Statin use and chronic lymphocytic leukemia incidence: A nested case-control study in Manitoba, Canada

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Abbreviations:
ATC: Anatomical Therapeutic Chemical
BCL2: B cell lymphoma-2
CI: Confidence interval
CLL: chronic lymphocytic leukemia
DDD: Defined daily dose
DPIN: Drug Program Information Network
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme
ICD-O-3: the third edition of the International Classification of Diseases for Oncology
MBL: monoclonal B lymphocytosis
MCR: Manitoba Cancer Registry
MH: Manitoba Health

MPR: Manitoba Population Registry
MVA: mevalonate
NSAIDs: Nonsteroidal anti-inflammatory drugs
NHL: Non-Hodgkin lymphoma
OR: Odds ratio
PHIN: personal health identification number
SLL: small lymphocytic lymphoma
WHO: World Health Organization

Abstract

Background: Recent studies have reported reduced risk of chronic lymphocytic leukemia (CLL) among statin users. However, the possibility that the effect of statins may differ by their chemical or pharmacodynamic properties has not been investigated.

Methods: In this nested case-control study, all Manitobans aged ≥ 40 years when diagnosed with CLL (as a first cancer) from 1999 to 2014 (n=1,385) were matched (on gender, age, residence, and duration of insurance coverage) to cancer-free controls (n=6,841). Using conditional logistic regression, statin use was analyzed by individual statins and groups: hydrophilic, low-potency lipophilic (fluvastatin and lovastatin) and high-potency lipophilic statins.

Results: Statin users constituted 27% and 28% of the CLL cases and controls. After adjusting for potential confounding by indication, patterns of healthcare utilization and use of other drugs, CLL incidence was not associated with use of hydrophilic (odds ratio: 1.08; 95% confidence interval: 0.86-1.34) or high-potency lipophilic statins (0.94; 0.79-1.11). Low-potency lipophilic statins were associated with a lower risk of CLL (0.64; 0.45-0.92), with stronger association (0.44; 0.22-0.88) observed with more regular use (half to full standard dose on average).

Conclusions: We found an association between low-potency lipophilic statin use and reduced CLL risk, with a possible dose-response effect.

Impact: While requiring replication in future studies, our findings suggest that the effect of statins on CLL risk may depend on their specific chemical or pharmacodynamic properties.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world, with the incidence increasing as the population ages. In Canada, 2,465 new CLL cases were reported in 2013 with 90 cases from the province of Manitoba (1). The incidence rate of CLL in Canada per 100,000 population has increased steadily from 4.2 in 1992 to 6.6 in 2010 (1). The etiology of CLL remains poorly understood, although certain chemicals, infections, blood transfusions, organ transplantation, and variations in certain loci have been associated with increased CLL risk (2, 3).

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, block the mevalonate (MVA) pathway and are widely prescribed for the prevention and management of cardiovascular disease. Both *in vitro* and *in vivo* studies have shown that statins have a direct anti-tumor effect through blocking of the MVA pathway in various tumor types (4, 5). Statins have been shown to induce apoptosis in B-CLL cells (6) and lower expression of low density lipoprotein receptor activity in CLL patients (7). Statin use has also been associated with a reduced risk of various cancer types in numerous observational studies and meta-analyses (8-12).

The results of studies of statin use and the risk of non-Hodgkin lymphoma (NHL), a heterogeneous group of cancers of the immune system that includes CLL, are mixed, with some studies identifying a risk reduction and others detecting no association (10-15). Thus, it is possible that the effects of statins depend on the subtype of NHL studied. A small (~15% reduction) non-statistically significant association between statin use and CLL risk has been found in two previous studies (16, 17). These studies were, however, limited by small sample size: 410 CLL cases including 22 statin users (16) and 326 cases including 114 users (17). They were further limited by reliance on questionnaires for measuring statin use; by lack of information about dose, duration and timing of use; and by grouping all statins regardless of their chemical or pharmacokinetic properties. We recently studied the effects of statins, as a class, on the incidence of several NHL subtypes, including CLL, and estimated an odds ratio(OR) of 0.89 (95% confidence interval [CI] 0.77–1.04) for CLL (18). In this paper, we report on the

association between CLL and use of several commonly used statins with different chemical structures, pharmacodynamics and lipid-lowering effects.

Methods

We conducted a population-based nested case-control study using the cancer registry and health service administrative databases of Manitoba.

Data sources

Manitoba Health (MH) is the publicly funded health insurance agency providing comprehensive health insurance, including coverage for hospital and outpatient physician services, to the province's 1.3 million residents. Coverage is universal, with no eligibility distinction based on age or income, and participation rates are very high (>99%) (19). Insured services include hospital, physician and preventive services including vaccinations. MH maintains several centralized, administrative electronic databases that are linkable using a unique personal health identification number (PHIN). The completeness and accuracy of MH administrative databases are well established (20, 21). These databases have been used extensively in studies of cancer epidemiology and post-marketing evaluation of various vaccines and drugs.

CancerCare Manitoba maintains one of the oldest population-based cancer registries in the world (Manitoba Cancer Registry [MCR], in operation since 1956). Reporting of cancer cases is mandated by provincial regulations and required for payment of physicians' service claims. The MCR is regularly audited by the North American Association of Central Cancer Registries. The quality of cancer registration has been consistently very high (21). Most cases are pathologically-confirmed (94% for cases registered between 2003 and 2007) and less than 2% of registrations originate from death certificates (21).

The MH Population Registry (MHPR) tracks addresses and insurance status (including end of coverage due to death or emigration) for all insured persons. Since 1971, the Hospital Abstracts database

recorded virtually all services provided by hospitals in the province, including admissions and day surgeries (20). The data collected comprise demographic as well as diagnosis and treatment information including primary diagnosis and service or procedure codes, coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before April 2004, and the ICD-10-CA (Canadian adaptation of the ICD-10) and the Canadian Classification of Health Interventions (CCI) afterwards. The Medical Services database, also in operation since 1971, collects similar information on services provided by physicians in offices, hospitals and outpatient departments across the province (20).

The Drug Program Information Network (DPIN), in operation since 1995, records all prescription drugs dispensed to Manitoba residents, including most personal care home residents (22). The DPIN database captures data from pharmacy claims for formulary drugs dispensed to all Manitobans even those without prescription drug coverage. However, prescriptions dispensed to Registered First Nations, who receive their prescription benefits from the federal government, tend to be under-reported by up to 20% (22). Because information is submitted electronically at the "point-of-sale", the accuracy of the recorded prescription information is excellent (22).

This study was approved by the University of Manitoba Research Ethics Board and by MH's Health Information Privacy Committee.

Source cohort

We used the MHPR to assemble a cohort comprised of all adults aged 40 years or older (statins are rarely prescribed for younger people) who were registered with MH between 1999 and 2014. Cohort members were followed from the latest of the study start date (January 1, 1999), their 40th birthday or the date of immigration to Manitoba until the study end date (December 31, 2014), or the date of diagnosis of CLL, death or emigration, whichever occurred first.

Definition of cases and controls

To be eligible for inclusion in the nested case-control analysis, a participant must have been: (1) free of cancer (except non-melanoma skin cancer) before the *index date*, defined as the date of diagnosis for a case or the matching date for a control, and (2) be covered by MH for a minimum of 5 years prior to the index date (to ensure that all participants had a reasonable opportunity to fill statin prescriptions before the index date).

Cases, identified by linking with the MCR, were members of the source cohort diagnosed with a pathologically-confirmed CLL (ICD-O-3 histology codes 9670 and 9823) (23). We also included small lymphocytic lymphoma (SLL) in the cases group, because SLL has similar clinical and pathological characteristics to CLL (24). Using incidence density sampling (25), we matched each case to up to five controls on birth date (±1 year), region of residence (one of five health regions with populations ≥40 between 25,000 and 375,000) and length of coverage with insurance before the *index date* (to ensure a comparable length of residence in the province).

Measurement of prescription drug use

For each participant, detailed histories of dispensed statins and other drug classes were obtained from the DPIN for the period between January 1, 1995, or the coverage initiation date if it was later, and the index date. The length of these histories was ≥10 years in 59% of participants (median 11.4 years, interquartile range 7.7–15.2 years). The WHO Anatomic Therapeutic Chemical (ATC) classification was used to classify drugs, e.g., statins were defined as all drugs in the Manitoba drug formulary with ATC codes C10AA (Supplementary Table 1-2). Statins were further classified, a priori, according to their potency and lipophilicity, into hydrophilic (pravastatin and rosuvastatin), high-potency (simvastatin and atorvastatin) and low-potency (lovastatin and fluvastatin) statins.

Exposure to individual and grouped statins (henceforth the index class) was characterized in two ways: (1) As a binary ("ever-use") variable indicating whether a participant ever filled a prescription of any drug in the index class at any point before the index date, and (2) as continuous and ordinal variable

representations of the average annual dose of the index class calculated by dividing the total dispensed quantity of the class by its overall duration of use (measured from the dispensing date of the first prescription that included a drug in that class). All drug use in the year immediately prior to the index date was excluded to avoid protopathic bias (26). Because different drugs in the same class may have different pharmacologic potency, the total dispensed quantity for each drug was expressed as a proportion of the WHO's defined daily dose (DDD) for that drug before summing up all these proportions as the total dispensed quantity of the class (see Supplementary Table 1 for list of DDDs). The DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (27).

Covariates

We identified ischemic and other chronic cardiovascular diseases and diabetes (indications or proxies for indications for statin use) from the hospital abstracts and medical services databases, using previously validated algorithms (Supplementary Table 3). We also measured the number of physician visits within the 5-year period before the index date as a proxy for propensity to access healthcare services. Neighborhood average household income quintiles, which are correlated with self-reported household incomes, were determined based on place of residence and 2011 Canadian census data (28, 29).

Statistical analysis

We used conditional (to account for individual matching) logistic regression (CLR) models to calculate ORs and 95% CIs of the association between statin use and CLL diagnosis. Selection of covariates for the final models was driven by a causal diagram analysis (30) and an empirical search for confounders: a variable was considered a confounder if its inclusion in adjusted models resulted in a >10% change in OR estimates of the main exposure. The final model was adjusted for history of chronic cardiovascular disease, ever-use of non-statin lipid-lowering drugs, aspirin, non-aspirin NSAIDs, household income, and number of physician visits in the 5-year period before the index date. To test for effect modification,

we stratified our analysis by each confounder and used likelihood-ratio tests to assess the statistical significance of the interaction terms. When appropriate, models also included mutual adjustment for statin groups and individual statins.

Given the long exposure histories in this cohort, participants had highly variable statin use histories. To reduce the effect of this heterogeneity, and to assess the presence of an "induction period" for statin effects (the time interval between an exposure exerting its causal effects and disease initiation or prevention (31)), we repeated all analyses after dividing the exposure history into 3 successive periods: 2–5, 6–10, and 11+ years before the index date. A separate exposure index was computed for each period by limiting exposure measurements to prescriptions dispensed during that period (32). As before, CLR models were used to estimates ORs associated with drug use in each period with mutual adjustment for exposure in other periods. We used SAS 9.4 (SAS Institute, Cary, North Carolina) and Stata 14 (Stata Corp. LLC., College Station, Texas) for all analyses.

Results

We included 1,385 CLL patients, matched to 6,841 cancer-free controls (Table 1). Most patients were male (60%) and older than 65 (65%), but CLL incidence seemed unrelated to income. CLL patients had a slightly higher prevalence, at diagnosis, of chronic cardiovascular disease than controls (42% vs 40%) and more physician visits in the 5-year period before the index date.

About 27% of cases and 28% of controls received at least one statin prescription prior to the index date, mostly atorvastatin (~16%). A similar percentage of cases and controls received hydrophilic and high-potency lipophilic statins (Table 1). There were only minor differences in the relative duration of use or the average dose between cases and controls. The dose was the typical dose for hydrophilic statins (median use of 365 DDD/year) but lower than the typical dose for high-potency lipophilic (243 DDD/year) and low-potency lipophilic statins (162 DDD/year) (Table 2). Low-potency lipophilic statin users were typically older (50% were 75+ compared to 42% for high-potency lipophilic statin users) and

more likely to have chronic cardiovascular disease (68% versus 57%-59% for users of other statins and 33% for never-users) (Supplementary Table 4).

After adjusting for several variables, including cardiovascular disease, propensity to use healthcare, and use of non-statin lipid-lowering drugs, aspirin and other NSAIDs (Table 3), ever-use of any statin was associated with small non-statistically significant reduced risk of CLL (OR = 0.89; 95% CI 0.76-1.04). When grouped by lipophilicity and potency, only use of low-potency lipophilic statins (lovastatin and fluvastatin) was associated with reduced risk, 0.64 (0.45-0.92). Neither high-potency lipophilic statins (0.94; 0.79-1.11) nor hydrophilic statins (1.08; 0.86-1.34) were associated with CLL risk. The analysis lacked power to detect a statistically significant association of individual statins use and CLL. However, the effects of individual low-potency statins, fluvastatin (0.71; 0.40-1.26) and lovastatin (0.66; 0.43-1.02), were consistent with their group effect.

More regular use (181–365 DDDs/year) of low-potency lipophilic statins was associated with a clinically and statistically significant reduction in CLL risk (0.44; 0.22-0.88) (Table 4). Both higher cumulative dose (≥ 1201 DDDs) and longer relative duration of use (≥ 76% of the time) of low-potency lipophilic statins were associated with greater risk reduction, possibly suggesting a dose- and duration-response effect. Individual low-potency statins displayed similar trends (Supplementary Table 5), although the estimates were not precise. Generally, there were no clear dose or duration-response trends for use of other statins. None of the variables we adjusted for in our analysis was an effect modifier (Supplementary Table 6).

Discussion

In an a priori hypothesis-driven analysis, we found that use of low-potency lipophilic statins was associated with lower CLL risk, OR=0.64 (0.45-0.92), with some indication of a dose-response effect. We did not detect a similar association with the use of either high-potency lipophilic statins or hydrophilic statins.

The association between statin use and CLL risk has been studied before. Employing questionnaires to measure statin use, a study conducted in 6 European nations (including 410 CLL patients) reported an OR of 0.83 (0.51-1.34) for all statins combined (16). A prospective US cohort study found, based on biannual questionnaires, that cholesterol-lowering drugs (93% of which were statins) had a risk ratio of 1.01 (0.59–1.74) for former users, and 0.91 (0.66–1.27) and 0.85 (0.58–1.23) for current users for less and more than five years of use, respectively (17). The number of CLL patients in this study was relatively small (326) with only 50 recent statin users and 49 long-term users) (17). Our estimates for statin use as a class (OR=0.89; 0.76-1.04) are in line with these results, despite differences in study design and data sources.

To the best of our knowledge, this is the first study to examine the association between low-potency lipophilic statins and CLL incidence (the analyses in the abovementioned studies were limited to studying the effects of statins as a class). Pharmacokinetic differences between lipophilic and hydrophilic statins may explain the differences in their association with CLL risk. The water solubility of statins affects their absorption and distribution in tissue (33, 34). Hydrophilic statins cannot easily penetrate cell plasma membranes through passive transport and their distribution is more hepatoselective (4, 35). However, this does not explain differences we observed between low-potency and high-potency lipophilic statins. The indications for individual statins are overlapping and clinical guidelines do not recommend certain types over others (36, 37), even though high-potency statins are prescribed when a larger reduction of low-density lipoprotein cholesterol (LDL-C) levels is desired (38). There is no clear connection between the type of statin and its effect on the MVA pathway in CLL cells. But this remains unexamined area as most animal and laboratory studies are often limited to studying a particular statin (39).

Simvastatin has shown cytotoxicity against cultured B-CLL cells with higher levels of apoptosis with increased dosage (6). Fluvastatin showed higher cytotoxicity against lymphoma cells than atorvastatin and simvastatin (39). The statins have been shown to down-regulate the anti-apoptotic protein BCL2 in

some leukemias (40), and the complete remission rate in CLL is increased when simvastatin is combined with venetoclax, another agent that selectively reduces BCL2 levels in CLL cells (41, 42). Elevated LDL levels in CLL cells may decrease apoptosis of CLL cells; this was not observed for acute leukemia cells or normal lymphocytes (43).

Strengths and limitations

A major strength of this study is the availability of high-quality, population-based health administrative databases in Manitoba. The completeness and accuracy of the MCR and MH databases are well established (20, 21). We had a relatively large number of cases compared to other CLL studies, but some of our estimates were imprecise due to infrequent use of certain statins (especially low-potency lipophilic statins). Reporting of cancer cases to the MCR is mandated by provincial law (44). The MCR currently obtains data for all persons diagnosed with CLL cells using flow cytometry (but excludes cases with monoclonal B lymphocytosis). CLL incidence was underreported before reporting of flow cytometry became a standard practice (45). It is possible that some diagnosed cases during that time were not included in the MCR, this misclassification was likely non-differential with respect to statin use.

A limitation of this study is that the DPIN database started in 1995. Statins prescribed before that time could not be identified. Statins were not, however, frequently prescribed before 1995 (46, 47) and have only been available since around 1990 (Supplementary Table 1). Also, any resulting misclassification is likely non-differential with regard to the outcome (CLL diagnosis) as it excludes all exposure information before 1995. Although we adjusted our analysis for several confounding factors, we could not adjust for undiagnosed chronic cardiovascular disease. We also lacked information on aspirin use unless it was prescribed which is the likely the case for regular users. As a result, we cannot rule out residual confounding. We did not have information on some potential confounders, such as smoking, alcohol use and environmental exposures, albeit the literature suggests this does not cause significant confounding (2).

While dyslipidemia has been associated with the development of CLL (48), the effect of severity of dyslipidemia has not been studied. Our study is limited by a lack of data on cytokine and lipid levels; we could not stratify our analysis by severity of dyslipidemia. The low-potency statin users in our study used a relatively low dose of statins and were generally older and more likely to have chronic cardiovascular disease and other comorbidities. Confounding by indication may have biased our results if risk factors for CLL influenced statin prescriptions.

In summary, our results suggest that use of low-potency lipophilic statins might be associated with a lower risk of CLL, possibly in a dose-dependent manner. Even though a causal relationship cannot be proven, a 35% reduction in CLL risk is a promising, clinically relevant result that warrants further investigation into the effects of low-potency lipophilic statins on CLL risk.

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Conflicts of Interest

SMM has received unrestricted research grants from Merck, GlaxoSmithKline, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies. JBJ and VB have received unrestricted research grants from Lundbeck, Gilead and Janssen Pharmaceuticals for unrelated projects and sit on advisory boards for Gilead, Janssen, and Abbvie Pharmaceuticals. VB received consulting fees from Astra Zeneca.

Data sharing

Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at Manitoba Centre for Health Policy (MCHP). The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository. The original data source and approval for use has been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies.

Authors' contribution

XY and SMM designed and supervised the study, GZ and CHR analyzed the data, CHR, GZ, and SMM wrote the manuscript, all other authors contributed to interpretation of the results and draft revisions. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

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451 **Tables**

452 **Table 1: Number (%) of CLL cases and their matched controls by certain socio-economic and**
453 **clinical characteristics**

	Case (N=1,385)	Control (N=6,841)
Male	825 (59.6%)	4,100 (59.9%)
Age group		
40-54	151 (10.9%)	737 (10.8%)
55-64	328 (23.7%)	1,621 (23.7%)
65-74	403 (29.1%)	2,009 (29.4%)
75+	503 (36.3%)	2,474 (36.2%)
In top 60% of household income distribution	800 (57.8%)	3,804 (55.6%)
Rural residence	521 (37.6%)	2,472 (36.1%)
Comorbidities		
Diabetes	229 (16.5%)	1,231 (18.0%)
Chronic cardiovascular disease (excluding hypertension)	579 (41.8%)	2,719 (39.7%)
Ischemic heart diseases	261 (18.8%)	1,284 (18.8%)
Stroke	33 (2.4%)	200 (2.9%)
Ever-use of statins		
Any statin	371 (26.8%)	1,918 (28.0%)
Any statin 2-5 years prior to the index date	341 (24.6%)	1,739 (25.4%)
Any statin 6-10 years prior to the index date	219 (15.8%)	1,139 (16.6%)
Any statin 11+ years prior to the index date	93 (6.7%)	462 (6.8%)
Hydrophilic statins	131 (9.5%)	591 (8.6%)

High-potency lipophilic statins	290 (20.9%)	1,500 (21.9%)
Low-potency lipophilic statins	40 (2.9%)	287 (4.2%)
Pravastatin	67 (4.8%)	299 (4.4%)
Rosuvastatin	73 (5.3%)	330 (4.8%)
Simvastatin	113 (8.2%)	572 (8.4%)
Atorvastatin	218 (15.7%)	1,113 (16.3%)
Fluvastatin	15 (1.1%)	111 (1.6%)
Lovastatin	28 (2.0%)	199 (2.9%)
Ever-use of other prescription drugs		
Non-statin lipid-lowering drugs	101 (7.3%)	464 (6.8%)
Metformin	123 (8.9%)	681 (10.0%)
Insulin	32 (2.3%)	169 (2.5%)
Other oral hypoglycemic drugs	113 (8.2%)	604 (8.8%)
Aspirin	249 (18.0%)	1,392 (20.3%)
Non-aspirin NSAID	844 (60.9%)	4,340 (63.4%)
Any NSAID	911 (65.8%)	4,721 (69.0%)
No. of physician visits in the 5-year period before index date		
0 — 19	261 (18.8%)	1,495 (21.9%)
20 — 39	388 (28.0%)	2,014 (29.4%)
40 — 64	380 (27.4%)	1,656 (24.2%)
65+	356 (25.7%)	1,676 (24.5%)

454

455 **Table 2: Relative duration (percent of time) and average annual dose (DDD/year) of statin use**
456 **prior to the index date excluding the year before the index date, for CLL cases and their**
457 **matched controls according to statin subgroup.**

	Cases			Controls		
	Q1	Median	Q3	Q1	Median	Q3
Average annual dose (DDD/year)						
Hydrophilic	350.3	365.0	392.2	365.0	365.0	429.0
High-potency lipophilic	182.5	243.3	365.0	182.5	251.8	365.0
Low-potency lipophilic	162.2	162.2	233.4	162.2	165.1	243.3
Relative duration (%)						
Hydrophilic	5.1	14.5	34.2	3.4	11.8	28.6
High-potency lipophilic	6.0	20.3	42.1	6.0	20.6	41.3
Low-potency lipophilic	7.1	23.4	53.0	5.9	23.1	63.7

DDD = defined daily dose, Q1 = first quartile, Q3 = third quartile.

458

459 **Table 3: Adjusted odds ratios (95% confidence interval) of the association between CLL**
460 **incidence and ever-use of statins, excluding the year before the index date.**

Ever-use of statins	Model A[a]	Model B[b]
Any statin	0.94 (0.82-1.08)	0.89 (0.76-1.04)
Hydrophilic[c]	1.14 (0.93-1.41)	1.08 (0.86-1.34)
Pravastatin[d]	1.18 (0.89-1.55)	1.13 (0.84-1.51)
Rosuvastatin[d]	1.12 (0.85-1.47)	1.06 (0.79-1.42)
High-potency lipophilic[c]	0.96 (0.82-1.12)	0.94 (0.79-1.11)
Simvastatin[d]	1.02 (0.82-1.27)	1.03 (0.82-1.29)
Atorvastatin[d]	0.99 (0.84-1.18)	0.96 (0.80-1.16)
Low-potency lipophilic[c]	0.68 (0.48-0.96)	0.64 (0.45-0.92)
Fluvastatin[d]	0.72 (0.41-1.25)	0.71 (0.40-1.26)
Lovastatin[d]	0.70 (0.47-1.06)	0.66 (0.43-1.02)

a: Model A includes the matching variables (age, gender, residence and duration of coverage). b: Model B includes the matching variables, chronic cardiovascular disease (excluding hypertension), income quintiles and number of physician visits 5 years before index date, non-statin lipid-lowering drugs, non-aspirin NSAIDs and aspirin and derivatives. c: Also adjusted for ever-use of the other statin subgroups. d: Also adjusted for ever-use of the other individual statins.

461

462 **Table 4: Adjusted[a] odds ratios (95% confidence interval) of the association between CLL**
463 **diagnosis and statin use, excluding the year before the index date, by statin subgroup according**
464 **to period, duration and dose.**

Statin use	Hydrophilic	High-potency lipophilic	Low-potency lipophilic
Time of first use (years prior to the index date)[b]			
2-5	1.07 (0.79-1.44)	0.96 (0.77-1.19)	0.62 (0.28-1.40)
6-10	0.93 (0.64-1.34)	0.90 (0.71-1.14)	0.61 (0.33-1.12)
11+	1.42 (0.90-2.24)	0.96 (0.69-1.34)	0.65 (0.39-1.11)
Relative duration (fraction of drug history)[b]			
1 - 25%	1.03 (0.79-1.33)	0.91 (0.74-1.12)	0.69 (0.43-1.12)
26 - 50%	1.10 (0.68-1.77)	0.85 (0.64-1.13)	0.56 (0.22-1.43)
51 - 75%	1.60 (0.84-3.04)	1.10 (0.76-1.59)	0.70 (0.29-1.68)
≥ 76%	0.99 (0.34-2.91)	1.40 (0.81-2.41)	0.42 (0.15-1.17)
Continuous use[b]			
< 12 months	1.00 (0.77-1.30)	0.97 (0.80-1.18)	0.65 (0.43-1.01)
≥ 12 months	1.23 (0.85-1.78)	0.90 (0.70-1.15)	0.60 (0.32-1.14)
Duration (months)[b]			
1 - 6	0.91 (0.60-1.40)	0.95 (0.70-1.29)	0.41 (0.16-1.06)
7 - 24	1.06 (0.73-1.52)	0.85 (0.63-1.13)	0.81 (0.43-1.52)
25 - 48	1.04 (0.65-1.67)	1.00 (0.75-1.34)	0.60 (0.27-1.32)
≥ 49	1.39 (0.93-2.09)	0.97 (0.75-1.26)	0.67 (0.36-1.23)
Cumulative dose (DDD)[b]			
1 - 120	0.87 (0.53-1.42)	0.92 (0.67-1.25)	0.68 (0.34-1.35)
121 - 480	0.87 (0.56-1.33)	0.92 (0.70-1.22)	0.71 (0.37-1.35)
481 - 1200	1.39 (0.93-2.07)	0.97 (0.73-1.29)	0.71 (0.35-1.44)
≥ 1201	1.18 (0.83-1.70)	0.94 (0.72-1.23)	0.47 (0.20-1.09)

Average annual dose (DDD/year)[b]			
1 - 180	2.81 (0.83-9.50)	0.97 (0.65-1.43)	0.74 (0.47-1.16)
181 - 365	1.46 (0.96-2.22)	0.96 (0.79-1.17)	0.44 (0.22-0.88)
≥ 366	0.96 (0.74-1.23)	0.89 (0.68-1.15)	0.88 (0.30-2.58)

a: Adjusted for the matching variables (age, gender, residence and duration of coverage), chronic cardiovascular disease (excluding hypertension), income quintiles and number of physician visits 5 years before index date, non-statin lipid-lowering drugs, non-aspirin NSAIDs, aspirin and derivatives, and other statin subgroups. b: Compared to never use of the specific statin subgroup.

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