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P124: Assessing the Relationship Between Statin Therapy and Incidence of Complications Associated with New-Onset Atrial Fibrillation: Findings from a Population-Based Study

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Background

Although anticoagulation has been identified as the primary preventive therapy for IS/SE among patients with AF, which could reduce up to 70% of incident IS/SE,[1, 2] a residual risk of AF complications remains.[3]

Table 1:

Residual Thromboembolic Risk in Landmark Clinical Trials of AF

Study	Year	No. Patients	Mean $CHADS_2$ score	Residual thromboembolic Risk*	
				DOAC	Warfarin
RE-LY[20]	2008	18,113	2.1	1.11–1.53†	1.69
ROCKET AF[21]	2011	14,264	3.5	2.10	2.40
ARISTOTLE[19]	2011	18,201	2.1	1.27	1.60
ENGAGE AF-TIMI 48[18]	2013	21,105	2.8	1.18–1.61†	1.50

**Expressed as percentage per year or event rate per 100 patient-years. †Dose dependent. DOAC = direct oral anticoagulant.*

1. *Can J Cardiol*. 2016;32:1170-1185.
2. *Europace*. 2012;14:1385-413.
3. *J Am Heart Assoc*. 2022;11:e026410.
Figure. Arrhythm Electrophysiol Rev. 2021 Oct; 10(3): 147–153.

Background

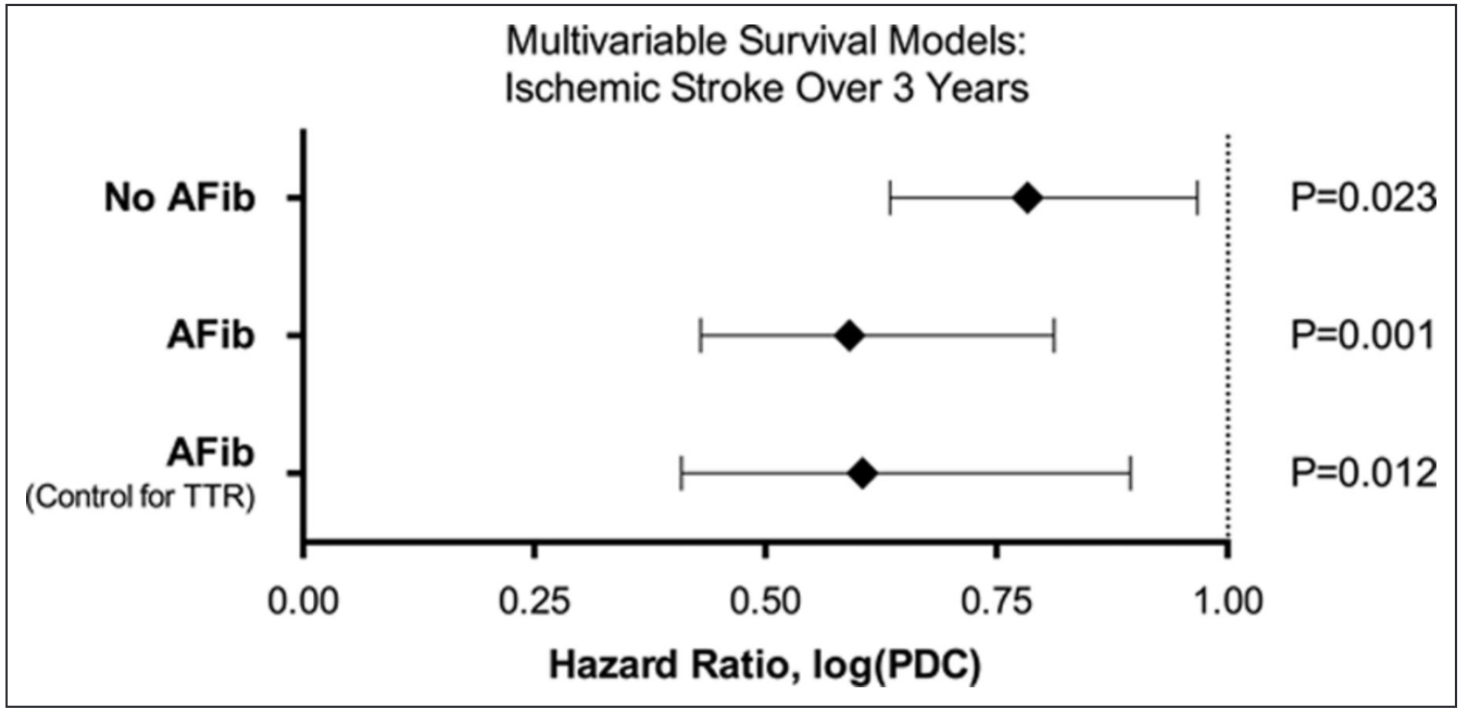


Figure 3. Multivariable survival models showing the relationship between statin adherence and ischemic stroke, according to atrial fibrillation (AFib) status. Three

Figure. Stroke. 2017;48:1788–1794

Background

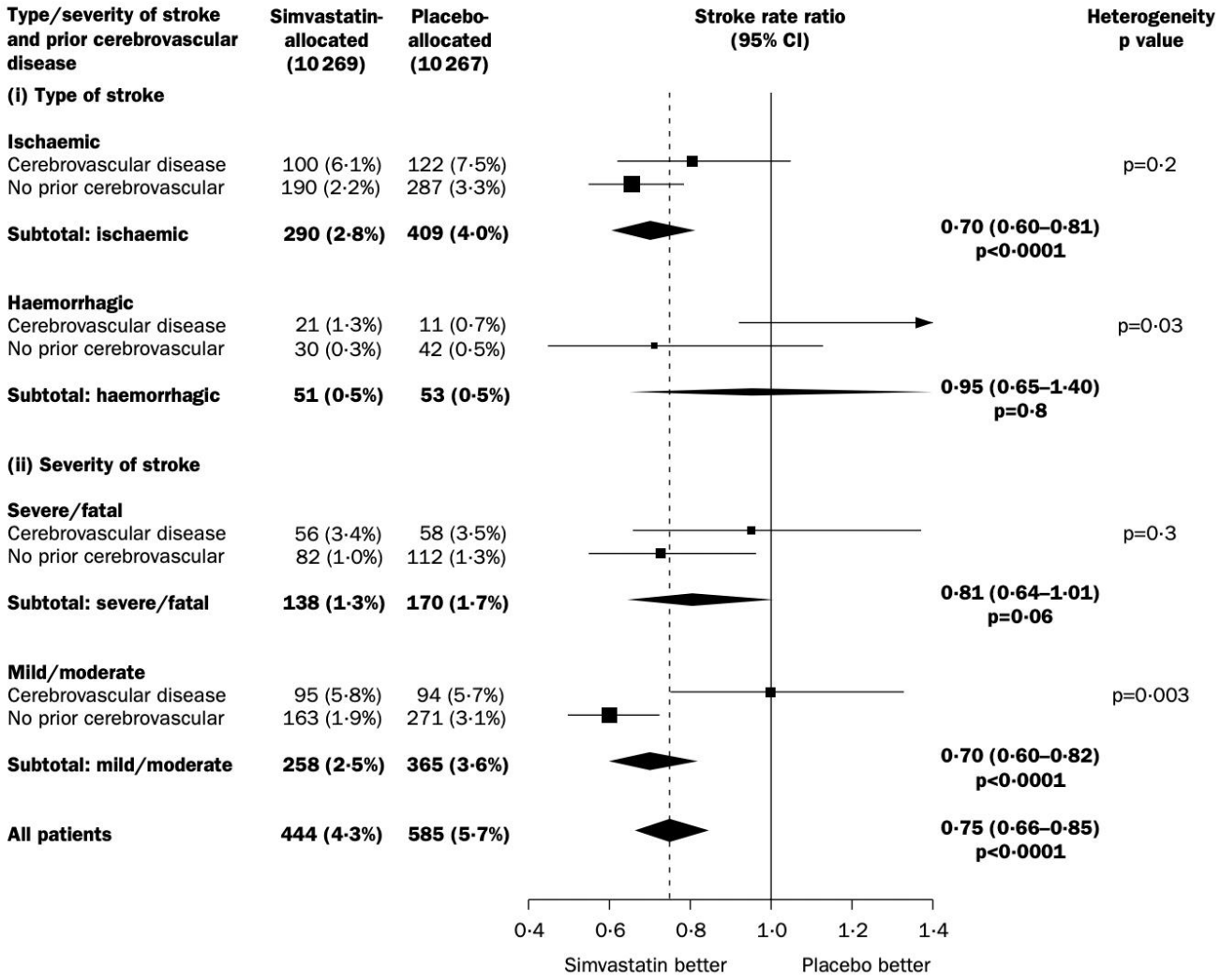
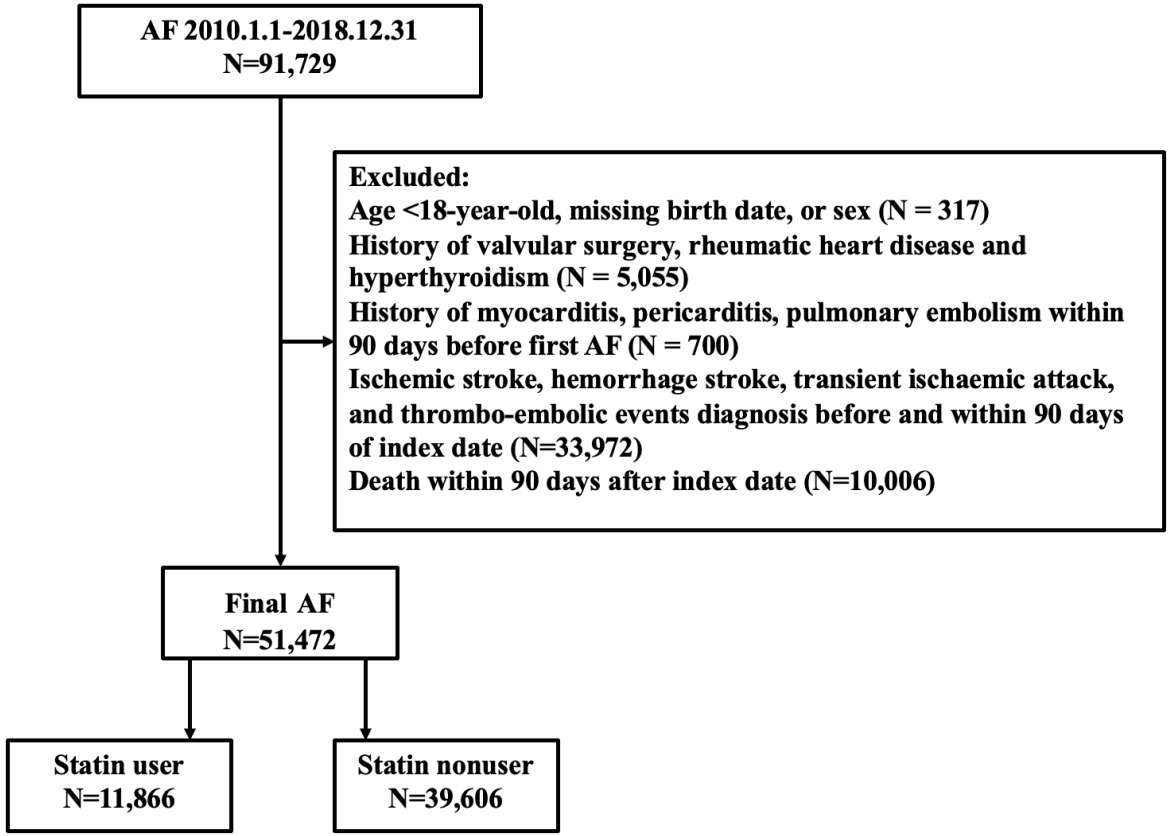


Figure 2: **Effects of simvastatin allocation on type and severity of stroke in participants subdivided by prior cerebrovascular disease**

Lancet. 2004 Mar 6;363(9411):757-67.

Methods

Figure 1. Flow chart of study cohort selection.



The primary outcomes included ischaemic stroke (IS) and systemic embolism (SE), haemorrhagic stroke (HS), transient ischaemic attack (TIA) and all-cause mortality.

An inverse probability of treatment weighting was used to balance baseline covariates between the two groups.

The Fine and Grey competing risks model was applied to evaluate the association between statin use and the risk of outcomes, with death defined as the competing event.

Results

Table 1. Baseline characteristics.

	Overall N=51,472	Stain non-users N=39,606	Statin users N=11,866	SMD before IPTW	SMD after IPTW
Age, mean (SD)	74.91 (12.50)	74.91 (13.08)	74.88 (10.32)	0.003	0.012
Female, No. (%)	24,542 (47.7)	18,944 (47.8)	5,598 (47.2)	0.013	0.004
Smoking, No. (%)	3,424(6.7)	1,696 (4.3)	1,728 (14.6)	0.086	0.005
CHA_2DS_2-VASc score, median (IQR)	2.71 (1.44)	2.68 (1.48)	2.81 (1.28)	0.094	0.009
High-risk (≥2) , No. (%)	40,435 (78.6)	30,484 (77.0)	9,951 (83.9)	0.062	0.006
Intermediate (=1), No. (%)	7,417 (14.4)	5,963 (15.0)	1,454 (12.2)	0.057	0.005
Low-risk (=0) , No. (%)	3,620 (7.0)	3,159 (8.0)	461 (3.9)	0.083	0.006
Medical conditions, No. (%)					
Hypertension	13,398 (26.0)	9,324 (23.5)	4,074 (34.3)	0.240	0.007
HF	10,226 (19.9)	7,260 (18.3)	2,966 (25.0)	0.333	0.004
CAD	8,347 (16.2)	4,779 (12.1)	3,568 (30.1)	0.453	0.032
Diabetes	20,511 (39.8)	13,715 (34.6)	6,796 (57.3)	0.467	0.011
CKD	2,592 (5.0)	1,834 (4.6)	758 (6.4)	0.077	0.010
PVD	673 (1.3)	330 (0.8)	343 (2.9)	0.153	0.004
Autoimmune diseases*	5,506 (10.7)	3,749 (9.5)	1,757 (14.8)	0.163	0.007
Liver cirrhosis	252 (0.5)	209 (0.5)	43 (0.4)	0.025	0.006
Anaemia	3,420 (6.6)	2,234 (5.6)	1,186 (10.0)	0.163	0.002

Results

Table 1. Baseline characteristics

(continued).

	Overall N=51,472	Stain non-users N=39,606	Statin users N=11,866	SMD before IPTW	SMD after IPTW
Cancer	6,367 (12.4)	4,294 (10.8)	2,073 (17.5)	0.191	0.012
GIB	4,165 (8.1)	2,808 (7.1)	1,357 (11.4)	0.150	0.004
Dyslipidaemia	3,852 (7.5)	1,753 (4.4)	2,099 (17.7)	0.433	0.020
Obesity	498 (1.0)	311 (0.8)	187 (1.6)	0.073	0.001
Medication use, No. (%)					
NOAC	20,469 (39.8)	14,581 (36.8)	5,888 (49.6)	0.261	0.001
Warfarin	10,732 (20.9)	8,169 (20.6)	2,563 (21.6)	0.024	0.003
Aspirin	13,608 (26.4)	6,384 (16.1)	7,224 (60.9)	1.036	0.017
Beta Blockers	16,216 (31.5)	11,657 (29.4)	4,559 (38.4)	0.191	0.006
ACEI/ARB	17,342 (33.7)	9,264 (23.4)	8,078 (68.1)	1.004	0.018
Procedure, No. (%)					
Ablation	291 (0.6)	208 (0.5)	83 (0.7)	0.022	0.002
Cardioversion	183 (0.4)	136 (0.3)	47 (0.4)	0.009	0.003

Abbreviations: N, number; SMD, Standardized mean difference; IPTW, inverse probability of treatment weighting; SD, standard deviation; IQR, interquartile range; HF, heart failure; CAD, coronary artery disease; CKD, chronic kidney disease; PVD, peripheral vascular disease; GIB, gastrointestinal bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; ACEI/ARB, angiotensin-converting enzyme/ angiotensin II receptor blocker.

*Autoimmune diseases include rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis.

The standardised mean difference is calculated across normoglycaemia, pre-diabetes and diabetes groups.

A variable is considered balanced between users and non-users where the standardized mean difference is ≤0.1.

Results

Table 2. Effects of statin use on the risk of different outcomes with IPTW.

N= 51,472	Statin non-user (N=39,606)	[a]Statin user (N=11,866)
Ischaemic stroke/ SE		
Event No.	5,473 (13.8%)	1,597 (13.5%)
Incidence rate per 100-person years	3.15	2.94
[b]SHR (95%CI) P	Ref.	0.83 (0.78-0.89) <0.01
Haemorrhagic stroke		
Event No.	918 (2.3%)	297 (2.5%)
Incidence rate per 100-person years	0.52	0.46
[b]SHR (95%CI) P	Ref.	0.93 (0.89-0.98) <0.01
Transient ischaemic attack		
Event No.	643 (1.6%)	219 (1.9%)
Incidence rate per 100-person years	0.38	0.32
[b]SHR (95%CI) P	Ref.	0.85 (0.80-0.90) <0.01
All-cause mortality		
Event No.	19,237 (48.6%)	4,726 (40.4%)
Incidence rate per 100-person years	9.58	8.17
[b]HR (95%CI) P	Ref.	0.96 (0.93-0.98) 0.04

Abbreviations: IPTW, inverse probability of treatment weighting; N, number; SHR, substitutional hazard ratio; SE, systematic embolism; CI, confidential interval; Ref, reference; HR, hazard ratio.

[a]Statin user was defined by a filled prescription for at least 90 consecutive days of statin use after the index date. The cumulative duration of statin use was modelled as a time-varying exposure. Hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment-weighted cohort that accounted for competing risk; the model was conditioned on age at index date.

[b]A multivariable adjusted model further accounted for the following prognostic covariates: age at index date, sex, smoking, CHA_2DS_2-VASc score, comorbidities, including diabetes, hypertension, heart failure, coronary artery disease, chronic kidney disease, peripheral vascular disease, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, liver cirrhosis, anaemia, cancer, gastrointestinal bleeding, dyslipidaemia, obesity and baseline use of non-vitamin K antagonist oral anticoagulant, warfarin, aspirin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, ablation, cardioversion.

Results

Table 3. Effect of duration of statin use on the risk of subsequent ischaemic stroke or SE and Haemorrhagic stroke among [a]statin users (N=11,423).

	Incident rate of 100-person years	SHR (95% CI) P	
		Unadjusted	[b]Adjusted
Ischaemic stroke/ SE			
3m to < 2 years	3.32	1.00(Ref.)	1.00(Ref.)
2 to < 4 years	3.02	0.84 (0.78-0.90) <0.01	0.90 (0.85-0.94) <0.01
4 to < 6 years	2.47	0.80 (0.65-0.76) <0.01	0.88 (0.80-0.95) <0.01
≥6 years	2.22	0.78 (0.53-0.68) <0.01	0.82 (0.76-0.88) <0.01
Haemorrhagic stroke			
3m to < 2 years	0.59	1.00(Ref.)	1.00(Ref.)
2 to < 4 years	0.49	0.92 (0.85-0.99) 0.04	0.90 (0.85-0.95) <0.01
4 to < 6 years	0.32	0.83 (0.78-0.89) <0.01	0.82 (0.78-0.86) <0.01
≥6 years	0.25	0.73 (0.67-0.79) <0.01	0.74 (0.69-0.80) <0.01
TIA			
3m to < 2 years	0.41	1.00(Ref.)	1.00(Ref.)
2 to < 4 years	0.32	0.93 (0.87-0.99) 0.03	0.91 (0.86-0.96) <0.01
4 to < 6 years	0.19	0.84 (0.77-0.91) <0.01	0.85 (0.78-0.93) <0.01
≥6 years	0.14	0.71 (0.66-0.76) <0.01	0.73 (0.68-0.79) <0.01

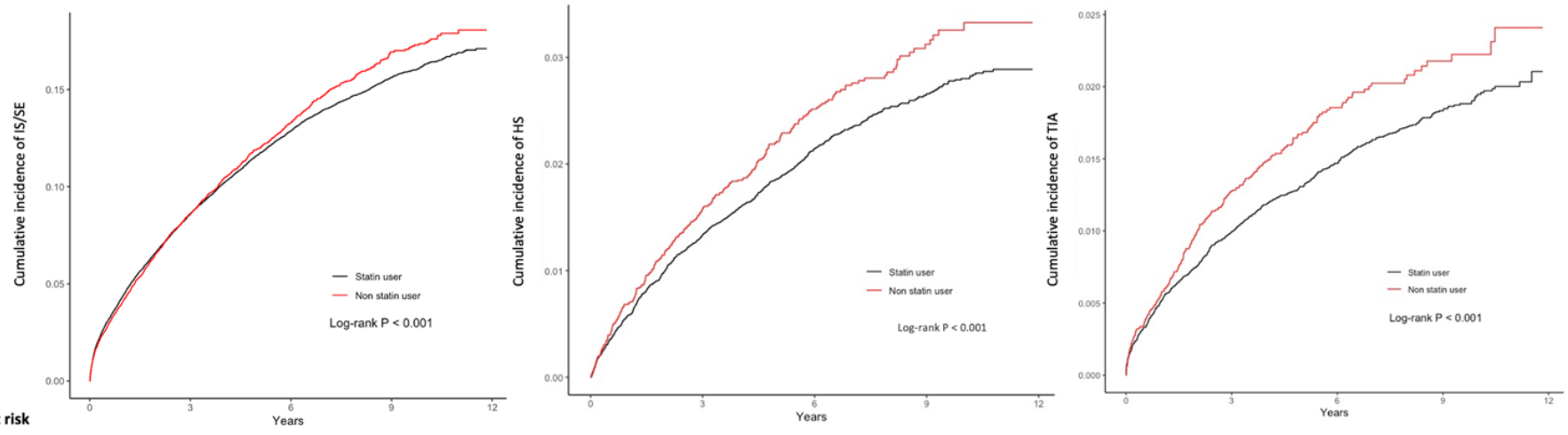
Abbreviations: SHR, substitutional hazard ratio; CI, confidential interval; SE, systematic embolism; m, month; Ref, reference; TIA, Transient ischaemic attack.

[a]Statin user was defined by a filled prescription for at least 90 consecutive days of statin use after the index date (n=9,695). The cumulative duration of statin use was modelled as a time-varying exposure. Hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment-weighted cohort that accounted for competing risk; the model was conditioned on age at index date.

[b]A multivariable adjusted model further accounted for the following prognostic covariates: age at index date, sex, smoking, CHA_2DS_2-VASc score, comorbidities, including diabetes, hypertension, heart failure, coronary artery disease, chronic kidney disease, peripheral vascular disease, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, liver cirrhosis, anaemia, cancer, gastrointestinal bleeding, dyslipidaemia, obesity and baseline use of non-vitamin K antagonist oral anticoagulant, warfarin, aspirin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, ablation, cardioversion.

Results

Figure 2. Cumulative incidence of different outcomes between statin users and non-users.

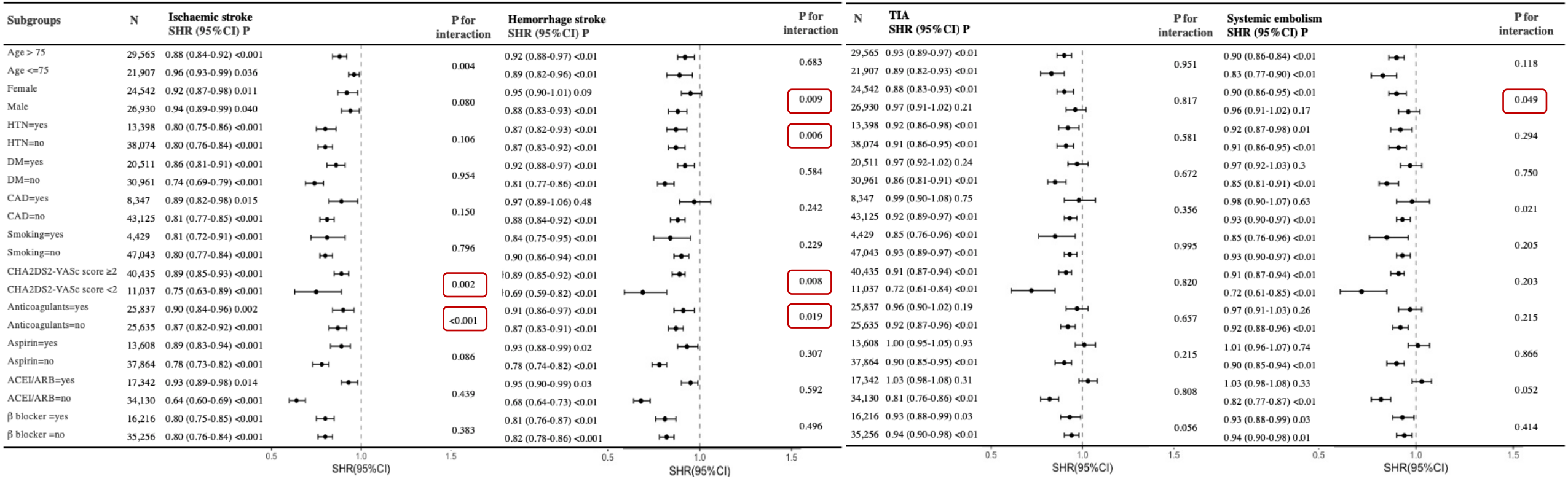


Number at risk	IS/SE					HS					TIA				
Statin users	11866	8972	4075	1484	234	11866	8906	3683	1180	0	11866	8857	3647	1169	0
Statin nonusers	39606	27812	15301	7133	1393	39606	27975	14498	5805	0	39606	27870	14426	5746	0

Abbreviation: IS, ischaemic stroke; SE, systematic embolism; HS, Haemorrhagic stroke; TIA, transient ischaemic attack.
We calculated the P-value using the Log-rank test for the equality of the cumulative functions between each exposure group after the inverse probability of treatment weighting, accounting for competing risks of all-cause mortality.

Results

Figure 3. Subgroup analysis.



Abbreviation: IS, ischaemic stroke; SE, systematic embolism; HS, Haemorrhagic stroke; TIA, transient ischaemic attack.
We calculated the P-value using the Log-rank test for the equality of the cumulative functions between each exposure group after the inverse probability of treatment weighting, accounting for competing risks of all-cause mortality.

Conclusion

- The use of statins can decrease the risk of adverse thromboembolic events in patients newly diagnosed with AF.
- Treatment with statins was linked to a reduced risk of stroke, independent of both anticoagulation therapy and CHA_2DS_2-VASc score.
- Statin use was associated with a lower risk of new-onset incident IS/SE, HS and TIA in a duration-dependent manner among AF patients.

Thank You !