Title: Association between Post-Diagnosis Statin Use and Survival in Patients with Esophageal Carcinoma: a Population-Based Cohort Study.

Short Title: Statins use and survival in esophageal cancer

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Key words: Esophagus; adenocarcinoma; HMG-CoA.

Author contributions

LA, ARH, MPNL, SC and AC conceived and designed the study. ARH, HB and AC were involved in data acquisition. AC and LA conducted the statistical analysis. LA, ARH, MPNL and AC were involved in interpretation of the data. LA drafted the manuscript. All co-authors contributed to and approved the final manuscript.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Abstract

Background & aims: Esophageal cancer (EC) is a significant cause of cancer-related mortality worldwide. Statins have anti-carcinogenic effects in EC cell lines. The aim of this study was to determine whether statin use following diagnosis of EC, including the histological subtypes, is associated with reduced EC-specific and all-cause mortality.

Methods: A cohort of 4445 men and women in the United Kingdom diagnosed with EC between January 2000 and November 2009 and followed-up until November 2011 were identified using the General Practice Research Database. Cox proportional hazard regression analysis with time-dependent exposures estimated the association between post-diagnostic statin use and EC-specific and all-cause mortality.

Results: The median survival of the whole cohort was 9.2 months (IQR 3.7-23.2). The median survival in post-diagnostic statin users was 14.9 months (IQR 7.1-52.3) and in non-users was 8.1 months (IQR 3.3-20). Post-diagnostic statin use was associated with a decreased risk of EC-specific mortality (adjusted Hazard Ratio [HR] 0.62, 95% CI 0.44-0.86) and all-cause mortality (HR 0.67, 95% CI 0.58-0.77) for the full cohort. In patients with esophageal adenocarcinoma (EAC), post-diagnostic use of statins was associated with decreased risk of EC-specific mortality (HR 0.61, 95% CI 0.38-0.96) and all-cause mortality (HR 0.63, 95% 0.43-0.92). This effect was not observed in patients with esophageal squamous cell carcinoma (ESCC). There was no evidence of effect modification on associations by pre-diagnostic statin use.

Conclusions: In a large population-based cohort, post-diagnostic statin use in patients with EC was associated with reduced EC-specific and all-cause mortality, specifically in those with EAC but not ESCC.

Keywords: HMG-CoA; esophagus

Introduction

Esophageal cancer (EC) is the 5th and 8th most common cause of cancer-related death in men and women respectively worldwide[1]. Of the two main histological subtypes, esophageal squamous cell carcinoma (ESCC) is globally predominant, while esophageal adenocarcinoma (EAC), the incidence of which has rapidly risen since the 1970s, is the most common form in the west[1, 2]. Most patients with EC present with advanced disease and are often only amenable to palliative management. Consequently, the overall 5-year survival rate is approximately only 15%[3].

Novel clinical interventions to improve prognosis in patients with EC are required. There has been a considerable research focus on the potential anti-cancer effects of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors), which are commonly prescribed for the primary and secondary prevention of cardiovascular disease[4]. A body of basic research has demonstrated that statins promote apoptosis and limit proliferation in EAC and ESCC cell lines[5-8]. Epidemiological investigations have demonstrated that use of statins post-diagnosis is associated with reduced risk of cancer-specific mortality in a number of malignancies, including prostate, breast and colorectal carcinoma[9-11]. Furthermore, at a population level their use is inversely associated with development of the histological subtypes of EC[12]. A population-based cohort study in Denmark demonstrated that statin use prior to diagnosis of EC was associated with a 19% decrease in cancer-specific mortality[13]. Whether statin use following diagnosis of EC, a more relevant time period for clinical intervention, improves survival is unknown. Furthermore, whether or not statins exert differential effects on survival for the two main histological subtypes, EAC and ESCC, is unknown. Therefore, the primary aim of this

epidemiological study was to determine whether statin use following diagnosis of EC, including the histological subtypes, is associated with reduced EC-specific and all-cause mortality. Secondary aims were to determine whether pre-diagnostic statin use is an effect modifier on the association between post-diagnostic statin use and survival; determine whether a dose-response relationship exists; and determine whether differential effects exist according statin type.

Methods

Data sources

This study was conducted using three databases: the United Kingdom (UK) General Practice Research Database (GPRD), the UK National Cancer Registry (NCR) and the Office of National Statistics (ONS) database. The GPRD is the world's largest electronic database of prospective demographic, lifestyle and medical data in a primary care setting[14]. At the time of data extraction, 4 million patients were registered at 488 general practices, covering 6% of the UK population. The age and sex distributions of participants in the GPRD are comparable with the National Population Census, and the distribution of participating practices is representative of the UK population[15]. General Practitioners (GPs) prospectively record incident diagnoses and medical procedures using a modified Read/Oxford Medical Information System (OXMIS) classification system. Filled drug prescriptions issued by GPs are automatically recorded and coded using the UK Prescription Pricing Authority Dictionary. Data recorded on diagnostic codes to identify diseases, including EC, and drug prescriptions in the GPRD have been shown to be valid in independent studies[16-18]. Linkage between databases used a deterministic algorithm based on the patient National Health Service number, postcode, gender and date of birth. The NCR contains information on tumour site (coded using the International Classification of Diseases, 10th Revision [ICD-10]), histology, cancer stage and treatment modalities. Approximately half of GPRD practices were linked to the NCR at the time of data extraction. For patients with data linked to the NCR, ONS data was available to determine cause of death. The GPRD group have obtained blanket approval from a multi-centre ethics committee for observational research conducted within the database.

Study cohort

Participants with incident esophageal or esophagogastric junction cancers, diagnosed between 1st January 2000 to 30st November 2009, and followed-up until 1st November 2011 were identified from the GPRD. Patients were included with no prior history of cancer. All patients were required to be diagnosed at least one year after the contributing practice had received its "up-to-standard" date: the time from which the practice was considered to generate continuous high quality data fit for research. The histological subtype for a subset of patients was determined through linkage to the NCR. ICD codes were used to confirm esophageal (C15) and esophago-gastric junctional (C16) cancers, and specific morphology codes were used to obtain the histological subtypes: EAC, esophagogastic junctional adenocarcinoma (EGJA) and ESCC. Follow-up was from the date of diagnosis until death, or until they were transferred out of the GPRD or the date of last data entry, whichever came first.

Statin use

Exposure to the following statins currently in clinical use in the UK were extracted: Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin and Fluvastatin. Post-diagnostic statin use was defined as a prescription of any of these statins recorded in the GPRD at any time after the date of diagnosis. Post-diagnostic statin use was included as a time-dependent covariate in the models to avoid immortal-time bias: whereby a span of cohort follow-up during which death could not occur (i.e. between diagnosis and the first statin prescription) is inappropriately introduced due to the definition of the exposure of interest[19]. Patients were considered unexposed until the first post-diagnosis prescription, from which point they were considered continuously exposed until the end of follow-up. Deeming patients continuously exposed sought to minimize reverse causation bias,

whereby ultimately discontinuation could reflect poor prognosis and therefore death may otherwise be more likely inappropriately classified during an "unexposed" period[20]. Exposure to the individual statins listed above was also considered in survival analyses. To investigate the possibility of healthy survivor bias in the statin users post-diagnosis, the intervals between diagnosis and statin initiation for all statin users post-diagnosis were presented using a Kaplan-Meier plot (Supplementary figure 1).

Pre-diagnosis statin use was also an exposure of interest. It was defined as a prescription of any of the statins recorded above in the GPRD for a minimum of two months between 6 and 18 months prior to diagnosis. This definition sought to minimize reverse causation bias, whereby symptomatic EC (and hence likely more advanced disease) could influence prescribing practice or medication use. Pre-diagnosis statin use was determined for the following three reasons: it was entered as a covariate in models of post-diagnostic statin use to determine whether it modifies the effect of post-diagnosis statin use on survival; in sensitivity analyses the association between pre-diagnosis statin use on survival was determined to consider an exposure to statin use, alternative to post-diagnosis statin use, in which the potential effect of reverse-causation bias would be expected to be minimal; and finally it was used to determine categories for dose-response analyses. Statin users were categorized as low (equivalent to ≤ 20mg simvastatin) or high (equivalent to > 20mg simvastatin) dose users based on the mean daily dose for statin prescriptions collected between 6-18 months prior to diagnosis. Cumulative statin dose was determined using categories of cumulative defined-daily dose (DDD). The DDD, a standardized measure of drug exposure as defined by the World Health Organization, is the assumed average maintenance dose per day for a drug used for its main indication in adults[21]. For example, 1 DDD is equivalent to a single dose of 30mg Simvastatin or 20mg Atorvastatin. The

median cumulative DDD collected between 6-18 months prior to diagnosis in the whole cohort was the threshold for cumulative dose categories. Post-diagnostic mean or cumulative dose-response analyses were not examined *a priori* as the dose categories would be expected to be a function of survival time. In a post-hoc analysis we conducted dose-response analyses using the dose (expressed in DDDs) of the first statin prescribed post-diagnosis to determine the dose category.

Covariates

The following covariates which could plausibly confound associations between post-diagnostic statin use and survival were extracted from the GPRD: age at diagnosis, gender, body mass index (BMI) at the time closest to and preceding diagnosis, smoking status, cardiovascular diseases (coronary artery, cerebrovascular and peripheral vascular disease) and diabetes mellitus, surgery (either esophagectomy, esophago-gastrectomy or extended gastrectomy) recorded within 6 months of diagnosis and medication use (aspirin, angiotensin converting enzyme inhibitors [ACEi] and angiotensin 2 receptor blockers [ARBs], beta-blockers and non-steroidal anti-inflammatory drugs [NSAIDs]). Use of these medications were extracted both post-diagnosis and pre-diagnosis using the same exposure definitions as for statin use. The following covariates were extracted from the NCR: chemotherapy, radiotherapy and surgery (either esophagectomy, esophago-gastrectomy or extended gastrectomy) recorded within 6 months of diagnosis.

Outcome measures

The outcome measures were EC-specific and all-cause mortality. All-cause mortality was determined for all study patients in the GPRD. EC-specific mortality was determined for

the subset of participants with data linked to the NCR and ONS datasets where EC was listed in part one of the death certificate.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort, including the histological subtypes; and separately for pre and post-diagnosis statin users. The characteristics between statin users and non-users were compared using the Chi-squared test for categorical data, two sample t-test for age and the Mann-Whitney U test for survival time. Crude rates of EC-specific and all-cause mortality were calculated which reflect time-dependent exposure to statins. To account for the time-varying nature of drug exposures, Cox proportional hazard regression with time-dependent exposures, estimated the associations between statin use (versus non-use) post-diagnosis on EC-specific and all-cause mortality for the full cohort and the histological subtypes. Concomitant medication use and surgery were included as time-dependent covariates in the models. Surgery was not included in multivariable analyses of the full cohort (total EC, n= 4445) as it was under-recorded in the GPRD, however it was included with cohorts linked to the NCR, where it was more comprehensively recorded. Survival curves according to post-diagnosis statin use were constructed using Cox proportional hazard regression with time-dependent exposures. For analyses of pre-diagnosis statin use, follow-up began from the date of diagnosis, and all included covariates were measured prior to this date. Cancer stage was incomplete for 95.9% of the cohort and was therefore not included in multivariable analyses. Tests for interaction examined for any effect modification of pre-diagnosis statin use on the association between post-diagnostic statin use and mortality. A test for linear trend was applied across dose categories.

Sensitivity analyses

We performed a number of sensitivity analyses to determine the robustness of our findings. As previously outlined, the association between pre-diagnosis statin use on EC-specific and all-cause mortality for the full cohort and the histological subtypes was examined. To determine whether treatment modality (surgery, chemotherapy and radiotherapy) was an important confounder in the relationship between post-diagnostic statin use and EC-specific and all-cause mortality, analyses were repeated with and without these covariates in the model. To explore the potential impact of reverse causation bias on analyses of post-diagnostic statin use and consider latency, the cohort was restricted to those surviving at least three months, all drug exposures were lagged for at least three months and all new prescriptions in the final three months of life were ignored. In a post-hoc analysis, the effect of post-diagnosis statin use on-cause and EC-specific mortality stratified by pre-diagnosis cardiovascular disease status were performed as effect sizes could differ according to their indication (primary versus secondary prevention). All analyses were performed with STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Cohort

In total, 4676 patients identified from the GPRD with esophageal or esophago-gastric junctional carcinoma met the inclusion criteria (figure 1). From these, 231 (5%) patients were excluded as they had no follow-up from diagnosis. The main cohort (total EC) comprised 4445 patients of whom 3655 died during follow-up. In total, 1530 (34.4%) patients were linked to the NCR in whom there were 1323 all-cause and 805 EC-specific deaths. Of these 1165 had complete information on both histology and site including 602 with EAC, 221 with EGJA and 342 with ESCC.

Clinical characteristics

Overall, patients in the whole cohort were more likely to be male, smokers and overweight or obese (table 1). Median survival for the whole cohort was 9.2 months (inter-quartile range 3.7-23.2). Post diagnosis statin use was observed in 18.7% of patients. Accounting for immortal-time, the median survival in post-diagnosis statin users was 14.9 months (IQR 7.1-52.3) and in non-users was 8.1 months (IQR 3.3-20). Most patients with EAC and EGJA were male and overweight, whereas the majority of patients with ESCC were female and had a normal or low BMI. Data on surgery was more complete for the histological subtypes (as additional surgical data was available from the NCR) than the whole cohort. Pre and post-diagnosis statin use was more common among patients with EAC and EGJA than for those with ESCC.

Pre and post-diagnosis statin users (compared to no pre and no post-diagnosis statin users respectively) were more likely to be older, male, overweight, smokers, have

associated cardiovascular diseases or diabetes, and use aspirin, ACEi/ARBs or beta-blockers (all p values < 0.001) (table 2). Post-diagnosis statin users were more likely to have undergone surgery compared to those who did not use statins post-diagnosis (24.9% vs. 21.2% respectively, p = 0.018); whereas pre-diagnosis statin users were less likely to have undergone surgery than those who did not use statins pre-diagnosis (17.5% vs. 23% respectively, p < 0.001). 830 patients were prescribed statins post-diagnosis in the whole cohort, of whom 163 were new users. Of these 117 (72%) were started without a prior history of cardiovascular disease (suggesting their indication for primary prevention), and 46 (28%) were started after a record of cardiovascular disease (suggesting their indication for secondary prevention). Of all patients who used statins following diagnosis, 90% were prescribed within 6 months of diagnosis (supplementary figure 1).

Post-diagnosis statin use and survival

In the full cohort post-diagnosis statin use was associated with decreased EC-specific (HR 0.62, 95% CI 0.44-0.86) and all-cause mortality (HR 0.67, 95% CI 0.58-0.77) (table 3, figure 2 and 3). Post-diagnosis statin use was associated with reduced EC-specific (HR 0.61, 95% CI 0.38-0.96) and all-cause mortality (HR 0.63, 95% CI 0.43-0.92) in patients with EAC only, but not for the other subtypes. There was no significant interaction of pre-diagnosis statin use on the effect of post-diagnostic statin use on EC-specific or all-cause mortality for whole cohort or the subtypes. Post-diagnosis use of Simvastatin and Atorvastatin, but not the other statins, was associated with reduced EC-specific mortality (supplementary table 2). Post-diagnosis use of each of the individual statins investigated was associated with decreased all-cause mortality.

Dose-response associations

No significant dose-response associations for either mean dose or cumulative dose in the 6-18 months prior to diagnosis were observed in the cohort for which EC-specific mortality data was available (n=1530) (p for trend 0.486 and 0.718 respectively) (table 4). However, for all-cause mortality (n = 4445) there were significant dose-response associations for mean and cumulative dose categories (p for trend 0.003 and 0.002 respectively). For the dose response analyses defined by the first prescribed statin dose post diagnosis, while there were significant trends across dose categories, the point estimates did not consistently decrease from low to high dose use.

Sensitivity analyses

Pre-diagnosis statin use was associated with decreased all-cause mortality (HR 0.87, 95% CI 0.78-0.96) but not EC-specific mortality (HR 0.90, 95% CI 0.71-1.16) for the full cohort (supplementary table 1). No significant associations were observed between pre-diagnosis statin use and EC-specific and all-cause mortality for the histological subtypes. Including and excluding treatment modality (surgery, chemotherapy, radiotherapy) as individual covariates in models in analyses of post-diagnostic statin use did not materially alter the strength or precision of estimates (supplementary table 3). Restricting the cohort to those who survived at least 3 months from diagnosis had a variable impact on associations between post-diagnostic statin use and survival: associations remained a similar magnitude in the full cohort for the assessment of all-cause mortality (main analysis: HR 0.67, 95% CI 0.58-0.77; sensitivity analysis: HR 0.70, 95% CI 0.60-0.82), however lost significance in the assessment of EC-specific mortality (main analysis: HR 0.62, 95% CI 0.44-0.86; sensitivity analysis HR 0.84, 95% CI 0.58-1.20). Lagging drug exposures weakened associations with EC-specific and all-cause mortality in the full

cohort while they were strengthened for associations in patients with EAC. Ignoring new prescriptions in the final three months of follow-up did not materially alter associations for: EC-specific mortality for the full cohort (main analysis: HR 0.62, 95% CI 0.44-0.86; sensitivity analysis: HR 0.60, 95% CI 0.43-0.84); all-cause mortality for the full cohort (main analysis: HR 0.67, 95% CI 0.58-0.77; sensitivity analysis: HR 0.54, 95% CI 0.47-0.63); EC-specific mortality in patients with EAC (main analysis: HR 0.61, 95% CI 0.38-0.96; sensitivity analysis: HR 0.53, 95% CI 0.32-0.85); or for all-cause mortality in patients with EAC (main analysis: HR 0.63, 95% CI 0.43-0.92; sensitivity analysis: HR 0.49, 95% CI 0.33-0.73). For sensitivity analyses which stratified for pre-diagnosis cardiovascular disease status, risk of EC-specific mortality with post-diagnosis statin use was HR 0.66, 95% CI 0.44-1.00 (no cardiovascular disease) and HR 0.35, 95% CI 0.20-0.63 (with cardiovascular disease); and for all-cause mortality with post-diagnosis statin use HR 0.66, 95% CI 0.56-0.79 (no cardiovascular disease) and HR 0.66, 95% CI 0.52-0.83 (with cardiovascular disease).

Discussion

This large population-based cohort study of patients with incident EC found that post-diagnosis statin use was associated with a 39% reduction in EC-specific mortality and 33% reduction in all-cause mortality. In patients with EAC specifically, post-diagnosis statin use was associated with a 39% reduction in EC-specific mortality and 37% reduction in all-cause mortality. There were no significant improvements in survival associated with post-diagnosis statin use for ESCC or EGJA. Pre-diagnosis statin use did not significantly modify effects observed for post-diagnosis statin use on mortality. Significant dose and cumulative dose-response relationships were observed for pre-diagnosis statin use and all-cause mortality in the whole cohort. Estimates of the association between statin use and mortality for the histological subtypes, EGJA and ESCC, including the dose-response analyses with EC-specific mortality as the outcome, lacked precision. It therefore may not be possible to exclude a weak or moderate effect in these groups. While there were significant trends across dose categories defined by the first prescribed statin dose post-diagnosis, the estimated hazard ratios did not consistently decrease from low to high dose use suggesting that we should cautiously interpret this finding. It should be noted this approach would not take into account changes in dose or a cumulative exposure.

Biological mechanisms

Our findings are consistent with experimental studies which have demonstrated that statins promote apoptosis and limit proliferation in EAC cell lines[5-8]. Inhibition of HMG-CoA reductase by statins decreases production of downstream intermediates of the mevalonate pathway, including farnesyl pyrophosphate, which are required for the

prenylation and consequent membrane localisation of guanosine-triphosphate-bound proteins, including Ras[22]. Through limiting Ras farnesylation, statins reduce two protein kinases, extracellular signal-related protein kinase and protein kinase B/Akt, both of which are responsible for promoting cell survival and growth signal transduction in EAC cell lines[5]. Statins also reduce, in a dose-dependent manner, intracellular adhesion molecule-1[6], an adhesion molecule involved in trans-endothelial tumour cell migration and metastatic spread[23, 24]. Whether these mechanisms operate to explain the associations observed in this study is not clear.

Comparison with previous work

As far as we are aware, this is the first observational study to investigate the effect of statin use post-diagnosis on survival in patients with EC. However, one large observational study of 295, 925 patients diagnosed with cancer of any site within the entire Danish population examined the effect of statin use pre-diagnosis on cancer-specific mortality[13]. This study used the definition of pre-diagnosis statin exposure employed in our study. In a sub-analysis of 4, 398 cases of EC (as a composite diagnosis), pre-diagnosis statin use was associated with reduced cancer-specific mortality (adjusted HR 0.81, 95% CI 0.69-0.95). This was similar to the effect size that we observed (HR 0.87, 95% CI 0.78-0.96) on all-cause mortality (n = 4445). However, while the effect size for pre-diagnosis statin use on EC-specific mortality in our study was similar, the estimate lacked precision, likely reflecting limited power to detect associations (HR 0.90, 95% CI 0.71-1.15) (n = 1530). Similarly to our study, significant amounts of data were missing for cancer stage, radiotherapy and chemotherapy. Use of concomitant medications that could plausibly confound associations were not included in multivariable

analyses. The effect of dose-response on EC mortality specifically was not reported. This study did not determine associations according to the histological subtype.

Strengths and limitations

This study had several strengths. Read codes used to identify patients with EC in the GPRD have been shown to be valid (positive predictive value 0.97, sensitivity 0.92, and specificity 0.99)[18]. Overall five-year survival was 12.5%, consistent with UK data, suggesting the disease identified was clinically representative[3]**.** Participants with EC identified from the GPRD represent a large cohort with a median 9 (IQR 3.7 – 22.7) months follow-up post diagnosis to enable meaningful survival analyses. In a subset of patients, linkage with the NCR enabled associations between statin use and mortality for the histological subtypes of EC; and linkage with the ONS database enabled EC-specific mortality to be examined. Prospective prescription records within the GPRD avoid recall bias compared to self-reported medication use. Measurement error of drug exposures is likely to be minimal given the accuracy of prescription records in the GPRD[17]. While the GPRD does not record purchased over-the-counter medications, exposure misclassification for statin use is unlikely as such purchases account for only 0.7% of total statin use in the UK[25]. While the GPRD records prescribed medications, exposure misclassification could foreseeably arise where patients did not adhere to treatment: while prescriptions are accurately recorded by the GPRD, drug adherence is not directly captured. However, exposure misclassification through both sources would be expected to attenuate associations and underestimate the associations observed in this study. For analyses of post-diagnosis statin use, the time-varying nature of drug exposures were accounted for and therefore avoided immortal time bias, which would have otherwise likely exaggerated associations. A form of selection bias, healthy survivor bias, could

have influenced results for individuals who were prescribed their first statin after a substantial interval following diagnosis: this group would by definition have an improved prognosis as their risk of death due to the index cancer would be expected to diminish as the interval lengthened. However, this potential bias would seem unlikely to have influenced results overall as 90% of patients who were prescribed statins post-diagnosis, did so within 6 months (supplementary figure 1).

This study has several limitations. There were substantial amounts of missing data for treatment modality and cancer stage. Completeness of treatment modality approached that expected for surgery and radiotherapy but not chemotherapy for patients linked to the cancer registry. For example, for EAC patients the proportion receiving surgery, chemotherapy, and radiotherapy, respectively, was 33%, 24% and 15% and national audit data indicate the approximate expected proportions to be 35%, 47% and 12%[26]. While treatment modality and stage are important predictors of outcomes, it is not clear as to whether they operate as confounders in the association between statin use and mortality. As clinical staging and treatment modality are closely related, treatment modality could be regarded as a proxy for staging: with surgery expected to be most discerning from the three captured modalities. Therefore, sensitivity analyses were conducted (outlined above), to explore whether treatment modality, and by extension cancer staging, could operate as confounders in the association between statin use and mortality. Effect sizes and the precision of the estimates were similar for post-diagnosis statin use in analyses which did and did not adjust for surgery, chemotherapy and radiotherapy; suggesting that unmeasured confounding by treatment modality or clinical stage was not operating.

Reverse causation bias could theoretically operate in the association between post-diagnosis statin use and mortality. New users could represent a group with a more favorable prognosis, as determined by their GP, such that for these individuals prevention of cardiovascular disease (particularly primary prevention), a long-term outcome, is deemed a clinical priority, as opposed to adopting a more palliative approach. Although we cannot exclude this, our findings would suggest this mechanism of reverse causation bias is not a prominent explanation for the associations observed. First, of all statin users post-diagnosis, new statin users who were likely prescribed statins for primary prevention accounted for a minority (14%). Second, there was no significant interaction with statin use prior to diagnosis for the association between post-diagnosis statin use and EC-specific and all-cause mortality. Third, restricting the whole cohort to those surviving greater than three months from diagnosis did not materially alter associations in the whole cohort (associations examined with linked data were likely underpowered to assess this). Restricting the cohort to those surviving longer periods would have been underpowered: the prognosis from EC overall is poor and the remaining cohort size would be too small to permit meaningful analyses. Fourth, one would expect reverse causation bias to operate in the same manner as for other medications exposures used in the treatment of cardiovascular diseases (assuming they do not cause harm): indeed significant associations were not observed (all p values > 0.05). Fifth, pre-diagnosis statin use, a measure of statin exposure which would be expected to be free of reverse causation bias, was associated with reduced all-cause mortality. Deeming patients continuously exposed to statins once a prescription was issued until the end of follow-up prevented another guise of reverse causation bias, whereby treatment decisions made at the end-of-life, such as withdrawing regular medications, ensured patients were correctly classified as exposed. Similarly, sensitivity analyses which ignored all new prescriptions in the final

three months' of follow-up, an exposure which may not plausibly influence outcomes but which could reflect a GP's assessment of prognosis, did not materially alter the strength or significance of associations.

The analyses may be susceptible to unmeasured confounding mediated by a healthy-user effect: statin users could represent a more health conscious group, whereby associated behaviors, either on the part of the patient or health-professional, may be associated with improved survival. For example, more health-conscious individuals may present and be diagnosed with an earlier stage of cancer; and GP have been reported to selectively under-prescribe lipid-lowering medications to obese patients or smokers[27], both of which are associated with increased cancer-related mortality[28, 29]. However, contrary to this, statin users appeared less healthy: they were more likely to be overweight or obese, smoke and have diabetes or cardiovascular disease than non-users - factors which independently predict mortality. Nevertheless, we attempted to minimize potential confounding from a healthy-user effect by including smoking, BMI, cardiovascular disease and concomitant medication use in multivariable analyses. Nevertheless, as with all observational studies, residual confounding is still possible.

Conclusions

In summary, post-diagnosis statin use was associated with large and significant reductions in EC-specific and all-cause mortality, specifically in those with EAC. There was evidence of significant dose and cumulative dose-response relationships with pre-diagnosis statin use on all-cause mortality in patients with EC. These results require replication in other large cohorts and provide further evidence in support of the conduct of randomized controlled trials of statins as adjuvant agents in patients with EC.

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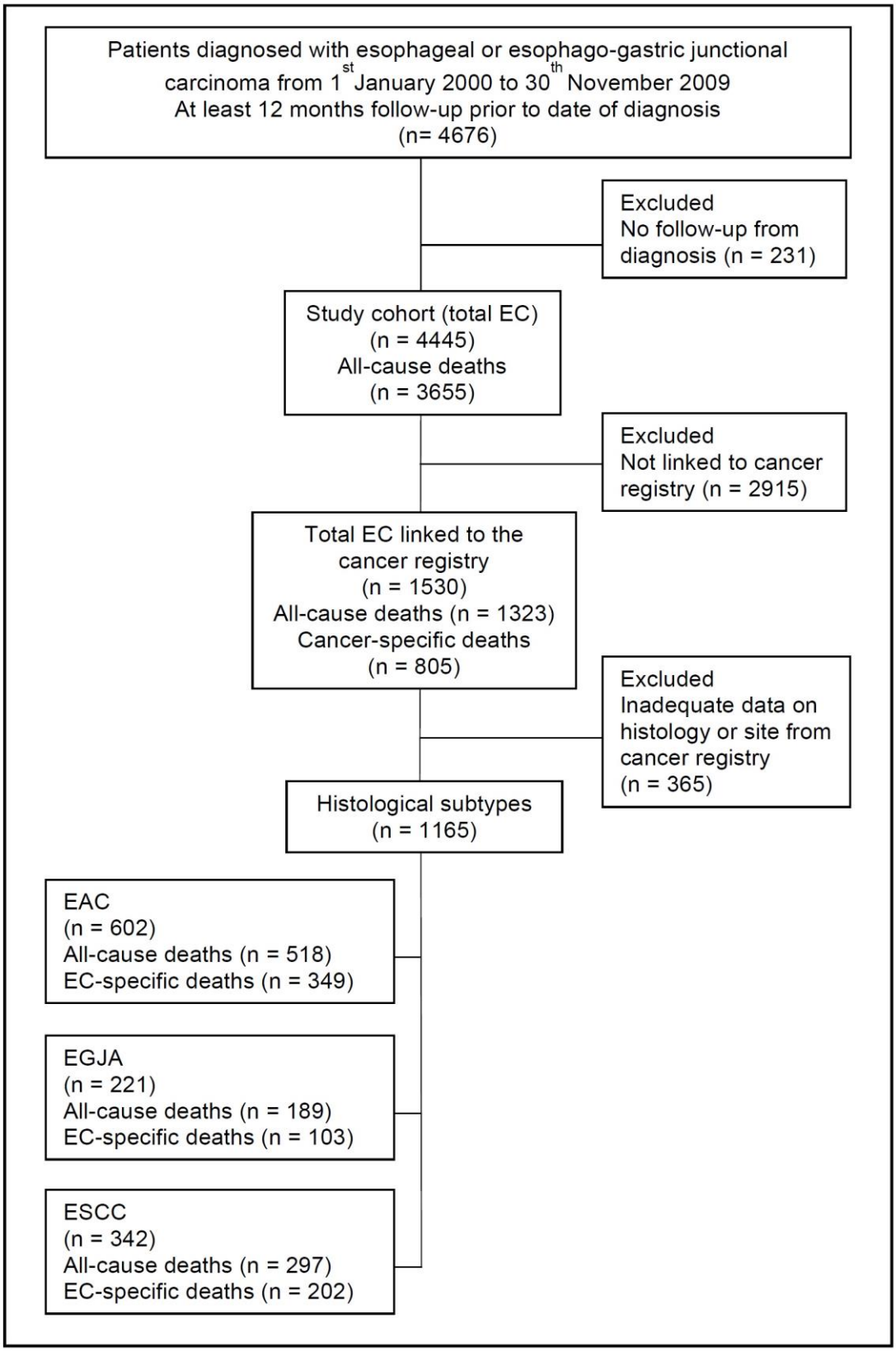
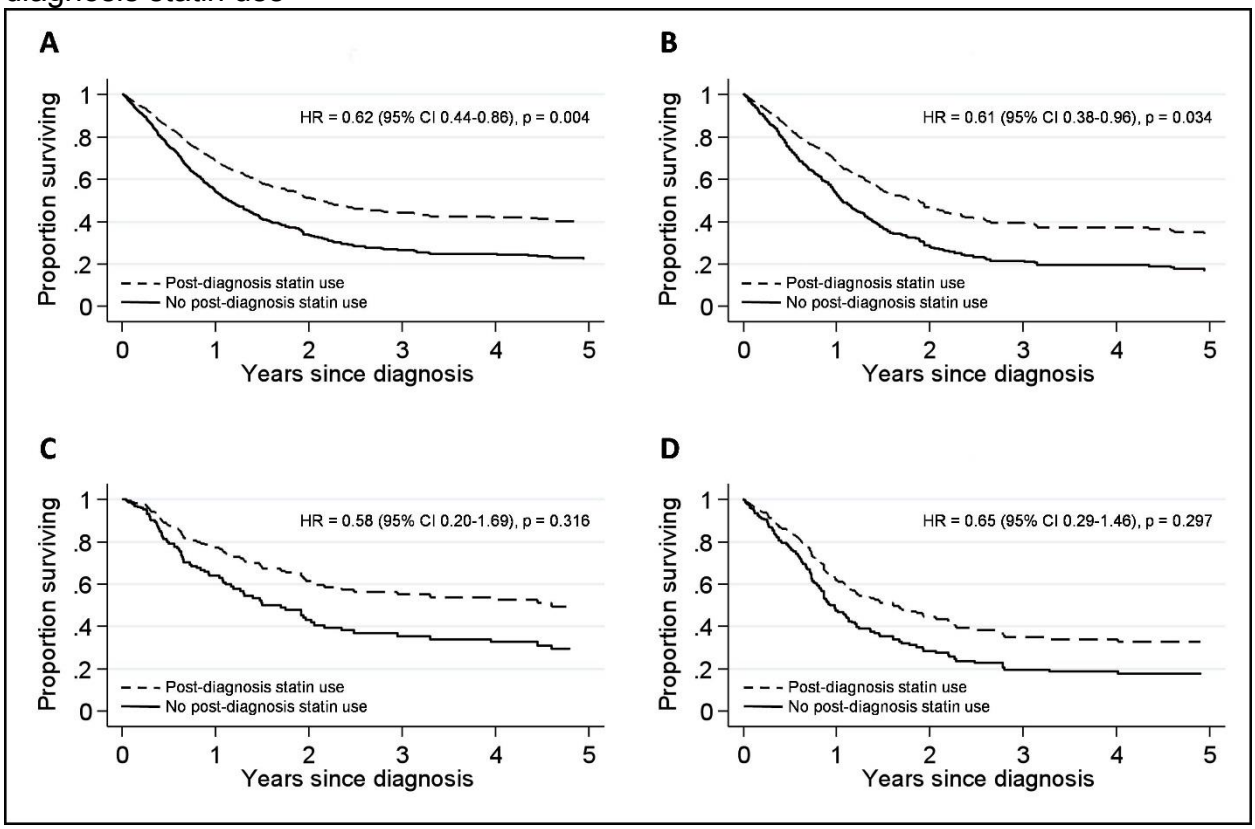
Figure 1. Flow chart of study participants



Abbreviations: EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma

Figure 2. Adjusted time-dependent Cox proportional hazard regression survival curves with hazard ratios for esophageal cancer-specific mortality stratified according to post-diagnosis statin use

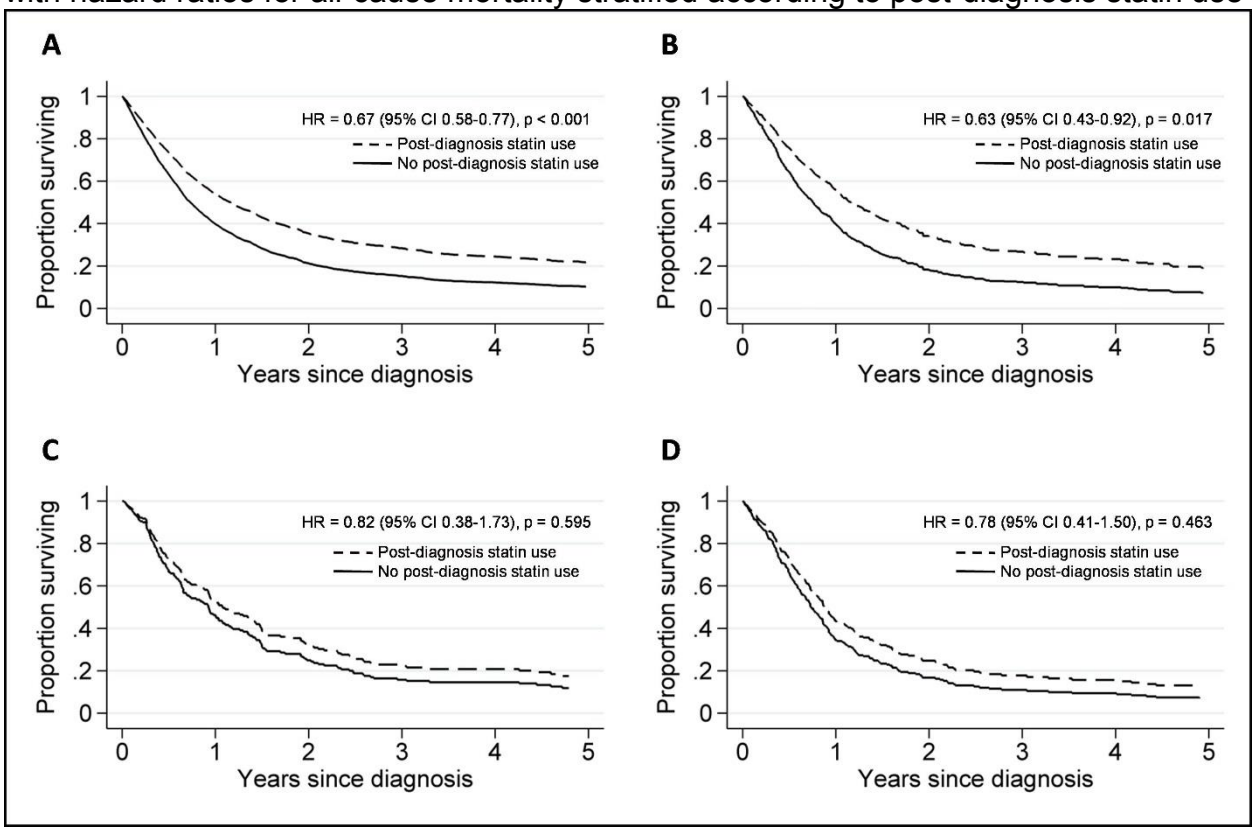


Abbreviations: ACEi, angiotensin conversing enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; NCR, National Cancer Registry; NSAID, non-steroidal anti-inflammatory drugs

A – Total esophageal carcinoma cases linked to NCR (n = 1222)
B – Esophageal adenocarcinoma (n=470)
C – Esophagogastric junctional adenocarcinoma (n=184)
D – Esophageal squamous cell carcinoma (n = 267)
All adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, pre-diagnosis statin use, post-diagnosis use of aspirin, beta-blockers, ACEi/ARBs and NSAIDs

Only cases with complete body mass index and smoking data included

Figure 3. Adjusted time-dependent Cox proportional hazard regression survival curves with hazard ratios for all-cause mortality stratified according to post-diagnosis statin use



Abbreviations: ACEi, angiotensin conversing enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drugs

A – Total esophageal carcinoma cases (n = 3595)
B – Esophageal adenocarcinoma (n=470)
C – Esophagogastric junctional adenocarcinoma (n=184)
D – Esophageal squamous cell carcinoma (n = 267)
A adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, pre-diagnosis statin use, post-diagnosis use of aspirin, beta-blockers, ACEi/ARBs and NSAIDs

B, C, D adjusted for above including surgery

Only cases with complete body mass index and smoking data included

Table 1. Baseline demographic and clinical characteristics of the cohort and stratified by histological subtype and site

Characteristics	Total EC (n=4445)	EAC (n=602)	EGJA (n=221)	ESCC (n=342)
Age (years), mean (SD)	70.8 (11.5)	70.7 (11.3)	68.3 (11.6)	71.8 (12.1)
Male gender, n (%)	2913 (65.5)	468 (77.7)	171 (77.4)	136 (39.8)
Smoking status, n (%)				
Ever	2701 (64.3)	348 (62.0)	127 (60.2)	187 (59.2)
Unknown[1]	244 (5.5)	41 (6.8)	10 (4.5)	26 (7.6)
Body mass index (kg/m^2), n (%)				
< 25	1460 (40.2)	168 (35.0)	58 (31.4)	160 (59.0)
≥ 25 < 30	1435 (39.5)	215 (44.8)	76 (41.1)	80 (29.5)
≥ 30	737 (20.3)	97 (20.2)	51 (27.6)	31 (11.4)
Unknown[1]	813 (18.3)	122 (20.3)	36 (16.3)	71 (20.8)
Comorbidities, n (%)				
Diabetes mellitus	347 (7.8)	52 (8.6)	17 (7.7)	18 (5.3)
Cardiovascular diseases	771 (17.3)	99 (16.4)	28 (12.7)	57 (16.7)
Esophageal cancer treatment, n (%)				
Surgery	973 (21.9)	196 (32.6)	98 (44.3)	92 (26.9)
Chemotherapy	325 (7.3)	146 (24.3)	60 (27.1)	68 (19.9)
Radiotherapy	231 (5.2)	88 (14.6)	9 (4.1)	78 (22.8)
Median survival, months (IQR)	9.2 (3.7-23.2)	9.6 (4.0-23.3)	10.6 (4.2-24.8)	8.6 (4.0-18.7)
Prior medication use				
Statin prescription, n (%)	908 (20.4)	101 (16.8)	30 (13.6)	39 (11.4)
Aspirin prescription, n (%)	998 (22.5)	130 (21.6)	44 (19.9)	74 (21.6)
Beta-blocker prescription, n (%)	685 (15.4)	96 (15.9)	36 (16.3)	51 (14.9)
ACEi or ARB prescription, n (%)	947 (21.3)	117 (19.4)	31 (14.0)	58 (17.0)
NSAID prescription, n (%)	391 (8.8)	51 (8.5)	16 (7.2)	29 (8.5)
Post diagnosis medication use				
Statin prescription, n (%)	830 (18.7)	104 (17.3)	35 (15.8)	31 (9.1)
Aspirin prescription, n (%)	839 (18.9)	116 (19.3)	39 (17.6)	48 (14.0)
Beta-blocker prescription, n (%)	709 (16.0)	99 (16.4)	32 (14.5)	43 (12.6)
ACEi or ARB prescription, n (%)	889 (20.0)	109 (18.1)	38 (17.2)	33 (9.6)
NSAID prescription, n (%)	793 (17.8)	128 (21.3)	41 (18.6)	65 (19.0)

Abbreviations: ACEi, angiotensin conversing inhibitor; ARB, angiotensin receptor blocker; EC, esophageal cancer; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NSAID, non-steroidal anti-inflammatory drugs;

[1]Percentages presented for unknown categories reflect overall proportion of missing data for the relevant covariate; while percentages presented for known categories refer to complete data only

Table 2. Baseline demographic and clinical characteristics of the whole cohort stratified by statin use

Characteristics	No pre-diagnostic statin use (n=3537)	Pre-diagnostic statin use (n=908)	p-value	No Post-diagnostic statin use (n=3615)	Post-diagnostic statin use (n=830)	p-value
Age (years), mean (SD)	70.4 (12.0)	72.3 (9.3)	<0.001	70.7 (11.9)	71.3 (9.2)	0.137
Male gender, n (%)	2249 (63.6)	664 (73.1)	<0.001	2291 (63.4)	622 (74.9)	<0.001
Smoking status, n (%)						
Ever	2037 (61.6)	664 (74.4)	<0.001	2102 (62)	599 (73.7)	<0.001
Unknown n[1]	229 (6.5)	15 (1.7)		227 (6.3)	17 (2.0)	
Body mass index (kg/m^2), n (%)						
< 25	1202 (43.1)	258 (30.7)		1246 (43.3)	214 (28.4)	
≥ 25 < 30	1085 (38.9)	350 (41.7)		1109 (38.5)	326 (43.2)	
≥ 30	505 (18.1)	232 (27.6)	<0.001	523 (18.2)	214 (28.4)	<0.001
Unknown n[1]	745 (21.1)	68 (7.5)		737 (20.4)	76 (9.2)	
Comorbidities, n (%)						
Diabetes Mellitus	180 (5.1)	167 (18.4)	<0.001	236 (6.5)	111 (13.4)	<0.001
Cardiovascular diseases	419 (11.8)	352 (38.8)	<0.001	491 (13.6)	280 (33.7)	<0.001
Esophageal cancer treatment, n (%)						
Surgery	814 (23.0)	159 (17.5)	<0.001	766 (21.2)	207 (24.9)	0.018
Chemotherapy	282 (8.0)	43 (4.7)	0.323	280 (21.4)	45 (20.5)	0.786
Radiotherapy	202 (5.7)	29 (3.2)	0.265	203 (15.5)	28 (12.8)	0.302
Median survival, months (IQR)	9.2 (3.7-23.3)	9.5 (4.0-23.1)	0.913	8.1 (3.3-20.0)	14.9 (7.1-52.3)	<0.001
Prior medication use						
Statin prescription, n (%)	0 (0)	908 (100)	N/A	262 (7.2)	646 (77.8)	<0.001
Aspirin prescription, n (%)	470 (13.3)	528 (58.1)	<0.001	572 (15.8)	426 (51.3)	<0.001
Beta-blocker prescription, n (%)	371 (10.5)	314 (34.6)	<0.001	417(11.5)	268 (32.3)	<0.001
ACEi or ARB prescription, n (%)	483 (13.7)	464 (51.1)	<0.001	567 (15.7)	380 (45.8)	<0.001
NSAID prescription, n (%)	296 (8.4)	95 (10.5)	0.047	306 (8.5)	85 (10.2)	0.103
Post diagnosis medication use						
Statin prescription, n (%)	184 (5.2)	646 (71.1)	<0.001	0 (0)	831 (100)	NA
Aspirin prescription, n (%)	456 (12.9)	383 (42.2)	<0.001	390 (10.8)	449 (54.1)	<0.001
Beta-blocker prescription, n (%)	419 (11.8)	290 (31.9)	<0.001	385 (10.7)	324 (39.0)	<0.001
ACEi or ARB prescription, n (%)	493 (13.9)	396 (43.6)	<0.001	437 (12.1)	452 (54.5)	<0.001
NSAID prescription, n (%)	635 (18.0)	158 (17.4)	0.698	598 (16.5)	195 (23.5)	<0.001

Abbreviations: ACEi, angiotensin conversing inhibitor; ARB, angiotensin receptor blocker; EC, esophageal cancer; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NSAID, non-steroidal anti-inflammatory drugs;

[1]Percentages presented for unknown categories reflect overall proportion of missing data for the relevant covariate; while percentages presented for known categories refer to complete data only

Table 3. Esophageal cancer-specific and all-cause mortality according to post-diagnostic use of statins

Cohort	Statin exposure	Number of patients, n (%)	Person-Years	Mortality rate (95% CI) (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p for interaction[3]
EC-specific mortality							
Total EC	No post-diagnosis statin use	1311 (85.7)	1848.3	38.9 (36.2-41.9)	1.00 (reference)	1.00 (reference)	
(n=1530)	Post-diagnosis statin use	219 (14.3)	426.8	20.1 (16.3-24.9)	0.71 (0.57-0.89)	0.62 (0.44-0.86)[1]	0.817
EAC	No post-diagnosis statin use	498 (82.7)	728.6	41.5 (37.0-46.4)	1.00 (reference)	1.00 (reference)	
(n = 602)	Post-diagnosis statin use	104 (17.3)	237.4	19.8 (14.9-26.4)	0.70 (0.51-0.96)	0.61 (0.38-0.96)[1]	0.374
EGJA	No post-diagnosis statin use	186 (84.2)	303.1	42.3 (36.6-48.8)	1.00 (reference)	1.00 (reference)	
(n = 221)	Post-diagnosis statin use	35 (15.8)	66.9	34.6 (21.2-56.5)	0.63 (0.33-1.21)	0.58 (0.20-1.69)[1]	0.062
ESCC	No post-diagnosis statin use	310 (90.6)	440.0	30.7 (25.0-37.6)	1.00 (reference)	1.00 (reference)	
(n = 342)	Post-diagnosis statin use	31 (9.1)	46.2	15 (8.0-27.8)	1.08 (0.65-1.81)	0.65 (0.29-1.46)[1]	0.756
All-cause mortality							
Total EC	No post-diagnosis statin use	3615 (81.3)	4905.9	62.2 (60.0-64.5)	1.00 (reference)	1.00 (reference)	
(n=4445)	Post-diagnosis statin use	830 (18.7)	1379.5	43.7 (40.4-47.3)	0.82 (0.75-0.89)	0.67 (0.58-0.77)[2]	0.599
EAC	No post-diagnosis statin use	498 (82.7)	728.6	60.7 (55.3-66.6)	1.00 (reference)	1.00 (reference)	
(n = 602)	Post-diagnosis statin use	104 (17.3)	237.4	32.0 (25.6-40.1)	0.75 (0.59-0.96)	0.63 (0.43-0.92)[1]	0.290
EGJA	No post-diagnosis statin use	186 (84.2)	303.1	61.8 (54.9-69.6)	1.00 (reference)	1.00 (reference)	
(n = 221)	Post-diagnosis statin use	35 (15.8)	66.9	54.1 (36.5-80.0)	0.80 (0.51-1.24)	0.82 (0.38-1.73)[1]	0.418
ESCC	No post-diagnosis statin use	311 (90.9)	440.0	54.8 (47.0-63.8)	1.00 (reference)	1.00 (reference)	
(n = 342)	Post-diagnosis statin use	31 (9.1)	46.2	34.4 (22.9-51.8)	1.12 (0.74-1.68)	0.78 (0.41-1.50)[1]	0.751

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin conversing enzyme inhibitor; EC, esophageal cancer; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NSAID, non-steroidal anti-inflammatory drugs

[1]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, pre-diagnosis statin use, post-diagnosis use of aspirin, beta-blockers, NSAIDs, and ACEi/ARBs

[2]Adjusted for [1] except surgery

[3]p for interaction between pre and post-diagnosis statin use on survival

Table 4. Dose-response associations between statins use and risk of esophageal cancer-specific and all-cause mortality

Statin exposure	Number of patients, n (%)	Person-Years	Mortality rate (95% CI) (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
EC-specific mortality					
Post-diagnosis statin use[3]					
No statin use	1311 (85.69)	1848.3	38.9 (36.2-41.9)	1.00 (reference)	1.00 (reference)
Low dose statin use[4]	118 (7.71)	245.1	18.8 (14.1-25.1)	0.70 (0.52-0.95)	0.56 (0.38-0.83)[1]
High dose statin use[4]	101 (6.6)	181.7	22 (16.1-30.0)	0.73 (0.53-1.00)	0.69 (0.46-1.03)[1]
P for trend				0.007	0.029
Pre-diagnosis statin use[5]					
No statin use	1301 (85.0)	1980.6	34.8 (32.3-37.5)	1.00 (reference)	1.00 (reference)
Low dose statin use[4]	149 (9.7)	232.8	42.4 (33.9-53.1)	1.08 (0.85-1.36)	0.90 (0.68-1.19)[1]
High dose statin use[4]	80 (5.2)	61.7	34.5 (25.2-47.2)	0.89 (0.65-1.23)	0.92 (0.64-1.33)[1]
P for trend				0.770	0.486
≥ 1 < 224 DDD[6]	146 (9.5)	191.2	36.6 (29.0-46.3)	0.97 (0.76-1.24)	0.89 (0.67-1.20)[1]
≥ 224 DDD[6]	83 (5.4)	103.2	44.6 (33.4-59.5)	1.07 (0.79-1.44)	0.99 (0.70-1.39)[1]
P for trend				0.820	0.718
All-cause mortality					
Post-diagnosis statin use[3]					
No statin use	3615 (81.3)	4905.9	62.2 (60.0-64.5)	1.00 (reference)	1.00 (reference)
Low dose statin use[4]	379 (8.5)	691.4	39.5 (35.1-44.5)	0.80 (0.70-0.90)	0.64 (0.54-0.75)[2]
High dose statin use[4]	451 (10.2)	688	48.0 (43.1-53.4)	0.83 (0.74-0.93)	0.70 (0.60-0.82)[2]
P for trend				<0.001	<0.001
Pre-diagnosis statin use[5]					
No statin use	3537 (79.6)	5128.2	56.8 (54.8-58.9)	1.00 (reference)	1.00 (reference)
Low dose statin use[4]	463 (10.4)	570.5	66.6 (60.2-73.7)	1.06 (0.95-1.18)	0.90 (0.80-1.02)[2]
High dose statin use[4]	445 (10.0)	586.6	61.7 (55.7-68.4)	0.95 (0.86-1.07)	0.83 (0.73-0.94)[2]
P for trend				0.706	0.003
≥ 1 < 224 DDD[6]	463 (10.4)	581.2	65.6 (59.3-72.5)	1.04 (0.94-1.16)	0.91 (0.80-1.02)[2]
≥ 224 DDD[6]	445 (10.0)	575.9	62.7 (56.5-69.5)	0.97 (0.87-1.08)	0.82 (0.72-0.93)[2]
P for trend				0.789	0.002

Abbreviations: ACEi, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DDD, defined daily dose; EC, esophageal cancer;

[1]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, aspirin, beta-blockers, ACEi/ARB use and NSAIDs

[2]Adjusted for [1] except surgery

[3]Dose categories determined using the first statin dose prescribed post-diagnosis

[4]Low dose equivalent to ≤ 20mg Simvastatin; high dose equivalent to > 20mg Simvastatin

[5]Measured between 6-18 months prior to diagnosis of EC

[6]Cut off of 224 DDDs selected as the median value in whole cohort

Supplementary table 1. Esophageal cancer-specific mortality according to pre-diagnostic use of statins

Cohort	Statin exposure	Number of patients, n (%)	Person-Years	Mortality rate (95% CI) (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
EC-specific mortality						
Total EC	No pre-diagnosis statin use	1301 (85.0)	1980.6	34.8 (32.3-37.5)	1.00 (reference)	1.00 (reference)
(n=1530)	Pre-diagnosis statin use	229 (15.0)	294.5	39.4 (32.8-47.3)	1.01 (0.83-1.22)	0.91 (0.71-1.16)
EAC	No pre-diagnosis statin use	501 (83.2)	817.6	35.5 (31.6-39.8)	1.00 (reference)	1.00 (reference)
(n = 602)	Pre-diagnosis statin use	101 (16.8)	148.3	39.8 (30.8-51.3)	1.07 (0.81-1.41)	0.81 (0.55-1.20)
EGJA	No pre-diagnosis statin use	191 (86.4)	326.7	27.2 (22.1-33.5)	1.00 (reference)	1.00 (reference)
(n = 221)	Pre-diagnosis statin use	30 (13.6)	43.3	32.3 (19.2-54.6)	0.96 (0.55-1.69)	0.82 (0.40-1.69)
ESCC	No pre-diagnosis statin use	303 (88.6)	444.2	39.8 (34.4-46.2)	1.00 (reference)	1.00 (reference)
(n = 342)	Pre-diagnosis statin use	39 (11.4)	42.0	59.6 (40.3-88.2)	1.21 (0.79-1.84)	1.08 (0.65-1.79)
All-cause mortality						
Total EC	No pre-diagnosis statin use	3543 (79.6)	5128.2	56.8 (54.8-58.9)	1.00 (reference)	1.00 (reference)
(n=4445)	Pre-diagnosis statin use	908 (20.5)	1157.1	64.1 (59.7-68.9)	1.00 (0.93-1.09)	0.86 (0.78-0.95)
EAC	No pre-diagnosis statin use	501 (83.2)	817.6	52.6 (47.8-57.8)	1.00 (reference)	1.00 (reference)
(n = 602)	Pre-diagnosis statin use	101 (16.8)	148.3	59.3 (48.1-73.1)	1.08 (0.86-1.35)	0.77 (0.56-1.06)
EGJA	No pre-diagnosis statin use	191 (86.4)	326.7	50.2 (43.1-58.5)	1.00 (reference)	1.00 (reference)
(n = 221)	Pre-diagnosis statin use	30 (13.6)	43.3	57.8 (39.0-85.5)	0.96 (0.63-1.46)	0.72 (0.42-1.24)
ESCC	No pre-diagnosis statin use	303 (88.6)	444.2	59.0 (52.3-66.6)	1.00 (reference)	1.00 (reference)
(n = 342)	Pre-diagnosis statin use	39 (11.4)	42.0	83.4 (59.9-116.2)	1.18 (0.83-1.68)	0.95 (0.62-1.46)

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin conversing enzyme inhibitor; EC, esophageal cancer; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NSAID, non-steroidal anti-inflammatory drugs

Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, aspirin, beta-blockers, ACEi/ARB use and NSAIDs

Supplementary table 2. Mortality according to first statin type used post-diagnosis of esophageal carcinoma

Statin type	Number of patients, n (%)	Person-Years	Mortality rate (95% CI) (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
EC-specific mortality					
No statin	1311 (85.69)	1703.91	42.2 (39.2-45.4)	1.00 (reference)	1.00 (reference)
Simvastatin	128 (8.37)	381.4	11.8 (8.8-15.8)	0.67 (0.50-0.91)	0.61 (0.41-0.89)[1]
pravastatin	20 (1.31)	29.8	33.6 (18.1-62.5)	1.00 (0.54-1.87)	1.09 (0.56-2.12)[1]
Atorvastatin	63 (4.12)	137.1	21.9 (15.3-31.3)	0.81 (0.56-1.17)	0.56 (0.35-0.90)[1]
rosuvastatin	3 (0.2)	8.7	0	NA	NA
fluvastatin	5 (0.33)	14.3	7 (1-49.8)	0.23 (0.03-1.63)	0.24 (0.03-1.76)[1]
All-cause mortality					
No statin	3615 (81.33)	4592.4	66.5 (64.1-68.9)	1.00 (reference)	1.00 (reference)
Simvastatin	516 (11.61)	1066.3	34.4 (31.1-38.1)	0.83 (0.75-0.93)	0.68 (0.58-0.79)[2]
pravastatin	57 (1.28)	132.6	30.9 (22.8-42)	0.69 (0.51-0.94)	0.58 (0.41-0.82)[2]
Atorvastatin	214 (4.81)	397.6	42.3 (36.3-49.2)	0.87 (0.74-1.02)	0.70 (0.58-0.85)[2]
rosuvastatin	32 (0.72)	56.4	39 (25.7-59.2)	0.68 (0.45-1.04)	0.63 (0.40-0.99)[2]
fluvastatin	11 (0.25)	40.0	12.5 (5.2-30)	0.36 (0.15-0.88)	0.33 (0.14-0.80)[2]

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin conversing enzyme inhibitor; EC, esophageal cancer; NSAID, non-steroidal anti-inflammatory drugs

[1]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, surgery, diabetes, aspirin, beta-blockers, ACEi/ARB use and NSAIDs

[2]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, aspirin, beta-blockers, ACEi/ARB use and NSAIDs

Supplementary table 3. Sensitivity analyses for post-diagnostic statin use and esophageal cancer-specific and all-cause mortality

Supplementary table 3. Sensitivity analyses for post-diagnostic statin use and esophageal cancer-specific and all-cause mortality

	Statin users		Non users			
Sesnitivity analyses (post-diagnostic statin use vs. non-use)	Number of patients, n (%)	Mortality rate (95% CI) (per 100 person-years)	Number of patients, n (%)	Mortality rate (95% CI) (per 100 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Total EC						
Esophageal cancer-specific mortality						
Adjusted for surgery (main analysis)	219 (14.3)	15.1 (12.2-18.6)	1311 (85.7)	42.2 (39.2-45.4)	0.71 (0.57-0.89)	0.62 (0.44-0.86)[1]
Adjusted for surgery, chemotherapy and radiotherapy	219 (14.3)	15.1 (12.2-18.6)	1311 (85.7)	42.2 (39.2-45.4)	0.71 (0.57-0.89)	0.61 (0.44-0.85)[3]
Not adjusted for surgery	219 (14.3)	15.1 (12.2-18.6)	1311 (85.7)	42.2 (39.2-45.4)	0.71 (0.57-0.89)	0.65 (0.47-0.90)[2]
All patients surviving longer than three months from diagnosis	201 (16.7)	19.1 (15.3-23.7)	1001 (83.3)	30 (27.6-32.6)	0.71 (0.57-0.89)	0.84 (0.58-1.20)[1]
Exposure to precriptions lagged by three months	191 (12.5)	20.2 (16.2-25.3)	1339 (87.5)	38.4 (35.7-41.3)	0.84 (0.66-1.07)	0.66 (0.41-1.07)[1]
All prescriptions in the final three months of follow -up ignored	191 (12.5)	13.5 (10.8-16.9)	1339 (87.5)	42.6 (39.6-45.8)	0.64 (0.50-0.81)	0.60 (0.43-0.84)[1]
All-cause mortality						
Adjusted for surgery	830 (18.7)	43.7 (40.4-47.3)	3615 (81.3)	62.2 (60-64.5)	0.82 (0.75-0.89)	0.66 (0.58-0.76)[1]
Adjusted for surgery, chemotherapy and radiotherapy	830 (18.7)	43.7 (40.4-47.3)	3615 (81.3)	62.2 (60-64.5)	0.82 (0.75-0.89)	0.66 (0.58-0.76)[3]
Not adjusted for surgery (main analysis)	830 (18.7)	43.7 (40.4-47.3)	3615 (81.3)	62.2 (60-64.5)	0.82 (0.75-0.89)	0.67 (0.58-0.77)[2]
All patients surviving longer than three months from diagnosis	764 (21.8)	32 (29.4-34.8)	2749 (78.3)	49.4 (47.4-51.5)	0.88 (0.80-0.96)	0.70 (0.60-0.82)[2]
Exposure to precriptions lagged by three months	723 (16.3)	42.4 (38.9-46.3)	3722 (83.7)	61.8 (59.7-64.0)	0.92 (0.83-1.01)	0.85 (0.74-0.98)[2]
All prescriptions in the final three months of follow -up ignored	723 (16.3)	30.4 (27.9-33.2)	3722 (83.7)	68.1 (65.7-70.5)	0.67 (0.61-0.74)	0.54 (0.47-0.63)[2]
EAC						
Esophageal cancer-specific mortality						
Adjusted for surgery (main analysis)	104 (17.3)	19.8 (14.9-26.4)	498 (82.7)	41.5 (37-46.4)	0.70 (0.51-0.96)	0.61 (0.38-0.96)[1]
Adjusted for surgery, chemotherapy and radiotherapy	104 (17.3)	19.8 (14.9-26.4)	498 (82.7)	41.5 (37-46.4)	0.70 (0.51-0.96)	0.61 (0.38-0.98)[3]
Not adjusted for surgery	104 (17.3)	15.5 (11.6-20.6)	498 (82.7)	41.5 (37-46.4)	0.70 (0.51-0.96)	0.60 (0.37-0.98)[2]
All patients surviving longer than three months from diagnosis	98 (20.3)	19.8 (14.9-26.4)	385 (79.7)	32.1 (28.2-36.5)	0.78 (0.56-1.08)	0.83 (0.50-1.36)[1]
Exposure to precriptions lagged by three months	93 (15.5)	19.7 (14.6-26.7)	509 (84.6)	40.8 (36.5-45.6)	0.81 (0.58-1.13)	0.47 (0.23-0.98)[1]
All prescriptions in the final three months of follow -up ignored	93 (15.5)	14.1 (10.4-19.0)	509 (84.6)	46 (41.1-51.4)	0.63 (0.45-0.87)	0.53 (0.32-0.85)[1]
All-cause mortality						
Adjusted for surgery (main analysis)	104 (17.3)	32 (25.6-40.1)	498 (82.7)	60.7 (55.3-66.6)	0.75 (0.59-0.96)	0.63 (0.43-0.92)[1]
Adjusted for surgery, chemotherapy and radiotherapy	104 (17.3)	32 (25.6-40.1)	498 (82.7)	60.7 (55.3-66.6)	0.75 (0.59-0.96)	0.65 (0.44-0.94)[3]
Not adjusted for surgery	104 (17.3)	32 (25.6-40.1)	498 (82.7)	60.7 (55.3-66.6)	0.75 (0.59-0.96)	0.63 (0.43-0.94)[2]
All patients surviving longer than three months from diagnosis	98 (20.3)	23.1 (18.3-29.2)	385 (79.7)	50.7 (45.6-56.5)	0.80 (0.62-1.04)	0.73 (0.48-1.09)[1]
Exposure to precriptions lagged by three months	93 (15.5)	30.5 (23.9-38.9)	509 (84.6)	60.2 (54.9-66)	0.82 (0.62-1.07)	0.59 (0.40-0.88)[1]
All prescriptions in the final three months of follow -up ignored	93 (15.5)	21.8 (17.1-27.8)	509 (84.6)	67.9 (61.9-74.4)	0.63 (0.49-0.82)	0.49 (0.33-0.73)[1]

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin conversing enzyme inhibitor; EC, esophageal cancer; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NA, not applicable; NSAID, non-steroidal anti-inflammatory drugs

[1]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, pre-diagnosis statin use, aspirin, beta-blockers, ACEi/ARB and NSAID use

[2]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, pre-diagnosis statin use, aspirin, beta-blockers, ACEi/ARB and NSAID use

[3]Adjusted for age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, chemotherapy, radiotherapy, pre-diagnosis statin use, aspirin, beta-blockers, ACEi/ARB and NSAID use

Supplementary figure 1. Kaplan-Meier plot of time to first statin prescription following diagnosis of esophageal carcinoma among post-diagnosis statin users