Statin use and survival in 16 098 patients with non-Hodgkin lymphoma or chronic lymphocytic leukaemia treated in the rituximab era

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Introduction

Statins are among the most widely prescribed medications in the Western world, used to treat hypercholesterolaemia. In Sweden statins were used by 31% of the population aged ≥60 years in 2018.1 and in the USA by 26% of adults ≥40 years in 2012.2 Statins inhibit the rate-limiting enzyme of the mevalonate pathway, thereby reducing synthesis of cholesterol and isoprenoids that affect function of Ras family and other oncogenic proteins.3 Pro-apoptotic, anti-angiogenic, and immunomodulatory effects of statins have also been described in vitro, as has modulation of B-cell leukaemia/lymphoma 2 (BCL2) proteins, which promote cell survival in multiple cancer types.4–6 Many epidemiological studies support these in vitro data, suggesting an anti-cancer effect in several cancers including the lymphoproliferative malignancy multiple myeloma.7–11

Summary

Statin use has been associated with reduced mortality from several cancers but also suggested, in vitro, to diminish the effectiveness of lymphoma treatments including rituximab. The present study aimed to assess the association of statin use with mortality in patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). We identified all incident NHLs and CLLs in Sweden from 2007 to 2013 with subtype information in the Swedish Lymphoma and Cancer Registers. Using Cox regression, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of pre- or post-diagnosis statin use (yes/no, intensity) with lymphoma-specific, cardiovascular, or all-cause mortality; and for follicular lymphoma (FL) by initial treatment strategy (active/watch-and-wait). Among 16 098 incident NHL/CLL patients, 20% used statins at diagnosis. Pre- and post-diagnosis statin use, and statin intensity were not consistently associated with any mortality outcome in patients with NHL, overall or for any subtype. For actively treated patients with FL, statin use did not appear to increase lymphoma-specific mortality (vs. non-users, HR [95% CI] after diagnosis 0.87 [0.45–1.67]). For CLL, statin use was associated with all-cause and cardiovascular but not consistently with lymphoma-specific mortality. In conclusion, statin use was not associated with improved lymphoma survival but appears safe to use during lymphoma treatment.

Keywords: statins, lymphoma, survival, prognosis.
the other hand, given their wide use, any negative effect of statins on rituximab treatment would have huge implications. Published epidemiological studies have included selected patients from specialised centres or have had limited statistical power.\textsuperscript{18–21} In the present study, we aimed to assess statin use in non-Hodgkin lymphoma (NHL) subtypes or CLL in a population-based setting in Sweden and to evaluate implications for rituximab-treated patients by assessing patients with follicular lymphoma (FL) separately by treatment strategy (active vs. watch-and-wait).

**Patients and methods**

**Study population**

We identified all incident NHL and CLL patients in Sweden from 1 January 2007 until 31 December 2013 and followed them until death, emigration, or 31 December 2013, whichever came first. We used the Cancer Register to identify patients with CLL and the Swedish Lymphoma Register (SLR) to identify NHL diagnoses other than CLL (Figure S1). The SLR contains detailed NHL subtype classification, as well as patient and disease characteristics such as components of the International Prognostic Index (IPI): age, disease stage, presence of elevated serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group Performance Status (ECOG PS), and presence and specification of any extra-nodal manifestations. The SLR also contains information on lymphoma treatment initiation (i.e. active vs. a watch-and-wait strategy) and type of treatment, if given. The SLR coverage is ~95\% of the Swedish Cancer Register,\textsuperscript{22} to which reporting is mandatory by law. For persons with two or more lymphoma diagnoses during follow-up, only the earliest was included. If two different NHL diagnoses were reported on the same day, we considered them discordant (Figure S1).

We linked the cohort to additional population-based registers for covariate information. We used the longitudinal integration database for health insurance and labour market studies\textsuperscript{23} to obtain socioeconomic data and the Swedish Patient Register\textsuperscript{24} to retrieve information on healthcare utilisation.

**Statin use and concomitant medications**

Data on use of statins and other concomitant medications were retrieved from the Prescribed Drug Register (PDR), which covers all prescriptions dispensed at Swedish pharmacies since July 2005.\textsuperscript{25} All statins marketed in Sweden during the study period were included; statins are not available over-the-counter in Sweden. Patients were considered statin users before diagnosis if they had at least one statin dispensation during the 6-month period before diagnosis, and users after diagnosis if they had at least one statin dispensation during the 6-month period after diagnosis.

To assess statin use at any time during follow-up, we performed a 1:5 matched nested case-control analysis within the cohort. The ‘case’ patients, e.g. those experiencing lymphoma-specific death were matched on lymphoma subtype and time since diagnosis to five ‘controls’, e.g., participants still alive on the case’s date of death (index date). In this analysis, we assessed all statin dispensations from date of lymphoma diagnosis until 6 months before death/index date.

We also characterised statin dose intensity and statin use duration. Based on average mg/day dispensed, statin dose intensity was classified into high-, moderate- and low-intensity therapy according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines;\textsuperscript{26} intensity corresponds to the degree of cholesterol reduction achieved (Table SI). In the nested case-control analysis, we calculated the cumulative duration of statin use from date of the first post-diagnosis dispensation to 6 months after the last.

We also retrieved data from the PDR on use of anticoagulants, β-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers and diabetes medications, to adjust for potential confounding by comorbidities. Further, we collected dispensations of proton-pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs) (Table SII), which are commonly used by frequent utilisers of healthcare services, for use in sensitivity analyses to assess healthy user bias in statin users.

**Lymphoma-specific, cardiovascular and all-cause mortality**

Information on deaths was retrieved from the Cause-of-Death Register. The primary outcome was lymphoma-specific death, which was defined as deaths listing any NHL/CLL International Classification of Diseases (ICD) code as the main cause (Table SIII). In a random subset of 103 patients with NHL from the SLR, we performed a validation study of lymphoma-specific mortality in the Cause-of-Death Register. Using medical records as the ‘gold standard’, the positive predictive value (PPV) was calculated as described previously.\textsuperscript{11,27,28} Cardiovascular disease (CVD) and all-cause mortality were analysed as secondary outcomes.

**Statistical analysis**

In the cohort analysis, we used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95\% confidence intervals (CIs) for risk of lymphoma-specific, cardiovascular or all-cause mortality for statin users compared to non-users. Models were estimated for NHL overall and separately for diffuse large B-cell lymphoma (DLBCL), FL, the latter further subclassified as treated and non-treated FL at diagnosis, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), T/natural killer (NK)-cell
lymphomas, lymphoplasmacytic lymphomas/Waldenström macroglobulinaemia (LPL) and discordant and other lymphomas. Because CLL is not included in the SLR and therefore lacked some covariate data, CLL was analysed separately. All models were adjusted for age at diagnosis (<50, 50–60, 60–70, 70–80, ≥80 years), sex, year of diagnosis, highest education level (elementary school, high school, college/university), and comorbidity (concomitant medication vs. none, based on the medications previously mentioned). Models for all NHL and subtypes other than CLL were also adjusted for age- and region-specific IPI and treatment status at diagnosis (initial active treatment vs. not). In analyses of statin use before diagnosis, follow-up started at diagnosis of NHL/CLL. In analyses of statin use after diagnosis, follow-up started 6 months after the exposure measurement period (using a 6-month exposure lag) to attenuate any reverse causation due to discontinuation of prophylactic medications (such as statins) near end of life. Analyses of statin dose intensity and duration of use were performed only for all NHL and CLL, not for individual subtypes. We performed dose intensity trend tests among statin users. We assessed potential healthy user bias with sensitivity analyses further adjusting for use of PPIs and SSRIs and number of outpatient specialist doctor visits during the 3-year period before diagnosis. In an additional sensitivity analysis, we excluded patients aged <40 years given their expected low frequency of statin use.

In the nested case-control analyses, we used multivariable conditional logistic regression models conditioned on the matching factors and adjusted for the same covariates as the cohort analyses to estimate odds ratios (ORs) and 95% CIs of lymphoma-specific mortality for statin users compared to non-users. We also calculated ORs for duration of statin use [non-use (reference category), >0–1, >1–2, >2 years] in similarly adjusted models and performed trend tests across the duration categories among users.

Only participants with complete information on all variables were included in the main analyses. All statistical tests were two-sided, and all \( P < 0.05 \) were considered significant. Data preparation and analyses were performed with the Statistical Analysis System (SAS) version 9.3 (SAS Institute, Inc., Cary, NC, USA) and survival analyses with Stata version 14 (StataCorp., College Station, TX, USA). The study was approved by the regional ethics review board at the Karolinska Institute.

Results

Patient characteristics

We identified 16,098 patients diagnosed with NHL \((N = 12,819)\) or CLL \((N = 3,279)\) in Sweden during the study period (Figure S1). The NHLs included 4,130 DLBCL, 1,751 FL (989 actively treated and 762 followed with a watch-and-wait strategy at diagnosis), 769 MCL, 766 MZL, 952 T/NK-cell lymphomas, 755 LPL and 3696 discordant and other lymphomas. We ascertained 3,040 lymphoma-specific and 608 CVD deaths among a total of 4,743 deaths from any cause during follow-up.

Among all study participants, 3,184 (19.8%) used statins during the 6-month period before diagnosis, and of those 2,370 (74%) continued taking statins during the 6-month period after diagnosis (Table I). Statin users were older at diagnosis, more likely to be male and had a considerably higher usage of all other medications investigated. Most lymphoma-specific characteristics were similar between the groups, but fewer statin users than non-users were asymptomatic at diagnosis (ECOG PS 0, 46% vs. 55%) (Table I).

Statin use (yes/no) and survival

We excluded 814 patients with incomplete data from the main cohort analyses. In adjusted analyses, statin use before diagnosis was not associated with lymphoma-specific mortality in all NHL (HR 0.95, 95% CI 0.85–1.06), CLL (HR 0.91, 95% CI 0.69–1.21) or any other major NHL subtype (Fig. 1A, Table SIV). For post-diagnosis statin use, we observed no association with lymphoma-specific mortality for all NHL (HR 0.93, 95% CI 0.77–1.12), CLL (HR 0.79, 95% CI 0.55–1.12) or most other subtypes. For T/NK-cell lymphoma, we observed a statistically significantly reduced lymphoma-specific mortality (HR 0.42, 95% CI 0.18–0.98) (Fig 1B). Results excluding individuals aged <40 years yielded similar results, i.e. post-diagnosis statin use, all NHL (HR 0.93, 95% CI 0.77–1.13).

In the nested case-control analysis, patients with CLL with statin use at any time during follow-up had a statistically significantly reduced lymphoma-specific mortality (HR 0.59, 95% CI 0.41–0.87) (Fig 1C). Statin use was not associated with lymphoma-specific mortality for any other NHL subtype; the smaller sample size precluded assessment of patients with FL under the watch-and-wait approach (Fig 1C). The sensitivity analyses additionally adjusted for correlates of health service utilisation did not suggest a strong influence of healthy user bias (Table SIV).

In the secondary outcome analyses, there was a statistically significant reduction of CVD mortality for CLL, both for statin users before diagnosis (HR 0.67, 95% CI 0.46–0.96) and after diagnosis (HR 0.51, 95% CI 0.31–0.84) (Table SV). In analyses of all-cause mortality, statin use before diagnosis was statistically significantly associated with reduced all-cause mortality in patients with T/NK-cell lymphomas (HR 0.70, 95% CI 0.50–0.97) and CLL (HR 0.83, 95% CI 0.69–0.99) (Fig. 2A). In CLL, post-diagnosis use also had a significant association (HR 0.73, 95% CI 0.59–0.91) (Fig 2B, Table SVI). Post-diagnosis statin-use patients with FL on watch-and-wait had an increased all-cause mortality (Fig. 2B).

Intensity and duration of statin use and survival

Most statin users received moderate intensity statin therapy as categorised by the ACC/AHA (Table SVII). Statin
Table I. Characteristics of patients diagnosed with first incident non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) from 2007 to 2013 in Sweden by statin use before diagnosis.

| Characteristic                              | No statin use* | Statin use* |
|---------------------------------------------|----------------|-------------|
|                                             | n = 12         | n = 3184    |
| Duration of follow-up, years, median (range)| 2.28 (0.0–7.00) | 1.90 (0.0–7.00) |
| Age at diagnosis, years, median (range)     | 68 (18–105)    | 73 (34–95)  |
| Sex, n (%)                                  |                |             |
| Female                                      | 5704 (44.2)    | 1185 (37.2) |
| Male                                        | 7210 (55.8)    | 1999 (62.8) |
| Education level, n (%)                      |                |             |
| Elementary school                           | 4452 (34.5)    | 1398 (43.9) |
| High school                                 | 5042 (39.0)    | 1135 (35.7) |
| College/university                          | 3226 (25.0)    | 591 (18.6)  |
| Missing                                     | 194 (1.5)      | 60 (1.9)    |
| Major subtypes, n (%)                       |                |             |
| DLBCL                                       | 3257 (25.2)    | 873 (27.4)  |
| FL, treated                                 | 805 (6.2)      | 184 (5.8)   |
| FL, watch and wait                          | 600 (4.6)      | 162 (5.1)   |
| MCL                                         | 592 (4.6)      | 177 (5.6)   |
| MZL                                         | 642 (5.0)      | 124 (3.9)   |
| T/NK-cell                                   | 801 (6.2)      | 151 (4.7)   |
| LPL                                         | 637 (4.9)      | 118 (3.7)   |
| Discordant                                  | 252 (1.9)      | 69 (2.2)    |
| Other                                       | 2802 (21.7)    | 573 (18.0)  |
| CLL                                         | 2526 (19.6)    | 753 (23.7)  |
| Clinical characteristics**                  |                |             |
| Stage, n (%)                                |                |             |
| I–II                                        | 2511 (24.2)    | 527 (21.7)  |
| III–IV                                      | 5941 (57.2)    | 1387 (57.1) |
| Primary extra-nodal                         | 1230 (11.8)    | 327 (13.5)  |
| Other/missing                               | 706 (6.8)      | 190 (7.8)   |
| ECOG Performance                            |                |             |
| Status, n (%)                               |                |             |
| Asymptomatic                                | 5735 (55.2)    | 1121 (46.1) |
| Symptomatic, ambulatory                     | 2880 (27.7)    | 789 (32.5)  |
| <50% in bed days                            | 723 (7.0)      | 210 (8.6)   |
| >50% in bed days                            | 550 (5.3)      | 162 (6.7)   |
| Bedbound                                    | 266 (2.6)      | 95 (3.9)    |
| Missing                                     | 234 (2.3)      | 54 (2.2)    |
| Bulky disease, n (%)                        |                |             |
| Yes                                         | 1355 (13.0)    | 290 (11.9)  |
| No                                          | 8482 (81.7)    | 2004 (82.4) |
| Unclear/missing                             | 551 (5.3)      | 137 (5.6)   |
| Age-adjusted IPI, n (%)                     |                |             |
| 0–1, <60 years                              | 3189 (30.7)    | 210 (8.6)   |
| 0–1, ≥60 years                              | 3930 (37.8)    | 1248 (51.3) |
| ≥2, <60 years                               | 212 (2.0)      | 20 (0.8)    |
| ≥2, ≥60 years                               | 2410 (23.2)    | 786 (32.3)  |
| Unclear/missing                             | 647 (6.2)      | 167 (6.9)   |
| B-symptoms at diagnosis, n (%)              |                |             |

Table I. (Continued)

| Characteristic                              | No statin use* | Statin use* |
|---------------------------------------------|----------------|-------------|
|                                             | n = 12         | n = 3184    |
| LDH at diagnosis, n (%)                     |                |             |
| Elevated                                    | 4208 (40.5)    | 1099 (41.5) |
| Normal                                      | 5547 (53.4)    | 1278 (52.6) |
| Not taken/missing                           | 635 (6.1)      | 144 (5.9)   |
| No. of outpatient specialist doctors’ visits during the 3 years pre-diagnosis, median (range) | 4 (0–484) | 6 (0–290) |
| Other medications before diagnosis**, n (%) |                |             |
| β-blockers                                  | 2407 (18.6)    | 1732 (54.4) |
| Diuretics                                   | 2267 (17.6)    | 1126 (35.4) |
| ACE inhibitors                              | 2454 (19.0)    | 1778 (55.8) |
| Calcium blockers                            | 1432 (11.1)    | 929 (29.2)  |
| Anticoagulants                              | 2661 (20.6)    | 2183 (68.6) |
| Diabetes medications                       | 667 (5.2)      | 780 (24.5)  |
| PPIs                                        | 2370 (18.4)    | 879 (27.6)  |
| SSRIs                                       | 834 (6.5)      | 284 (8.9)   |

ACE, angiotensin-converting enzyme; CLL, chronic lymphocytic leukaemia; DLBCL, Diffuse Large B-Cell Lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, Follicular Lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LPCL, lymphoplasmacytic lymphoma; MCL, Mantle Cell Lymphoma; MZL, Marginal Zone Lymphoma; NK Cell, natural killer cell; PPIs, proton-pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

*Note: categorical variables presented as counts and percentage, n (%); continuous variables as median (range).

**Information available only in the Swedish Lymphoma Register, percentage presented as part of total lymphoma patients except CLL (12 819 patients, 2691 lymphoma-specific deaths).

***Numbers may add to >100% because patients can contribute to several categories when using several types of medications concomitantly.

Treatment intensity showed no evidence of a dose–response relationship with lymphoma-specific mortality for all NHL or CLL (Table SVII, Fig 3), whereas post-diagnosis statin intensity was significantly inversely associated with all-cause mortality in patients with NHL (multivariable adjusted P_{trend} = 0.001) (Table SVII). Duration of statin use did not show any association with lymphoma-specific mortality for all NHL or CLL in trend tests in the nested case-control sample, but patients with CLL with >2 years statin use had a statistically significantly reduced lymphoma-specific mortality (HR 0.51, 95% CI 0.30–0.86) (Table SVIII).
Validation of lymphoma-specific mortality

In the random subset of 103 lymphoma-specific deaths reviewed for cause-of-death validation, medical records confirmed 94, whereas two deaths were adjudicated as non-lymphoma related and seven had inadequate information, yielding a PPV in evaluable patients of 97.9% (Table SIX).

Discussion

Accumulating preclinical and epidemiological evidence suggests that statins may have anti-cancer effects.3,7 However, for lymphoma the evidence has indicated improved survival for certain NHL subtypes,13 while also raising concern about adverse interaction with the widely used rituximab.
In this population-based study of 16,098 incident cases of NHL/CLL in Sweden 2007–2013, we confirm that statins appear safe to use during lymphoma treatment. In NHL subtype-specific analyses, we saw no reduction in lymphoma-specific mortality for statin-using patients. For CLL, we found no consistent association of statin use with lymphoma-specific mortality across time windows, but a reduction in all-cause mortality for both pre- and post-diagnosis statin use, perhaps driven by the even more pronounced reduction in cardiovascular mortality. In all, we found no clear evidence of improved lymphoma-specific survival for statin-using patients with NHL or CLL.

**Subtype-specific findings**

Non-Hodgkin lymphoma and CLL are heterogeneous diseases for which diagnostics are increasingly driven by immunohistochemical and genetic information. BCL2, nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and other oncogenic mechanisms important in the pathogenesis of certain NHL subtypes are affected by products of the mevalonate pathway, raising the question whether statins, which inhibit the key mevalonate pathway enzyme, could selectively improve survival of those NHL subtypes. A reported association of statin use with improved event-free survival for patients with FL (n = 293 patients) but not for those with DLBCL (n = 228) illustrated the importance of assessing the lymphoma subtypes separately. In contrast, a large clinical trial with 1135 patients with FL on immuno-chemotherapy observed similar treatment response rates and overall survival (OS) regardless of statin use. However, the latter study was restricted to patients with high-risk FL requiring immediate treatment. The present population-based study included 1751 patients with FL with and without lymphoma treatment indication and found a similar lack of clear survival benefit for statin users. Importantly, for the patients with FL starting lymphoma therapy, we did not find evidence of adverse outcome for statin users compared to non-users. The lymphoma treatment administered in these patients almost exclusively included rituximab,
consistent with clinical guidelines that have recommended rituximab for all patients requiring systemic treatment since 2006. Thus, the present findings argue strongly against an adverse effect of statins on rituximab treatment in this real-world FL cohort. Patients with FL followed with a watch-and-wait approach and using statins post-diagnosis had a statistically significant increased all-cause mortality, possibly explained by reverse causation by this group’s excess comorbidity.

For DLBCL, a recent large Canadian population-based study of patients aged ≥66 years at diagnosis of de novo DLBCL or transformed lymphoma and treated with a rituximab-containing regimen, found improved OS (n = 4913 patients). A Korean study found impaired progression-free survival (PFS) and OS of non-germinal centre (non-GC) DLBCL (n = 208) with statin use, a subgroup that we could not evaluate separately due to missing DLBCL subtype information. However, most studies show no association between statin use and DLBCL survival, consistent with our present study.

For CLL, contrary to in vitro studies, clinical studies have not shown a benefit for statin users overall. One study found a prolonged time to first treatment for statin-using patients with CLL without a 17p deletion, and another found a prolonged time to first treatment for statin-using lymphoma-specific mortality in patients with T/NK-cell lymphoma. Little is published with pre- and/or post-diagnosis statin use, and analyses of cardiovascular mortality showed an even more pronounced reduction for statin users. Collectively, we interpret these findings as likely explained by cardiovascular protection rather than a direct effect of statins on CLL progression.

Among the less common NHL subtypes, we had limited statistical power to detect significant associations. We observed a novel finding of significantly decreased lymphoma-specific mortality for statin use at any time during follow-up (the nested case-control analysis) but not for statin use specifically in the 6-month period before/after diagnosis. All-cause mortality in CLL significantly improved with pre- and/or post-diagnosis statin use, and analyses of cardiovascular mortality showed an even more pronounced reduction for statin users. Collectively, we interpret these findings as likely explained by cardiovascular protection rather than a direct effect of statins on CLL progression.

Statin intensity and duration of statin use
When assessing association of statin treatment intensity, we found a dose–response relationship with all-cause but not lymphoma-specific mortality. This may partly be driven by the cardiovascular benefits, particularly for indolent lymphomas, for which a larger proportion of patients are expected to die from non-lymphoma causes. We found no significant trend in either patient group for duration of statin use and lymphoma-specific mortality, although patients with CLL with >2 years of use had a reduced lymphoma-specific mortality.

Our present study is, to our knowledge, the largest population-based study assessing statins and prognosis of NHL/CLL. We included a highly generalisable patient population of both aggressive and indolent lymphomas, with both treated patients and those under a watch-and-wait strategy. We used high-quality Swedish registers with detailed subtype classification and adjustment for relevant clinical variables. Furthermore, the PDR provided assessment of all dispensed statin prescriptions during the study period, enabling exposure classification with intensity categories according to the well-validated ACC/AHA guidelines. Additionally, we demonstrated excellent validity of the register data for classifying lymphoma-specific mortality.

Limitations include a lack of clinical data for patients with CLL and a lack of time to progression data. Additionally, despite the large overall size, the study had limited power for analyses of less common subtypes. Furthermore, a longer follow-up period would have been preferred to facilitate exploration of longer statin exposure periods in indolent lymphomas.

In summary, this population-based study did not support the in vitro studies that suggested improved survival of NHL with statin use and did not clearly support a lymphoma-specific mortality reduction for CLL. However, statins did appear safe to use during rituximab treatment. Further research is warranted to evaluate whether statins are beneficial for certain subtypes of lymphoma, with longer exposure periods, or in combination with other medications.

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Disclosures
The authors have nothing to disclaim.

Author contributions
Karin E. Smedby was chief investigator. Elsa Bränvall, Sandra Eloranta, Sara Ekberg and Karin E. Smedby conceived and designed the study. Elsa Bränvall performed literature search. Sandra Eloranta and Sara Ekberg designed the statistical analysis. Tove Wästerlid performed the validation study. Elsa Bränvall, Sandra Eloranta, Sara Ekberg and Karin E. Smedby analysed and interpreted data. Elsa Bränvall, Sandra Eloranta, Tove Wästerlid, Brenda M. Birmann and Karin E. Smedby
wrote the manuscript. All authors have reviewed and approved the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Identification of cohort of NHL and CLL patients in the Swedish Lymphoma and Cancer Registers.

Table SI. ACC/AHA categories of statin therapy intensity*.

Table SII. Medications and ATC codes included as concomitant medications.

Table SIII. Diagnosis codes included in the definitions.

Table SIV. Hazard ratios (HR)* and 95% confidence intervals (CI) for the association of statin use with lymphoma-specific mortality for major lymphoma subtypes in Sweden, 2007-2013.

Table SV. Hazard ratios (HR)* and 95% confidence intervals (CI) for the association of statin use with cardiovascular mortality for lymphoid neoplasm patients in Sweden, 2007-2013.

Table SVI. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of statin use with all-cause mortality in 16,098 non-Hodgkin lymphoma patients in Sweden, 2007-2013.

Table SVII. Hazard ratios (HR)* and 95% confidence intervals (CI) for the association of intensity of statin use with lymphoma-specific mortality for major lymphoma subtypes in Sweden, 2007-2013.

Table SVIII. Diagnosis codes included in the definitions.

Table SVI. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of intensity of statin use with cardiovascular mortality for lymphoid neoplasm patients in Sweden, 2007-2013.

Table SVII. Hazard ratios (HR) and 95% confidence intervals (CI) for lymphoma-specific mortality in relation to duration of statin therapy in the 1:5 matched nested case-control study.

Table SIX. Validation of lymphoma-specific mortality.

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