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Letter to the Editor

Statin and the Risk of Ischemic Stroke or Transient Ischemic Attack in Head and Neck Cancer Patients with Radiotherapy

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Dear Sir:

We read with great interest the study entitled "Incidental statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer" by Addison et al.[1] The study, which included 1,011 head and neck cancer (HNC) patients with 288 (28%) on statins, found that statin was protective against the development of transient ischemic attack (TIA) and ischemic stroke after radiotherapy during a median follow-up of 3.4 years.

With the aim to examine the association between statin and stroke risk after radiotherapy in a larger cohort of HNC patients, we conducted a nationwide population-based study using data from the National Health Insurance Research Database. International Classification of Diseases, Ninth Revision, Clinical Modification was used for disease identification and the cancer status was confirmed using the catastrophic illness registry. We identified newly diagnosed HNC patients receiving radiotherapy from January 1, 2000 to December 31, 2010 (n=48,548), and patients with previous cancer or radiotherapy history were excluded for further analysis. Statin user was defined as use of statin during the entire course of radiotherapy. After propensity score matching of the selected comorbidities, there were 1,073 patients receiving statin (user group) and 1,073 matched patient not receiving statin (nonuser group) during radiotherapy and follow-up. The demographics were not different between the user and nonuser groups except for the use of antithrombotics and antihypertensives, which were of higher incidence in the user group (Table 1). In total, TIA or ischemic stroke developed in 64 patients in the user group and 45 in the nonuser group during the study period, respectively. Cumulative incidences of developing TIA or ischemic stroke in the user and nonuser groups were presented in Figure 1, and no significant difference was observed (log-rank test, P=0.29). The risk of TIA or ischemic stroke was also similar in the competing-risk regression model (adjusted subhazard ratio, 1.35; 95% confidence level, 0.95 to 1.91). Further subgroup analysis showed that statin was associated with reduced risk of TIA or ischemic stroke in patient over 65 years of age, but with elevated risk of TIA or ischemic stroke in female patients (Supplementary Table 1). We also found no significant difference between different statins on the TIA or ischemic stroke incidence.

The preliminary findings from this study showed that the legacy effect of statin during radiotherapy does not lower the subsequent risk of TIA and ischemic stroke in patient with HNC, which is contradictory to the report by Addison et al.[1] Our study population, which comprised mostly of Asians, was different from that of Addison's, and the different ethnic background may contribute to divergent statin resistance. Moreover, nasopharyngeal carcinoma consisted of a significant proportion of HNC in Taiwan.[2] The different treatment field in radiotherapy for HNC may result in different carotid artery pathology. The large sample size and wide coverage (>99%) of the National Health Insurance are the strong points of this study, while the study limi-

Table 1. Comparisons in demographic characteristics and comorbidities in head and neck cancer patient with and without statin during radiotherapy

Characteristic	Statin		*P*
	No (n=1,073)	Yes (n=1,073)	
Gender			0.21
Women	124 (11.6)	143 (13.3)	
Men	949 (88.4)	930 (86.7)	
Age stratified (yr)			0.69
≤49	149 (13.9)	163 (15.2)	
50–64	549 (51.2)	539 (50.2)	
≥65	375 (35.0)	371 (34.6)	
Age (yr)*	60.5±10.2	60.6±10.5	0.90
Comorbidity			
Hypertension	840 (78.3)	830 (77.4)	0.60
Hyperlipidemia	882 (82.2)	882 (82.2)	0.99
Diabetes	531 (49.5)	524 (48.8)	0.76
Congestive heart failure	102 (9.5)	123 (11.5)	0.14
Hypercoagulability	4 (0.4)	4 (0.4)	0.99
Atrial fibrillation	19 (1.8)	25 (2.3)	0.36
Coronary artery disease	449 (41.9)	467 (43.5)	0.43
Chronic kidney disease and ESRD	170 (15.8)	181 (16.9)	0.52
Previous stroke	175 (16.3)	180 (16.8)	0.77
Medication			
Aspirin	891 (83.0)	937 (87.3)	0.01
Clopidogrel	89 (8.3)	248 (23.1)	<0.01
ACEI	627 (58.4)	706 (65.8)	<0.01
ARB	463 (43.2)	604 (56.3)	<0.01
Warfarin	42 (3.9)	61 (5.7)	0.06
Treatment			
Surgery	181 (16.9)	182 (17.0)	0.95
Chemotherapy	776 (72.3)	765 (71.3)	0.60
Cetuximab	18 (1.7)	25 (2.3)	0.28

Values are presented as number (%) or mean±SD. Chi-square test.
ESRD, end-stage renal disease; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
*t-test.

tation is the potential insufficient adjustments for the various confounding factors from its retrospective design.

In summary, statin use during radiotherapy was not associated with reduced risk of TIA or ischemic stroke in Taiwanese patients with HNC. Possible difference in statin resistance and types of HNC might be the explanation for the inconsistent result with the previous study. Future large-scale prospective studies are necessary to determine effectiveness of statin in preventing radiation-induced vascular disease and stroke.

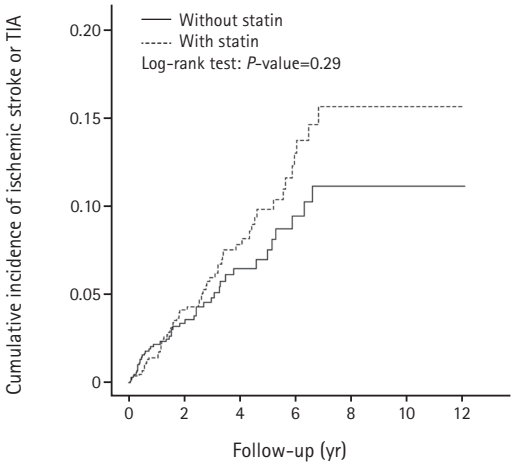

Figure 1. Cumulative incidence of ischemic stroke or transient ischemic attack (TIA) in the user and nonuser group during follow-up.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2018.01585.

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Supplementary Table 1. Incidences and subhazard ratios of ischemic stroke or TIA in head and neck cancer patient with and without statin during radiotherapy stratified by demographics and comorbidity in the competing-risk regression model

Ischemic stroke or TIA	Statin						Crude SHR (95% CI)	Adjusted SHR† (95% CI)
	No			Yes				
	Event	PY	Rate*	Event	PY	Rate*		
Overall	45	2,708	16.6	64	3,090	20.7	1.45 (1.04–2.00)‡	1.35 (0.95–1.91)
Age group (yr)								
≤49	4	444	9.00	9	511	17.6	1.12 (0.70–1.80)	1.15 (0.67–1.95)
50–64	23	1,430	16.1	25	1,550	16.1	0.77 (0.62–0.97)‡	0.83 (0.65–1.05)
≥65	18	834	21.6	30	1,028	29.2	0.69 (0.53–0.91)§	0.74 (0.56–0.99)‡
P for interaction								0.87
Gender								
Women	3	371	8.08	9	453	19.9	4.37 (0.70–27.5)	4.19 (1.03–17.0)‡
Men	42	2,337	18.0	55	2,636	20.9	1.15 (0.80–1.65)	1.02 (0.69–1.52)
P for interaction								0.24
Comorbidity								
No	0	44	0.00	1	52	19.3	-	-
Yes	45	2,664	16.9	63	3,038	20.7	1.23 (0.86–1.76)	1.09 (0.74–1.61)
P for interaction								<0.001
Medication								
Aspirin								
No	4	413	9.68	3	345	8.69	-	-
Yes	41	2,295	17.9	61	2,744	22.2	1.17 (0.80–1.71)	1.10 (0.74–1.64)
P for interaction								0.28
Clopidogrel								
No	42	2,497	16.8	50	2,370	21.1	1.17 (0.79–1.74)	1.00 (0.63–1.57)
Yes	3	211	14.2	14	719	19.5	2.00 (0.56–7.09)	3.85 (0.36–41.7)
P for interaction								0.26
ACEI								
No	11	1,171	9.39	15	1,090	13.8	2.07 (0.71–6.03)	1.53 (0.46–5.07)
Yes	34	1,537	22.1	49	1,999	24.5	1.13 (0.74–1.74)	1.10 (0.70–1.71)
P for interaction								0.26
ARB								
No	22	1,469	15.0	34	1,276	26.7	2.16 (1.09–4.28)‡	1.89 (0.92–3.89)
Yes	23	1,239	18.6	30	1,814	16.5	0.93 (0.51–1.70)	0.74 (0.36–1.51)
P for interaction								0.36
Warfarin								
No	44	2,607	16.9	61	2,879	21.2	1.45 (1.00–2.09)‡	1.31 (0.88–1.94)
Yes	1	101	9.92	3	210	14.3	-	-
P for interaction								0.10
Treatment								
Surgery	37	2,187	16.9	56	2,513	22.3	1.34 (0.90–1.99)	1.32 (0.86–2.01)
No	8	521	15.3	8	577	13.9	0.81 (0.23–2.91)	0.85 (0.27–2.61)
Yes								0.23
P for interaction								
Chemotherapy								
No	9	853	10.6	24	1,031	23.3	2.53 (0.99–6.44)	2.05 (0.74–5.69)

Supplementary Table 1. Continued

Ischemic stroke or TIA	Statin						Crude SHR (95% CI)	Adjusted SHR† (95% CI)
	No			Yes				
	Event	PY	Rate*	Event	PY	Rate*		
Yes	36	1,855	19.4	40	2,059	19.4	1.11 (0.69–1.77)	1.03 (0.58–1.84)
P for interaction								0.12
Cetuximab								
No	45	2,689	16.7	64	3,042	21.0	1.27 (0.89–1.81)	1.13 (0.76–1.67)
Yes	0	19	0.00	0	47	0.00	-	-
P for interaction								0.82

TIA, transient ischemic attack; PY, person-year; SHR, subhazard ratio; CI, confidence interval; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
*Incidence rate per 1,000 person-years; †Variable found to be significant in the Table 1 were further examined in the multivariable analysis (use of aspirin, clopidogrel, ACEI, and ARB); ‡$P<0.05$; §$P<0.01$.

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