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Letters

RESEARCH LETTER

Statin Use Is Associated With Reduced Heart Failure and Risk of Death in Non-Hodgkin Lymphoma

A recent study showed that statin exposure reduced the risk of anthracycline-related cardiac dysfunction in lymphoma patients.[1] However, limited data are available regarding the association between statin use and heart failure (HF) events and overall survival in lymphoma patients.[2,3] We conducted a retrospective cohort study using the Taiwan National Health Insurance Research Database and the National Cancer Registry to evaluate the effect of statin use on clinical outcomes in patients with non-Hodgkin lymphoma (NHL).

We identified 20,471 patients with newly diagnosed NHL from the NHIRD between 2012 and 2019. After excluding individuals <18 years of age with a prior history of lymphoma, missing data, or outcomes occurring before enrollment, 15,466 patients were included. Outcomes were HF events (defined as any HF hospitalization or a new HF diagnosis on 2 or more instances within a 30-day period in the ambulatory setting), major arterial (myocardial infarction or ischemic stroke) or venous events (deep vein thrombosis or pulmonary embolism), and overall survival. NHL histology and staging information were obtained from the National Cancer Registry. We performed propensity score matching to balance demographics, comorbidities, NHL cell type (B vs T cell), NHL aggressiveness (indolent vs aggressive according to the fifth edition of the World Health Organization classification), and staging between statin users and nonusers. Statin users were defined as those who received a statin within the 6 months preceding the lymphoma diagnosis and took statins for more than 90% of the subsequent 30-day period. Those who had no documented statin use in the same period were defined as nonstatin users. Multivariable cause-specific Cox proportional hazards models determined the association between statin use and clinical outcomes. Cumulative incidence function (Gray's test) compared overall survival and HF for propensity-matched statin groups. Sensitivity analyses, including modeling statin exposure time as a segmented time-dependent covariate and considering death as a competing risk using the Fine-Gray method (subdistribution hazard), were conducted. The study was approved by the Institutional Review Board of the National Cheng Kung University Hospital.

Among the patients (mean age 62.7 ± 15.5 years, 55.0% male), 14.6% were statin users. Overall, 70.4% of NHLs were considered aggressive by histology; 88.0% were B-cell lymphoma, with the majority being diffuse large B-cell lymphoma (54.3%) followed by follicular lymphoma (12.9%) and marginal zone lymphoma (11.5%). After 1:2 propensity score matching between statin users and nonusers, most covariates were well-balanced, except for slightly higher proportions of coronary artery disease and diabetes in statin users (**Table 1**). Covariates that remained imbalanced (coronary artery disease and diabetes) were included in each Cox model.

Among nonstatin users, the cumulative incidence for HF was 9.3% (95% CI: 8.3%-10.4%) after a mean follow-up of 3.4 ± 2.7 years, whereas 7.7% (95% CI: 6.4%-9.1%) of statin users experienced HF events. Statin use was associated with fewer HF events with an adjusted HR of 0.81 (95% CI: 0.66-0.99). All sensitivity analyses showed similar results. In analysis considering time-varying exposure of statins, longer statin exposure had an HR of 0.68 (95% CI: 0.52-0.86). The effect of statins for HF remained consistent in competing risk analysis (subdistribution HR: 0.81; 95% CI: 0.66-0.99).

The cumulative incidence of death was 45.6% (95% CI: 42.6%-48.9%) in statin users and 50.3% (95% CI: 48.0%-52.6%) in nonstatin users; statin users demonstrated improved overall survival (HR: 0.89; 95% CI: 0.82-0.96). This effect was even more pronounced in the time-dependent analysis of statin exposure (HR: 0.36; 95% CI: 0.31-0.41). There were 44 cardiovascular (CV) deaths, with a cumulative incidence of 0.6% (95% CI: 0.3%-1.1%) in statin users and 0.9% (95% CI: 0.6%-1.3%) in nonstatin users.

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TABLE 1 Baseline Characteristics of Statin Users and Nonusers Among Non-Hodgkin Lymphoma Patients Before and After Propensity Score Matching

	Propensity Score Matching							
	Before				After			
	Total (N = 15,466)	Statin Users (n = 2,263)	Statin Nonusers (n = 13,203)	ASMD	Total (N = 5,358)	Statin Users (n = 1,786)	Statin Nonusers (n = 3,572)	ASMD
Age, y				0.58				0.07
	63.0 (20.0)	69.0 (15.0)	62.0 (21.0)		66.0 (15.0)	69.0 (15.0)	69.0 (18.0)	
Sex				0.06				0.03
Female	6,968 (45.1)	1,073 (47.4)	5,895 (44.7)		2,566 (47.9)	840 (47.0)	1,726 (48.3)	
Monthly income, NTD				0.28				0.03
Dependent	5,100 (33.0)	968 (42.8)	4,132 (31.3)		2,242 (41.8)	732 (41.0)	1,510 (42.3)	
<20,000	3,000 (19.4)	419 (18.5)	2,581 (19.6)		1,008 (18.8)	338 (18.9)	670 (18.8)	
20,000-29,999	4,341 (28.1)	570 (25.2)	3,771 (28.6)		1,373 (25.6)	461 (25.8)	912 (25.5)	
≥30,000	3,025 (19.6)	306 (13.5)	2,719 (20.6)		735 (13.7)	255 (14.3)	480 (13.4)	
Stage				0.11				0.06
1	3,506 (22.7)	565 (25.0)	2,941 (22.3)		1,242 (23.2)	428 (24.0)	814 (22.8)	
2	3,141 (20.3)	501 (22.1)	2,640 (20.0)		1,121 (20.9)	390 (21.8)	731 (20.5)	
3	2,833 (18.3)	401 (17.7)	2,432 (18.4)		983 (18.4)	314 (17.6)	669 (18.7)	
4	5,986 (38.7)	796 (35.2)	5,190 (39.3)		2,012 (37.6)	654 (36.6)	1,358 (38.0)	
Histology								
Cell type				0.04				0.03
B-NHL	13,615 (88.0)	2,014 (89.0)	11,601 (87.9)		4,822 (90.0)	1,598 (89.5)	3,224 (90.3)	
T/NK-NHL	1,851 (12.0)	249 (11.0)	1,602 (12.1)		536 (10.0)	188 (10.5)	348 (9.7)	
Aggressiveness				0.03				0.03
Indolent	4,577 (29.6)	645 (28.5)	3,932 (29.8)		1,558 (29.1)	505 (28.3)	1,053 (29.5)	
Aggressive	10,889 (70.4)	1,618 (71.5)	9,271 (70.2)		3,800 (70.9)	1,281 (71.7)	2,519 (70.5)	
Anticancer therapy								
Rituximab	8,906 (57.6)	1,300 (57.5)	7,606 (57.6)	0.003	3,088 (57.6)	1,033 (57.8)	2,055 (57.5)	0.01
Anthracycline	7,912 (51.2)	1,066 (47.1)	6,846 (51.9)	0.10	2,501 (46.7)	852 (47.7)	1,649 (46.2)	0.03
Cyclophosphamide	10,154 (65.7)	1,430 (63.2)	8,724 (66.1)	0.06	3,360 (62.7)	1,137 (63.7)	2,223 (62.2)	0.03
Vinca alkaloid	9,801 (63.4)	1,378 (60.9)	8,423 (63.8)	0.06	3,227 (60.2)	1,094 (61.3)	2,133 (59.7)	0.03
Steroid	12,706 (82.2)	1,834 (81.0)	10,872 (82.3)	0.03	4,333 (80.9)	1,452 (81.3)	2,881 (80.7)	0.02
Etoposide	1,268 (8.2)	152 (6.7)	1,116 (8.5)	0.07	384 (7.2)	119 (6.7)	265 (7.4)	0.03
Platinum	331 (2.1)	45 (2.0)	286 (2.2)	0.01	119 (2.2)	39 (2.2)	80 (2.2)	0.004
Cytarabine	911 (5.9)	142 (6.3)	769 (5.8)	0.02	340 (6.4)	108 (6.1)	232 (6.5)	0.02
Radiotherapy	617 (4.0)	95 (4.2)	522 (4.0)	0.01	221 (4.1)	70 (3.9)	151 (4.2)	0.02
HSCT	111 (0.7)	13 (0.6)	98 (0.7)	0.02	39 (0.7)	12 (0.7)	27 (0.8)	0.01
CV medications								
ACE inhibitor/ARB	3,286 (21.3)	1,056 (46.7)	2,230 (16.9)	0.67	2,083 (38.9)	689 (38.6)	1,394 (39.0)	0.01
Beta-blocker	2,848 (18.4)	751 (33.2)	2,097 (15.9)	0.41	1,568 (29.3)	520 (29.1)	1,048 (29.3)	0.005
Digoxin	185 (1.2)	37 (1.6)	148 (1.1)	0.04	93 (1.7)	30 (1.7)	63 (1.8)	0.01
MRA	867 (5.6)	149 (6.6)	718 (5.4)	0.05	374 (7.0)	116 (6.5)	258 (7.2)	0.03
Comorbidities								
CAD	1,513 (9.8)	601 (25.6)	912 (6.4)	0.54	977 (18.2)	373 (20.9)	604 (16.9)	0.10
Hypertension	5,561 (36.0)	1,495 (63.7)	4,066 (28.4)	0.72	3,189 (59.5)	1,034 (57.9)	2,155 (60.3)	0.05
Diabetes mellitus	3,079 (19.9)	1,269 (54.1)	1,810 (12.6)	0.96	2,174 (40.6)	794 (44.5)	1,380 (38.6)	0.12
Valve disease	348 (2.3)	92 (3.9)	256 (1.8)	0.13	211 (3.9)	69 (3.9)	142 (4.0)	0.01
Atrial fibrillation	238 (1.5)	53 (2.3)	185 (1.3)	0.07	147 (2.7)	43 (2.4)	104 (2.9)	0.03
CKD/ESRD	1,325 (8.6)	359 (15.3)	966 (6.7)	0.26	704 (13.1)	238 (13.3)	466 (13.1)	0.01

Values are n (%) except age which is median (IQR).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASMD = absolute standardized mean difference; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; ESRD = end-stage renal disease; HSCT = hematopoietic stem cell transplantation; MRA = mineralocorticoid-receptor antagonist; NHL = non-Hodgkin lymphoma; NTD = new Taiwan dollar; PAD = peripheral artery disease.

Although numerical reductions in both CV deaths and cancer-related deaths were observed in statin users, only the reduction in cancer-related deaths reached statistical significance. The cumulative incidence of cancer death was 29.8% (95% CI: 27.4%-32.5%) in statin users and 35.0% (95% CI: 33.1%-37.0%) in nonstatin users, with an adjusted HR of 0.83 (95% CI: 0.75-0.92) for statin users compared to nonstatin

users. There were no differences in the risk for arterial events (HR: 1.05; 95% CI: 0.86-1.28) and venous events (HR: 0.86; 95% CI: 0.59-1.25) between statin groups.

The exact mechanisms for the potential benefit of statins in cancer remain unknown. Our previous study showed that statins were associated with a lower risk of breast cancer-related death.[4] It has been hypothesized that the pleiotropic effects of statins on inflammation and oxidation play important roles in cancer outcomes.

Our study had several strengths. First, the data were derived from a national insurance system which allowed for tracking of clinical information in a large sample. Second, staging and histology data were available, allowing us to consider this important prognostic factor. Third, consistent results were demonstrated by sensitivity analyses. Nevertheless, we acknowledge limitations. First, as a retrospective study, despite careful matching of comorbidities and medications, unmeasured confounding may still exist. Second, certain information including body mass index, smoking, and laboratory data were unavailable. Third, most of the deaths in our study were cancer related. Because physicians tend to attribute the cause of death solely to cancer in cancer patients, the true number of CV deaths may be underestimated. In conclusion, statin use was associated with a lower risk of HF events and improved survival in NHL patients. Further randomized trials are needed to further verify the potential benefits of statins in this specific population.

Chao-Yu Chen, MD[a,b]
Wei-Ting Chang, MD[c,d]
Hui-Wen Lin, BSc[a,e]
Sheng-Hsiang Lin, PhD[e,f,g]
***Yi-Heng Li, MD, PhD**[a]

*Department of Internal Medicine
National Cheng Kung University Hospital
138 Sheng Li Road
Tainan, Taiwan
E-mail: heng@mail.ncku.edu.tw

From the [a]National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [b]Madou Sin-Lau Hospital, Tainan, Taiwan; [c]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan; [d]Chi Mei Medical Center, Tainan, Taiwan; [e]Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [f]College of Medicine, National Cheng Kung University, Tainan, Taiwan; and the [g]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

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