

# Statin Use and Risk of Vascular Events Among Cancer Patients After Radiotherapy to the Thorax, Head, and Neck

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**Background**—This study aimed to explore whether statins reduce radiation-induced vascular complications in cancer patients postradiotherapy to the thorax, head, and neck.

**Methods and Results**—We conducted a retrospective cohort study within a provincial linked database of 5718 cardiac patients with thorax and head or neck cancer having undergone radiotherapy between 2000 and 2011. One thousand five hundred fifty-two patients were identified as nonstatin users and 4166 as statin users. The primary outcome of interest was the composite of cerebrovascular (transient ischemic attack, and fatal or nonfatal stroke) or cardiovascular events (fatal or nonfatal myocardial infarction). Time-dependent Cox proportional hazard analyses were performed. The crude event rate was 10.31% for nonusers and 9.03% for statin users (hazard ratio of 0.92 [95% CI 0.76–1.10,  $P=0.3451$ ]), over a mean time to event/censoring of  $534\pm 687$  days for nonusers and  $594\pm 706$  days for the statin users. After adjusting for age, sex, prior history of stroke/transient ischemic attack or myocardial infarction, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic kidney disease, heart failure, and hypertension, statin use postradiotherapy was associated with a nonsignificant 15% relative risk reduction, but a strong trend toward reducing the primary outcome (hazard ratio=0.85 95% CI 0.69–1.04,  $P=0.0811$ ). The use of statins was associated with a significant reduction of 32% for the outcome of stroke alone (hazard ratio=0.68, 95% CI 0.48–0.98,  $P=0.0368$ ).

**Conclusions**—Statin use post radiation therapy was associated with a significant reduction in stroke, with a trend toward significantly reducing cardiovascular and cerebrovascular events. (*J Am Heart Assoc.* 2019;8:e005996. DOI: 10.1161/JAHA.117.005996.)

**Key Words:** cancer and stroke • myocardial infarction • radiotherapy • statin

Radiation therapy (RT) remains an effective treatment for many different types of cancers. However, the net clinical benefit of RT may be attenuated by an increased risk of cardiovascular and cerebrovascular disease (CVD) associated with RT exposure. Cardiovascular disease is the leading cause of morbidity and mortality among cancer survivors.<sup>1</sup> In one of the larger observational studies of childhood cancer survivors, the relative risk for cardiac death was 3.1 times that expected for the general population (CI, 2.4–3.7).<sup>2</sup> In

addition to cardiovascular death, RT has also been associated with increased risk of ischemic stroke, transient ischemic attack, carotid stenosis, and general carotid injury post cervical irradiation.<sup>3–6</sup> The mechanism of RT-induced vascular disease is incompletely understood, but appear to be independent of conventional vascular risk factors with data suggesting a key role for inflammation and accelerated atherosclerosis.<sup>7,8</sup> Furthermore, the pattern of plaque generation within affected arteries (ie, carotid and coronary

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Accompanying Tables S1 through S4 and Figures S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.117.005996>

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## Clinical Perspective

### What Is New?

- Radiation-induced atherosclerosis is a risk factor for cardiovascular and cerebrovascular events.
- There are no studies exploring whether statins reduce vascular complications in cancer patients post thorax, head, and neck radiotherapy.
- In this retrospective cohort study of cardiac patients post radiotherapy, we demonstrate that statin use was associated with a significant 32% reduction in stroke, and a strong trend toward reducing the composite outcome of cardiovascular and cerebrovascular events.

### What Are the Clinical Implications?

- This raises the need for prospective randomized controlled trials to definitively establish the benefit of statins in this at-risk population and to define guidelines on the management of radiation-induced vascular disease.

arteries) appears to be distinct from that generated solely by traditional atherosclerosis.<sup>3,8–10</sup> There is extensive literature illustrating the vascular impact of statin therapy in both primary and secondary prevention of cardiovascular diseases and CVD among the general population.<sup>11</sup> Additionally, statins reduce inflammation. However, despite this plausibility, no study has been conducted in humans addressing whether statin therapy reduces the risk of vascular events after RT, particularly among patients with thorax, head, and neck cancers. Therefore, the aim of this observational study was to test whether statins are protective against vascular events among patients who have received RT to the thorax, head, and neck.

## Methods

### Data Sources

The data, analytic methods, or study materials will not be available to other researchers, given that the government agencies who released the database to us do not allow data sharing, even for this anonymized information.

The administrative, computerized health insurance databases of Quebec constituted the primary data source. All Quebec residents have access to universal care, and the medical and drug services database was merged with the vital status and hospitalization databases by means of a unique anonymous identifier. These databases are now widely used for research purposes and provide suitable clinical granularity (with unlimited procedural codes) to allow for substantial control of confounding variables. The pharmaceutical

database has been evaluated and its validity was confirmed.<sup>12</sup> Moreover, validity studies have been done for several medical services claims.<sup>13,14</sup> Approval for the construction and use of the database was granted by the McGill University Health Center ethics board and the Quebec government agency responsible for privacy of access. Given that patient data were collected and tracked anonymously, individual informed consent was not required.

### Study Patient Population

The study population was derived from a sample of the total Quebec population. Specifically, we had a data set of 380 000 patients >45 years old who had coronary angiography, acute coronary syndrome, or undergone a coronary revascularization procedure—either percutaneous angioplasty or coronary artery bypass surgery—between August 2000 and March 2011. Only patients >65 years old were included in this study as only this subset has access to universal drug coverage and hence, documentation of a prescribed medication list. From this study population, all patients with thorax and head or neck cancer having undergone radiotherapy were identified using *International Classification of Diseases (ICD), Ninth and Tenth Revision codes* and were included in the present study (Table S1). Baseline demographic data were collected, including diagnosis, medical comorbidities, and age on entry into the cohort (Table S2).

### Ascertainment of Radiation and Statin Exposure

For each patient in the cohort, all healthcare medical visits and exposure to head, neck, and mediastinal radiotherapy were identified (Table S1).<sup>15–17</sup> Because this database does not include treatments administered in the hospital, RT exposure was also derived from physicians' billing codes, by identifying corresponding procedure codes for RT. Exposure to statins was measured as the first statin prescription starting from 1 year before time zero (radiation exposure) to event or censor. The subjects were considered not exposed to statins until exposed. For sake of fluidity, patients prescribed statin were considered statin users.

### Ascertainment of Outcomes and Comorbidities

The primary outcome of interest was the occurrence of any of cerebrovascular events (including transient ischemic attack, stroke, carotid revascularization, or stroke death) or cardiovascular events (including myocardial infarction [MI] or fatal MI). The secondary outcome of interest was the occurrence of stroke alone. Multivariate Cox proportional hazard model analyses were conducted to identify predictors of worst outcome. Potential predictors analyzed included age at first

RT exposure, sex, prior history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, heart failure, chronic kidney disease, peripheral vascular disease, coronary artery disease (CAD), and CVD. Age was analyzed both as a continuous and a categorical variable. Age was treated as a categorical variable: 66 to 70 (reference group), 71 to 75 years old, 76 to 80 years old, and >81 years old.

Diagnostic codes for cardiovascular outcomes adhered to the ICD-9 (before 2005) and 10th revisions. For these codes, high positive predictive values have been reported in the general population.<sup>18–20</sup> Survival time was calculated from the index date, the first occurrence to RT until the date of study outcomes, or end of follow-up, whichever occurred first.

Comorbidities were ascertained based on ICD-9 and -10 codes from both inpatient and outpatient medical databases. Statin-associated side effects (hepatitis, transaminitis, myopathy, myositis, myalgia, rhabdomyolysis, and sleep disorders) were identified based on ICD-9 and ICD-10 codes from both inpatient and outpatient medical databases (Table S3).

### Statistical Analyses

Baseline characteristics according to treatment assignment were compared using  $\chi^2$  test for categorical variables and Wilcoxon rank sum test for continuous variables.

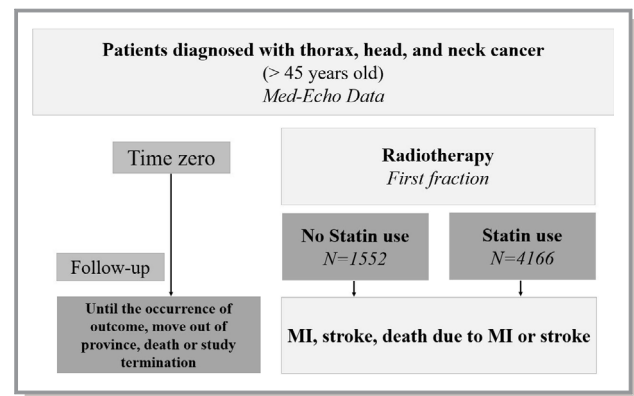
Cox proportional hazards models were used to calculate the hazard ratio and 95% CI for the comparison of event rates in the 2 groups. In the Cox proportional hazards model, time zero was taken as the first occurrence of the exposure (RT). Exposure to statins was measured as the first statin prescription starting from 1 year before time zero to event or censor. Initial statin exposure was analyzed in a time-dependent manner to avoid immortal time bias. Once initial exposure was ascertained, it was analyzed in a time-invariant fashion. Proportional hazards assumption was tested statistically and verified.

Statin-associated side effects were assessed using logistic regression where time zero was the time of radiotherapy exposure. Side effects were categorized by whether they occurred after or before statin exposure to verify a temporal association with exposure. Statistical analyses were performed using SAS (SAS Proprietary Software 9.4 [TS1M1] Institute, Inc, Cary, NC).

## Results

### Baseline and Clinical Characteristics

We identified a total of 5718 patients with thorax, head, or neck cancer who had exposure to RT. The patient cohort was divided into 2 groups according to statin use (Figure 1). There were 1552 subjects in the nonuser group and 4166 subjects



**Figure 1.** Study design—retrospective data collection. MI indicates myocardial infarction.

in the statin-user group. Table 1 summarizes the baseline characteristics and comorbidities for statin-users and nonusers. Overall the mean age for the statin-user group was  $75 \pm 5.8$  years and  $76 \pm 6.8$  for the nonusers ( $P < 0.0001$ ), with females comprising 43% and 51% of the 2 cohorts, respectively ( $P < 0.0001$ ). Mean time to event/censoring was  $534 \pm 687$  days for nonusers and  $594 \pm 706$  days for the statin-users.

The burden of baseline cardiovascular risk factors (Table 1) and most comorbidities (carotid artery disease, CAD, prior MI, peripheral vascular disease, diabetes mellitus, dyslipidemia, and hypertension) was higher in the statin-user group than the nonusers group ( $P < 0.0001$ ). Of the statin-users, 89% had known prior CAD versus 80% of nonusers ( $P < 0.0001$ ). The additional use of chemotherapy was similar in both statin-users and nonusers ( $P = 0.42$ ). Overall, statin use was reported in 73% of the total study cohort. The statin-user group was also more commonly using other medications such as aspirin, clopidogrel, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, calcium-channel blocker ( $P < 0.0001$  for all), and warfarin ( $P = 0.02$ ).

### Predictors of Cardiovascular and Cerebrovascular Outcomes

The hazard ratios (HR) of stroke, MI, and death caused by MI or stroke for statin use among cancer patients post RT is shown in Table 2. The crude event rate of the primary outcome was 10.3% in nonusers and 9.0% in statin-users, with a univariable HR of 0.80 (95% CI 0.67–0.96,  $P = 0.019$ ). The annualized event incidence of the primary outcome was 5.74% among statin-users and 6.41% among nonusers ( $P = 0.24$ ). The annualized event incidence of stroke alone was 1.62% among statin-users and 2.19% among nonusers ( $P = 0.07$ ). In a multivariable model with statin use as a time-dependent variable, after adjusting for age, sex, prior history of transient

**Table 1.** Baseline Characteristics of Statin-Users and Nonusers

	Total (n=5718)	Statin Users (n=4166) N (%)	Nonusers (n=1552) N (%)	P Value
<b>Demographics</b>				
Age (median) (y)	74	74	75	<0.0001
Mean age (SD)	75 (6.1)	75 (5.8)	76 (6.8)	
<b>Age categories (y)</b>				
66–70	1610 (28)	1223 (29)	387 (25)	<0.0001
71–75	1619 (28)	1201 (29)	418 (27)	
76–80	1375 (24)	1027 (25)	348 (22)	
81 and over	1114 (19)	715 (17)	399 (26)	
Sex (female)	2595 (45)	1807 (43)	788 (51)	<0.0001
<b>Cardiovascular risk factors</b>				
Hypertension	4062 (71)	3075 (74)	987 (64)	<0.0001
Diabetes mellitus	1702 (30)	1322 (32)	380 (24)	<0.0001
Dyslipidemia	3572 (62)	3079 (74)	493 (32)	<0.0001
Carotid artery disease	286 (5)	237 (6)	49 (3)	<0.0001
CAD	4942 (86)	3696 (89)	1246 (80)	<0.0001
PVD	388 (7)	316 (8)	72 (5)	<0.0001
Heart failure	1261 (22)	925 (22)	336 (22)	0.65
CKD	836 (15)	632 (15)	204 (13)	0.0538
Atrial fibrillation	1195 (21)	846 (20)	349 (22)	0.07
Prior stroke	597 (10)	466 (11)	131 (8)	0.002
Prior MI	1773 (31)	1397 (34)	376 (24)	<0.0001
Prior MI/CAD	5199 (91)	3855 (93)	1344 (87)	<0.0001
Cancer type				0.10
Head and neck	689 (12)	520 (12)	169 (11)	
Chest and mediastinal	5029 (88)	3646 (88)	1383 (89)	
<b>Cancer therapy</b>				
Chemotherapy	1138 (20)	840 (20)	298 (19)	0.42
<b>medication</b>				
Aspirin	3280 (57)	2754 (66)	526 (34)	<0.0001
ACEI	2735 (48)	2300 (55)	435 (28)	<0.0001
ARB	1130 (20)	948 (23)	182 (12)	<0.0001
BB	1563 (27)	1298 (31)	265 (17)	<0.0001
CCB	1565 (27)	1316 (32)	249 (16)	<0.0001
Clopidogrel	827 (14)	751 (18)	76 (5)	<0.0001
Warfarin	859 (15)	654 (16)	205 (13)	0.02

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, β-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; MI, myocardial infarction; PVD, peripheral vascular disease.

ischemic attack or MI, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic kidney disease, heart failure, and hypertension, statin-use at the time of RT was associated with a nonsignificant 15% relative risk reduction in the subsequent stroke, MI, and death (HR=0.85, 95% CI 0.69–1.04). The

crude and adjusted HR for the secondary outcome of stroke alone were 0.75 (95% CI 0.55–1.04,  $P=0.0860$ ) and 0.68 (95% CI 0.48–0.95,  $P=0.0368$ ), respectively. Figures 2 and 3 depict the Kaplan–Meier event-free survival curves following RT, according to statin use, for the primary composite outcome of

**Table 2.** Effect of Statin Use on Outcomes

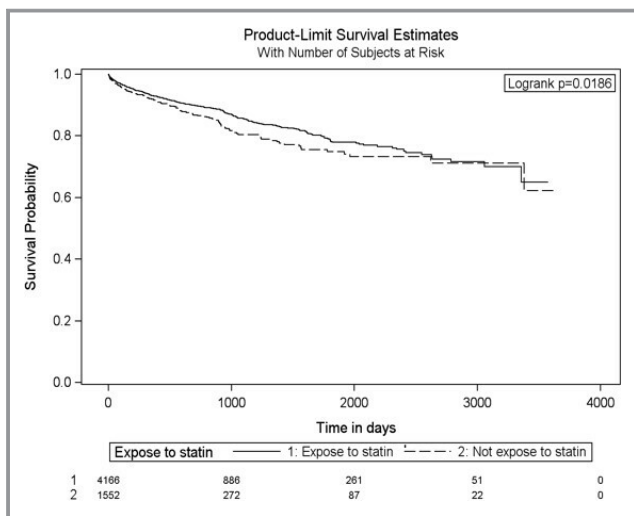
	Statin Users (n=4166) N (%)	Nonusers (n=1552) N (%)	Hazard Ratio (95% CI)	P Value
<b>MI/stroke/death</b>				
Crude	376 (9.0)	160 (10.3)	0.92 (0.76–1.10)	0.3451
Adjusted*	...	...	0.85 (0.69–1.04)	0.1068
	Statin Users (n=4186) N (%)	Nonusers (n=1532) N (%)	Hazard Ratio (95% CI)	P Value
<b>Stroke</b>				
Crude	110 (2.6)	56 (3.7)	0.75 (0.55–1.04)	0.0860
Adjusted*	...	...	0.68 (0.48–0.98)	0.0368

MI indicates myocardial infarction.

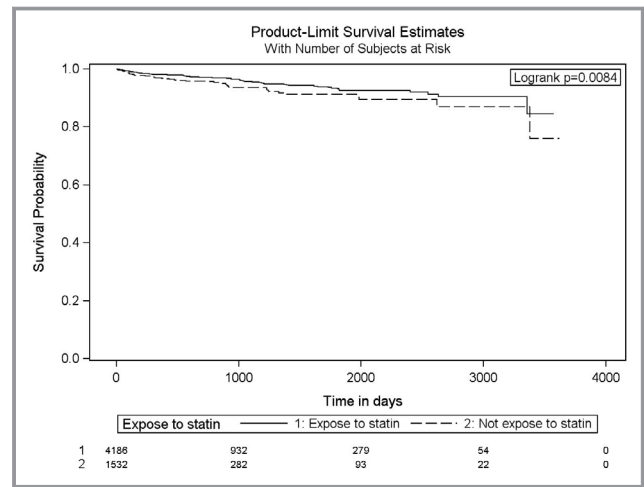
\*Adjusted for age, sex, atrial fibrillation, coronary artery disease, previous myocardial infarction, chronic kidney disease, cerebrovascular disease, diabetes mellitus, dyslipidemia, heart failure, and hypertension.

MI, stroke, and death caused by MI and stroke (Figure 2), as well as for secondary outcome of stroke alone (Figure 3). The Cox proportional hazard model for the multivariate MI-free survival analysis is shown in Table S4. The Kaplan–Meier event-free survival curve for the secondary outcome of MI alone is shown in Figure S1. The overall all-cause mortality was lower in the statin group ( $P<0.0001$ , Figure 4) compared with the nonstatin group.

Predictors of vascular outcomes and death independent of statin use in patients’ medical regimen were explored. Results of the multivariable Cox regression analysis for post RT cardiovascular and CVD events are shown in Tables 3 through 6. Forest plots of hazard ratios according to baseline covariates for the



**Figure 2.** Adjusted Kaplan–Meier survival curves for the composite outcome of MI, stroke, and death from MI or stroke for statin users and nonusers. MI indicates myocardial infarction.



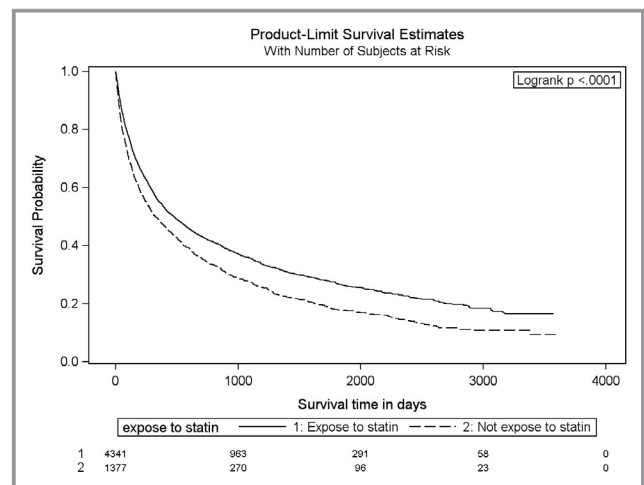
**Figure 3.** Adjusted Kaplan–Meier survival curves for the outcome of stroke for statin users and nonusers.

combined primary outcome and for the outcome of stroke alone are shown in Figure S2–S3.

Overall, the prevalence of potential statin-associated side effects (Table 7) was low in both study groups (308 [7%] in statin users and 34 [2%] in nonusers). There was no significant difference between the 2 study groups regarding the rate of hepatitis, transaminitis, myositis, or myalgia. The rate of myopathy and sleep disorder was higher in the statin group.

## Discussion

In the largest study to date assessing the impact of statin use on vascular outcomes in a cohort of 5718 cardiac patients who had undergone radiotherapy to the thorax, head, or neck, we have shown that statins were associated with a



**Figure 4.** Adjusted Kaplan–Meier survival curves for all-cause mortality for statin users and nonusers. Age: continuous variable×reference category is from ages 66 to 70 inclusively.

**Table 3.** Multivariate Disease-Free Survival Analysis of Patients With Thorax, Head, or Neck Cancer Treated With Radiotherapy by the Cox Proportional Hazard Model for the Composite Outcome of Stroke, MI, and Death From MI or Stroke With Age as a Continuous Variable

	Hazard Ratio	95% CI	P Value
Age (continuous)	1.04	1.03–1.06	<0.0001
Sex*	1.56	1.30–1.86	<0.0001
Atrial fibrillation	1.00	0.81–1.24	0.9989
CAD/MI	1.52	1.03–2.24	0.0357
CKD	1.29	1.02–1.63	0.0353
CVD	1.71	1.36–2.17	<0.0001
Diabetes mellitus	1.22	1.01–1.47	0.0421
Dyslipidemia	1.10	0.90–1.34	0.3656
Heart failure	1.44	1.18–1.76	0.0005
Hypertension	0.88	0.72–1.08	0.2186
Statin use	0.85	0.69–1.08	0.1068

CAD indicates coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; MI, myocardial infarction.

\*Reference female sex.

nonsignificant but strong trend in reducing the composite end point of stroke, MI, or death caused by stroke or MI. After adjusting for comorbidities, statin use was associated with a significant reduction in the secondary outcome of stroke. Most of this cohort population were patients with underlying CAD, for which the benefits of statins persisted mostly for the prevention of cerebrovascular events, even with the added risk of RT. This study demonstrated that statin therapy could be favorable even with the competing risks of cancer and cancer-associated mortality.

There is a growing body of evidence showing increasing burden of vascular events post RT to the thorax, head, or neck. Evidence of CAD was seen in Hodgkin’s lymphoma patients in their 20s post mediastinal RT, with higher risks observed in patients treated at younger ages.<sup>21</sup> Studies have demonstrated up to a 5-fold increase in ischemic stroke post cervical irradiation at 5 years in cancer survivors.<sup>3</sup> In patients >65 years of age treated with RT for head and neck squamous cell carcinoma, the HR for ischemic stroke was 1.5,<sup>22</sup> similar to what was found in this cohort of patients.

With improvement in cancer therapies, patient survival has significantly increased post cancer diagnoses. This has left a dearth of evidence in the management of the longer-term complications of cancer therapies. Despite the presence of data showing the association between RT and vascular disease, be it additive or multiplicative to traditional cardiovascular risk factors, there currently exist no guidelines for the treatment or prevention of RIA (radiation-induced atherosclerosis). Current revascularization strategies are particularly challenging in this

**Table 4.** Multivariate Disease-Free Survival Analysis of Patients With Thorax, Head, or Neck Cancer Treated With Radiotherapy by the Cox Proportional Hazard Model for the Composite Outcome of Stroke, MI, and Death From MI or Stroke With Age as a Categorical Variable

	Hazard Ratio	95% CI	P Value
Age (categories) (y)*			
71–75	1.37	1.07–1.76	0.0124
76–80	1.54	1.19–1.98	0.001
81 and over	2.04	1.57–2.65	<0.0001
Sex†	1.53	1.28–1.83	<0.0001
Atrial fibrillation	1.01	0.81–1.25	0.9522
CAD/MI	1.52	1.03–2.24	0.0348
CKD	1.30	1.02–1.65	0.0305
CVD	1.70	1.35–2.15	<0.0001
Diabetes mellitus	1.21	1.00–1.46	0.047
Dyslipidemia	1.09	0.89–1.33	0.399
Heart failure	1.44	1.17–1.76	0.0005
Hypertension	0.89	0.73–1.08	0.2498
Statin use	0.84	0.68–1.02	0.0811

CAD indicates coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; MI, myocardial infarction.

\*Reference category ages 66 to 70 inclusively.

†Reference female sex.

population, given that RIA tends to cause more ostial coronary artery lesions including the left anterior descending artery with involvement of proximal artery segments compared with age-

**Table 5.** Multivariate Stroke-Free Survival Analysis of Patients With Thorax, Head, or Neck Cancer Treated With Radiotherapy by the Cox Proportional Hazard Model With Age as a Continuous Variable

	Hazard Ratio	95% CI	P Value
Age (continuous)	1.03	1.01–1.06	0.0101
Sex*	1.30	0.94–1.78	0.1086
Atrial fibrillation	1.42	0.999–2.03	0.0506
CAD/MI	1.17	0.62–2.20	0.6212
CKD	1.63	1.09–2.44	0.0168
CVD	3.76	2.66–5.33	<0.0001
Diabetes mellitus	1.06	0.75–1.50	0.7308
Dyslipidemia	1.07	0.75–1.53	0.7034
Heart failure	1.15	0.79–1.67	0.4618
Hypertension	0.83	0.58–1.18	0.4618
Statin use	0.68	0.48–0.98	0.0368

CAD indicates coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; MI, myocardial infarction.

\*Reference female sex.

**Table 6.** Multivariate Stroke-Free Survival Analysis of Patients With Thorax, Head, or Neck Cancer Treated With Radiotherapy by the Cox Proportional Hazard Model With Age as a Categorical Variable

	Hazard Ratio	95% CI	P Value
Age (categories) (y)*			
71–75	1.430	0.920–2.221	0.1116
76–80	1.207	0.751–1.939	0.4375
81 and over	1.854	1.161–2.960	0.0097
Sex†	1.266	0.923–1.737	0.1432
Atrial fibrillation	1.447	1.014–2.064	0.0418
CAD/MI	1.165	0.622–2.183	0.6334
CKD	1.660	1.109–2.483	0.0137
CVD	3.730	2.634–5.282	<0.0001
Diabetes mellitus	1.050	0.745–1.482	0.7794
Dyslipidemia	1.071	0.750–1.530	0.7052
Heart failure	1.135	0.780–1.650	0.5078
Hypertension	0.842	0.589–1.203	0.3434
Statin use	0.67	0.472–0.962	0.0296

CAD indicates coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; MI, myocardial infarction.

\*Reference category ages 66 to 70 inclusively.

†Reference female sex.

associated atherosclerosis.<sup>7,10,23,24</sup> In CVD, carotid lesions have been described as being more extensive and involving longer arterial segments compared with traditional atherosclerosis.<sup>9</sup> Endarterectomies are often complicated by increased scar tissue overlying diseased arterial segments.<sup>25</sup> This draws attention to the need for better primary and secondary preventive therapies for RIA.

Multiple studies have revealed the beneficial effects of statin therapy on reducing the risk of vascular mortality and morbidity

**Table 7.** Side Effect Profile Between Users (From First Statin Exposure) and Nonusers of Statins (From Time Zero of Radiotherapy)

Side effects	Statin Users (N=4332)	Non-Statins Users (N=1386)	Odds Ratio	CI
	N (%)	N (%)		
Hepatitis	20 (0.46)	2 (0.14)	3.2	0.7–13.7
Transaminitis	16 (0.37)	1 (0.07)	5.1	0.7–38.5
Myopathy	75 (1.73)	12 (0.86)	2.0	1.1–3.7
Myositis/myalgia	23 (0.53)	4 (0.29)	1.8	0.6–5.3
Sleep disorders	173 (4.01)	15 (1.06)	3.9	2.3–6.6
Rhabdomyolysis	1 (0.02)	0 (0)	NA	NA

NA indicates quasi-complete separation.

in a variety of different populations. For instance, intensive statin therapy in stable CAD patients with dyslipidemia yielded a HR for major adverse cardiac events of 0.78.<sup>26</sup> In a cohort of patients with stroke/ transient ischemic attack, high-dose statins were associated with HRs of 0.84 and 0.80 for nonfatal/fatal stroke and major cardiovascular events, respectively.<sup>27</sup> In addition, evidence has also demonstrated the benefit of statins in the primary prevention in subjects without known underlying CAD. In the CTT (Cholesterol Treatment Trialists’) Collaboration study,<sup>28</sup> primary prevention with statins was associated with the proportional reductions per 1.0 mmol/L reduction in low-density lipoprotein cholesterol in major vascular events for both women (rate ratio 0.84, 99% CI 0.78–0.91) and men (rate ratio 0.78, 99% CI 0.75–0.81). The growing body of literature on cardiovascular prevention and lipid-lowering strategies now favors intensive statin therapy with lower low-density lipoprotein targets. In most trials, elderly patients tend to be underrepresented and are at increased risk of statin-associated side effects. Despite the mean age for our study population being >70 years old, the total number of side effects was small overall in both groups (Table 7). There was no significant difference observed between the 2 groups for most common side effects (myalgia, myositis, and myopathy). Sleep disorders and hepatitis were reported more frequently in the statin-user group. Keeping in mind the unsuitability of our database for quality of life and medication compliance assessment, these results are in keeping with current guidelines suggesting that statin therapy may be suitable for older adults.

However, there have been no studies assessing the effect of statin therapy in subjects post RT on combined cardiovascular and cerebrovascular morbidity and mortality. In our study, statin therapy post RT was associated with a nonsignificant 15% reduction in stroke, MI, or death caused by stroke or MI. Although there was a strong trend, the result was not statistically significant, likely because of the high-risk population of patients, with a crude event incidence of 9.03% and 10.31% over a 1- to 2-year follow-up. The secondary outcome of stroke alone post RT to the thorax, head, or neck was found to be reduced by 32% in patients on statin therapy. The results of our analysis complement the findings by Addison and colleagues, who demonstrated the salutary effect of statins on CVD in a younger cohort of patients with head and neck cancers and fewer comorbidities.<sup>29</sup> Within a group of relatively low vascular risk patients undergoing head and neck radiation, statin use may lower risk of cerebrovascular accidents. Within a much higher vascular risk group of patients, as in our study, statins may also lower the risk of cerebrovascular accidents but the effect size is blunted by the much higher baseline risk of disease.

The 2018 American College of Cardiology and American Heart Association cardiovascular disease prevention guidelines recommend preventive therapy with statins in patients with

high risk of atherosclerotic cardiovascular disease ( $\geq 20\%$ , Class I indication).<sup>30</sup> There are also new recommendations for primary prevention in patients with intermediate ( $\geq 7.5\%$  to  $< 20\%$ , Class I) and borderline risks ( $5\%$  to  $< 7.5\%$ ), guided by risk enhancers to facilitate the decision to initiate statin therapy. These risk-enhancing factors carry a greater lifetime risk of atherosclerotic cardiovascular disease, but do not yet include the exposure to RT to the thorax, head, and neck. The recent US Preventive Services Task Force recommendation sets this threshold at  $10\%$ .<sup>30</sup> These data support the continuation of statins among those having received RT and who have an indication for statins. Our data act as hypothesis generating as to whether individuals who do not meet Class I indications for statin therapy would benefit from it through risk enhancement from radiotherapy, and whether prospective randomized controlled trials are needed to strongly support statin therapy in the population who do not meet current criteria for statins.

The results of this study should be considered in the context of its inherent limitations. Importantly, this study is retrospective and observational in design, making it impossible to rule out residual and unmeasured confounding between nonrandomized groups as an explanation for observed results. The statin-user and nonuser groups were largely different from each other. The statin subgroup of patients had significantly more underlying comorbidities, such as CAD, with the added risk factor of RT, which could also explain why they had higher overall all-cause mortality compared with the nonstatin group. This would be expected to bias the statin group toward having higher risk of vascular events, although the contrary was observed for the outcome of stroke alone (Table 2 and Figure 3). While there was a greater burden of cardiovascular risk factors among statin users who underwent RT, there was greater use of other cardiac medications in this group as well. Despite rigorous attempts to adjust for identified confounders, differences in statin users versus nonusers because of a nonrandomized design may have contributed to the noted beneficial effect of statins in patients post RT. There were also limitations imposed by the database used in this study. While it offered access to a large group of patients, having access to information on smoking status, low-density lipoprotein levels, statin dosing, and radiation dosing would have greatly added to the analysis but was unavailable. Despite these limitations, this study offers a promising insight into the potential benefits of lipid-lowering therapies post RT.

## Conclusion

This retrospective observational study demonstrated that in a large cohort of patients, with a heavy burden of CAD and having undergone radiation to the thorax, head, or neck, the use of statins was associated with a trend for a 15% reduction in the composite outcome of cardiovascular and cerebrovascular

events. The use of statins was associated with a significant reduction of 32% for the outcome of stroke alone. This study supports a benefit of statin therapy in prevention of vascular events. There is a need for prospective randomized control trials to explore the role of statins post RT in less selected populations and to establish more definitive guidelines on the management of radiation-induced vascular disease.

## Disclosures

The views expressed are those of the author and do not reflect official policy of Fort Belvoir Community Hospital, the Defense Health Agency, the Department of Defense, or the US Government.

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# **Supplemental Material**

**Table S1. Definitions of covariates-Interventions.**

Covariates	ICD-9 codes	ICD-10 codes	CCI	Intervention CCP	Code d'Acte (Act Code)
<b>Radiotherapy</b>	V580 V661 V671	Z510 Z541 Z081	1.xx.27.xx	0639	8510,8511,8507,8508,8553,8509,9477,200,8518,8519,8520,8554,7648,8516,746,635,8564,8565,9150,9162,9134,9144,9152,9164,9141,9146,9160,9170,9168,9143,8504
<b>Chemotherapy</b>	V66.2 V67.2	Z54.2 Z08.2		13.55	583,603, 734,94,95,15012,15013,470,472,475,476,7000,15272,15403,15699,15702

CCI: Canadian Classification of Health Interventions, CCP: Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures

**Table S2. Definitions of covariates-Comorbidities and Outcomes.**

Covariates	ICD-9 codes	Disease	ICD-10 codes
<b>Atrial Fibrillation</b>	427.31	Atrial fibrillation	148.0
<b>Hypertension</b>	401.x	Essential hypertension	I10.x
<b>Diabetes (DM)</b>	250.x	Diabetes mellitus	
		Type I DM	E09.x
		Type II DM	E10.x
		Malnutrition-related DM	E11.x
		Other specified diabetes mellitus	E12.x
		Unspecified diabetes mellitus	E13.x
			E14.x
<b>Dyslipidemia</b>	272.0	Pure hypercholesterolemia	E78.x
<b>Coronary artery disease</b>	414.0X	Coronary atherosclerosis	I25.1x
	414.2X	Chronic total occlusion of coronary artery	
	414.3X	Coronary atherosclerosis due to lipid rich plaque	
	414.8X	Other specified forms of chronic ischemic heart disease	
	414.9X	Chronic ischemic heart disease, unspecified	I25.9x
		Atherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris	I25.7x
		Other forms of chronic ischemic heart disease	I25.8x
<b>Myocardial infarct</b>	410.x	Acute myocardial infarction	
		ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I21.x
		Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I22.x
	411	Other acute and subacute of ischemic heart disease	I24
<b>Heart failure</b>	428.0	Heart failure, unspecified	
	428.1	Left heart failure	150.1
	428.2x	Systolic heart failure	150.2x
	428.3x	Diastolic heart failure	150.3x
	428.4x	Combined systolic and diastolic heart failure	150.4x
	428.9	Heart failure, unspecified	150.9

<b>Peripheral Arterial Disease</b>	443.9	Peripheral vascular disease, unspecified	I73.9
<b>Stroke</b>	433	Occlusion and stenosis of precerebral arteries	I63, I65
	434	Occlusion of cerebral arteries	I66
	434.1	Cerebral embolism	
	434.9	Unspecified occlusion	
	436	Acute but ill-defined cerebrovascular disease	I67.89
	438	Late effects of cerebrovascular disease	I69
<b>TIA</b>	435	Transient cerebral ischemia	G45
<b>Chronic Kidney Disease</b>	585	Chronic kidney disease (CKD)	N18
<b>Heart Failure</b>	428	Heart Failure	I50

**Table S3. Definition of Statin side effects.**

	<b>ICD code 9</b>	<b>ICD code 10</b>
<b>Hepatitis</b>	070, 573.3	K71.6, K75.9
<b>Transaminitis</b>	790.4	R74.0, R94.5
<b>Myopathy</b>	359.4-359.9, 728	G71, G72, M60, M63
<b>Myositis/Myalgia</b>	729.1	M60.9, M79.1
<b>Sleep disorders</b>	780.50- 780.59	G47
<b>Rhabdomyolysis</b>	728.88	M62.82

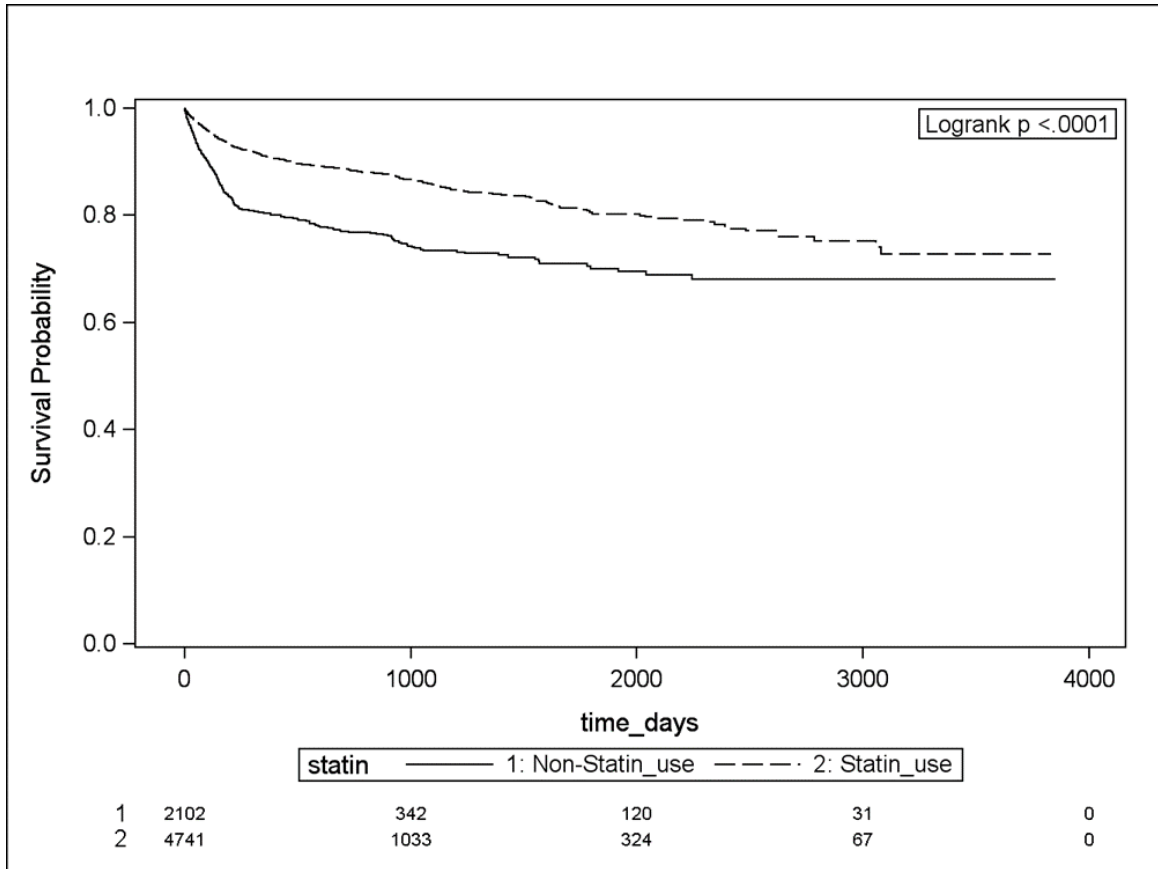
**Table S4. Multivariate MI free survival analysis of patients with thorax, head or neck cancer treated with radiotherapy by the Cox proportional hazard model (age continuous).**

	<b>Hazard Ratio</b>	<b>95% Confidence Interval</b>	<b>P Value</b>
<b>Age</b>	1.04	1.03-1.06	<0.0001
<b>Sex*</b>	1.62	1.31-20..	<.0001
<b>Atrial fibrillation</b>	0.87	0.67-1.13	0.2928
<b>CAD/MI</b>	1.69	1.04-2.73	0.0334
<b>CVD</b>	1.14	0.84-1.56	0.4024
<b>CKD</b>	1.17	0.88-1.55	0.2910
<b>Diabetes</b>	1.33	1.07-1.66	0.0101
<b>Dyslipidemia</b>	1.14	0.90-1.45	0.2692
<b>Heart Failure</b>	1.55	1.22-1.96	0.0003
<b>Hypertension</b>	0.93	0.74-1.18	0.5449
<b>Statin use</b>	0.91	0.72-1.16	0.4562

CAD: coronary artery disease, CVD: cerebrovascular disease, CKD: chronic kidney disease, MI: myocardial infarction

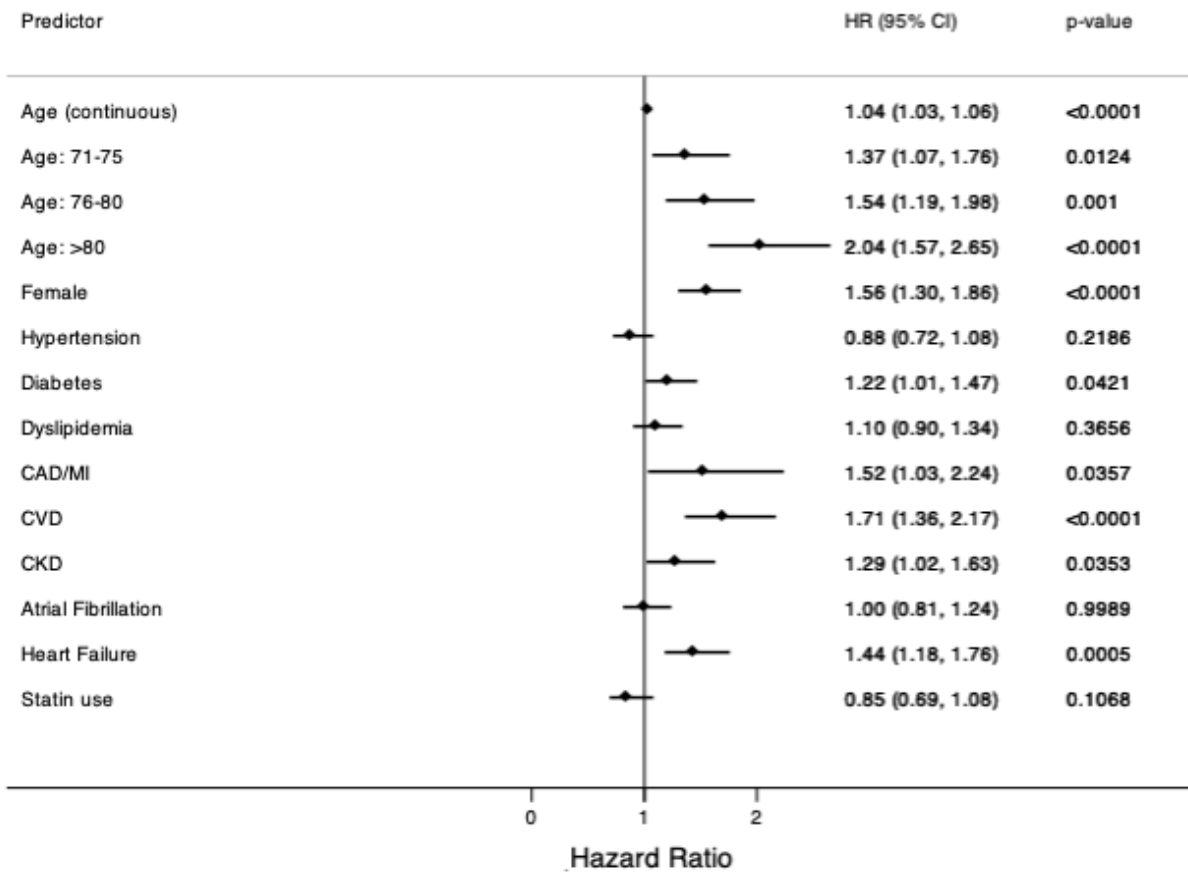
\*Reference female sex

**Figure S1. Adjusted Kaplan Meier Survival Curves for the Outcome of Myocardial Infarction between Statin users and non-Statin users.**



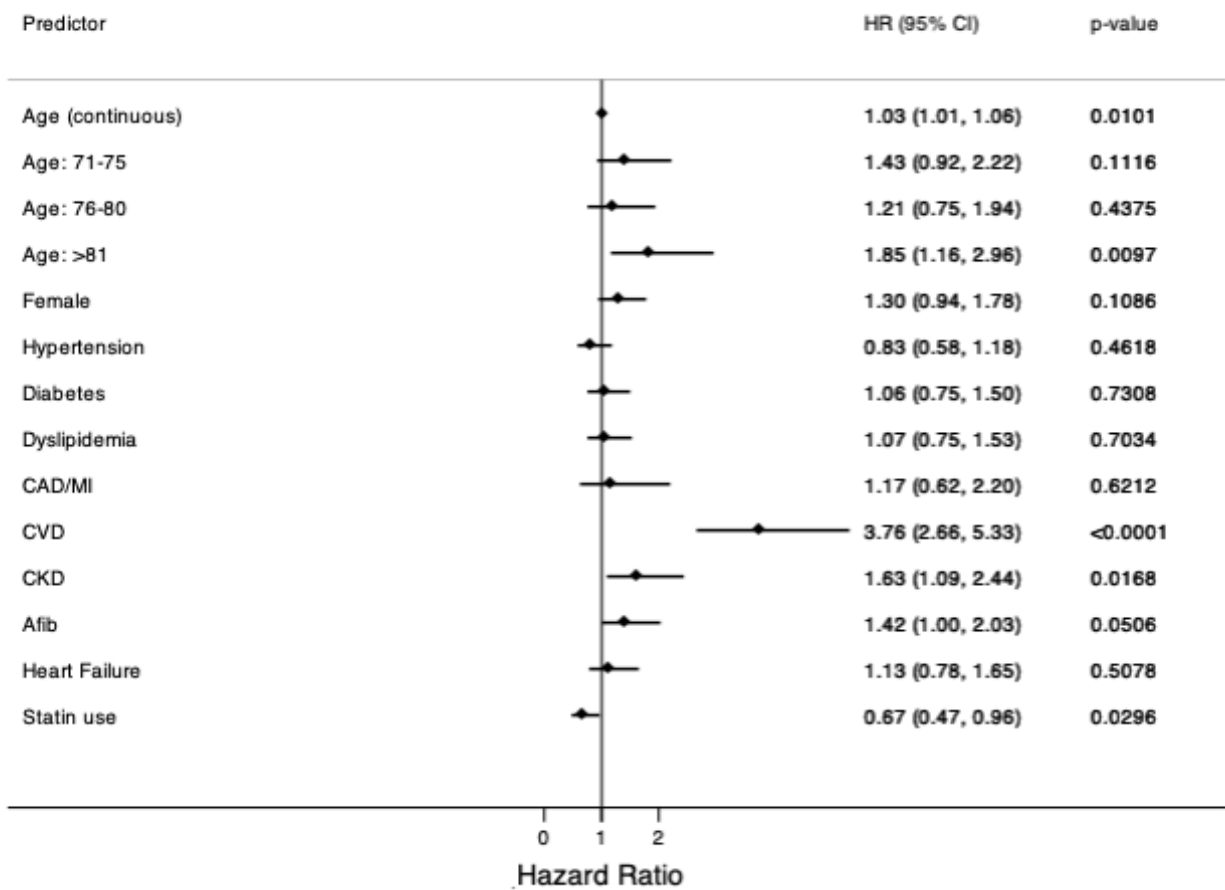


**Figure S2. Forest Plot of Hazard Ratio for the Combined Outcome of Stroke and Myocardial Infarction according to Baseline Covariates.**



CAD: coronary artery disease, CKD: chronic kidney disease, CVD: cerebrovascular disease, MI: myocardial infarction

**Figure S3. Forest Plot of Hazard Ratio for the Outcome of Stroke according to Baseline Covariates**



CAD: coronary artery disease, CKD: chronic kidney disease, CVD: cerebrovascular disease, MI: myocardial infarction