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COMMON MEDICATIONS IN THE RISK AND PROGNOSIS OF LYMPHOID NEOPLASMS AND EPIDEMIOLOGY OF PRIMARY CNS LYMPHOMA

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COMMON MEDICATIONS IN THE RISK AND PROGNOSIS OF LYMPHOID NEOPLASMS AND EPIDEMIOLOGY OF PRIMARY CNS LYMPHOMA

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To Petter, Stella, Lisa and Ines

POPULAR SCIENCE SUMMARY OF THE THESIS

Lymphoid neoplasms are cancers stemming from the lymphocyte, a type of white blood cell, and include the different subtypes of lymphomas, including chronic lymphocytic leukemia as well as multiple myeloma. They arise at different stages in the development of the lymphocyte with different genetic markers and give rise to varying disease scenarios and treatment needs.

Towards the end of the last century, the incidence (the number of new cases per 100 000 persons and year) increased rapidly, for mostly unknown reasons. During the same period, many new medications were increasingly used in Europe and North America. Among the most common are aspirin (used as protection against heart attacks and stroke) and statins (used to lower blood cholesterol). Both of these medications have been described to be able to interfere with cancer development.

In study I and II we used Swedish health-care registers to investigate if statin use improved survival in myeloma (study I) and lymphoma (study II). We found that statins seemed to improve survival in myeloma, but there did not seem to be a protective effect in subtypes of lymphoma. It is not possible to draw firm conclusions from our study about whether statin use improves survival in myeloma patients, as other analytical reasons could have contributed as well. However, we believe the result should be followed up in further studies.

In study III we used data from patients in a large American cohort, the Nurses' Health study. We made detailed calculations of their aspirin use, and found that users of many aspirin tablets/week (5 or more on average) had an increased risk of the follicular lymphoma subtype. We could not find evidence that persons using aspirin for longer periods of time had a higher risk of developing lymphoma.

In study IV, we investigated primary central nervous system lymphoma (PCNSL), an uncommon lymphoma subtype that arises within the brain or spinal cord. PCNSL traditionally has a dismal prognosis, but many new treatments have been introduced lately. We calculated the incidence (number of new PCNSL diagnoses /100,000 persons and year) in Sweden, and found that the incidence is increasing among persons 70 years and older, but that other brain tumors are increasing in this age group as well. We therefore suspect that the increase, at least in part, is caused by more diagnostic procedures and reporting in this age group. We also investigated survival in PCNSL, and we did not find any improvement in survival during the study period.

ABSTRACT

Lymphoid neoplasms are malignancies arising from the lymphocyte, and include lymphoma subtypes, chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). It is a heterogenous group of diseases, with different molecular pathogenesis, clinical characteristics, treatments and outcome. There is increasing understanding that risk factors may differ between the subtypes.

The incidence of the non-Hodgkin subtypes of lymphoma (NHL) increased rapidly for several decades during the end of the 20th century, for mostly unknown reasons. Concurrently the use of many prophylactic medications such as statins and aspirin became common in Europe and North America. Anti-carcinogenic properties have been described in both these medications, but for statins there has also been concern about a potential conflicting effect of statins in lymphoma treatments that include the widely used monoclonal antibody rituximab.

In **study I and II** we investigated the association between statin use and disease-specific mortality in lymphoid neoplasms. We assessed statin exposure in 6-month periods before and after diagnosis of a lymphoid neoplasm in cohort studies, and at any time during follow-up in nested case-control studies. We assessed the dose-response relationship by categories of intensity of statin use (according to American College of Cardiology/American Heart Association guidelines as low, moderate and high intensity) and duration. In **study I**, we found that among patients with MM, statin use was associated with improved myeloma-specific mortality in all time-windows assessed. There was however no significant trend for dose intensity or duration. In **study II**, we found no association between statin use and lymphoma-specific survival in NHL overall or in CLL and other subtypes. We found improved lymphoma-specific survival in Burkitt lymphoma and in CLL patients that used statins for >2 years, but these findings could also be due to chance. We found no evidence of reduced efficacy of rituximab treatment for patients with statin use, which is reassuring.

In **study III** we used the American cohort the Nurses' Health Study to assess detailed information on aspirin use over 25+ years and risk of NHL and its subtypes. We investigated both cumulative average quantity and duration of aspirin use. We found no association between aspirin use and risk of NHL overall, but there was an increased risk of follicular lymphoma for users of large quantities of aspirin (5+ tablets/week), as well as a significant trend across increasing categories of quantity.

In **study IV** we investigated the incidence of primary central nervous system lymphoma (PCNSL), a rare NHL subtype located in the CNS. PCNSL has traditionally had a dismal prognosis, but many new treatment schemes have been introduced lately. We found an increasing incidence primarily in the elderly (70+) that was consistent with an increasing trend of brain tumors of all types in the same age group, suggesting that this can, at least in part, be due to increased diagnostic procedures and reporting. We did not find any improvement in survival during the study period, indicating that the new treatments have not yet improved the prognosis in a population-based setting.

LIST OF SCIENTIFIC PAPERS

I. Elsa Brånvall, Sara Ekberg, Sandra Eloranta, Tove Wästerlid, Brenda M. Birmann. Karin E. Smedby
Statin use improves survival in multiple myeloma: A Swedish population-based study of 4,315 patients
American Journal of Hematology, 2020 Jun;95(6):652-661

II. Elsa Brånvall, Sara Ekberg, Sandra Eloranta, Tove Wästerlid, Brenda M. Birmann. Karin E. Smedby
Statin use and survival in 16,098 patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia in the rituximab era
Manuscript

III. Elsa Brånvall, Karin E. Smedby, Julie Batista, Bernard A. Rosner, Edward Giovannucci, Jan-Peter Glossmann, Kimberly A. Betrand, Honglei Chen, Francine Laden, Shumin Zhang, Brenda M. Birmann
Regular aspirin use and risk of non-Hodgkin lymphoma subtypes: A prospective analysis in the Nurses' Health Study
Manuscript

IV. Sandra Eloranta, Elsa Brånvall, Fredrik Celsing, Karin Papworth, Maria Ljungkvist, Gunilla Enblad, Karin E. Smedby
Increasing incidence of primary central nervous system lymphoma but no improvement in survival Sweden 2000-2013
European Journal of Haematology, 2018 Jan;100(1):61-68

CONTENTS

LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACNU	Active Comparator New User design
AIDS	Acquired Immunodeficiency Syndrome
AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
COX	Cyclooxygenase enzyme
DDD	Defined Daily Dose
DLBCL	Diffuse Large B-Cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
EBER	Epstein Barr Virus early RNA transcripts
EBV	Epstein Barr Virus
EMRR	Excess Mortality Rate Ratio
FL	Follicular Lymphoma
HD-MTX	High-Dose Methotrexate
HIV	Human Immunodeficiency Virus
HMD	Human Mortality Database
HR	Hazard Ratio
ICD	International Classification of Diseases
IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LISA	Longitudinal integration database for health insurance and labor market studies
LPL	Lymphoplasmacytic Lymphoma
MALT	Mucosa Associated Lymphoid Tissue
MCL	Mantle Cell Lymphoma
MGUS	Monoclonal Gammopathy of Undetermined Significance

MM	Multiple Myeloma
MZL	Marginal Zone Lymphoma
NHL	Non-Hodgkin lymphoma
NHS	Nurses' Health Study
NK-cell	Natural Killer Cell
NPR	The National Patient Register
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds Ratio
PCNSL	Primary Central Nervous System Lymphoma
PDR	The Prescribed Drug Register
PG	Prostaglandin
PIN	Personal identification number, 10-digit "person-nummer"
PPI	Proton Pump Inhibitors
PPV	Positive Predictive Value
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RS	Relative survival
SEER	Surveillance, Epidemiology and End Results Program (provides American Cancer statistics)
SLR	Swedish Lymphoma Register
SNOMED	Systematized Nomenclature of Medicine
SSRI	Selective Serotonin Reuptake Inhibitor
TPR	The Total Population Register
WHO	World Health Organization
WHOCC	WHO Collaborating Centre for Drug Statistics Methodology

1 INTRODUCTION

Lymphoid neoplasms are cancers stemming from the lymphatic white blood cell (Fig 1.1). The traditional division in myelomas and lymphomas, the latter further divided in Hodgkin and non-Hodgkin lymphomas (NHL) has gradually developed, mainly based on histopathology, molecular genetics and clinical course. Due to new insights in the genetic alterations in these malignant cells, the NHL entity was finally replaced entirely in the WHO 2008 classification, and substituted by a division in mature B- and T-/natural killer (NK)-cell lymphoid neoplasms.[1] Here multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) are included in the "mature B-cell lymphoid neoplasms" group, which was additionally modified in the latest 2016 edition.[2,3] The term NHL is, however, still widely used in the current literature and cancer statistics of today, and will also be referred to in this thesis, whereas Hodgkin lymphoma will not be addressed further. Primary central nervous system lymphoma (PCNSL), a lymphoma arising within the brain or spinal cord, is not recognized as a separate entity by the WHO, given that it is not possible to distinguish morphologically from the common NHL subtype diffuse large B-cell lymphoma (DLBCL) that is located in other parts of the body.[1]

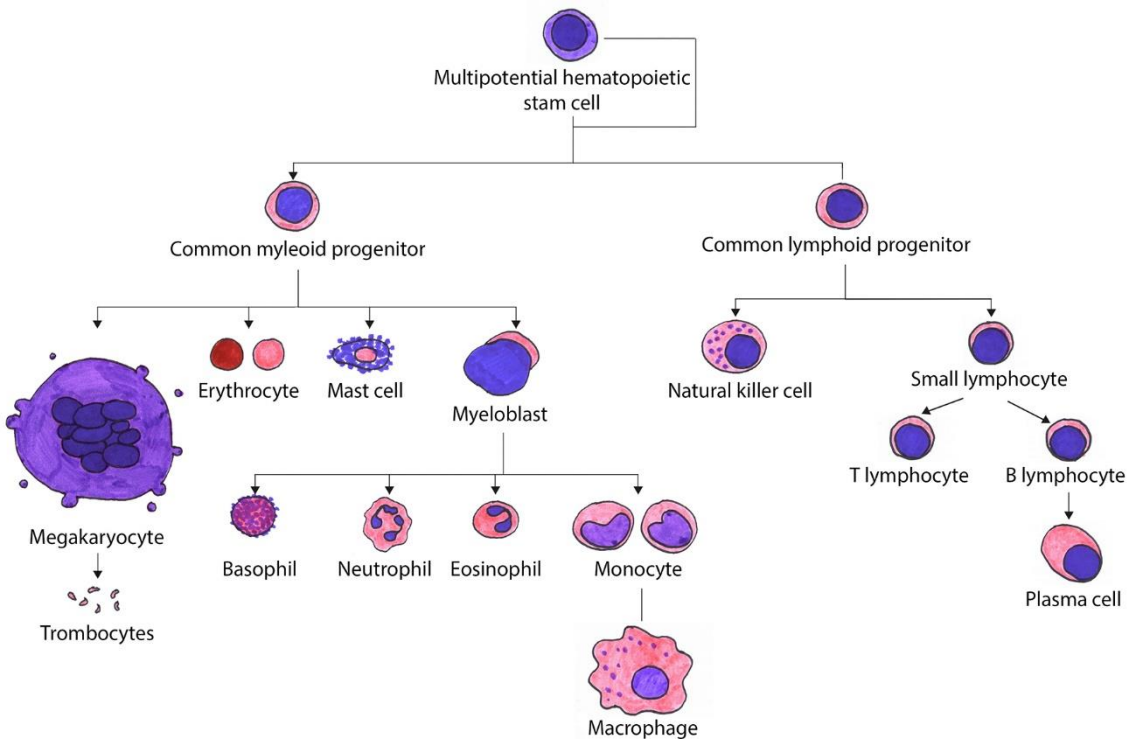


Fig 1.1 The principles of hematopoiesis. Illustration by Hanna Närding

The clinical manifestations of lymphoma span from indolent disease to highly proliferative disease, requiring immediate treatment. The prognosis varies considerably between subtypes of lymphoma, with a reported relative 5-year survival for NHL overall at around 73%, translating to approximately 600 deaths yearly in Sweden[4] and 20,000 deaths yearly in the US.[5] The age-adjusted incidence rate of NHL in the US is approximately 19.6 per 100,000

person-years (cases diagnosed from 2013–2017) with an estimated 77,240 new cases in 2020, accounting for 4.3% of all new cancers in the US in 2020.[5] The corresponding incidence rate of CLL is 5.0 per 100,000 person-years with an estimated new 21,040 cases in the US in 2020.[6] The incidence rates in Sweden are similar, and 1,907 incident diagnoses of NHL and 670 of CLL were reported in 2017.[7] In the uncommon subtype primary central nervous system lymphoma (PCNSL), only approximately 30 new cases are diagnosed yearly in Sweden,[8] accounting for approximately 1% of NHLs and about 3% of all primary brain tumors[9].

For MM, many new treatments have been introduced during the last decade, and survival has improved considerably.[10] For the period 2010-2016 the relative 5-year survival was 54% in the US[11] and the age-adjusted incidence rate 7.0 per 100,000 person-years, or an estimated 32,270 new cases in 2020.[11] The incidence rate in Sweden is similar, with 849 MM diagnoses reported in 2017.[7] A Swedish study has shown that 2.7% of MM patients have a previous diagnosis of a monoclonal gammopathy of undetermined significance (MGUS), the precursor state of MM, in which the monoclonal (M)-protein concentration typical for MM has been diagnosed in the blood but without the patient fulfilling other criteria of MM.[12] These patients are followed with regular testing of their M-protein in order to identify a potential progression to MM, and to provide early treatment and improve survival.

Whereas the incidence of MM has remained relatively stable in recent decades, NHL incidence in Europe and North America was increasing steeply between 1970 and 2000, when it plateaued, and since 2008 has been slightly decreasing.[5] Little is still known about the reasons for these changes in either direction (Fig 1.2).

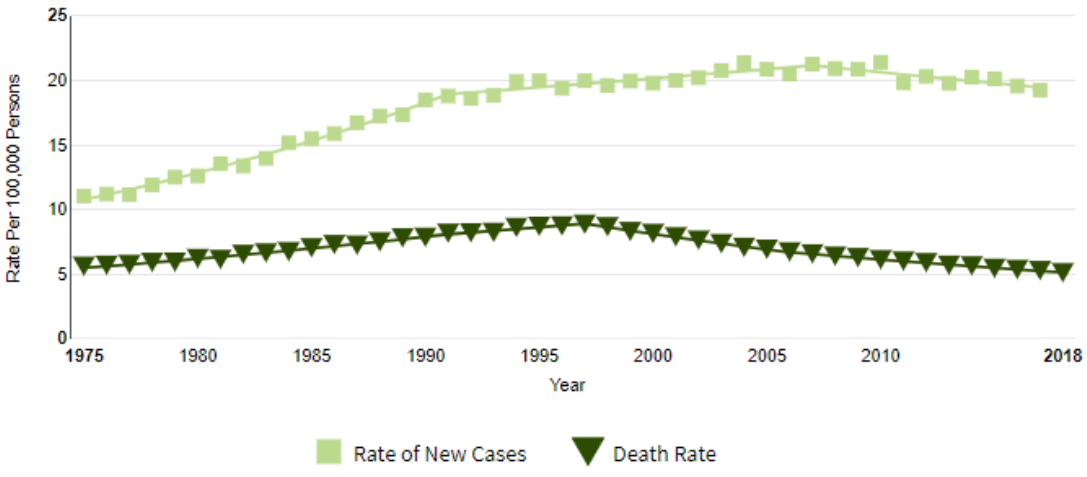


*Fig 1.2 Age-adjusted NHL incidence and death rates per 100,000 person-years in the US Reprint from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018).*

Among the NHL subtypes, a special interest has been a potential increase in the uncommon subtype of primary central nervous system lymphoma (PCNSL), a type of diffuse large B-cell lymphoma (DLBCL) that arises within the CNS.[13,14] This subtype has traditionally had a dismal prognosis, but new treatments have been introduced in the last decades, raising the hope of improved outcomes for patients with this subtype.[15]

During the same period, use of certain medications has increased in Europe and North America, among these, the common drugs aspirin and statins.[16,17] Interesting potential interactions of these medications in carcinogenesis and cancer proliferation have been hypothesized in several other cancer forms, but little is known about these medications in the etiology and prognosis of lymphoid neoplasms. A potential protective effect of aspirin in risk of lymphoma, equivalent to what has been shown in colorectal cancer, would be highly valuable. At the same time, a possible interaction between concomitant medications such as statins with other antitumoral treatments, thus inhibiting their effect, would also have large implications.

In this thesis we aimed to analyze the role of common medications in the etiology and prognosis of lymphoid neoplasms, and investigate the incidence and prognosis of PCNSL. Specifically, we have used the Swedish population-based registers to investigate if statin use affects the prognosis of myeloma or subtypes of lymphoma including CLL, and we have used American prospective cohort data to explore if regular use of aspirin affects the risk of lymphoma. We have also used the Swedish registers to calculate recent incidence rates of PCNSL and assess any recent changes in survival corresponding to the newly introduced treatment schemes.

2 LITERATURE REVIEW

2.1 ETIOLOGY AND RISK FACTORS

Lymphomas of B-cell origin constitute about 95% of all lymphomas; the rest are T-cell malignancies. The latest WHO classification includes 17 different main subtypes among the mature B-cell neoplasms, among them CLL and MM (Table 2.1).[3] The different B-cell subtypes arise at different stages in the normal development of the B cell (Fig 2.1) and have different behaviors in terms of pathogenesis, clinical presentation and treatment.

Table 2.1 Human mature B-cell neoplasms according to the WHO classification

Lymphoma subtype	Frequency among lymphomas (%)*
B-cell chronic lymphocytic leukemia (B-CLL)	7
Mantle-cell lymphoma	5
B-cell prolymphocytic leukemia	<1
Follicular lymphoma	20
Hairy-cell leukemia	<1
Mucosa associated lymphoid tissue (MALT) lymphoma	7
Nodal marginal-zone lymphoma	2
Splenic marginal-zone lymphoma	1
Burkitt's lymphoma	2
Diffuse large B-cell lymphoma	30-40
Primary mediastinal B-cell lymphoma	2
Post-transplant lymphoma	<1
Primary effusion lymphoma	<0.5
Lymphoplasmacytic lymphoma	1
Multiple myeloma	10
Classical Hodgkin's lymphoma	10
Lymphocyte-predominant Hodgkin's lymphoma	0.5

*These numbers refer to the frequencies in Europe and North America.

Known risk factors for lymphoma include immune suppression, such as after organ transplantation,[18] and certain infections, such as Epstein-Barr virus (EBV)[19] and Human Immunodeficiency virus (HIV),[20] or infection with helicobacter pylori in gastric mucosa associated lymphoid tissue lymphoma (MALT)[21] and chlamydia psittaci in ocular adnexal marginal zone lymphoma.[22] Constitutive inflammatory activation is also believed to increase the risk of lymphoma, as exemplified by an increased lymphoma incidence in patients with inflammatory diseases such as Sjögren's syndrome, rheumatoid arthritis (RA) and inflammatory bowel disease.[23,24]

Prognostic risk factors include both clinical and tumor molecular characteristics. The tumor microenvironment and more broadly the host background in terms of heredity, tumor genetics, and co-morbidity may also be additional critical factors in lymphoma progression. Concurrent medications used for other diseases may thus play a role in NHL progression as well. There is growing appreciation that, given the large morphological and molecular differences between the subtypes, risk factors may also differ between them, underscoring the importance of investigating different subtypes separately.[25]

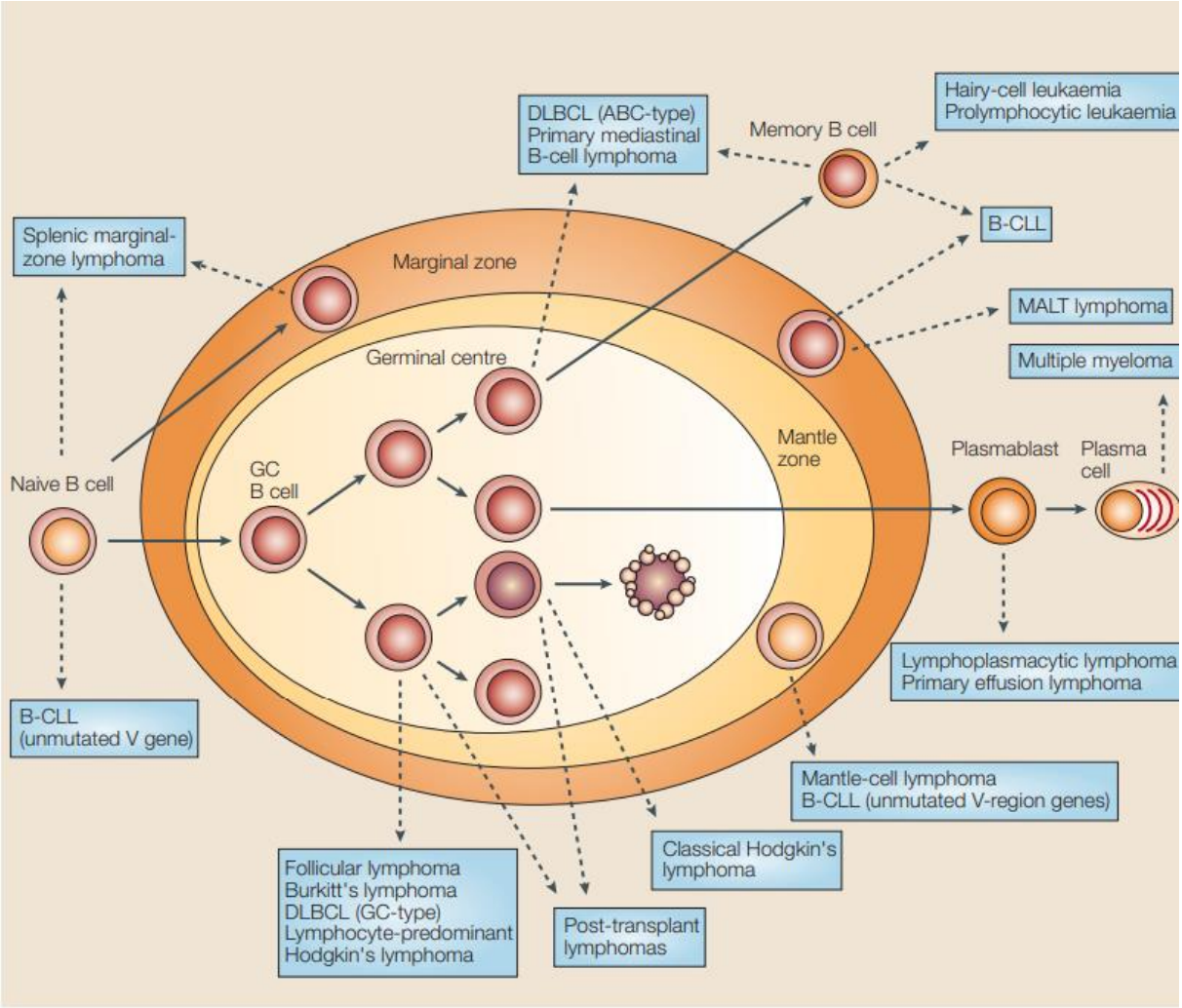


Fig 2.1 Cellular origin of human B-cell lymphomas. Reprint from Ralph Kuppers: Mechanisms of B-cell lymphoma pathogenesis, Nature Reviews cancer, 2005 [26]

2.2 STATINS

Statins are among the most frequently prescribed classes of drugs in Europe and North America,[16,17] primarily indicated in the treatment of hyperlipidemia. An estimated one in 10 adults and one in four individuals ≥ 60 years old are currently on statin therapy in the US.[27] Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway, thereby reducing cholesterol synthesis (Fig 2.2). The impact of statins on cholesterol and isoprenoid synthesis may have anticancer effects

through several mechanisms important for tumor survival.[28] Consistent with this hypothesis, many epidemiological studies support an anti-cancer effect in several solid cancers.[29-31]

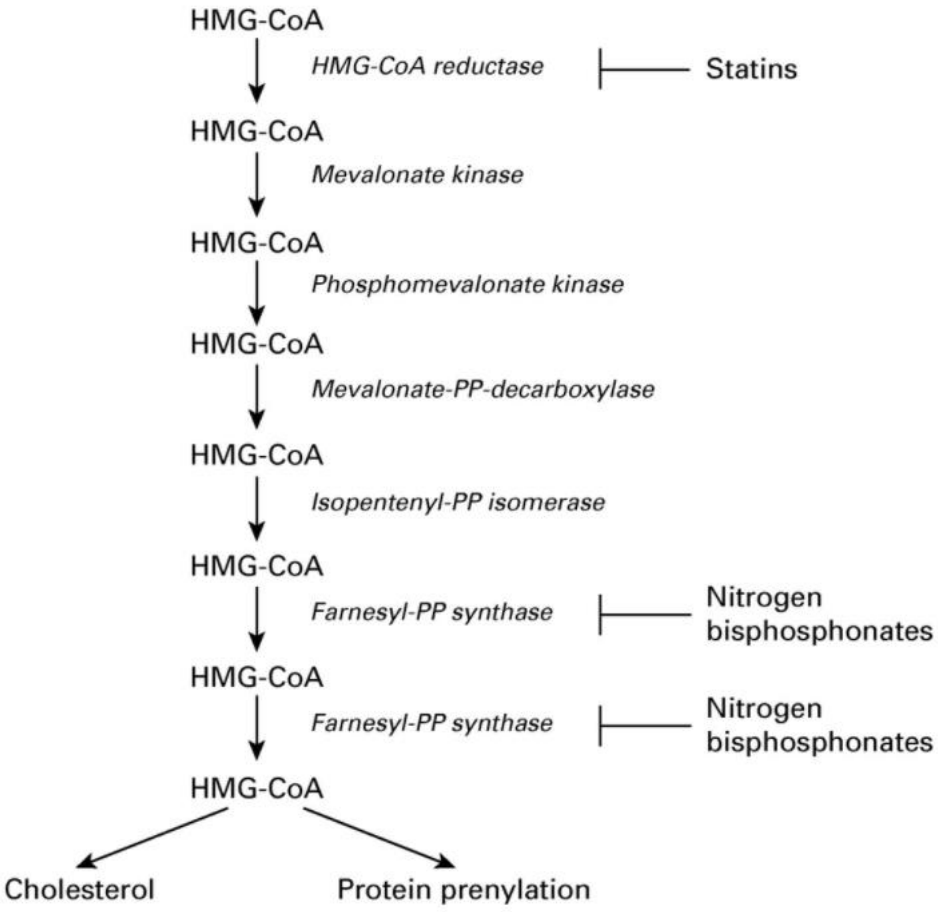


Fig 2.2 Statin and nitrogen-containing bisphosphonate mechanism of action on the mevalonate pathway. Reprint from Sanfilippo: Statins are associated with reduced mortality in multiple myeloma, Journal of Clinical Oncology, 2016.[32]

2.2.1 Statins and prognosis in lymphoid neoplasms

Statins have been shown to inhibit lymphoma cell proliferation *in vitro*.[33] There has been concern, however, that statins may also inhibit the effect of the monoclonal antibody rituximab, which is widely used in lymphoma treatment, given that *in vitro* data have shown inhibited binding of rituximab to its effector receptor, CD20, in the presence of statins.[34] This negative effect has not been confirmed *in vivo*, but most studies have included few or highly selected patients.[35-38] Most authors suggest that associations with statins are likely to be different in different subtypes of lymphoma, and possibly also context-dependent, e.g. with associations depending on the treatment combination. A summary of the results of previously published studies assessing statin use and prognosis of lymphoma overall, or subtypes, can be found in Table 2.2.

In patients with MM, several small studies (n=9 to 146) in the relapsed and refractory setting have suggested that statins are well tolerated in combination with other therapies,[39-41] but only

one large study has been published, in American veterans (n=4,957), which reported improved survival for statin users.[32]

There are several possible pathways suggested for statins to interfere in the progression of lymphoid neoplasms, such as its ability to down-regulate NF-κB signaling, which is a therapeutic target of interest in MM.[42-44] Furthermore, statins are suggested to be able to modulate the BCL2 family proteins which promote cell survival and chemoresistance in multiple cancer types including lymphoma.[45] Moreover, in vitro studies have shown that statins affect the same anti-osteoclast mechanisms as bisphosphonates,[46] a medication included as prophylaxis and treatment of osteolytic lesions in MM patients.

Table 2.2 Studies on statin and NHL survival

Author	Title	Data source	Study population	NHL subtype(s)	Findings
Bachy E. *Am J Hematol* 2016[38]	Statin use is safe and does not impact prognosis in patients with de novo follicular lymphoma treated with immunochemotherapy: An exploratory analysis of the PRIMA cohort study	The PRIMA cohort, patients with de novo follicular lymphoma treated with immunochemotherapy (international multicenter)	1,135 study participants (119 statin users at diagnosis)	FL	Comparable treatment response and survival in terms of all investigated outcome measures, EFS, TTNLT, TTNCT, OS
Ennishi D. *Annals of Oncology* 2009[47]	Statin-independent prognosis of patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP therapy	Newly diagnosed DLBCL patients with R-CHOP treatment at the Cancer Institute Hospital and Okayama University Hospital, Japan	256 patients, including 35 statin users	DLBCL	No significant influence on PFS or OS
Nowakowski G. *JCO* 2010[48]	Statin use and prognosis in patients with DLBCL and FL in the rituximab era	Consecutive patients from the Mayo Clinic Rochester and the University of Iowa	228 DLBCL + 293 FL (21% of DLBCL and 19% of FL patients were statin users)	DLBCL + FL	For DLBCL no association with ORR, EFS, OS For FL, improved EFS for statin users at baseline (HR = 0.45, 95% CI: 0.26, 0.77), including both rituximab-treated (HR = 0.38, 95% CI: 0.14, 1.07) and watch and wait HR = 0.38, 95% CI: 0.17, 0.84)
Koo XS. *Leukemia and Lymphoma* 2011[36]	Effect of concomitant statin, metformin or aspirin on rituximab treatment for DLBCL	DLBCL receiving rituximab-based chemoimmunotherapy at the National Cancer Centre, Singapore	213 (47 (22.1%) were statin users)	DLBCL	Response rate and EFS similar, the same for OS after adjusting for age.
Song MK. *Leukemia Research* 2014[49]	Statin use has negative clinical impact on non-germinal center in patients with diffuse large B cell lymphoma in rituximab era	De novo DLBCL receiving R-CHOP therapy from five medical centers in Korea	409 (146 patients (35.7%) statin users at start of follow-up)	DLBCL (GC and non-GC type)	Statin had significant negative impact on survival of the non-GC type (3-year PFS, multivariate adj HR = 1.55, 95% CI: 1.06, 2.28, p = 0.024) OS (HR = 1.53, 95% CI: 1.04, 2.26, p = 0.023)
Samaras P. *Annals of Hematology* 2009[35]	Concomitant statin use does not impair the clinical outcome of patients with diffuse large B cell lymphoma treated with rituximab-CHOP	DLBCL with first line R-CHOP treatment at University Hospital Zürich or Triemli City Hospital Zürich; Switzerland	145 patients (21 (15%) received statins throughout therapy)	DLBCL	No adverse impact on response to chemotherapy, EFS, and OS

Smyth L. *Br J Haematol* 2020[50]	Statin and cyclooxygenase-2 inhibitors improve survival in newly diagnosed diffuse large B-cell lymphoma: a large population-based study of 4913 subjects	Patients >66 years diagnosed with DLBCL or transformed FL treated with rituximab-containing regimen as first line therapy with curative intent, Population-based study Ontario, Canada	4,913 patients, 46% statin users	DLBCL + transformed FL (if treatment naïve)	Statin exposure for 30 days (HR = 0.97, 95% CI: 0.96, 0.98), Exposure 180 days (HR = 0.84, 95%CI: 0.80, 0.89), Exposure 365 days (HR = 0.71, 95% CI: 0.63, 0.79)
Shanafelt TD. *Leukemia and Lymphoma* 2010[51]	Statin and non-steroidal anti-inflammatory drug use in relation to clinical outcome among patients with Rai stage 0 chronic lymphocytic leukemia	Newly diagnosed CLL with Rai stage 0	686 patients (136 (20%) statin users and 230 (34%) used daily aspirin, ibuprofen, or naproxen at diagnosis)	CLL Rai 0	No difference in time to treatment. No difference in time to salvage treatment for patients starting first-line rituximab-containing treatment
Mozessohn L. *J Natl Cancer* 2017[52]	The association of dyslipidemia with chronic lymphocytic leukemia: a population-based study	Population-based case-control study in Ontario, Canada, using administrative databases	2,124 persons with CLL	CLL	Statins (modeled separately) (adjusted HR = 0.53, 95% CI: 0.46, 0.60), P < .001)
Friedman D. *Leukemia and Lymphoma* 2010[53]	Statin use and need for therapy in chronic lymphocytic leukemia	CLL patients at diagnosis or at start of first treatment at the Duke University and Durham VA Medical Centers	254 (65 (26%) on statins at time of diagnosis)	CLL	No difference in TFS
Chow S. *Leukemia and Lymphoma* 2016[54]	A link between hypercholesterolemia and chronic lymphocytic leukemia	CLL patients at the specialized CLL clinic at Sunnybrook, Canada	231 (107 (46.3%) used statins at the start of the study)	CLL	Excluding patients with del 17p, TFT was prolonged for statin users (57.5 (IQR = 32, 8) vs 36 (IQR = 11, 1) months, p<0.02).
Chae, YK. *Blood* 2014[55]	Statin and aspirin use is associated with improved outcome of FCR therapy in relapsed/refractory chronic lymphocytic leukemia	Relapsed/refractory CLL treated with salvage FCR	280 patients (58 patients received statins, aspirin, or both, 17 (6%) statins only)	CLL	Users of statins and aspirin had improved PFS (HR = 0.34, 95% CI: 0.18, 0.65), OS (HR = 0.40, 95% CI: 0.21, 0.79) Not significant for statin alone.

Abbreviations: EFS= Event-Free Survival, TTNLT = Time to Next Lymphoma Treatment, TTNCT = Time to Next Chemotherapy, OS = Overall Survival, PFS = Progression-Free Survival, ORR = Overall Response Rate, TFS = Treatment-Free Survival, TFT = Time to First Treatment

2.3 ASPIRIN

Aspirin is also one of the most commonly used drugs in Europe and North America, used regularly by approximately half of the adult population according to a recent nationwide US survey.[56] The most common indication is as a platelet inhibitor in the secondary prevention of cardiovascular disease. Aspirin has anti-inflammatory properties through the inhibition of cyclooxygenase 2 (COX-2), thereby inhibiting prostaglandin (Pg) biosynthesis. Prostaglandins, most notably PgE2, are necessary for carcinogenesis and tumor proliferation.[57,58] The inhibition of prostaglandins would thus offer a possible explanation for the reduced cancer incidence seen in pooled randomized controlled trials (RCTs) of aspirin use for cardiovascular prevention.[59] An alternative protective mechanism may be through inhibition of COX-1, which create an antiplatelet effect that potentially modifies the tumor microenvironment by releasing antiangiogenetic agents, diminishing tumor aggressiveness and proliferation.[60] The most evidence for cancer preventive properties of aspirin have been found in colorectal cancer, which has been reported by several clinical and epidemiological studies. Among the first cohort studies in America to report this were the Nurses' Health Study and the Health Professionals' Study.[61-63]

2.3.1 Aspirin and risk of lymphoma

The observed associations between aspirin use and NHL risk have been more mixed. In the pooled RCTs of aspirin use for cardiovascular prevention discussed above, a statistically significant reduction in risk of lymphoma overall was seen for aspirin users, but data was too sparse to allow for subtype-specific analyses.[59] Some authors have suggested that the associations may vary by lymphoma subtype. The largest prospective cohort study published so far reported a null association for NHL overall but an increased risk for the subtype of follicular lymphoma (FL).[64] An overview of previously published studies with prospectively collected data that assess aspirin use and risk of lymphoma is presented in Table 2.3.

Table 2.3 Prospective studies on aspirin and risk of lymphoma

Author	Title	Data source	Study population	Findings
Cerhan. *Int J Cancer* 2003 [65]	Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma	Iowa Women's Health Study cohort	27,290 women, 1992–99 132 NHL cases	Suggestive positive association between NHL overall and use of non-aspirin NSAIDs or non-aspirin NSAIDs *and* aspirin, but no association with aspirin use alone.
Jacobs. *JCNI* 2007[66]	A Large Cohort Study of Long-Term Daily Use of Adult-Strength Aspirin and Cancer Incidence	Cancer Prevention Study II Nutrition Cohort	146,113 participants (69810 men and 76303 women) 132 NHL cases	No association (1992-2003) with NHL
Teras. *Cancer Epidemiol Biomarkers Prev*[64]	Aspirin and other nonsteroidal anti-inflammatory drugs and risk of non-hodgkin lymphoma	Cancer Prevention Study-II Nutrition cohort	149,570 participants, 1,709 incident NHLs, 1992-2007	60+ NSAID pills/month associated with FL, lagged (HR = 1.76, 95% CI: 1.04, 2.98), similar for aspirin and non-aspirin NSAIDs
Walter. *JCO* 2011[67]	Long-Term Use of Acetaminophen, Aspirin, and Other Nonsteroidal Anti-Inflammatory Drugs and Risk of Hematologic Malignancies: Results From the Prospective Vitamins and Lifestyle (VITAL) Study	Vitamins and Lifestyle (VITAL) study	64,839 men and women, recruited 2000-2002 389 cases of mature B-cell neoplasms (incl 66 plasma cell disorders)	High use of low-dose aspirin was associated with an increased risk of CLL/SLL (HR = 2.26; 95% CI: 1.35, 3.79) No clear association with use of regular-dose aspirin.

Abbreviations: NHL= non-Hodgkin lymphoma, NSAID= Non-Steroidal Anti-inflammatory Drug, FL= Follicular Lymphoma, HR= Hazard Ratio, CLL= Chronic Lymphocytic Leukemia, SLL= Small Lymphocytic Lymphoma

2.4 PRIMARY CNS LYMPHOMA

As mentioned initially, the vast majority of PCNSL (>90%) are of the DLBCL subtype, and most commonly of non-germinal center (non-GC) type.[68] They usually have a very high proliferative activity with Ki67 of 70–90%. In immunocompetent patients the tumor most often is EBV early RNA transcripts (EBER) negative. PCNSL occurs more frequently in immunocompromised individuals such as patients with immunodeficiency syndromes,[69] organ transplant recipients receiving immunosuppressive therapy, and in particular in association with HIV, where PCNSL is one of the four defining malignancies for acquired immunodeficiency syndrome (AIDS).

The incidence of PCNSL increased coinciding with the HIV epidemic until the mid-90ies and several reports from other parts of the world have suggested an increasing incidence even after that.[13,14,70] However, population-based levels of both incidence and survival of PCNSL are strongly influenced by cases in HIV positive individuals, and the corresponding incidence and survival in immunocompetent PCNSL have been difficult to unravel.

PCNSL poses particular clinical problems due to its location in the brain. It may be associated with substantial neurological symptoms, and can be hard to reach for biopsies and histological diagnosis. Despite high chemo- and radiosensitivity, it is challenging to treat and has a dismal prognosis. Most used radiotherapy regimens have caused severe sequelae, and the blood brain barrier has made it hard to access with conventional chemotherapy. Chemotherapeutic agents used in PCNSL treatment must be able to cross the blood-brain barrier and reach therapeutic concentrations in the CNS, either in conventional doses like corticosteroids, or like methotrexate (MTX), to able to do so in escalated, rapid intravenous doses. During the first decade of the 2000s, different regimens including high-dose methotrexate (HD-MTX) were introduced, where leucovorin rescue is used to interrupt the MTX effect outside the CNS, enabling higher doses of MTX to reach the CNS. These regimens have shown promising results in RCTs but, in addition to leucovorin rescue, they require pre- and post-hyperhydration, urine alkalinization, and MTX concentration monitoring, and thus careful balancing of this therapy intensification with side-effects control is needed[71].

In this thesis, we wanted to investigate a possible increasing incidence of immunocompetent PCNSL in the Swedish population, and also to evaluate if the new treatment schemes introduced have contributed to any improvement in survival in a population-based setting.

3 RESEARCH AIMS

3.1 SPECIFIC AIMS

Study I
To assess if statin use is associated with improved myeloma-specific survival for patients with MM.

Study II
To assess if statin use is associated with improved lymphoma-specific survival for NHL patients overall or those with common subtypes including CLL.

To assess if concomitant statin use during rituximab treatment is associated with decreased lymphoma-specific survival in patients treated with rituximab.

Study III
To investigate if aspirin use is associated with the risk of developing NHL or common subtypes.

Study IV
To characterize the epidemiology of PCNSL among immunocompetent individuals by investigating if an increased incidence can be established in the past 15 years in Sweden.

To investigate if any survival benefits can be observed in a population-based setting following the development of intensified treatment regimens.

3.2 HYPOTHESES

Study I
Statin use will be associated with improved myeloma-specific survival.

Study II
Statin use will be associated with improved lymphoma-specific survival in NHL patients overall or those with common subtypes including CLL.

But patients treated with rituximab will have contrasting decreased survival based on a hypothesized interference of statins with rituximab treatment.

Study III
Aspirin use will be associated with a reduced incidence of NHL or subtypes.

Study IV
The recent incidence of PCNSL in Sweden will demonstrate increasing rates.

PCNSL survival in Sweden in recent years will demonstrate improvement.

4 MATERIALS AND METHODS

4.1 DATA SOURCES

Studies I, II and IV in this thesis use data from the Swedish population-based registers, whereas study III uses American cohort data. In this chapter, I will briefly describe these data sources. The Swedish population registers date back to the 17th century when the Swedish church started local registers of their parish members. Since 1991, the Swedish Tax Agency has the responsibility for this national registration. In addition, many new registers were started during the 20th century, including many with healthcare data. Since 1947, all Swedish citizens are assigned a personal 10-digit identification number (PIN) at birth or at registration if immigrating to the country.[72] This PIN code enables linkage between the registers, creating excellent possibilities for register-based medical research. The registers are somewhat different in administration and coverage, and the ones used in this thesis are the following:

The Swedish Cancer register was founded in 1958 and is held at the National Board of Health and Welfare. It includes information about all incident malignant diseases, including some benign tumors, in Sweden.[73] In addition to the personal information (PIN, age, sex), the register contains date of diagnosis and hospital, as well as the diagnosis by International Classification of Disease (ICD) code. For diagnoses from 1993 it also contains the more detailed histopathology codes according to the Systematized Nomenclature of Medicine (SNOMED). The register has a dual reporting system by law, where both the physician diagnosing a malignant condition and the pathologist/cytologist answering a pathology report with a malignancy are obliged to report it to the register. This results in a high completeness and accuracy. According to a study performed among the lymphoid malignancies, their overall accuracy was 98% and completeness a bit more varying by aggressiveness of the malignancy, 98% for NHL overall, 97% for myeloma and slightly lower for indolent lymphoma such as CLL, 87%.[74] Studies I, II and IV use data from this register.

The Swedish Lymphoma register (SLR) is a quality register established in 2000, and includes all NHL diagnoses except CLL (that has its own quality register). The SLR contains detailed records of patient- and lymphoma-specific factors such as age at diagnosis, subtype according to SNOMED, diagnostic method, localization of the tumor and factors relevant to calculation of international prognostic index (IPI) score (disease stage, presence of elevated serum lactate dehydrogenase [LDH], performance status according to Eastern Cooperative Oncology Group (ECOG), and presence and specification of any extranodal manifestations). From 2007 onwards the SLR also contains information on treatment type as reported by clinicians in a specific electronic form. The coverage of the SLR has been reported to be >95% as compared to the Swedish Cancer Register.[75] Studies II and IV use data from this register.

The Swedish Cause-of-Death register was founded in 1961 and is kept by Statistics Sweden.[76] It contains information on all deaths in Sweden based on the causes of death reported on the death certificate issued by the physician stating the death. Following a

definition by WHO an underlying (or "main") cause of death is chosen depending on the severity, combination and order of causes of death listed on the death certificate. This process is facilitated by the Automated Classification of Medical Entities (ACME), a specific international algorithm provided by the US National Center for Health Statistics. While the Cause-of-death register is considered almost 100% complete in terms of the actual death and date of death, the accuracy of the underlying cause of death is more varying, reportedly highest among malignant disorders, where a validation study of the diagnoses in the register in 1995 found a 90% agreement with hospital data.[77] Studies I, II and IV used data from this register.

The National Patient register (NPR) was founded in 1964, with more complete coverage since 1987, and is administered by the National Board of Health and Welfare. It originally included the discharge diagnoses from all Swedish hospitals, thus inpatient diagnoses, now called The Swedish National Inpatient Register (IPR). A study from 2011 found that 99% of all hospital discharge diagnoses were registered in the IPR.[78] From 2001, diagnoses from visits to physicians at non-primary outpatient care units are also included, a part called The Swedish National Outpatient Register (OPR). The completeness of this register is lower but no recent validation data are published. However, comparisons with statistics of outpatient visits from "Sveriges kommuner och regioner" (SKR) approximate that somewhere between 1-29% of the non-primary outpatient care is not covered in the register during the period 2005-2018, with missing data mainly in the early years and from visits in the private sector (personal communication, statistician Karin Skölding at the National Board of Health and Welfare). Both the IPR and OPR contain main and contributing ICD codes from hospital discharge/doctors' visits together with information about clinic and date. Studies I, II and IV used data from this register.

The Longitudinal integration database for health insurance and labor market studies (LISA) was established in 1990 and is maintained by Statistics Sweden.[79] The data are collected from several national registers with detailed individual socioeconomic information, including highest attained level of education, available in >98% of individuals aged 25-64 years, with an estimated accuracy of 85%.[79] Studies I, II and IV used data from this register.

The Prescribed Drug register (PDR) was established in July 2005 and contains data on all dispensed prescriptions at Swedish pharmacies.[80] Each dispensed drug is listed with product name, type of medication according to the Anatomical Therapeutic Chemical Classification System (ATC code), strength, pack size, prescribed quantity/number of packages and date of prescription and purchase. Medications administered at hospitals and all over-the-counter medications are not included in the register. For prescribed medications, however, the reporting to the register is automated, and the completeness is considered very high. Missing variables are reported to be found in only 0,2-0,4% of the individuals, slightly higher among antibiotic and antiparasitic medications, up to 1,4% (2019 data). Studies I and II used data from this register.

The Total Population register (TPR) was started in 1968 and is held by Statistics Sweden.[81] It contains data on all citizens of Sweden, including births, deaths, immigration and emigration, and an updated version is provided monthly. Virtually all births and deaths are reported to this register within 30 days. A slightly lower capture of immigration and in particular, of emigration, results in an estimation of up to 0,5% over-coverage of TPR.[81] Studies I and II used immigration and emigration data from this register.

The Cancer incidence database (Statistikdatabasen), a publicly available cancer incidence database, held by Statistics Sweden. Study IV used data from this database.

The Human Mortality Database (HMD) is an international database that began in year 2000 as a collaboration between the Department of Demography at the University of California, Berkeley, USA and the Max Planck Institute for Demographic Research in Rostock, Germany. HMD was created in order to provide detailed mortality and population data and currently includes data from 41 countries or areas. Statistics Sweden provide Swedish data to HMD. Study IV used data from this database.

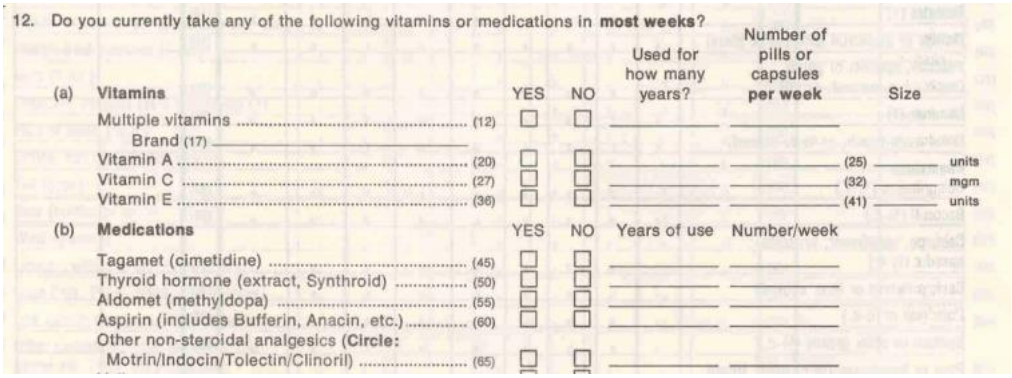
In the US, **the National Death Index** was established in 1979 by the National Center for Health Statistics, in order to provide collected information on deaths and causes of death from the different states. Other health information, however, is less coordinated. Data about health services and drug dispensations are divided in different systems of health plans or insurance providers. Instead, medical researchers have used other approaches for data collection, among them several ambitious cohorts.

The Nurses' Health Study (NHS) was established in the seventies when the oral contraceptives became increasingly used, and researchers wanted to assess possible long-term consequences such as cardiovascular disease and breast cancer. Nurses were chosen as participants because of their dedication to human health and their medical knowledge, and as they were expected to be able to provide accurate information about medications and health issues. Only married nurses were included, as oral contraceptive use was sensitive at the time. So in 1976, 121,700 female, married, US registered nurses aged 30 to 55 years and residing in any of the 11 most populous US states, returned an enrollment questionnaire.[82] Since then biennial follow-up questionnaires have updated cohort members' information on an extensive number of risk factors and diseases. The response rate of the questionnaires has been ≥90% in most follow-up cycles.

The original focus of the cohort study was contraceptive methods, smoking, cancer and cardiovascular disease, but additional questionnaires have been added covering other life-style factors including dietary information, quality of life questions, as well numerous additional diseases and medications. As an example, detailed prospective data on regular use of aspirin, including over-the counter-use, is now available for >25 years of follow-up (Fig 4.1). Biological samples have later been added as well, such as blood, urine and buccal mucosal cells. Two off-spring cohorts have also followed, the NHS2, established in 1989, aiming to cover nurses that started contraceptive use earlier in their adolescence and study a

broader range of premenopausal risk factors and outcomes, and NHS3, initiated in 2010, aiming to include nurses from more diverse ethnical backgrounds and capture more current exposures and habits, also including other healthcare workers, both men and women. NHS3 is also the first NHS cohort to be entirely web based.

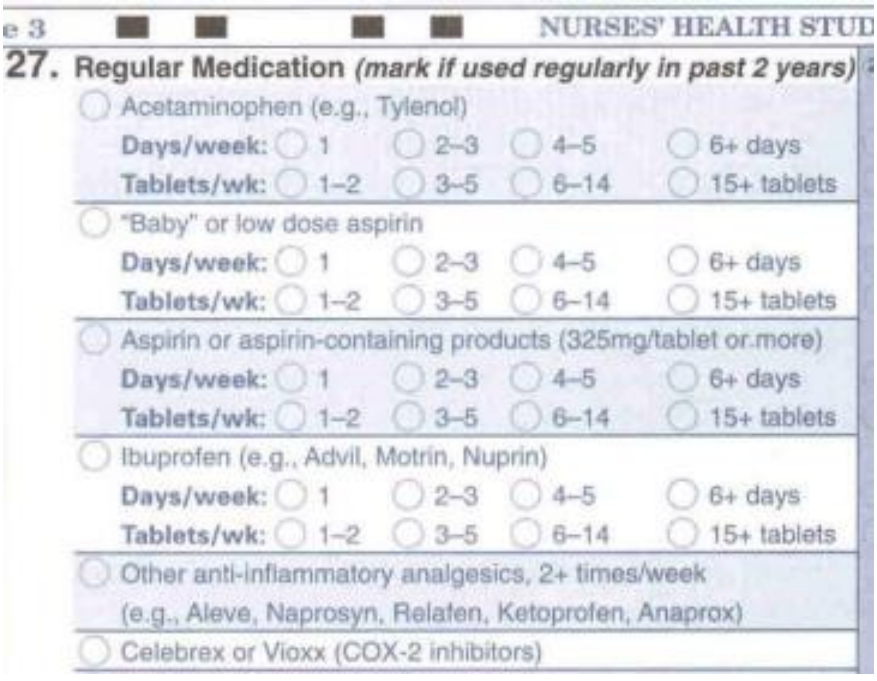
The quality of the NHS database is high, NHS staff perform reviews of medical records and pathology reports in order to confirm diagnoses self-reported by the participants. When medical records are not available, linkage to applicable cancer registers is used. Deaths among cohort members is identified by next-of-kin or by periodic searches of the National Death Index,[83,84] similarly followed by medical record review or linkage to state cancer registers to confirm cause of death or previously unreported diagnoses. Data from this cohort have been used in study III.



12. Do you currently take any of the following vitamins or medications in **most weeks**?

(a) Vitamins		YES	NO	Used for how many years?	Number of pills or capsules **per week**	Size
Multiple vitamins	(12)	☐	☐			
Brand	(17)					
Vitamin A	(20)	☐	☐		(25)	units
Vitamin C	(27)	☐	☐		(32)	mgm
Vitamin E	(36)	☐	☐		(41)	units

(b) Medications		YES	NO	Years of use	Number/week
Tagamet (cimetidine)	(45)	☐	☐		
Thyroid hormone (extract, Synthroid)	(50)	☐	☐		
Aldomet (methyldopa)	(55)	☐	☐		
Aspirin (includes Bufferin, Anacin, etc.)	(60)	☐	☐		
Other non-steroidal analgesics (**Circle:** Motrin/Indocin/Tolectin/Clinoril)	(65)	☐	☐		



e 3 NURSES' HEALTH STUD

27. Regular Medication ***(mark if used regularly in past 2 years)***

Acetaminophen (e.g., Tylenol)
Days/week: 1 2–3 4–5 6+ days
Tablets/wk: 1–2 3–5 6–14 15+ tablets

"Baby" or low dose aspirin
Days/week: 1 2–3 4–5 6+ days
Tablets/wk: 1–2 3–5 6–14 15+ tablets

Aspirin or aspirin-containing products (325mg/tablet or more)
Days/week: 1 2–3 4–5 6+ days
Tablets/wk: 1–2 3–5 6–14 15+ tablets

Ibuprofen (e.g., Advil, Motrin, Nuprin)
Days/week: 1 2–3 4–5 6+ days
Tablets/wk: 1–2 3–5 6–14 15+ tablets

Other anti-inflammatory analgesics, 2+ times/week
(e.g., Aleve, Naprosyn, Relafen, Ketoprofen, Anaprox)

Celebrex or Vioxx (COX-2 inhibitors)

Fig 4.1 Parts of the 1980 and 1990 NHS study questionnaires, showing the sections including the questions regarding aspirin use. Used with permission of NHS responsible Meir Stampfer and Walter Willett.

4.2 STUDY DESIGNS AND STUDY POPULATIONS

4.2.1 Cohort study

All the studies in this thesis use, at least in part, a cohort study design, although the types of cohorts differ slightly (Table 4.1). A cohort study is a study design in which a designated group of individuals are followed-up for exposures and outcomes over a well-defined period of time of time.[85] It measures and compares occurrence (i.e. incidence) of the outcome (i.e. disease). The selection or classification of subjects is based on exposure status, (i.e. citizens of Sweden or nurses in 11 US states). In an observational cohort study the investigator does not assign the exposure. The participants must be free of the outcome at beginning of follow-up, and must be at risk of developing the outcome.

4.2.2 Case-control study

This study design was used within the cohorts of studies I and II, more specifically the so called nested case-control study design. In a cohort study it is sometimes hard to obtain sufficient numbers of outcome events for a rare outcome, or it may be expensive or, as in our case, difficult to obtain or categorize exposure information from everyone in the cohort. Then a case-control study design may be more efficient.[86] Instead of, as in a cohort study, choosing participants based on their exposure status and compare the exposed participants against the unexposed, in a case-control study we select subjects that develop the outcome of interest (*cases*) and compare their exposure to that of the subjects that do not develop the outcome (*controls*). Controls are a sample from the source population that gave rise to the cases, and provide an estimate of the exposure in the source population. The key is to select controls *independently* of their exposure status, otherwise we may introduce selection bias. Further limitations with a case-control study is that there may be reduced precision due to sampling, although this loss can be kept small if the number of controls selected per case is large.

Unless time at risk is incorporated in the sampling, case control studies cannot directly measure risks or rates, instead Odds Ratios (ORs) is the only measure of association that is possible to calculate directly from any case-control study. However, if we sample our controls with risk set sampling, so that controls are matched to cases on time, the ORs equals Hazard Ratios (HRs).[86] In risk set sampling, the controls are sampled with replacement from a unique set of people in the source population who are at risk at the time each case is diagnosed. Thus, the risk set therefore changes from one case to the next, and theoretically a control can later become a case, and the same control may be selected by chance more than once. Risk set sampling also helps address secular trends in exposure over time.

Table 4.1 Overview of the design and data sources of the four studies of this thesis

Parameter	Study I	Study II	Study III	Study IV
Aim	Test association of statin use and survival in MM	Test association of statin use and survival in NHL and CLL	Test association of aspirin use and risk of NHL (including CLL but not MM)	Describe epidemiology and survival of PCNSL
Design	Cohort study and nested case-control study	Cohort study and nested case-control study	Cohort study	Cohort study
Data sources, study population	The Cancer register	The Cancer register, The Swedish Lymphoma register	The Nurses' Health Study (NHS) Cohort	The Cancer register
Study population	All incident diagnoses of MM, N=4,315.	All incident diagnoses of NHL and CLL,, N=16,098 (12,819 NHL + 3,279 CLL)	All women in the cohort with baseline data on aspirin use and without history of RA or cancer, N=78,233	All Swedish residents for study of incidence of PCNSL, all incident diagnoses of immunocompetent PCNSL for study of survival, N=359
Study period	2007-2013	2007-2013	1984-2012	2000-2013
Data sources, covariable and outcome information	**Total population register** (emigration and immigration) **Cause-of-death-register** (date and cause of death) **LISA database** (highest level of attained education) **National Patient Registers** (in- and outpatient, data on any previous MGUS diagnosis and number of outpatient specialist visits prior to diagnosis) **Prescribed drug register** (data on statin use and on concomitant medications used to adjust for comorbidity)	**Total population register** (emigration and immigration) **Swedish Lymphoma register** (patient- and disease-specific characteristics and treatment information) **Cause-of-death-register** (date and cause of death) **LISA database** (highest level of attained education) **National Patient Registers** (in- and outpatient), number of outpatient specialist visits prior to diagnosis) **Prescribed drug register** (data on statin use and on concomitant medications used to adjust for comorbidity)	All covariable data extracted from the **NHS database** (based on collected questionnaire data, previous searches in medical records and National Death index by the staff of the NHS).	**Human Mortality Database** (to identify person-time at risk for analysis of incidence rates) **Swedish Lymphoma register** (to identify PCNSL cases) **National Patient Registers** (in- and outpatient, to identify immunodeficient cases) **Cause-of-death register** (date and cause of death) **Statistikdatabasen** (to obtain age-standardized incidence rates of any brain tumor for comparison)
Outcome	Primary: MM-specific mortality, Seconday: all-cause mortality	Primary: Lymphoma-specific mortality, Seconday: all-cause mortality	Incident diagnoses of NHL (including subtypes DLBCL, FL, CLL, T-cell)	Incidence of PCNSL and mortality in PCNSL

Abbreviations: NHL= non-Hodgkin lymphoma, CLL= Chronic Lymphocytic Leukemia, MM= Multiple Myeloma, PCNSL= Primary Central Nervous System Lymphoma, DLBCL= Diffuse Large B-cell Lymphoma, FL= Follicular lymphoma, RA= Rheumatoid arthritis, NHS= Nurses' Health Study, MGUS= Monoclonal Gammopathy of Undetermined Significance

4.3 CLASSIFICATION OF EXPOSURES AND OUTCOMES

4.3.1 Statin exposure

In studies I and II, all statins available in Sweden during the study period were included: simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. Persons with at least one dispensation of a statin during the 6-month period before diagnosis were considered statin users at time of diagnosis, and persons with at least one dispensation during the period six months after diagnosis were considered statin users after diagnosis. We also assessed statin use at any time during follow-up in a nested case-control study, for which all statin dispensations during the period from diagnosis until six months before index date (death of the case) were included.

Statin dose intensity was classified according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines,[87] depending on the average mg/day dispensed during the period of interest. The ACC/AHA guidelines are based on pooled data from numerous RCTs of statin use in cardiovascular prevention, and categorize statin therapy into low, moderate and high intensity therapy corresponding to the average decrease of serum low-density lipoprotein cholesterol (LDL-C) attained with the respective statin dose (Table 4.3).

Table 4.3 ACC/AHA categories of statin therapy intensity

Intensity	LDL-C reduction	Included statins and doses
Low intensity	<30%	Simvastatin 10-15 mg Pravastatin 10-30 mg Fluvastatin 20-60 mg
Moderate intensity	30 to <50%	Atorvastatin 10-30 mg Simvastatin >15-80 mg Pravastatin>30-80 mg Fluvastatin >60-80 mg Rosuvastatin 5-15 mg
High intensity	≥50%	Atorvastatin >30-80 mg Rosuvastatin >15-40 mg

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association, LDL-C = Low-density lipoprotein cholesterol

Duration of statin use was calculated from time of first dispensation until six months after the last dispensation. If new dispensations occurred after that, they were added to the total duration. In Sweden, a dispensation by practice covers three months of use, so this allowed for some missed doses or uneven distribution of purchases.

4.3.2 Aspirin exposure

Questions about aspirin use were first queried in the 1980 NHS questionnaire, and thereafter in every questionnaire except in 1986. Of note, the question has been posed differently in different years, and a specific question separating low dose aspirin, “baby” aspirin (81 mg in the US) from high dose “adult” strength (325 mg) was not introduced until 2000, thus too late

to allow separate examination of low and high dose aspirin. In order to extract as much information as possible from the available data, we defined aspirin use in three ways in study III:

1. Current status regarding regular use of the equivalent of two "adult" strength (325 mg) tablets/week, classified as yes/no.
2. Cumulative average quantity of use (nonuse, <2, 2-<5, ≥5 tablets/week), for which we determined the average number of adult strength tablets/week at baseline and then computed an updated average each biennial follow-up cycle.
3. Duration of regular aspirin use, for which we summed the consecutive years of regular aspirin use reported (nonuse, ≤5, 6-10, ≥11 years).[88]

If aspirin information was missing on a questionnaire, the information from the previous questionnaire was carried forward. If the information was missing for two or more consecutive questionnaires, the variable was set to missing.

4.3.3 Disease-specific mortality

In study I the outcome was myeloma-specific mortality and in study II lymphoma-specific mortality, defined as any plasma cell- or lymphoma ICD10 codes respectively, as main (underlying) cause of death. In order to validate these outcomes, we also compared these causes of death in a subset of the patients to the information provided in medical records. For this, we followed an algorithm used previously in pediatric cancer.[89,90]

4.3.4 Relative survival and excess mortality

Relative survival (RS) is used as an outcome measure in study IV. RS is the ratio of the observed all-cause survival of a cohort of, in our case, PCNSL cancer patients to the expected survival of a comparable group of individuals in the general population that are assumed free of PCNSL.[91] So called life tables are typically used to represent the expected survival of the general population. We assume that the cancer patients would be exchangeable to the general population, had they not been diagnosed with cancer, so that the difference in mortality between the cancer and the cancer-free groups is explained by the PCNSL. The fact that the cancer patients are included also in the general population has been shown to introduce a very small bias in estimates of relative survival given that the proportion of e.g. PCNSL patients in the general population is so small.[92] In contrast to disease-specific survival/mortality, relative survival incorporates also indirect cancer mortality, such as treatment related mortality or mortality associated with other factors related to the cancer.

Excess mortality is the mortality analogue of relative survival, and is also used in study IV. It is defined as the ratio between the mortality rate in the group under observation, the PCNSL patients, compared to the general population.[91] The excess mortality can be modelled and contrasted by various groups using Poisson regression. In this setting the excess mortality rate ratios provide estimates of the relative difference in excess mortality between the groups. As such the EMRR aims to estimate the same quantity as disease-specific HRs from eg a Cox regression.

4.3.5 Diagnosis of NHL subtypes

Diagnoses of NHL in study III were self-reported by the women in the NHS cohort in the biennial questionnaires. The NHS staff then reviewed medical records and pathology reports in order to confirm the diagnoses. If this confirmatory data could not be accessed, linkage to applicable cancer registers was performed. Diagnoses of NHL from the period before the revised WHO classification of hematological diseases of 2008 were reassessed and reclassified according to the 2008 WHO classification and the guidelines of the International Lymphoma Epidemiology (InterLymph) Consortium Pathology Working Group.[93,94] In our analysis we included all confirmed primay incident diagnoses of NHL (ICD-8 codes 200, 202, 204.4), including CLL, but not multiple myeloma, that has been published earlier.[95]

4.4 STATISTICAL METHODS

4.4.1 A brief introduction to the methods and tests used in this thesis

When we want to estimate the association between an exposure (such as statins or aspirin) and an outcome (such as diagnosis of a lymphoid neoplasm or disease-specific death) in an observational study, we often need to adjust for several potential confounding factors, in multivariable models. Depending on our study design and research question there are several statistical methods we can use. Below, I will briefly discuss the rationale behind the methods used in this thesis as well as some of the statistical tests used. In several studies we will interpret and express the relative rates of the outcome obtained from the regression models as a relative risk.

Cox proportional hazards models (or Cox regression) are used in studies I, II and III in which we have a binary outcome with variable follow-up time and censoring.[96] Cox regression is the most common method for survival analysis. It estimates the ratio of the rates of the outcome (i.e. rate of diagnoses of lymphoid neoplasm or death) for the exposed / unexposed over time, the hazard function, and the outcome measure is Hazard Rate Ratio. With a Cox model, it is possible to evaluate the associations with several covariates at the time, upon the time it takes for the outcome to occur. The Cox model does not give us the baseline hazard, but the ratio of the hazards of the groups we compare. The levels of the variables we compare can change over time if we include time-varying covariates, but the model makes the assumption that the hazard ratio of the groups we compare is constant during the follow-up, i.e. the proportional hazards assumption. If this assumption is not satisfied, our results may not be valid.

Conditional logistic regression is used in the nested case-control analyses in study I and II. Logistic regression is suitable when we have a binary outcome and do not explicitly take follow-up time into account (in our case we used risk set sampling, thus conditioned or matched on time, so time is accounted for implicitly by the study design).[97] The outcome measure is Odds Ratio. Like in the Cox models, we can control for several other factors in the model.

Kaplan Meier curves were used in study I and II to visualize univariate cumulative survival estimates. Using this method it is not possible to adjust for confounders so this type of graph needs to be interpreted with much caution in observational studies.

Flexible parametric survival models were also used in study I and II in order to visualize adjusted survival graphs in comparison to the univariate, given that graphs are not possible to attain with the Cox models we used in our main analyses.[98]

Likelihood ratio tests were used in study I in order to evaluate any effect modification by sex**.** This test assesses the goodness of fit by comparing the log likelihoods of two competing nested statistical models, in this case where one is also adjusting for sex, and the other is not.

Positive Predictive Value is the number of true positive tests (or in our case, accurate diagnoses) divided by all the positive tests (or diagnoses), both true and false. This test was used in study I and II.

Poisson regression is used in study IV to estimate incidence rates of PCNSL. Poisson regression is typically a model for count outcomes but can also be adapted to accommodate survival data. This type of regression model assumes a Poisson distribution for the events, i.e. PCNSL diagnoses, because the event occurs equally likely at any point in time, and the probability of an event occurring is proportional to the length of time you wait.[99] For modelling the incidence rates (PCNSL diagnoses / person-time at risk), the risk time is incorporated in the model as an offset term (i.e. a constant that can vary from individual to individual).

Population attributable fraction is the proportion (fraction) of all cases in the population that can be attributed to the exposure**.** Or mathematically: (proportion of cases exposed) x (attributable proportion in the exposed). This test is used in study IV.

4.4.2 Methods by study

The study methodology applied in studies I and II is similar. The rationale behind these studies is the same, to investigate the associations between statin use and prognosis in lymphoid malignancies in a population-based setting. Because lymphoid malignancies are heterogeneous, with different treatments and putative mechanisms of association with statin use and different research questions, we decided in accordance with suggestions at the half-time seminar, to pursue these different research questions further in two different studies. In MM, with the only large published study being performed in American veterans of whom 98% were male,[32] we wanted to assess if population-based results were the same, and specifically if there was any effect modification by sex. We also wanted to assess whether a prior diagnosis of MGUS affected any possible association between statin use and survival. In NHL on the other hand, given the large differences by subtype in molecular biology and clinical course, we wanted to separate as many distinct subtypes as possible making use of the detailed histologic information available in the SLR. We also wanted to adjust NHL models for age-adjusted IPI score and whether active lymphoma treatment was started or not.

Furthermore, given previous *in vitro* data,[34] we wanted to assess whether there were indications of increased mortality in association with rituximab, one of the most frequently used treatments in lymphoma, but not used at all in MM. Beneath, I will describe the methods for study I, and then point out modifications done in study II.

Study I included all incident multiple MM diagnoses from 2007-2013 identified via the Swedish Cancer register 2007-2013. We followed the patients until the earliest among dates of death, emigration or December 31st 2013. Information on dates and causes of death was added from the Cause-of-Death register and socioeconomic data were retrieved from the LISA database.[79] Data on use of statins and other medications were retrieved from the Prescribed Drug register. Data on any previous MGUS and number of non-primary care doctors' visits during the 3-year period prior to diagnosis were retrieved from the Swedish inpatient and outpatient registers.

We used Cox proportional hazards models to contrast the risk of the primary outcome myeloma-specific mortality and secondary outcome all-cause mortality for statin users compared to non-users, using HRs and 95 % CIs. Analyses were calculated for statin use before and after diagnosis of MM respectively (as described previously, see "Exposure classification" section). In analyses of statin use during the period six months after diagnosis we used a 6-month exposure lag. We thus applied an additional six months delayed entry (beyond the 6 months exposure assessment period) in the analyses, after start of the timescale at time of MM diagnosis. Models were adjusted for age at diagnosis, sex, year of diagnosis, education level and concomitant medication with anticoagulants, diuretics, beta-blockers, ACE inhibitors, calcium blockers and anti-diabetics to capture comorbidity. In sensitivity analyses in order to assess potential healthy user bias we also adjusted for use of PPIs and SSRIs and number of non-primary care doctors' visits during the 3-year period before diagnosis. Separate analyses were also made for patients with previous MGUS diagnosis and we also performed analyses stratified by sex and formally tested potential effect modification by sex using a likelihood ratio test for the interaction parameters.

In order to assess statin exposure at any time during follow-up, we performed a 1:5 matched nested case-control analysis where all "cases" (myeloma-specific deaths) were matched to five controls, defined as participants of the cohort that were still alive and at risk at the date of the death of the case (index date). In this analysis, all statin dispensations during any time from diagnosis until 6 months before index date were included. A sensitivity analysis omitting a longer period before index date was also performed, thus including statin dispensations only up until one year before death of the case.

We also performed dose-response analyses assessing intensity of statin use (low, moderate, high) and performed trend tests across categories of dose intensity. In the nested case-control sample we also performed analyses of duration of statin use with trend tests.

Study II included all incident NHL patients identified in the SLR, and CLL patients identified in the Cancer register from 2007-2013. For persons with two or more lymphoma

diagnoses during follow-up, only the first chronological diagnosis from the SLR and/or cancer register was included in the cohort. If two different NHL diagnoses were reported on the same day, we considered them discordant.

Methods were similar to study I, using multivariable Cox proportional hazards models to compare rates of the primary outcome lymphoma-specific mortality and secondary outcome all-cause mortality for NHL overall, for subtypes, and for CLL. The same covariates as in study I were included in the models, and because of the detailed information in the SLR, we were also able to adjust for additional patient and disease characteristics in all models except CLL models. The risk factors included in the calculation of the international prognostic index score (IPI), including age, disease stage, presence of elevated serum lactate dehydrogenase [LDH], performance status according to Eastern Cooperative Oncology Group (ECOG), and presence and specification of any extranodal manifestations, were in the models as an age-adjusted IPI score. In all models except CLL and the stratified FL models we also adjusted for whether active lymphoma treatment was started or not. In order to investigate patients with or without rituximab treatment separately, we assessed the patients with FL that started treatment at diagnosis separately from those FL patients that did not start treatment but were instead followed with a watch-and-wait approach. We chose this subtype because of the uniform treatment recommendations in Swedish guidelines where rituximab is included in the treatment for all patients with indication for systemic treatment.

We performed a nested case-control analysis similar to the one in study I, except that in study II, we also matched on subtype. We also performed intensity and duration analyses similar to study I. In study II however, we also performed sensitivity analyses requiring two dispensations per 6-month period in order to be categorized as a statin-user. We also explored categorizing statin use in slightly different periods around the time of diagnosis (statin before diagnosis as dispensations 9-3 months before diagnosis), and we explored different exposure lags (3 and 9 months).

Study III was conducted in the Nurses' Health Study cohort (NHS). We included all women who answered the earliest relevant questions on aspirin use in the 1980 questionnaire and excluded those with a baseline history of cancer or RA. We followed the participants until the earliest among dates of NHL or other cancer diagnosis, diagnosis of RA, death or close of follow-up June 2012. We calculated HRs and 95% CIs using multivariable Cox proportional hazard regression models stratified by follow-up period and attained age (in months) to estimate the relative risk of NHL overall and of major subtypes DLBCL, FL, CLL and T-cell lymphoma associated with current regular aspirin exposure status and cumulative average quantity and duration of use (as described in the exposure classification section). Models were adjusted for potential confounding by region of residence, race, current BMI, smoking status and alcohol consumption and a 4-year exposure lag was applied in the analyses.

We also performed trend tests across categories of quantity and duration of aspirin use in order to assess dose-response relationship. Tests for trend were performed based on an ordinal version of the aspirin use variables, created from the category medians.

In the restricted follow-up period for which data were available (1994-2012), additional sensitivity analysis models were adjusted for concurrent use of acetaminophen and NSAIDs (yes, no).

Study IV included all incident cases of PCNSL from 2000-2013, identified in the SLR. To estimate any underreporting to the SLR we linked to an external case-series of confirmed PCNSL from the Uppsala region[100] and a clinical series from the Stockholm region in Sweden. Immunodeficient PCNSL-cases were identified through the Swedish Patient register and excluded. Date and causes of death were obtained from the Cause-of-Death Register. We calculated incidence (per 100,000 person-years) and 95% CIs by age, sex and calendar period, and used relative survival to estimate PCNSL-specific survival. The expected survival was obtained from publicly available life tables. We performed tests for temporal trends in excess mortality using Poisson regression. We used Statistikdatabasen to assess general trends in incidence of all brain tumors in Sweden over the study period, as a reflection of diagnostic intensity of malignancies with CNS location.

We calculated cumulative relative survival by sex, age at diagnosis, calendar period of diagnosis, and performance status and plotted graphs. We also used Poisson regression to estimate excess mortality rate ratios (EMRR) to contrast PCNSL-specific survival in these patient subgroups. We formally tested for statistically significant differences in excess mortality by subgroups using likelihood ratio tests.

4.5 METHODOLOGICAL CONSIDERATIONS

The Swedish population-based registers provide a great source of real-world evidence, but as in all observational research, methodological considerations are essential for the validity of our studies. When assessing potential associations with drug use in an observational study there are several possibilities, including multiple potential sources, of bias and exposure misclassification. Reverse causation (or protopathic bias), confounding by indication and immortal time bias are examples of biases with particular relevance in the studies of this thesis.[101]

Exposure classification is essential in pharmacoepidemiology. The plausibility of an association is strengthened by presence of a dose-response relationship and/or duration of use.[102] As for the dose intensity, the Swedish drug register contains a variable for defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication and it is decided by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) in Oslo, Norway.[103] The DDD would be the most accessible way to categorize statin exposure, but it is a unit of measurement that does not necessarily reflect the recommended or prescribed daily dose. For statins, the treatment intensity has been increasing over time, and the WHOCC has changed the DDDs twice, last in 2009 in order to reflect the changing prescription patterns. Furthermore, the different statins are not equipotent, making comparisons between the different types difficult. Numerous studies have been published about statins and cancer using DDDs to classify

intensity. The reasons for this are obvious: apart from being easily accessible the DDD is also easy to quantify and very few authors have had access to actual lipid levels in cancer patients,[47,54] given that this is not a variable included in the work-up for cancers. Although the correlation between levels of blood cholesterol and cancer is not known, it is reasonable to expect that any association with statin dose intensity would be correlated with the degree of reduction of blood cholesterol, as has been shown in cardiovascular disease.[104]

Using the ACC/AHA categories posed other challenges, however. Given that the different statins are not equipotent, the mean statin dose as a basis for mean intensity could not be used, instead the mean intensity needed to be recalculated every time a person changed statin ATC type. This made the time-dependent statin intensity categorization complicated, and because of this we finally decided to use a nested case-control study design rather than Cox models with time-dependent exposure of statin intensity categories when assessing exposure during the entire follow-up. In those nested case-control analyses, persons changing ATC code were evaluated manually.

Reverse causation, arises when the occurrence of the outcome leads to changes in the exposure or the way the exposure is measured. A common form of this is protopathic bias in pharmacoepidemiologic studies.[101] Potential examples of this in the thesis include that early symptoms of indolent lymphoma may give pain, causing the patient to use aspirin or other NSAIDs. This could create a false association between aspirin use and lymphoma risk, whereas in reality the initiation of the medication was a consequence of the outcome of interest even though the outcome was still undiagnosed.

Another example is that patients with malignant disorders may stop taking prophylactic medications such as statins when they are approaching the end of life.[105-107] This would create an association where non-use of statins would seem associated with reduced mortality, when in fact entering the late palliative phase causes the patient to stop the medication.

Both of these examples would thus induce false associations with the respective medications if not addressed properly. In the first example, one possibility to address this bias is by not classifying a person as having been "exposed" to aspirin until a certain amount of time has passed after the actual initiation of the medication, a so called "exposure lag".[108] In the statin example, the exposure period before the outcome (death) is where we expect the biased exposure to occur, and we need to exclude that exposure period in our analysis.[109,110] In this case as well, by "lagging" the statin exposure classification six months, the last six months of the exposure are not included in our analysis.

Challenges with this approach include making the right assumptions about time in order to use the right lag time. In the example of aspirin and lymphoma, we need to know how long before the clinical diagnosis of lymphoma a person may have symptoms causing them to take aspirin. We also need to make the right assumptions about how long the induction period is, i.e, how long does it take from one's exposure to aspirin before it may influence the risk of the outcome, lymphoma, as well as the latent period, i.e. the time it takes from the lymphoma

develops until it gets diagnosed.[108] Rothman calls the sum of these two periods the "empirical induction period". He argues that the longer it is, the more it will attenuate the effect-estimate because of increasing nondifferential misclassification.[108] Studies with exposures that have very long empirical latency periods will therefore get very different results depending on the length of the follow-up.

Confounding by indication arises because individuals who are prescribed a medication or an intervention are inherently different from those who are not; they get the prescription for a reason. Statin users are different than non-users of statin in that they may have higher blood cholesterol or more cardiovascular disease, and the reasons for *starting* statin treatment may be associated with our outcome of interest rather than the statin medication itself. This is a bias that is hard to fully address, but a frequently used method to attenuate these differences between the exposed and the non-exposed, is to use Propensity Score Matching. This tool allows us to match subjects according to their propensity to be statin users or not and, in so doing, to account for the indication bias.[111,112] However, this method only adjusts for the measured confounders included in the propensity score and not the unmeasured confounders. Also importantly and as discussed earlier, in a case-control study controls must not be selected based on their exposure status, so this method cannot be used in case-control studies.

Immortal time is a bias arising from the differential inclusion of "immortal person-time", a period of follow-up during which outcomes cannot occur because of the treatment definition (Fig 4.5).[113] In this thesis, when we define statin users as those filling at least one statin prescription during the 6-month period after diagnosis, if we would also start follow-up at diagnosis, all early deaths within the first few months would be assigned to the non-users, because the deaths occurred before some statin-users had filled their prescription.

However, if the patients lived long enough to fill their prescription, this time would be counted as person-time for the statin-users. This unbalance creates a period of statistical "immortality" for statin users that first period of up to six months. When added across all statin users, the person-time for statin users has the potential to include a considerable amount of "immortal" person-time, adding substantially to the total person-time of the statin-users, thus falsely lowering their mortality as compared to the non-user group. Studies have shown immortal time bias to be unproperly addressed in several observational studies of cancer survival and adjuvant medications or procedures.[114]

One way to adjust for immortal time bias is known as the landmark analysis, where we decide a (landmark) time point before which we assign/measure the exposure status, and after which we begin to count person-time for both the exposed and the unexposed, to avoid adding misclassified person-time to only one group.[114] In study I and II, the analyses assessing statin use during the period 6 months after diagnosis are landmark analyses, as the exposure status gets assigned *during* those six months, and the accrual of person-time begins only *after* those six months (plus a 6 months lag-time). In a landmark analysis, it is important to choose the right landmark timepoint. If we chose it too early, we may misclassify some statin users that do not have dispensations during that time. If we choose it too late, we

postpone the starting point of accrual of person-time and we may lose several patients and limit our statistical power.

In the landmark analysis however, we only make use of the exposure information during a short period of time. If we want to use the information about statin use during the entire follow-up, another way to avoid immortal time bias is to use time-dependent Cox models[115], in which exposure status can change during follow-up, and person-time gets assigned to the corresponding category of exposure status.

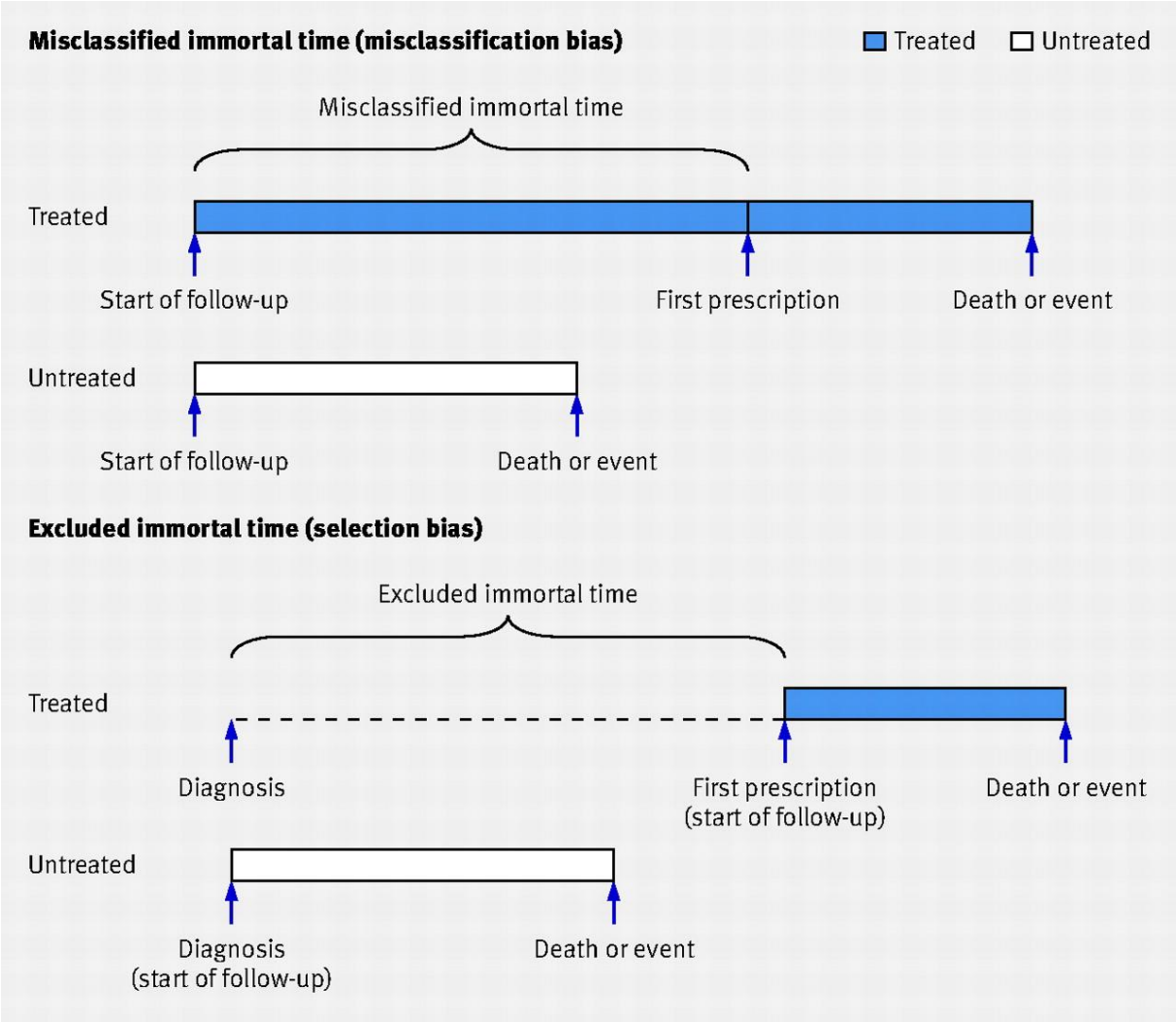


Fig 4.5 Immortal time bias is introduced in a cohort study when (top figure) the immortal time is either misclassified as time in the treated group in a time fixed analysis (although, by definition, if an event would have occurred during this period, it would have been attributed to the untreated group given that the person has not yet filled a prescription). It can also be introduced when (bottom figure) this person-time is excluded from the analysis, given that the start of follow-up is defined by the start of treatment it is by design later in the treated group as compared to the untreated group. (Illustration from Lévesque et al, BMJ 2010)[113]

4.6 ETHICAL CONSIDERATIONS

The patients in studies I, II and IV in this thesis have been identified via Swedish population-based registers and the quality register SLR. The registers have been linked at the National board of Health and welfare. They remove the personal identification number before sharing the data with the Division of Clinical Epidemiology, Karolinska Institutet, so that all data analyzed are pseudonymized. The only exception from this rule in this thesis (in which patients are directly identifiable) is the medical record review for the cause-of-death validation in study I (myeloma-specific death) and study II (lymphoma-specific death) in which we received the personal identification number for a small subset of the patients in order to access medical records and confirm or refute their reported cause-of -death. Given that these patients were all dead, an informed consent could not be asked. In addition, the validation part was performed by a physician at the hematology clinic at the Karolinska University Hospital, Stockholm, who only read the records necessary to adjudicate cause-of-death.

In order to process personal data there must be a "lawful basis for the processing", otherwise it is not considered legal according to GDPR. There are six lawful bases mentioned in GDPR, of which "Processing is necessary for the performance of a task carried out in the public interest" is applicable in our studies. We thus believe the benefits of the knowledge gained are considered to outweigh possible harm to the patients in terms of breach of integrity. The information gained is of general interest to many patients and clinicians, and the data presented is not of sensitive nature. As for the validation study, in which data were not pseudonymized, the data were not sensitive, and the cause-of-death validation attained will be of help for the interpretation of these and other studies to come.

Studies I, II and IV have been approved by the regional ethics review board at Karolinska Institutet.

The patients included in study III were all identified in the NHS cohort described above. The electronic study data archives did not include personal identifying information on study participants but utilized a unique study ID to link relevant data to the corresponding individuals. Informed consent was implied by the voluntary return of study questionnaires. The protocol for the present study was approved by the Human Subjects Research Committees at Brigham and Women's Hospital and the Harvard School of Public Health (Boston, MA), and those of participating cancer registries as required.

5 RESULTS

5.1 MAIN RESULTS OF STUDY I AND II

In **study I**, we identified 4,315 patients with an incident diagnosis of MM, of whom 5.3% had a previous diagnosis of MGUS. There were 1,496 myeloma-specific deaths among 1,913 deaths in total. In the cohort, 21% used statins during the 6-month period before diagnosis, "at baseline", and 86% of the dispensed statins were simvastatin. During the 6-month period after diagnosis 17% used statins. Baseline use of statins was associated with a 17% reduction in myeloma-specific mortality (multivariable adjusted HR = 0.83, 95% CI: 0.71, 0.96) and a 15% reduction in all-cause mortality (HR = 0.85, 95% CI: 0.75, 0.97) (Fig 5.1a), whereas use of statins during the 6-month period after diagnosis was associated with a 27% reduction in myeloma-specific mortality (HR= 0.73, 95% CI: 0.60, 0.89) and a 19% reduction in all-cause mortality (HR = 0.81, 95% CI: 0.69, 0.95) (Fig 5.1b). In the analysis of statin use during the 6-month period after diagnosis and association with myeloma-specific mortality, we performed additional analyses with longer exposure lags (Table 5.1). This did not change point estimates considerably, but confidence intervals got wider.

Table 5.1. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of statin use and myeloma-specific and all-cause mortality in Sweden 2007-2013 with increasing exposure lags

Statin use versus no use after diagnosis*	Myeloma-specific mortality		All-cause mortality	
Model	n-deaths/ N subjects	HR (95% CI)	n-deaths/ N subjects	HR (95% CI)
Adjusted, 6 months lag	855/2,955	**0.73 (0.60, 0.88)**	1,123/2,955	**0.81 (0.69, 0.95)**
Adjusted 1 year lag	689/2,518	**0.73 (0.59, 0.91)**	879/2,359	0.84 (0.70, 1.01)
Adjusted 2 years lag	408/1,690	0.78 (0.59, 1.04)	535/1,690	**0.78 (0.61, 0.99)**
Adjusted 3 years lag	226/1,046	0.84 (0.58, 1.23)	284/1,046	0.87 (0.63, 1.21)
Adjusted 4 years lag	101/619	0.79 (0.45, 1.40)	125/619	0.77 (0.46, 1.28)

Abbreviations: HR= Hazard Ratio, CI=Confidence interval, MM= Multiple myeloma

*During the period 6 month after diagnosis

Adjusted for age category, sex, year of diagnosis, highest education level, medication (yes/no) for: diabetes, anticoagulants, diuretics, beta-blockers, ACE inhibitors, Calcium channel blockers during same period as statin exposure.

We performed sex-stratified analyses in which statin use was significantly associated with a lower myeloma-specific mortality in women (statin use after diagnosis; 0.57, 0.42-0.79) but not in men (0.87, 0.68-1.11), but there was no statistically significant interaction by sex when assessed formally, (P = .094). Sensitivity analyses restricting the patients to those without previous MGUS diagnosis yielded similar results.

The case-control analysis of 855 cases of myeloma-specific mortality and 4,275 controls, showed that participants with a statin dispensation at least once at any time during follow-up had a 35% lower myeloma-specific mortality (HR 0.65; 95% CI 0.52-0.80) compared to non-users (Fig 5.1c). The sensitivity analysis restricting statin exposure to dispensations up until 1 year before index date did not substantially alter the results, although there was a slight attenuation (HR 0.71; 95% CI 0.56, 0.89).

In **study II** we identified 16,098 patients diagnosed with NHL (N=12,819) or CLL (N=3,279). The NHLs included 4,130 DLBCL, 1,751 FL (further divided into 989 FL starting treatment and 762 FL followed with a watch-and-wait strategy), 769 MCL, 766 MZL, 130 Burkitt lymphomas, 952 T/NK-cell lymphomas, 755 LPL and 3,566 discordant and other lymphomas. There were 3,040 lymphoma-specific deaths among a total of 4,743 deaths. In the cohort, 20% used statins during the 6-month period before diagnosis.

Statin use during the period 6 months before diagnosis was not associated with lymphoma-specific mortality in all NHL (multivariable adjusted HR = 0.95, 95% CI: 0.85, 1.06), CLL (HR = 0.91, 95% CI: 0.69, 1.21) or those with any other major NHL subtype, but for Burkitt lymphoma patients we observed a statistically significantly reduced lymphoma-specific mortality (HR = 0.19, 95% CI: 0.04, 0.83, n=20 statin users) (Fig. 5.1A).

Likewise, statin use during the period 6 months after diagnosis was not associated with lymphoma-specific mortality in all NHL patients (HR = 0.93, 95% CI: 0.77, 1.12), CLL patients (HR = 0.79, 95% CI: 0.55, 1.12) or those with the other subtypes except for T/NK-cell lymphoma patients, in whom we observed a statistically significant reduced lymphoma-specific mortality (HR = 0.42, 95% CI: 0.18, 0.98). The post-diagnosis statin use in Burkitt lymphoma could not be assessed due to sparse numbers. When stratifying FL patients by treatment or the watch-and-wait approach, lymphoma-specific mortality was not significantly different for statin users compared to non-users among actively treated patients (HR = 0.87, 95% CI: 0.45, 1.67) nor among patients followed with a watch-and-wait approach (HR = 1.30, 95% CI: 0.47, 3.63).

The nested case-control analysis assessing statin use at any time during follow-up included 896 cases (lymphoma-specific deaths) among NHL with 4,295 controls, and among CLL 235 cases and 1,177 controls. For CLL patients with statin use there was a statistically significant reduced lymphoma-specific mortality (HR = 0.59, 95% CI: 0.41, 0.87), but there was no association in all NHL or other major subtypes. However, Burkitt lymphoma and FL patients under the watch-and-wait approach could not be assessed because of sparse numbers.

When assessing all-cause mortality, in analyses of association with statin use before diagnosis there was a statistically significant reduction in all-cause mortality in T/NK-cell lymphoma patients (HR = 0.70, 95% CI: 0.50, 0.97) and in those with CLL (HR = 0.83, 95% CI: 0.69, 0.99). In CLL patients, this association was seen in analyses of statin use after diagnosis as well (HR = 0.73, 95% CI: 0.59, 0.91). Statin use after diagnosis was also associated with an increased all-cause mortality in FL patients with a watch-and-wait approach.

In neither study I or II did sensitivity analyses with additional adjustment for use of PPIs, SSRIs and number of non-primary outpatient doctors' visits (included together in the sensitivity models) considerably change the results (in MM HR = 0.74 [95% CI: 0.61, 0.90] for statin use after diagnosis with additional adjustment vs HR = 0.73 [95% CI: 0.60, 0.89] in main analyses, and in NHL HR = 0.93 [95% CI: 0.77, 1.12] for both sensitivity and main

analyses , and in CLL HR = 0.77 [95% CI: 0.54, 1.10] with additional adjustment vs HR = 0.79 [95% CI: 0.55, 1.12] in main analysis).

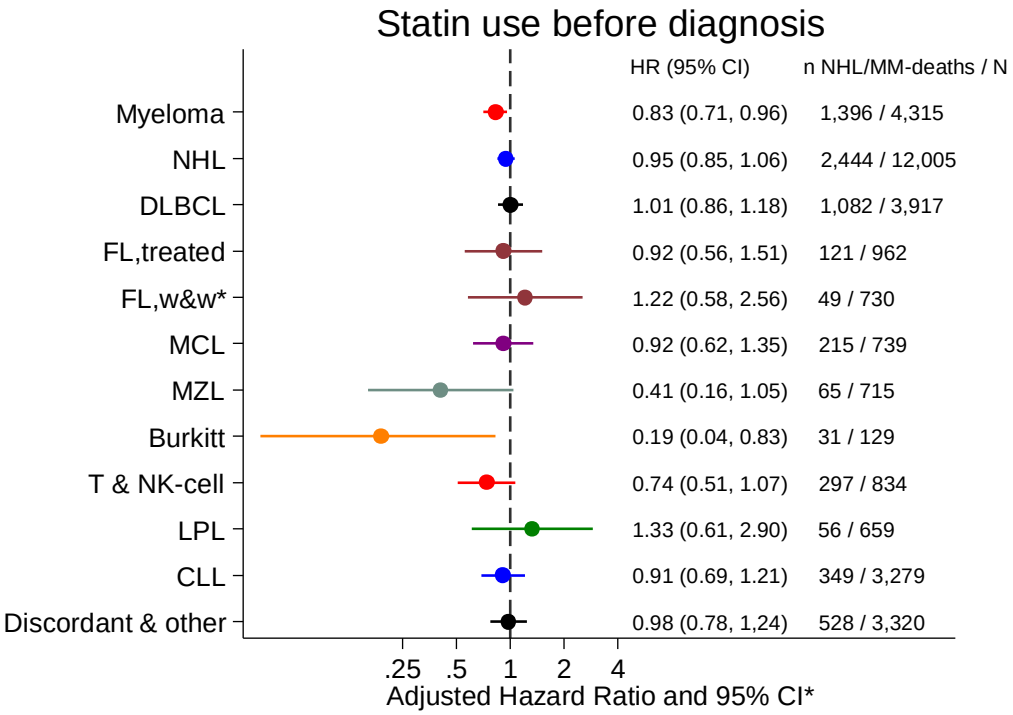
In study II we also explored different exposure lags, 3 and 9 months respectively, which did not considerably change the results. In further sensitivity analyses we required 2 dispensations of statins per 6-month period before and after diagnosis respectively in order to be considered as a statin user. This logically resulted in slightly fewer statin users, but effect estimates remained similar.

The majority of the patients in both study I and II used medium intensity statin therapy, at baseline 67% among both MM and lymphoma patients, compared to low intensity 29% in MM and 30% in lymphoma, and high intensity 4% in lymphoma and 3% in MM. In neither of the studies multivariable adjusted analyses showed any statistically significant evidence of a dose-response relationship with disease-specific mortality. As for all-cause mortality, in study II the trend test for intensity of statin treatment and all-cause mortality was significant for statin use after diagnosis of NHL (multivariable adjusted p_{trend}=0.001).

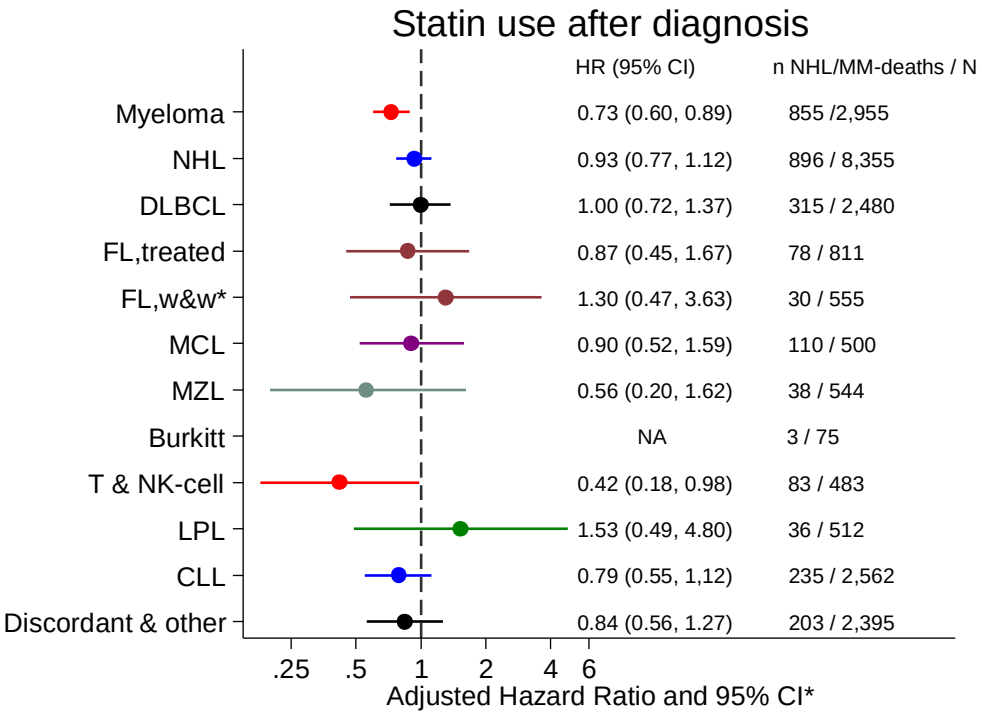
We found no association between duration of statin use and disease-specific mortality for patients with MM, all NHL or CLL in trend tests, but CLL patients with statin use >2 years had a statistically significant improved lymphoma-specific survival (HR = 0.51, 95% CI: 0.30, 0.86).

The validation study of disease-specific mortality showed excellent PPV for both myeloma-specific and lymphoma-specific mortality, 97% and 98% respectively, using the medical record review as the gold standard.

A


Statin use before diagnosis
HR (95% CI)
n NHL/MM-deaths / N
Myeloma
0.83 (0.71, 0.96)
1,396 / 4,315
NHL
0.95 (0.85, 1.06)
2,444 / 12,005
DLBCL
1.01 (0.86, 1.18)
1,082 / 3,917
FL,treated
0.92 (0.56, 1.51)
121 / 962
FL,w&w*
1.22 (0.58, 2.56)
49 / 730
MCL
0.92 (0.62, 1.35)
215 / 739
MZL
0.41 (0.16, 1.05)
65 / 715
Burkitt
0.19 (0.04, 0.83)
31 / 129
T & NK-cell
0.74 (0.51, 1.07)
297 / 834
LPL
1.33 (0.61, 2.90)
56 / 659
CLL
0.91 (0.69, 1.21)
349 / 3,279
Discordant & other
0.98 (0.78, 1,24)
528 / 3,320
.25
.5
1
2
4
Adjusted Hazard Ratio and 95% CI*

B


Statin use after diagnosis
HR (95% CI)
n NHL/MM-deaths / N
Myeloma
0.73 (0.60, 0.89)
855 /2,955
NHL
0.93 (0.77, 1.12)
896 / 8,355
DLBCL
1.00 (0.72, 1.37)
315 / 2,480
FL,treated
0.87 (0.45, 1.67)
78 / 811
FL,w&w*
1.30 (0.47, 3.63)
30 / 555
MCL
0.90 (0.52, 1.59)
110 / 500
MZL
0.56 (0.20, 1.62)
38 / 544
Burkitt
NA
3 / 75
T & NK-cell
0.42 (0.18, 0.98)
83 / 483
LPL
1.53 (0.49, 4.80)
36 / 512
CLL
0.79 (0.55, 1,12)
235 / 2,562
Discordant & other
0.84 (0.56, 1.27)
203 / 2,395
.25
.5
1
2
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6
Adjusted Hazard Ratio and 95% CI*

C

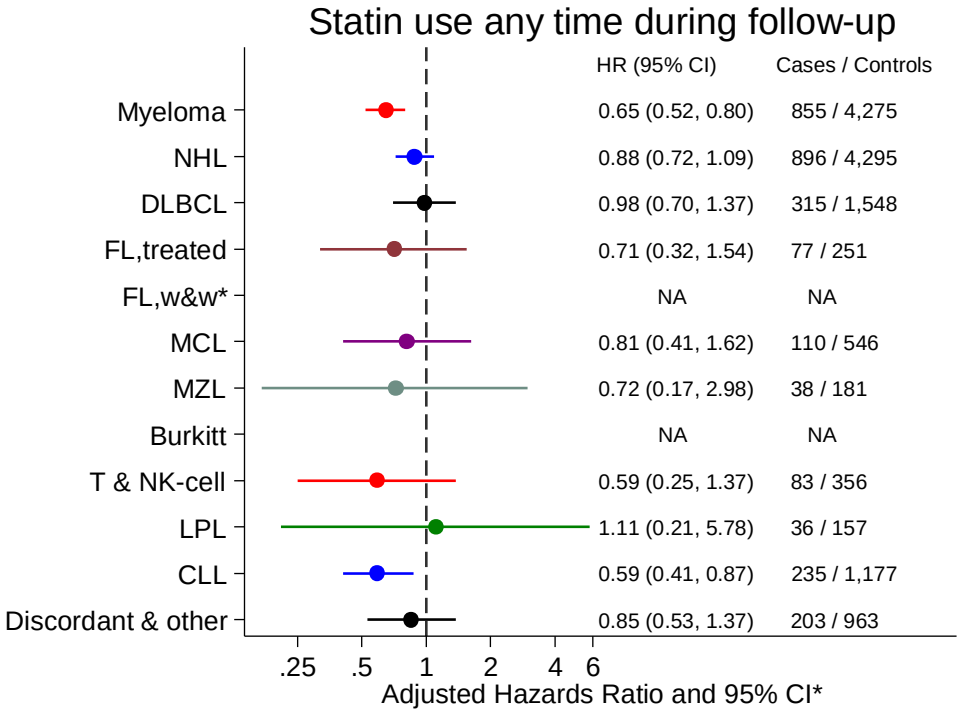

Fig 5.1. Hazard Ratios (HR) and 95% confidence intervals (CI) for the association of statin use in periods before (A), after (B) and any time during follow-up (C) with disease-specific mortality for lymphoid neoplasms including multiple myeloma in Sweden 2007-2013

***Notes**: HRs were calculated with Cox proportional hazards regression models in cohort analyses (A+B) and approximated by ORs in conditional logistic regression models (C) given that incidence density sampling was used when sampling the controls in the case-control-study*

***Abbreviations:** CI=Confidence Interval, NHL= non-Hodgkin lymphoma (except CLL), DLBCL= Diffuse Large B-Cell Lymphoma, FL= Follicular lymphoma, w&w= followed with a watch-and-wait approach (no rituximab treatment), MCL= Mantle Cell Lymphoma, MZL= Marginal Zone Lymphoma, NK Cell= Natural Killer Cell, LPL= Lymphoplasmacytic Lymphoma, CLL= Chronic Lymphocytic Leukemia*

***Adjusted**: Covariates adjusted for: Age category, sex, year of diagnosis, highest education level, concomitant medication (yes/no) for: diabetes, anticoagulants, diuretics, beta-blockers, ACE inhibitors, Calcium channel blockers. All models except CLL and myeloma also adjusted for age-adjusted IPI score and active treatment vs no treatment.*

5.2 MAIN RESULTS OF STUDY III

We identified 78,233 women in NHS who met the inclusion criteria, 46% of whom used aspirin at baseline. During 1,776,841 person-years we confirmed 868 incident NHL diagnoses including 128 with DLBCL, 148 with FL, 251 with CLL/SLL and 28 with T-cell lymphoma.

Overall, we observed no statistically significant associations of current aspirin use status (e.g., yes/no regular use) with risk of NHL overall or any of the subtypes. When categorizing aspirin use as cumulative average quantity of tablets/week, there was a statistically significant increased risk of FL for users of 5+ tablets/week, with a multivariable adjusted HR = 1.89 (95% CI: 1.03, 3.48) and with a significant trend across increasing category of cumulative average quantity (p=0.04) (Table 5.2). We saw no clear trends for the other subtypes.

In the analyses of duration of aspirin use, we did not observe any biologically plausible trends. Neither did we see any suggestion of confounding of the association of any aspect of aspirin use with risk of NHL or subtypes by concomitant use of other NSAIDs or acetaminophen.

Table 5.2 Hazard ratios (HR) and 95% confidence intervals (CI) for NHL in relation to cumulative average quantity of aspirin use

			Cumulative average quantity of tablets/week				
Parameter	**Model**	**Non-user**	**0 < to <2**	**2 ≤ to <5**	**5+**	**User, unknown quantity**	**P trend*** **
Person-years		352,941	654,687	364,095	354,446	50,671	
All NHL	Cases	110	336	198	195	29	
	Simple model*	ref	1.13 (0.90, 1.42)	1.13 (0.88, 1.45)	1.20 (0.94, 1.53)	**1.61 (1.06, 2.45)**	
	Fully adjusted model**	ref	1.12 (0.89, 1.41)	1.15 (0.89, 1.47)	1.21 (0.95, 1.55)	**1.63 (1.07, 2.49)**	0.17
DLBCL	Cases	19	45	28	30	6	
	Simple model*	ref	0.79 (0.45, 1.38)	0.78 (0.43, 1.43)	0.92 (0.51, 1.65)	2.12 (0.84, 5.38)	
	Fully adjusted model**	ref	0.74 (0.42, 1.31)	0.76 (0.42, 1.40)	0.88 (0.49, 1.60)	2.15 (0.85, 5.45)	0.79
Follicular lymphoma	Cases	17	52	35	38	6	
	Simple model*	ref	1.40 (0.78, 2.53)	1.60 (0.86, 2.97)	1.83 (1.00, 3.35)	1.89 (0.69, 5.20)	
	Fully adjusted model**	ref	1.39 (0.77, 2.51)	1.59 (0.85, 2.98)	**1.89 (1.03, 3.48)**	1.96 (0.71, 5.40)	**0.04**
CLL/SLL	Cases	33	83	74	55	6	
	Simple model*	ref	0.92 (0.60, 1.41)	1.38 (0.89, 2.12)	1.09 (0.70, 1.71)	1.17 (0.49, 2.81)	
	Fully adjusted model**	ref	0.93 (0.61, 1.43)	1.42 (0.91, 2.20)	1.10 (0.70, 1.74)	1.21 (0.50, 2.90)	0.27
T-cell lymphoma	Cases	3	15	4	5	1	
	Simple model*	ref	1.55 (0.44, 5,44)	0.82 (0.18, 3.75)	1.00 (0.24, 4.21)	2.11 (0.22, 20.6)	
	Fully adjusted model**	ref	1.70 (0.48, 6,00)	0.92 (0.20, 4.25)	1.16 (0.27, 4.95)	2.30 (0.23, 22.4)	0.57

Abbreviations: HR=Hazard Ratio, CI=Confidence Interval, NHL= non-Hodgkin lymphoma, DLBCL= Diffuse Large B-Cell Lymphoma, CLL= Chronic Lymphocytic Leukemia, SLL= Small Lymphocytic Leukemia

Notes: RA patients excluded. All models stratified on age (in months) and calendar period, calculated with Cox regression with a 4-year exposure lag.

*Simple model: No further adjustments

**Fully adjusted model: Adjusted for region of residence (Northeast, Midwest, South (MD, FL, TX), California), race (white, non-white), BMI (per 5kg/m^2 increase, continuous), smoking status (non-smoker, current smoker, past smoker), alcohol consumption (grams/day, continuous)

*** Trend tests include only aspirin users and also exclude users with unknown quantity

5.3 MAIN RESULTS OF STUDY IV

We identified 359 cases of incident immunocompetent PCNSL during the period. The overall incidence of PCNSL per 100,000 person-years was 0.26 (95% CI: 0.24, 0.29) and the average annual increase 4% (p=0.002). The increasing trend was primarily observed among elderly individuals (70+ years at diagnosis), in this group the average annual increase was 6% (95% CI: 1.02-1.10, p = 0.005) (Fig 5.2). This was consistent with a similar increasing incidence of brain tumors of any type primarily in the elderly.

There were 265 (74%) deaths during follow- up, the majority during the first year after diagnosis (73%), giving a median all-cause survival of 7.6 months (range: 0- 14.9 years). The overall 1- and 5- year relative survival was 0.43 (95% CI: 0.38- 0.48) and 0.24 (95% CI: 0.19- 0.29), respectively.

There was no significant improvement in relative survival across the study period although, for patients diagnosed in the first calendar period (2000- 2002), the relative survival curve appeared to flatten out after approximately 6 years of follow- up, and the same was seen among fit patients (with ECOG 0 at diagnosis) where survival also plateaued 6 years after diagnosis. However, there was little support for statistical cure in the group of patients aged <59 years at diagnosis, although relative survival was highest in this group compared to in other groups. No significant difference in the excess mortality rate for PCNSL patients was observed by sex (P = 0.23)

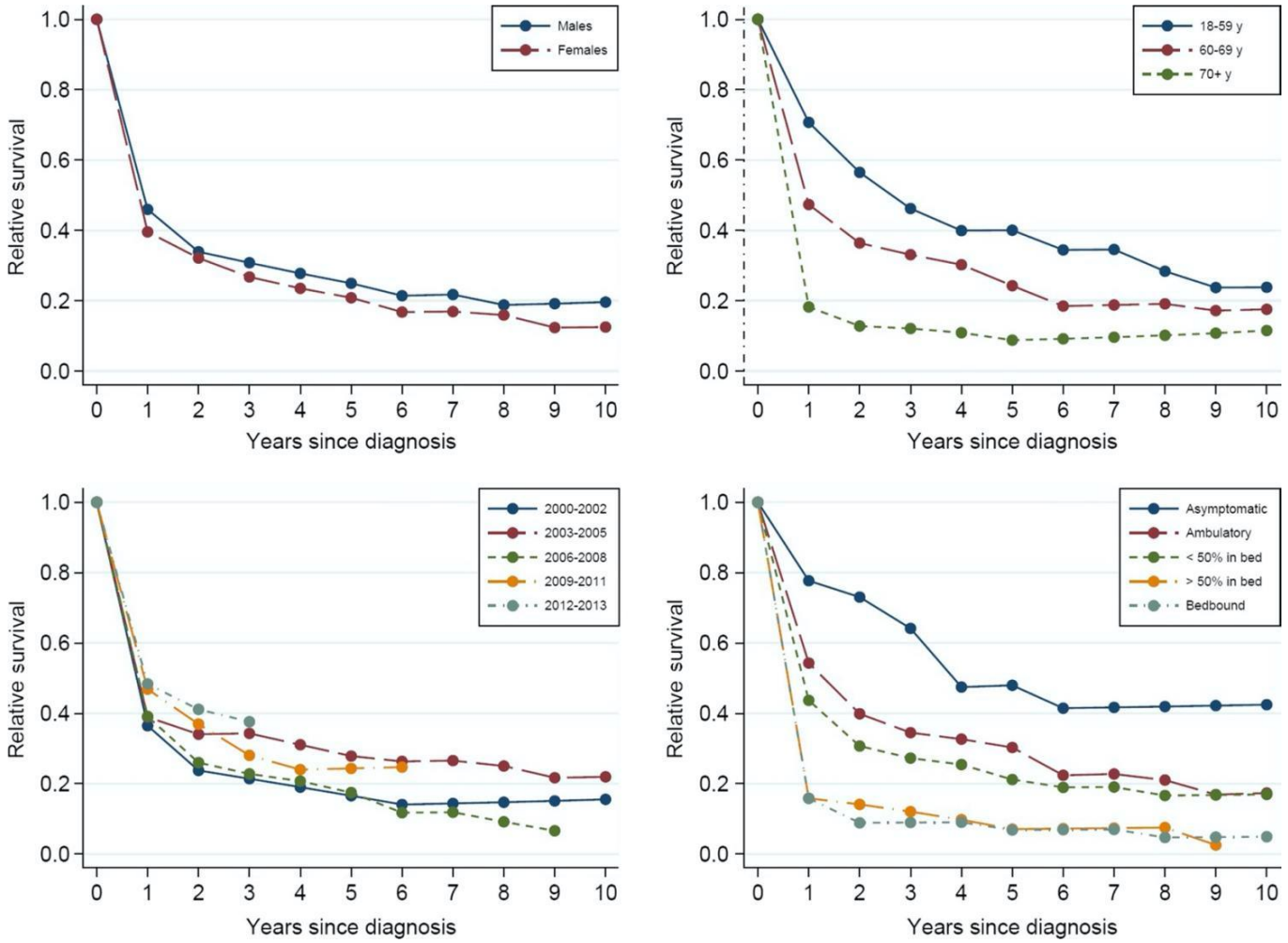

Fig 5.2. Relative survival by sex, age at diagnosis, calendar period of diagnosis and performance status in 359 patients with primary CNS lymphoma (PCNSL) in Sweden 2000 through 2013

6 DISCUSSION

In this thesis we build upon earlier studies of common medication use in relation to the risk and prognosis of lymphoid neoplasms, using Swedish population-based registers and detailed American cohort data. We also investigate the epidemiology of PCNSL in Sweden.

We found that statin use after diagnosis is associated with improved disease-specific survival in patients with MM, whereas no such consistent association was seen for NHL or major NHL subtypes including CLL. We found no evidence of reduced survival in the subset of rituximab-treated FL patients versus FL patients managed with watch-and-wait.

In analyses of aspirin use, we found no evidence of reduced incidence of NHL for aspirin users. Instead, when assessing subtypes separately, there was some evidence of increased risk of FL for higher quantity aspirin users.

There was an increasing incidence of PCNSL in the elderly in Sweden, which we believe is due at least in part to increased diagnostics and reporting in that age group. There was no overall improvement in PCNSL survival during this period, despite the new treatments introduced.

Although observational research inherently carries the risk of several types of biases, it can provide important information, and is an essential complement to RCTs. This is especially true for "old medications" like aspirin or statins in which pharmaceutical companies no longer make investments. It is also important for rare outcomes or for outcomes with long induction periods that are hard to capture within the time-frame of an RCT. There are several instances where observational studies have found clinically important associations that have later been confirmed in RCTs. Early examples include the strong negative association between aspirin and acute myocardial infarction (AMI) reported in in a 1974 study,[116] as well as the strong negative association between intake of folic-acid in the first trimester of pregnancy and neural tube defects[117] and the increased risk of thromboembolism in tamoxifen users.[118] Examples from the NHS cohort include, as previously mentioned, a reduced risk of colorectal cancer in aspirin users, but also the first indication of an increased risk of venous thromboembolism among estrogen users, the latter subsequently reported in several other observational studies.[119-123]

There are, of course, also examples in which the results of observational studies and RCTs have been conflicting,[124] and we need to rigorously consider both our study design and potential alternative explanations for findings in observational studies.

The demand for information about medication use and treatment outcomes in the real world is increasing. At the same time, the costs and time required for RCTs has increased, leading to fewer rather than more new drugs being approved (Fig 6.1). The information available in the Swedish population-based registers have a high coverage and quality, and can help fill these gaps, provided we handle our data with methodological rigor.

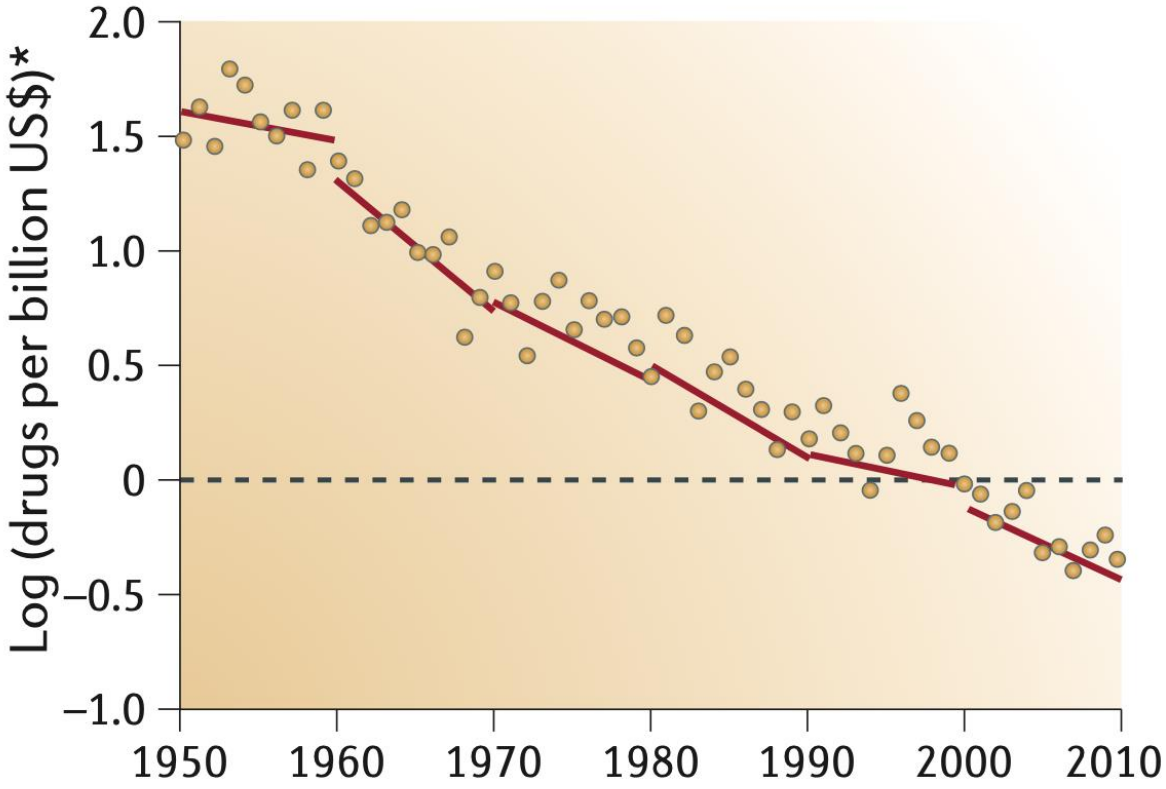

Fig 6.1. The number of new drugs approved by US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development has halved roughly every 9 years, a rate of decline that is fairly similar across recent decades. From Scannell J, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery 2012.[125]

6.1 STUDY I AND II

The association between statin use and improved myeloma-specific survival is intriguing. The consistency with the results of the only large study published so far[32] and the biological rationale with a potential mechanism of action similar to the well proven MM treatment with bisphosphonates add to the plausibility. However, with this study we cannot say whether the association is truly causative.

A strength of the studies is that we were able to evaluate the intensity of statin treatment in the most evidence-based way, using the ACC/AHA guidelines. We wanted to use an intensity scale that aligns with the biological response to statin dose in terms of cholesterol reduction in the blood. A disadvantage with this method was somewhat reduced statistical power, given that very few subjects were in the highest intensity category (3 and 4% respectively).

Some authors stress that when evaluating studies of associations between statin use and cancer mortality it is important to compare the magnitude of the inverse association to the results from studies of cardiovascular mortality prevention.[126] They argue that a stronger beneficial effect in cancer prevention as compared to in cardiovascular prevention is not

plausible. A meta-analysis of RCTs assessing statin use in adults at increased cardiovascular risk but without prior cardiovascular events, reported the RR (95% CI) for all-cause mortality to be 0.86 after 1-6 years (95% CI, 0.80, 0.93).[127] An observational study using American claims data to quantify the statin effect on AMI occurrence, used a 52-variable propensity score to match the statin-users and non-users, and found a 31 % risk reduction for AMI events.[128] Our results are within this spectrum, with lower point estimates for the association of statin use 6 months after diagnosis with myeloma-specific mortality (HR = 0.73, 95% CI: 0.60, 0.89) than with all-cause mortality (HR = 0.81, 95% CI: 0.69, 0.9).

Several biases need to be considered when interpreting these results. Ideally, in order to mitigate confounding by indication and healthy user bias, and seeking to approximate the design of a RCT in an observational study, we should have used an active comparator, new user design (ACNU).[129-131] Using an active comparator, the medication of interest is compared with another drug commonly used for the same indication, rather than with no treatment at all. However, given that virtually all lipid-lowering medications prescribed are statins, it is difficult to find an active comparator to statins.

With a new user design, only new users of the medication are included in the study. However, we had very few new users in our material, among MM patients only 77 (2.26%) were probable new users after diagnosis (i.e. had no statin dispensations during the 6 months before diagnosis but had statin dispensations during the 6-month period after diagnosis), and in the studied NHL/CLL cohort 295 (2.28%) were probable new users. A new user design would thus not have been feasible for the statin studies.

Not being able to use the ACNU design to address these possible biases, let us consider in what way our analyses would be distorted by them if present. Residual confounding by indication and healthy user bias typically would have affected our results in opposite ways. Whereas confounding by indication tends to lead to estimates showing increased risk (the medication under study thus seeming more harmful given that only those who are sick get the medication prescribed), the healthy user bias introduces a bias towards a more “protective” effect of the medication under study (given that the health-aware or healthy subjects are more prone to start using the medication as well as to adhere to it).

We aimed to assess possible healthy user bias in sensitivity analyses by adjusting for use of PPIs and SSRIs and number of non-primary care doctor outpatient visits, and we did not find evidence of a pronounced healthy user bias. Given that healthcare in Sweden is tax funded with a very low out-of-pocket cost, statins are accessible for all socioeconomic groups, and in our studies we did not find higher levels of attained education among statin users compared to non-users. In all, healthy-user bias does not appear to be the major explanation of our findings. As for confounding by indication, we should suspect some remaining confounding by indication by cardiovascular disease in our studies, despite having adjusted for use of medications for cardiovascular disease. If so however, this would likely distort our results towards a more harmful effect of statins.

We made efforts to avoid immortal time bias by using a landmark analysis excluding the period of statin exposure assessment in the cohort studies. We also excluded the period of exposure assessment before start of follow-up in the nested case control studies. The potential bias introduced by reverse causation, such as when cancer patients stop prophylactic medications near the end of life or initiate medication use to address symptoms of subclinical disease, is more complex. A Swedish study by Morin et al reported that patients with solid cancers stopped taking statins the month before death (as compared to their use 12 months before death) more frequently than, for example antihypertensive medications (4.7% absolute change for statins compared to 0.3% for medications used to treat hypertension).[105] However, the authors chose not to include hematological malignancies in the study because they reasoned that the prognosis of hematological malignancies is often unclear until late in the disease, and use patterns therefore less predictable. The potential bias introduced by reverse causation here would create an inverse association in which statins would falsely seem to improve survival. This potential bias is hard to account for other than by restricting the period of exposure assessment to avoid assessment of statin use during the last period of life or, as in the aspirin analyses of study III, implementing exposure lags that account for the potential influence of subclinical disease on use habits.

Although we used the same methodology for all lymphoid neoplasms in the statin studies, we found improved disease-specific survival in patients with MM but not in those with NHL. For those differences to be explained by reverse causation, MM patients would have had to stop their prophylactic medications longer before death than NHL patients. In order to explore this, we performed analyses with longer exposure lags in the MM cohort. These analyses have limited power, given that fewer patients survived long enough to remain in the analysis. Also, these studies likely carry a larger degree of statin exposure misclassification given that more patients change exposure status with time. However, in these studies we observed only a loss of precision rather than modifications of the associations of statin use and MM survival, arguing against this as a major explanation of our findings.

In NHL and CLL, there was no consistent evidence of association of statin use with reduced lymphoma-specific mortality in any subtype. The observed reduced lymphoma-specific mortality in Burkitt lymphoma is interesting, but could only be assessed in one time-interval and was based on very few patients, and could thus also have arisen due to chance. In patients with CLL, there was improved lymphoma-specific survival only for statin use at any time during follow-up, and for >2 years duration of statin use. Given that all-cause mortality was significantly improved for CLL patients with statin use in both of the time intervals investigated, the results for lymphoma-specific mortality could be driven by cardiovascular prevention. Another possibility however, considering the significant results for the longer duration, is that our follow-up time was too short to capture a possible longer-term reduction in mortality among statin users. Cancer progression is often slow, even more so for indolent lymphoma and CLL. As a comparison, the inverse association of aspirin with risk of colorectal cancer was only seen after 10 or more years of aspirin use in an RCT in the Women' Health Study.[132]

6.2 STUDY III

In **study III**, the finding of an increased risk for FL for users of high quantities of aspirin, was consistent with the only published large prospective study to date with detailed subtype data including analyses of FL, adding plausibility to our finding.[64] Despite the large cohort size however, we had a relatively small number of FL patients to analyze, illustrating that even larger sample sizes are needed to investigate this association further. In the analyses of duration of aspirin use, we did not observe any biologically plausible trends. Although there is no known mechanism for this putative association, FL etiology differs from that of other lymphomas in several aspects worth noting. It affects men and women equally[133,134], and there is no evidence of risk increase with immunosuppression[135]. Whether its risk may be increased by aspirin use warrants further investigation.

A limitation of the study is that we were not able to assess low (baby) and high (adult) strength aspirin use separately. However, detailed data about other aspects of the aspirin exposure such as quantity and duration of use was available for more than 25 years of follow-up. Also, our study is conservative in that we excluded patients with RA in order to avoid confounding. Also, in order to attenuate reverse causation by aspirin use for symptoms of subclinical disease in this indolent and slow growing lymphoma, we used a 4-year exposure lag in the analyses.

Regarding NHL overall, we did not find any associations with any aspect of aspirin use. In all, together with the results from previously published cohort studies, it does not seem likely that aspirin has a role in the prevention of lymphoma similar to what has been shown in colorectal cancer. The fact that we, equivalent with the previous large prospective study described above, found a possible risk increase for the indolent lymphoma subtype FL cannot outweigh the benefits aspirin adds in cardiovascular prevention, so this finding has no immediate clinical implications. However, if this finding is confirmed in larger studies, an increased awareness for longtime aspirin users could be warranted.

6.3 STUDY IV

In **study IV**, the increasing incidence of PCNSL in the elderly is consistent with studies based on SEER data (period of diagnosis 1980–2011), that also showed a continuously increasing incidence for the oldest patients.[9,14] In our study, this corresponded with an increasing trend in brain tumors of all kinds in Sweden in the same age group. This indicates that an increasing tendency to diagnose and report CNS tumors in the elderly may at least in part explain the findings. During this period, the possibilities to perform computer tomography (CT) and magnetic resonance imaging (MRI) scans, and also to perform some invasive diagnostic procedures have increased, making it accessible even for the elderly. In the SEER study, that unlike our study also included HIV positive and other immunocompromised patients, another possible explanation is that the increase could in part be due to the elderly population receiving more immunosuppressive treatments after transplantations and as treatments for autoimmune diseases. In our study, although we

excluded HIV positive cases and recipients of organ transplants, we were not able to exclude patients with other immunocompromizing conditions. More intensive immunosuppressing regimens used to treat i.e. rheumatoid arthritis and other autoimmune diseases could possibly also contribute to the increasing PCNSL incidence, although to a very minor degree.

Regarding survival, we found the overall 1- and 5- year relative survival to be 0.43 (95% CI: 0.38- 0.48) and 0.24 (95% CI: 0.19- 0.29), respectively, and the median all- cause survival was 7.6 months (range: 0- 14.9 years). This is lower than the SEER study, that for subjects diagnosed between 2000 and 2008, reported the overall 1- and 5-year relative survival estimates to be 51.4% and 31.2%, respectively, with a median relative survival of 14 months.[9] This is surprising, given that the SEER study also included HIV positive cases. An earlier American study that compared HIV positive cases of PCNSL from presumably HIV negative cases found a considerable difference in prognosis, with a median overall survival of only 2 months for HIV positive patients *vs* 12 months in the HIV negative[136].

To conclude, although our study disappointingly did now show evidence of improved survival, our study period included many patients from the period before modern HD-MTX-based regimens, and a more recent study period as well as a longer follow-up is warranted to evaluate survival with modern regimens. Also, the possible increase in incidence in the elderly needs to be followed further.

7 CONCLUSIONS

Study I

Statin use is associated with improved myeloma-specific survival. Whether this reflects a causal association requires assessment in a RCT setting.

Statin use is not associated with lymphoma-specific survival in NHL patients overall. Possible long-term mortality reductions in CLL patients or those with less common subtypes warrants further investigation in larger studies with longer follow-up. We found no evidence of interaction between statin use and rituximab treatment in patients with FL, suggesting that statins can be continued safely during FL treatment.

Study III

Aspirin use was not associated with risk of NHL overall, but a possible increase in risk of FL for users of larger quantities of aspirin warrants further study in larger populations.

Study IV

The incidence of PCNSL in the elderly is increasing in Sweden, but this may at least in part be due to increased diagnostics and reporting. While we observed no improvement in PCNSL survival during the study period, studies with longer follow-up are needed to evaluate the new treatment schemes introduced late during the study period.

8 POINTS OF PERSPECTIVE

Lymphoid neoplasms are relatively rare, and despite the fact that the studies in this thesis are all among the larger of their kinds, the statistical power for subtype-specific analyses is limited. Several questions that remain after this thesis would benefit from being tested in even larger study populations. A tempting next step would be to pool data from the registers of the other Nordic countries that also have excellent coverage by population-based registers organized in similar ways as the Swedish registers. This would provide better power, for example for studies of intensity of statin use, for which the limited number of high-intensity users hindered our detection of significant associations in dose-response tests. Pooling Nordic data would also be useful for subtype-specific analyses, for example in the Burkitt subtype. Furthermore, a longer follow-up would be desirable, especially for the indolent subtypes such as CLL.

To build further on our aspirin study, we plan to add the men from a similarly designed male cohort, the Health Professionals Follow-up Study (HPFS). We plan to pool our NHS data with the data from approximately 37,750 men with available comparable aspirin use information, adding an expected additional 450 cases of NHL during the follow-up period. In the future, aspirin use and NHL risk could also be evaluated in Nordic register data.

As for the PCNSL study, an updated study assessing the medical records of the PCNSL patients treated at the Karolinska hospital is ongoing. A complementary analysis in pooled data from the Nordic countries with added treatment information from the lymphoma registers of the respective countries would be highly informative, in particular to assess a larger study population treated with HD-MTX-based regimens. Also, a longer follow-up would enable us to assess long-term effects of these new treatments in a population-based setting. Furthermore, pooled data from the Nordic countries would enable us to assess treatment outcomes with the tyrosine kinase inhibitor ibrutinib in a population-based setting. This new treatment, taken as a pill, has shown promising results in small studies, but larger studies are still lacking.

A challenge with research in the SLR has been incomplete data for certain variables in the earlier years, such as treatment information. The completeness of this information is improving, which is reassuring and essential for register-based research on chemotherapy treatments and other treatments that are not covered by the drug register. However, many of the new medications are pills taken at home, which are thus possible to capture through the drug register.

Further possibilities with pooled Nordic data would be to assess combinations of treatments, which is often used in the hematology/oncology setting. The promising results reported for combinations of venetoclax and statins in NHL patients[137] and for, or statins acting as sensitization for anthracycline treatment in acute myeloid leukemia[138] are examples of this.

In order to further evaluate possible reverse causation in studies I and II of this thesis, patterns of deprescription of medications towards the end of life in the Swedish population ideally

should be better characterized. Future studies investigating these patterns are thus warranted. This would help disentangle mechanisms of possible reverse causation not only in the studies of this thesis, but of future studies of other medications and cancer survival as well.

As a next step, register-based controlled trials similar to those performed initially to evaluate cardiovascular interventions[139,140] would be ideal in the hematology/oncology setting, and an optimal approach for further confirmation of many of the results of this thesis. A possible RCT adding statin to any other physician's choice of MM treatment at time of MM diagnosis could be an example.

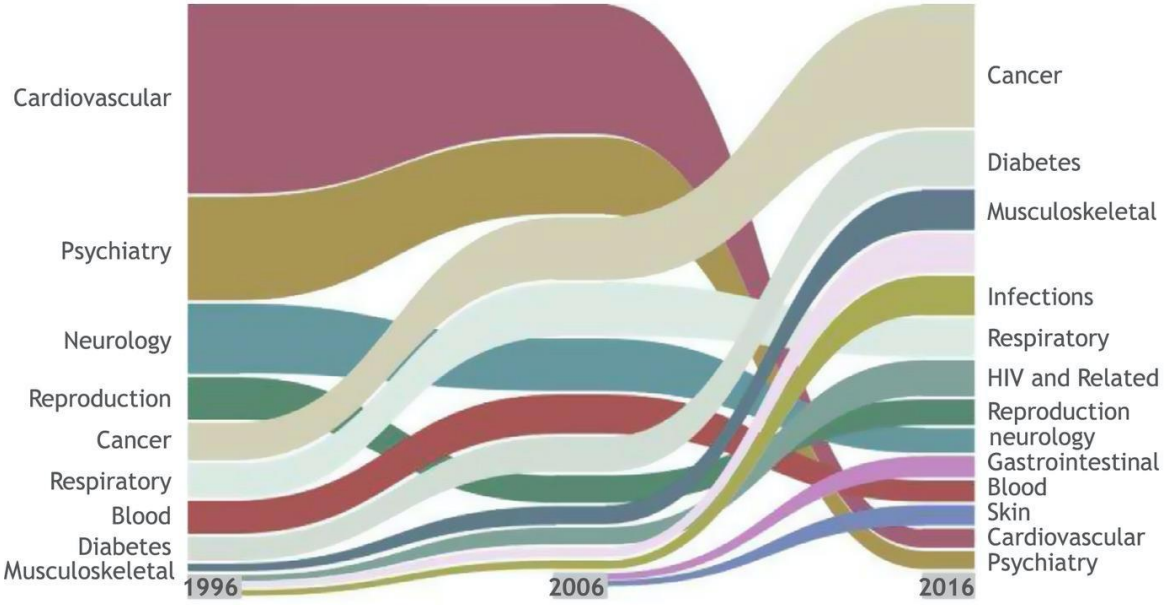

Fig 8.1 From Lee M et al: Innovation in Regulatory Science Is Meeting Evolution of Clinical Evidence Generation, Clinical Pharmacology and Therapeutics, 2019[141]

To conclude, considering the increasing challenges in terms of time and costs required for RCTs, the relative rarity of lymphoid neoplasms and the explosion of new treatment options available or in development for many conditions in the hematology/oncology setting[141] (Fig 8.1), the need to evaluate their benefits in a real-world setting is increasing. This is also important for intensive treatments like the HD-MTX regimens in PCNSL. We have a lot to gain by understanding the pitfalls and possibilities of our registers and available real-world data and use the wide palette of epidemiological methods with the greatest possible rigor.

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