RESEARCH LETTER

The association between statins and subsequent risk of bullous pemphigoid: A population-based cohort study

To the Editor: The incidence of bullous pemphigoid (BP) increases exponentially in the elderly and is associated with a significant health care burden. However, the measures for effective prevention among those with risk factors have yet to be identified. Statins, or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, have been implicated in suppressing BP-associated inflammation.[1,2] Additionally, statins were found to be inversely associated with the occurrence of BP in case-control studies.[3,4] We performed a population-based retrospective cohort study to examine the protective effect of statins against BP.

All data were collected from Taiwan's National Health Insurance Research Database (NHIRD). The study cohort consisted of patients aged ≥50 years with a history of statin therapy for ≥3 weeks per month for over 6 consecutive months between 1997 and 2010. The index date was defined as the date when the patient fulfilled the inclusion criteria. Statin nonusers were randomly selected from the NHIRD and matched to each statin user at a ratio of 4:1 by age, sex, and comorbidity-derived propensity score. The study outcome was the occurrence of BP (International Classification of Diseases, ninth revision, clinical modification code 694.5), confirmed by at least 3 outpatient diagnoses or 1 inpatient diagnosis by board-certified dermatologists. The diagnostic accuracy of this BP identification algorithm has been validated in a previous study.[5] All enrolled

Table I. Demographic data of statin users and nonusers

Parameters	Statin users N = 15,115	Statin nonusers N = 60,460	P value
Age at enrollment, mean (SD), y	64.1 (9.3)	64.2 (9.5)	.26
Sex, No. (%)			>.999
Females	7801 (51.6)	31,204 (51.6)	
Males	7314 (48.4)	29,256 (48.4)	
Comorbidities, No. (%)*			
Hypertension	11,715 (77.5)	47,115 (77.9)	.27
Diabetes mellitus	6307 (39.9)	24,020 (39.7)	.64
Chronic kidney disease	1239 (8.2)	4675 (7.7)	.06
Chronic liver disease	4634 (30.7)	18,736 (31.0)	.44
Coronary artery disease	6722 (44.5)	26,849 (44.4)	.89
Cerebrovascular disease	4567 (30.2)	18,088 (29.9)	.48
Dementia	1449 (9.6)	5656 (9.4)	.39
Parkinson's disease	765 (5.1)	3039 (5.0)	.88
Epilepsy	359 (2.4)	1331 (2.2)	.21
Statin therapy duration, mean (SD), d	1628 (1118)	0 (0)	<.001
Statin therapy duration, median (IQR), d	1463 (679-2344)	0 (0)	<.001
Users of DPP-4 inhibitors, No. (%)[†]	1278 (8.5)	1786 (3.0)	<.001
Users of loop diuretics, No. (%)[†]	1451 (9.6)	4673 (7.7)	<.001
Follow-up time, mean (SD), y	8.3 (2.7)	8.4 (2.8)	<.001

CNS, Central nervous system; *DPP-4,* dipeptidyl peptidase-4; *IQR,* interquartile range; *SD,* standard deviation.
*The listed comorbidities were used to calculate the propensity score for matching.
[†]Users of dipeptidyl peptidase-4 inhibitors and loop diuretics were defined as individuals taking these drugs for >1 day per week during the follow-up period.

Table II. The risk of bullous pemphigoid in statin users compared to nonusers calculated by multivariable subdistribution hazard models adjusted for the competing risk of death

	aHR (95% CI)*	P value
Statin users (vs nonusers)	1.12 (0.62-2.02)	.71
Age (per y)	1.09 (1.06-1.12)	<.001
Male (vs female)	1.66 (1.04-2.65)	.03
With comorbidities (vs without)		
Hypertension	0.77 (0.37-1.57)	.47
Diabetes mellitus	1.76 (1.07-2.87)	.03
Chronic kidney disease	0.69 (0.33-1.48)	.34
Chronic liver disease	1.31 (0.78-2.19)	.31
Coronary artery disease	0.49 (0.30-0.80)	.005
Cerebrovascular disease	2.84 (1.62-4.99)	<.001
Dementia	2.23 (1.39-3.58)	<.001
Parkinson's disease	0.65 (0.31-1.37)	.25
Epilepsy	2.70 (1.31-5.58)	.007
Users of the following drugs (vs nonusers)		
Loop diuretics[†]	2.21 (1.28-3.81)	.004
DPP-4 inhibitors[†]	1.26 (0.39-4.05)	.70

aHR, Adjusted hazard ratio; *CI*, confidence interval; *DPP-4*, dipeptidyl peptidase-4.
*Adjusted for age, sex, use of dipeptidyl peptidase-4 inhibitors, use of loop diuretics, and comorbidities including hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, coronary artery disease, cerebrovascular disease, dementia, Parkinson's disease, and epilepsy.
[†]Users of dipeptidyl peptidase-4 inhibitors and loop diuretics were defined as individuals taking these drugs for >1 day per week during the follow-up period.

subjects were followed-up from the index date until the first BP diagnosis, death, or December 31, 2013.

A total of 15,115 statin users and 60,460 well-matched nonusers were identified from the NHIRD (Table I). The incidence of BP per 1000 person-years during the follow-up period was 0.11 in both groups. This was 2-3 times higher than that in the age-matched population controls, probably due to a higher burden of neurologic comorbidities. After adjusting for potential confounders, the risk of BP in statin users was not significantly different from that in nonusers (adjusted hazard ratio: 1.12, 95% confidence interval [CI]: 0.62-2.02; *P* = .71) (Table II). Stratified analyses by age, sex, and comorbidities did not reveal any significant associations within the subgroups (data not shown).

As statins have a suppressive effect on leukocyte chemotaxis, antigen presentation, and lymphocyte activation, they may play a role in the prevention or treatment of BP.[1] Furthermore, statins inhibit the production of proinflammatory cytokines that have been found to be elevated in the sera and blister fluids of BP patients.[1,2] Both Bastuji-Garin et al[4] and Papadopoulou et al[3] found an inverse association between statins and BP, although the former's results were not statistically significant (Bastuji-Garin et al[4]: odds ratio [OR]: 0.66, 95% CI: 0.39-1.12; Papadopoulou et al[3]: OR: 0.4, 95% CI: 0.22-0.64). In

this nationwide population-based cohort study with adequate follow-up time, we failed to demonstrate a decreased risk of developing BP in statin users.

This study has some limitations. First, although descriptions regarding medications are included in the NHIRD, patient compliance may limit the accuracy. Second, the NHIRD lacks information on disease severity and laboratory studies. In conclusion, our study found no association between statin use and the risk of BP. Whether there are other drugs protective against BP warrants further investigation.

Tsung-Hsien Chang, MD,[a,b] Chun-Ying Wu, MD, PhD,[c,d,e] Yun-Ting Chang, MD, PhD,[a,b] Yi-Hsian Lin, MA,[c] and Chen-Yi Wu, MD, PhD[a,b,f]

From the Department of Dermatology[a] and Division of Translational Research, Taipei Veterans General Hospital, Taipei, Taiwan[c]; Department of Dermatology,[b] Instititue of Biomedical Informatics,[d] and Institute of Public Health and Department of Public Health, National Yang-Ming University, Taipei, Taiwan[f]; and Graduate Institute of Clinical Medicine, China Medical University Taichung, Taiwan.[e]

Correspondence to: Chen-Yi Wu, MD, PhD, Department of Dermatology, Taipei Veterans General Hospital, 201, sec. 2, Shih-Pai Road, Taipei, Taiwan

E-mail: chenyiok@gmail.com

Conflict of interest

None disclosed.

REFERENCES

1. Namazi MR. Statins: novel additions to the dermatologic arsenal? *Exp Dermatol*. 2004;13(6):337-339.
2. Kowalski EH, Kneibner D, Kridin K, Amber KT. Serum and blister fluid levels of cytokines and chemokines in pemphigus and bullous pemphigoid. *Autoimmun Rev*. 2019;18(5):526-534.
3. Papadopoulou A, Zafiriou E, Koukoulis GK, Roussaki-Schulze AV. Drugs associated with bullous pemphigoid: role of HMG-CoA reductase inhibitors. *J Eur Acad Dermatol Venereol*. 2020;34(6): e269-e270.
4. Bastuji-Garin S, Joly P, Lemordant P, et al. Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. *J Invest Dermatol*. 2011;131(3):637-643.
5. Wu CY, Wu CY, Li CP, Chou YJ, Lin YH, Chang YT. Association between dipeptidyl peptidase-4 inhibitors and risk of bullous pemphigoid in patients with type 2 diabetes: a population-based cohort study. *Diabetes Res Clin Pract*. 2021;171:108546.