass index and waist circumference tended to be higher in the Barrett's group.

Medication use and Barrett's esophagus

The results of medication used prior to enrolment in the study are shown in table 2. All subjects taking a statin and aspirin were taking their medication daily and were taking the standard circulatory-protective dose of aspirin (75 mg daily). Unadjusted odds ratios for drug exposure showed a lower use statins in the Barrett's oesophagus group compared to both the dyspepsia group (OR 0.58 (95% confidence intervals (CI) 0.38 – 0.89)($P < 0.01$) and reflux groups (OR 0.77 (95% CI 0.5 – 1.19) and the combined use of aspirin plus statin was associated with a lower risk of Barrett's esophagus: compared to the dyspepsia-control (OR 0.52 (95% CI 0.28 – 0.94) ($P < 0.05$) and compared to reflux-controls (OR 0.58 (95% CI 0.31 – 0.95) ($P < 0.05$)). Metformin use was associated with a lower risk of Barrett's esophagus when compared to the dyspepsia-controls but not the reflux-controls and beta-blockers were used less in the Barrett's group than the reflux-controls but not the dyspepsia controls. In the unadjusted analysis, the use of angiotension converting enzyme inhibitors was associated with a reduced incidence of Barrett's esophagus compared to both control groups. No medications were associated with an increased risk of Barrett's esophagus.

Use of statins and aspirin

Prior use of either aspirin or a statin for at least 6 months prior to index gastroscopy was associated with a reduced risk of Barrett's esophagus. After adjustment for confounding factors, statin use was associated with an overall significant reduction in Barrett's esophagus compared to dyspepsia-controls (adjusted odds ratio (aOR) 0.54 (95% confidence intervals 0.34 – 0.87) ($P < 0.01$) and non-significant reduction compared to reflux-controls (aOR 0.74 (95% CI 0.45 – 1.10) (table 3). There was no significant difference between statin use in the reflux and dyspepsia control groups and overall compared to all pooled controls prior statin use was associated with a reduced risk of Barrett's esophagus (aOR 0.62 (95% CI 0.37 – 0.93) ($P < 0.01$). Aspirin use was associated with consistent, but non-significant reduction in Barrett's esophagus compared to all control groups (as shown in table 3).

The combination of aspirin and a statin when taken for more than 6 months was associated with a consistent and significant reduction in the risk of Barrett's esophagus: compared to dyspepsia-controls (aOR 0.39 (95% CI 0.19 – 0.86)), reflux-controls (aOR 0.47 (95% CI 0.22 – 0.90)) and all controls (aOR 0.43 (95% CI 0.21 – 0.89))(all $P < 0.01$). In all cases the effect of combined aspirin and statin was greater than either alone.

After adjustment for potential confounders including statin and aspirin use, no other medications or risk factors were found to have a significant association with Barrett's esophagus. The number of subjects using non-aspirin NSAIDS was too small to analyse separately.

The vast majority of the current statin use (88%) was with simvastatin 40 mg once daily and no further attempt was made to examine the effects by statin dose, drug or pharmacological behaviour.

As shown in table 4, a longer duration of statin treatment or aspirin plus statin was associated with a lower risk of Barrett's esophagus. This was seen compared to both the dyspepsia controls and the reflux controls. Statin use for more than 5 years was associated with a lower risk of Barrett's esophagus (aOR 0.46 (0.13 – 1.28) in all controls, compared to 2 – 5 years (aOR 0.72 (0.40 – 1.15) or 6 months to 2 years (aOR 0.86 (0.51 – 1.46) ($P < 0.05$ for trend). Similarly the combined use of aspirin plus statin for 5 years was associated with a lower risk of Barrett's esophagus (aOR 0.34 (0.05 – 1.34) compared to 2-5 years (0.61 (0.25 – 1.09) or 6 months to 2 years (0.81 (0.24 – 1.56) when compared to all controls ($P < 0.05$ for trend).

Meta-analysis

Including the current study, 4 case-control studies were suitable for inclusion in the meta-analysis. The pooled results included 1089 Barrett's cases and 2085 controls, and demonstrated a significant inverse association between previous statin use and a new diagnosis of Barrett's esophagus pooled unadjusted OR 0.68 (95% CI 0.58 – 0.796) ($P < 0.0001$) (figure 1). A similar relationship was seen in the pooled adjusted OR 0.63 (95% CI 0.51 -0.778)($P < 0.0001$) (figure 2). Results were consistent across all studies with no heterogeneity ($I^2 = 0$) despite differing methodologies.

Discussion

In this study we have demonstrated that regular use of statin, or the statin and aspirin combination in men is associated with a reduced incidence of the diagnosis of Barrett's esophagus. There appeared to be a duration-response relationship with longer duration of treatment being associated with a greater degree of risk reduction and the combination of aspirin plus statin was always associated with a greater inverse association with risk of Barrett's compared to either drug alone. Although aspirin use was common, as reported previously in this population, regular (at least once a week) use of NSAIDs and selective COX-2 inhibitors is much less common. Therefore, we cannot examine whether these effects of aspirin are generalizable to all cyclo-oxygenase inhibitors or only seen with low-dose aspirin used for circulatory diseases (16).

Our data are limited to men and further studies are warranted in women. It is clear that there are important sex-related differences in the incidence and prognosis of Barrett's esophagus. Whether this relates to life-style, adipose tissue distribution or metabolism remains unclear and hence further follow up studies in women are required. A similar male preponderance was seen in other similar studies (21,22).

The main strengths of our study are the accurate and full records of medication exposure as reported previously (14,15,23) and the ability to correlate this with clearly defined endoscopic findings within the context of an adequately powered study. The main weakness, inherent in any observational study, is that of uncorrected bias. Although we have corrected for known and suspected confounders, it does remain possible that other factors are still influencing the results. Most specifically life-style factors related to a diagnosis of Barrett's esophagus may be undetected; for example the greater use of circulatory disease treatments (statins and anti-platelets) could reflect a more active engagement in health promotion in the non-Barrett's groups. In this study we did not specifically explore socioeconomic factors or

systematically assess current *H pylori* status. *H pylori* infection has a rather controversial relationship with gastroesophageal reflux and Barrett's esophagus: decreased acid secretion associated with infection may be protective against acid-related reflux disease (4). The overall prevalence of *H pylori* infection in patients undergoing gastroscopy in our unit is less than 10% (Beales, unpublished) and although this is an extra variable to be considered, we feel this is unlikely to significantly affect the relationship between statin use and Barrett's esophagus.

The other main weakness of our study is the definition of an incident case of Barrett's esophagus: we have used when this was first diagnosed endoscopically. Of course, the Barrett's metaplastic change could have been present for some time preceding the gastroscopy or even statin treatment. We have attempted to minimise this potential bias by only including cases and controls having their first gastroscopy for dyspeptic symptoms. The issue of how long any Barrett's segment has been present before discovery remains contentious and cannot be solved by either cross-sectional prevalence data or case-control studies such as the present study. However the similar case-control methodology has been widely employed to examine other risk factors for Barrett's (24-26).

Several individual studies (3-15,27) and 2 systematic reviews (that produced essentially identical results despite slightly different methodologies (16,17)) have reported that statin use, and particularly statin use combined with a cyclo-oxygenase inhibitor, is associated with a reduced incidence of esophageal adenocarcinoma. This has been reported in cohort studies and case-control studies of Barrett's patients and population-based studies compared to population-based controls, although not all studies are in agreement (28). Within the progression to cancer it is not clear whether the effects of statin (and aspirin) are seen mainly at the points of development and maintenance of the Barrett's segment or on preventing

progression to dysplasia and cancer. Whilst the cohort and case-control studies suggest statins and aspirin may prevent progression in an existing Barrett's segment; the current study suggests that statins and aspirin may prevent the development of the Barrett's segment as well.

We used two separate control groups: erosive reflux and those with no significant endoscopic findings. We found a similar pattern of reduced risk of Barrett's esophagus associated with statin use in both those with and without erosive reflux disease. This suggests that any effects of statins, or aspirin plus statins are not due to either prevention of reflux or development of erosive changes due to reflux (statins have well-recognised anti-inflammatory effects (29,30)). We recognise that our dyspepsia-control group inevitably contains patients with non-erosive reflux disease, but do not feel this demonstrably weakens our hypothesis that statin treatment (with or without aspirin) may be associated with a reduced risk of Barrett's esophagus, unrelated to any effects on esophageal acid exposure or the severity of endoscopic mucosal changes.

Perhaps due to the difficulties inherent in studying this area, there are relatively few studies examining prescribed and non-prescribed medications as risk factors for Barrett's esophagus compared to the number of studies examining esophageal cancer (16,17,20). Statin use as a risk factor for Barrett's specifically been examined in 3 other studies.

The most novel aspect of our current study is the meta-analysis of all the available data and this shows a significant and consistent inverse association between statin use and a new-diagnosis of Barrett's oesophagus. Regular statin use is associated with a 37% reduction in

the incidence of new diagnoses of Barrett's esophagus. This finding is consistent across the 4 studies, despite slightly different methods.

Nguyen et al (21) examined statin use from prescribing records and compared Barrett's cases to both non-Barrett's cases referred for diagnostic gastroscopy and a population-based cohort referred for colonoscopic cancer screening that had a gastroscopy purely for research purposes. In this, overwhelmingly male, cohort statin use was associated with a lower risk of Barrett's esophagus (aOR 0.57 (95% CI (0.38 – 0.87) and as in the current study a longer duration of statin use was associated with lower risk of Barrett's esophagus. Interestingly, in light of the results presented in our current study, the inverse association between statin use and a new diagnosis of Barrett's esophagus was more pronounced in those concurrently using aspirin (aOR 0.45 (95% CI 0.20 - 0.99) than those not using aspirin (aOR 0.73 (95% CI 0.32 – 1.65). A further case-control study using Barrett's-negative endoscopy patients as controls, including 242 male Barrett's patients, showed that statins were associated with a reduced rate of new diagnoses of Barrett's esophagus (aOR 0.53 (95% CI 0.35 – 0.81) (32). Interpretation of the results from this latter study are complicated by the retrospective, chart-review design and the absence of data on body habitus, smoking and other medications taken (32). One further study has attempted to examine the effects of the use of statins on the incidence of Barrett's esophagus. Omer et al reported that statin use was associated with a reduced rate of new diagnoses of Barrett's esophagus in the initial univariate analysis (OR 0.72 (95% CI 0.52 – 0.98)) but the statistical significance of this finding was not confirmed in the multivariate analysis (aOR 0.79 (95% CI 0.54 – 1.2) (22). Inaccuracies may be inherent in this study due to the purely retrospective nature of the data collection, lack of data on initiation of, or duration of statin use, relying on tertiary care centre endoscopy controls and the lack of matching in between cases and controls (there were significantly more females in the control group).

Although Nguyen et al (21) did stratify the effect of statin by aspirin use, the other studies did not. The available data on the effect of aspirin alone on the incidence of Barrett's esophagus are contradictory: an inverse association between aspirin use and Barrett's esophagus has been reported (22) but 2 other studies failed to find such an association (32,33).

The putative mechanisms of the effects of statins and aspirin in possibly preventing the development and establishment of Barrett's remain subject to conjecture. Experimentally statins inhibit proliferation and induce apoptosis in Barrett's cell lines and these effects are enhanced in an additive manner in combination with inhibition of the cyclo-oxygenase-2 pathway (10,11). Over-expression of COX-2 in Barrett's mucosa has been reported, and experimentally (34), and in clinical studies beneficial effects of COX-inhibitors on progression to cancer have been reported (13,16,35-37). Thus it is possible that statin and aspirin impair survival of the Barrett's clone at a very early stage and so impair establishment of a mature Barrett's segment. There are several putative mechanisms that could also be involved: aspirin reduced NF-kB signalling (38), which may in turn alter the nuclear transcription factor milieu that seems to be important in driving the development of Barrett's (39) and statins may influence the secretion of adipokines (such as adiponectin and leptin) which in turn seem to influence the behaviour of metaplastic Barrett's epithelial cells (40-44).

In conclusion, we have shown that statin use in men is associated with a significantly reduced rate of new diagnosis of Barrett's esophagus, this effect is more pronounced in concurrent aspirin users and there is greater effect with longer use of statins alone or combined with aspirin. Meta-analysis of pooled data confirms a significant reduction (37%) in the incidence

of Barrett's esophagus in statin users, with no heterogeneity in the results, despite differencing methodologies and control groups. Statins may protect against the development of Barrett's esophagus and this may contribute to the reduced risk of esophageal cancer seen in statin users in population studies. Further studies are required to determine if the relationship is causal and explore the mechanisms of action of statins on the esophageal mucosa.

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Table 1. Basic demographic data

	Barrett's esophagus	Dyspepsia controls	Reflux controls
N	134	268	268
Mean Age (±SD)	65.8 (13.8)	69.1 (11.3)	65.5 (11.4)
Smokers			
Current (%)	27 (20.1)	40 (14.9)	37 (13.8)
Ex- (%)	30 (22.4)	46 (17.1)	51 (19.0)
BMI (kg/m²)			
<25 (%)	37 (27.6)	86 (32.0)	89 (33.2)
25-30 (%)	64 (47.7)	115 (42.9)	107 (39.9)
>30 (%)	47 (35.1)	67 (25)	72 (26.8)
Waist Circumference			
<93 cm (%)	12 (8.9)	48 (17.9)	40 (14.9)
93.1-102 cm(%)	58 (43.3)	113 (42.1)	107 (39.9)
>102.1 cm (%)	64 (47.8)	107 (39.9)	121 (45.1)
Alcohol			
Never (%)	32 (23.9)	86 (32.1)	62 (23.1)
< 10 u/wk (%)	58 (43.3)	104 (38.8)	112 (41.8)
> 19 u/wk (%)	44 (32.9)	78 (29.1)	94 (35.1)

There were no significant differences in any basic demographic factor between any of the groups (all $P > 0.05$)

	Barrett's esophagus (134)	Dyspepsia controls (268)	OR Barrett's vs. Dyspepsia (95% CI)	Reflux controls (268)	OR Barrett's vs. Reflux (95% CI)
	N (%)	N (%)		N (%)	
Statin	48 (35.8)	131 (48.8)	0.58 (0.38 - 0.89)**	112 (41.7)	0.77 (0.50 - 1.19)
Aspirin	29 (21.6)	66 (24.6)	0.84 (0.51 - 1.38)	68 (25.3)	0.81 (0.40 - 1.32)
Statin and aspirin	18 (13.4)	60 (22.3)	0.53 (0.24 - 0.94)*	61 (22.8)	0.56 (0.31 - 0.95)*
CCM	17 (12.7)	36 (13.4)	0.94 (0.49 - 1.72)	38 (14.1)	0.87 (0.46 - 1.61)
ACE-I	18 (13.4)	92 (34.4)	0.29 (0.17 - 0.51)**	75 (27.9)	0.40 (0.22 - 0.69)**
ARB	6 (4.47)	15 (16.8)	0.79 (0.27 - 2.00)	14 (5.2)	0.85 (0.29 - 2.23)
Beta-blocker	18 (13.4)	45 (16.8)	0.77 (0.41 - 1.77)	64 (23.8)	0.49 (0.27 - 0.86)*
Insulin	4 (2.9)	12 (4.47)	0.65 (0.18 - 2.00)	34 (12.7)	0.56 (0.50 - 1.66)
Metformin	10 (7.4)	51 (19.0)	0.32 (0.16 - 0.68)**	10 (3.7)	0.55 (0.25 - 1.14)
Other diabetic meds	4 (2.9)	24 (8.9)	0.32 (0.23 - 2.89)	20 (7.4)	0.79 (0.21 - 2.52)
NSAIDs	5 (3.7)	9 (3.3)	1.15 (0.33 - 3.4)	24 (8.9)	0.48 (0.15 - 1.16)
Inhaled beta2-agonists	13 (0.9)	27 (10.1)	0.93 (0.44 - 1.89)	37 (13.8)	0.65 (0.32 - 1.25)
Inhaled steroids	14 (10.4)	33 (12.3)	0.80 (0.43 - 1.54)	27 (10.0)	1.00 (0.49 - 1.97)
Theophylline	0 (0)	3 (1.1)	-	0 (0)	-
Alpha blocker	10 (7.5)	30 (11.1)	0.64 (0.29 - 1.33)	31 (11.5)	0.62 (0.28 - 1.18)
Anti-cholinergic meds	8 (6.0)	15 (5.6)	1.08 (0.41 - 2.57)	20 (7.4)	0.79 (0.32 - 1.81)
Bisphosphonates	2 (1.5)	6 (2.23)	0.66 (0.09 - 3.17)	0 (0)	-

Table 2. Medication consumption

CCM, calcium channel modulator; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, non-aspirin non-steroidal anti-inflammatory drugs including non-selective and COX-2 selective agents, anti-cholinergic medications includes any with anti-cholinergic pharmacodynamics effects including inhaled anti-cholinergic drugs or tricyclic antidepressants.

* $P < 0.05$, ** $P < 0.01$

Table 3. Adjusted Odds ratios for use of statin and/or aspirin for at least 6 months prior to the diagnosis of Barrett’s esophagus compared to dyspepsia controls or erosive reflux controls.

	Barrett’s vs dyspepsia controls (95% CI)	Barrett’s versus reflux controls (95% CI)	Barrett’s versus all controls (95% CI)
Statin	0.54 (0.34 – 0.87)**	0.74 (0.45 -1.10)	0.62 (0.37-0.93)**
Aspirin	0.80 (0.51 – 1.30)	0.75 (0.46 – 1.19)	0.77 (0.46 – 1.14)
Statin + aspirin	0.39 (0.19 – 0.86)**	0.47 (0.22 – 0.90)**	0.43 (0.21 – 0.89)**

** $P < 0.01$

	Barrett's vs non-reflux controls (95% CI)	Barrett's versus reflux controls (95% CI)	Barrett's versus all controls (95% CI)
Duration of statin use			
6 months – 2 years (%)	0.79 (0.44 -1.42)	0.92 (0.51 – 1.65)	0.86 (0.51 – 1.46)
2 – 5 years (%)	0.56 (0.33 – 0.95)	0.87 (0.51 -1.49)	0.72 (0.40 – 1.15)
5 years + (%)	0.45 (0.12 -1.37)	0.48 (0.11 – 1.58)	0.46 (0.13 – 1.28)
Duration of aspirin used			
6 months – 2 years (%)	1.15 (0.47 – 2.7)	0.95 (0.39 – 2.17)	1.02 (0.46 – 2.19)
2 – 5 years (%)	0.78 (0.39 – 1.4)	0.78 (0.49 – 1.44)	0.78 (0.42 – 1.36)
5 years + (%)	0.70 (0.12 – 1.67)	0.69 (0.18 – 2.16)	0.69 (0.20 – 1.94)
Duration of Statin plus aspirin use			
6 months – 2 years (%)	1.04 (0.34 – 2.63)	0.66 (0.23 – 1.69)	0.81 (0.24 – 1.56)
2 – 5 years (%)	0.77 (0.32 – 1.72)	0.53 (0.25 – 1.19)	0.61 (0.25 – 1.09)
5 years + (%)	0.30 (0.06 – 1.60)	0.39 (0.02 – 0.85)	0.34 (0.05 – 1.34)

Table 4. Adjusted odds ratios for the use of statin and / or aspirin prior to the diagnosis of Barrett's oesophagus compared to all pooled (dyspepsia and reflux) controls

Figure legends**Figure 1**

Pooled unadjusted odds ratio for studies examining the association of statin use and incidence of Barrett's esophagus

Figure 2

Pooled adjusted odds ratio for studies examining the association of statin use and incidence of Barrett's esophagus

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