SUPPLEMENTAL MATERIAL

Table S1. Definition of covariates

Entity	Definition
Atrial fibrillation	ICD-9: 427.31
Heart Failure	ICD-9: 402, 404, 425, 428
Diabetes	ICD-9: 250
Hypertension	ICD-9: 401-405
Ischemic stroke	ICD-9: 430-434,436-438
Transient Ischaemic Attack	ICD-9: 435
Coronary Artery Disease	ICD-9: 410-414
Chronic Kidney Disease	ICD-9: 585
Peripheral Vascular Disease	ICD-9: 440-444, 447
Venous Thromboembolism	ICD-9: 415.1, 451, 453
Rheumatoid Arthritis	ICD-9: 714
Ankylosing Spondylitis	ICD-9: 720-724
Systemic Sclerosis	ICD-9: 710.1
Systemic Lupus Erythematosus	ICD-9: 710.0
Liver cirrhosis	ICD-9: 571.2, 571.5, 571.6, 572.2, 572.3, 572.4
Anaemia	ICD-9: 280,281-285
Cancer	ICD-9: 140-239
Gastrointestinal Bleeding	ICD-9: 456.0, 531-533, 578
Dyslipidaemia	ICD-9: 272, 272.1, 272.2, 272.3, 272.4
Obesity	ICD-9: 278
Smoke	ICD-9: 491, 492, 496

Abbreviation: ICD, international classification of disease.

Table S2. Events of incident heart failure, heart failure-related death and all-cause mortality among statin users and nonusers.

	Overall	Statin users	Statin nonusers
Heart failure, N (%)	9,268 (17.7)	3,673 (15.8)	5,595 (19.1)
Incidence rate per 100-person years	3.75	3.40	4.03
Heart failure-related death, N (%)	1,620 (3.1)	661 (2.8)	959 (3.3)
Incidence rate per 100-person years	0.66	0.61	0.69
All-cause mortality, N (%)	23282 (44.4)	9,537 (41.0)	13,745 (46.9)
Incidence rate per 100-person years	9.43	8.83	9.89

Abbreviation: N, number

Table S3. Characteristics of the inverse probability of treatment weighting treated cohort.

	Stain nonuser N=17,043.5	Statin user N=17,437.2
Age (SD)	74.77 (13.25)	74.71 (10.75)
Female, N (%)	8091.5 (47.5)	8263.6 (47.4)
Smoking, N (%)	1059.0 (6.2)	1102.3 (6.3)
CHA_2DS_2-VASc score (SD)	2.79 (1.57)	3.12 (1.61)
Medical conditions, N (%)		
Diabetes	7499.6 (44.0)	7733.7 (44.4)
Hypertension	4334.8 (25.4)	4467.4 (25.6)
Ischemic stroke	1794.9 (10.5)	1859.4 (10.7)
TIA	355.1 (2.1)	376.9 (2.2)
CAD	2149.7 (12.6)	2327.9 (13.3)
CKD	634.7 (3.7)	661.1 (3.8)
PVD	580.9 (3.4)	604.2 (3.5)
VTE	155.2 (0.9)	159.4 (0.9)
Autoimmune diseases*	2250.5 (13.2)	2322.6 (13.3)
Liver cirrhosis	67.8 (0.4)	69.1 (0.4)
Anaemia	1422.4 (8.3)	1475.4 (8.5)
Cancer	2552.2 (15.0)	2620.1 (15.0)
GIB	1783.1 (10.5)	1837.9 (10.5)
Dyslipidaemia	1216.1 (7.1)	1324.9 (7.6)
Obesity	126.2 (0.7)	131.5 (0.8)
Medication use, N (%)		
NOAC	7903.2 (46.4)	8037.0 (46.1)
Warfarin	3812.2 (22.4)	3858.9 (22.1)
Aspirin	7923.1 (46.5)	8135.6 (46.7)
Beta Blockers	5390.1 (31.6)	5501.5 (31.6)
ACEI/ARB	8448.0 (49.6)	8680.7 (49.8)
Procedure, N (%)		
Ablation (%)	101.6 (0.6)	103.5 (0.6)
Cardioversion (%)	63.0 (0.4)	63.6 (0.4)

Abbreviation: N, number; IPTW, inverse probability of treatment weighting; SD, standard deviation; TIA, transient ischaemic attack; CAD, coronary artery disease; CKD, chronic kidney disease; PVD, peripheral vascular disease; VTE, venous thromboembolism; 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.

Table S4. Association between LDL levels and heart failure (N=48,558).

LDL level (mmol/L)	Total / HF event (%)	*SHR (95% CI) P	
		Unadjusted	†Adjusted
As continuous variable			
	48,558/8685 (17.9%)	1.09 (1.07-1.11) <0.001	1.07 (1.05-1.09) <0.001
As categorical variable			
<1.8	9,424 (19.4%) / 1,745 (18.5%)	1.00(Ref.)	1.00(Ref.)
1.8-2.6	19,045 (39.2%) / 3,354 (17.6%)	1.06 (1.01-1.11) 0.01	1.03 (0.98-1.08) 0.15
>2.6	20,089 (41.4%) / 3,586 (17.9%)	1.17 (1.12 -1.22) <0.001	1.11 (1.07-1.17) <0.001

Abbreviation: LDL, low density lipoprotein; N, number; HF, heart failure; SHR, subdistribution hazard ratio; CI, confidence interval; Ref, reference.

*Subdistribution hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted with competing risks.

†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, ischemic stroke, transient ischaemic attack, coronary artery disease, chronic kidney disease, peripheral vascular disease, venous thromboembolism, 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.

Table S5. Effect of statin use between all-cause mortality and heart failure related death.

	Event number	Incident rate	Unadjusted *HR (95%CI) P	†Adjusted HR (95%CI) P
All-cause mortality				
Statin nonusers N=29,251	13,745 (47%)	9.89	Ref	Ref
Statin users N=23,239	9,537 (41%)	8.83	0.88 (0.86-0.90) <0.001	0.85 (0.82-0.87) <0.001
Heart failure-related death				
Statin nonusers N=29,251	959 (3.3%)	0.69	Ref	Ref
Statin users N=23,239	661 (2.8%)	0.61	0.88 (0.79-0.97) 0.009	0.85 (0.76-0.94) 0.002

Abbreviation: HR, hazard ratio; CI, confidence interval; N, number; Ref, reference.
*Hazard estimates were obtained with the use of a conventional Cox proportional hazards regression model fit to the inverse probability of treatment weighted.
†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, ischemic stroke, transient ischaemic attack, coronary artery disease, chronic kidney disease, peripheral vascular disease, venous thromboembolism, 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.

Table S6. Sensitivity analysis for the association between statin use and risk of incident heart failure.

Model	Statin nonuser	Statin user
IPTW treated	N=17,043.5	N=17437.2
Unadjusted SHR (95%CI) P	1	0. 84 (0.81-0.87) <0.001
Age and sex adjusted SHR (95%CI) P	1	0.82 (0.80-0.84) <0.001
Multivariable adjusted SHR (95%CI) P	1	0. 81 (0.78-0.85) <0.001
Competing risks without propensity score consideration SHR (95%CI) P	1	0.74 (0.70-0.77) <0.001
Conventional multivariable Cox regression HR(95%CI) P	1	0.75 (0.71-0.78) <0.001
Propensity score regressed	N=17,173	N=17,173
Unadjusted SHR (95%CI) P	1	0.72 (0.70-0.76) <0.001
Age and sex adjusted SHR (95%CI) P	1	0.73 (0.70-0.76) <0.001
Multivariable adjusted SHR (95%CI) P	1	0.75 (0.71-0.79) <0.001

Abbreviations: IPTW, inverse probability of treatment weighting; SHR, subdistribution hazard ratio; HR, hazard ratio; CI, confidential interval.

Subdistribution hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted with or without competing risks

Table S7. Characteristics of the alternative propensity score matched cohort according to statin use

	Stain nonuser N=17,173	Statin user N=17,173
Age (SD)	74.76 (12.17)	75.67 (10.94)
Female, N (%)	8172 (47.6)	8225 (47.9)
Smoking, N (%)	1046 (6.1)	1178 (6.9)
CHA_2DS_2-VASc score (SD)	2.84 (1.60)	3.00 (1.66)
Medical conditions, N (%)		
Diabetes	7666 (44.6)	7290 (42.5)
Hypertension	4394 (25.6)	4911 (28.6)
Ischemic stroke	1831 (10.7)	2414 (14.1)
TIA	358 (2.1)	479 (2.8)
CAD	2175 (12.7)	2620 (15.3)
CKD	645 (3.8)	849 (4.9)
PVD	586 (3.4)	809 (4.7)
VTE	143 (0.8)	166 (1.0)
Autoimmune diseases*	2240 (13.0)	2348 (13.7)
Liver cirrhosis	64 (0.4)	68 (0.4)
Anaemia	1366 (8.0)	1641 (9.6)
Cancer	2563 (14.9)	2690 (15.7)
GIB	1749 (10.2)	1969 (11.5)
Dyslipidaemia	1228 (7.2)	1816 (10.6)
Obesity	126 (0.7)	144 (0.8)
Medication use, N (%)		
NOAC	8338 (48.6)	7030 (40.9)
Warfarin	3863 (22.5)	3812 (22.2)
Aspirin	8138 (47.4)	8502 (49.5)
Beta Blockers	5485 (31.9)	5428 (31.6)
ACEI/ARB	8702 (50.7)	8726 (50.8)
Procedure, N (%)		
Ablation (%)	105 (0.6)	98 (0.6)
Cardioversion (%)	54 (0.3)	60 (0.3)

Abbreviation: N, number; IPTW, inverse probability of treatment weighting; SD, standard deviation; TIA, transient ischaemic attack; CAD, coronary artery disease; CKD, chronic kidney disease; PVD, peripheral vascular disease; VTE, venous thromboembolism; 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.

Table S8. The association between statin new user* and risk of incident heart failure and heart failure-related death after 1:1 propensity score matching (N=7740).

	Statin nonuser (N=3870)	Statin new user (N=3870)
Incident heart failure, N (%)	742 (19.2%)	623 (16.1%)
Unadjusted SHR (95% CI)	1	0.68 (0.62-0.74)
Age and sex adjusted SHR (95% CI)	1	0.71 (0.65-0.78)
Multivariable adjusted SHR (95% CI)	1	0.70 (0.64-0.77)
Heart failure-related death, N (%)	103 (2.7%)	96 (2.5%)
Unadjusted SHR (95% CI)	1	0.78 (0.71-0.85)
Age and sex adjusted SHR (95% CI)	1	0.78 (0.72-0.86)
Multivariable adjusted SHR (95% CI)	1	0.75 (0.68-0.82)

Abbreviation: N, number; SHR, subdistribution hazard ratio; CI, confidential interval.

*We excluded all patients with a history of statin use prior to the index date and statin new user was defined as never use of statin before index date.

Subdistribution hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the 1:1 propensity score matching cohort that accounted for competing risks.

Table S9. Association between statin use and a negative control outcome: incident gastrointestinal bleeding

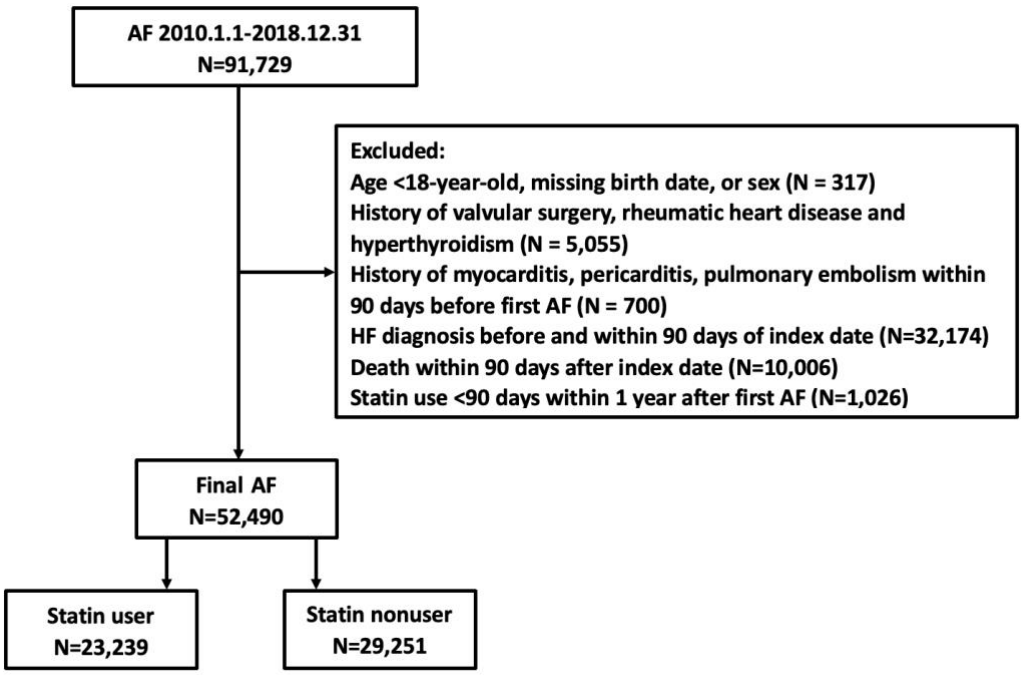
Event	Statin nonusers (Ref.) (N=29,251)	Statin users (N=23,239)	P
Incident gastrointestinal bleeding			
Number with event, N (%)	2,272 (7.8)	1,674 (7.2)	0.14
Incidence rate per 100-person years	1.64	1.55	<0.01
Unadjusted *SHR (95% CI)	1	1.03 (0.97-1.10)	0.34
†Multivariable adjusted SHR (95% CI)	1	1.01 (0.94-1.08)	0.77

Abbreviations: SHR, subdistribution hazards ratio; CI, confidence interval; ref., reference.

*Subdistribution hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted with competing risks.

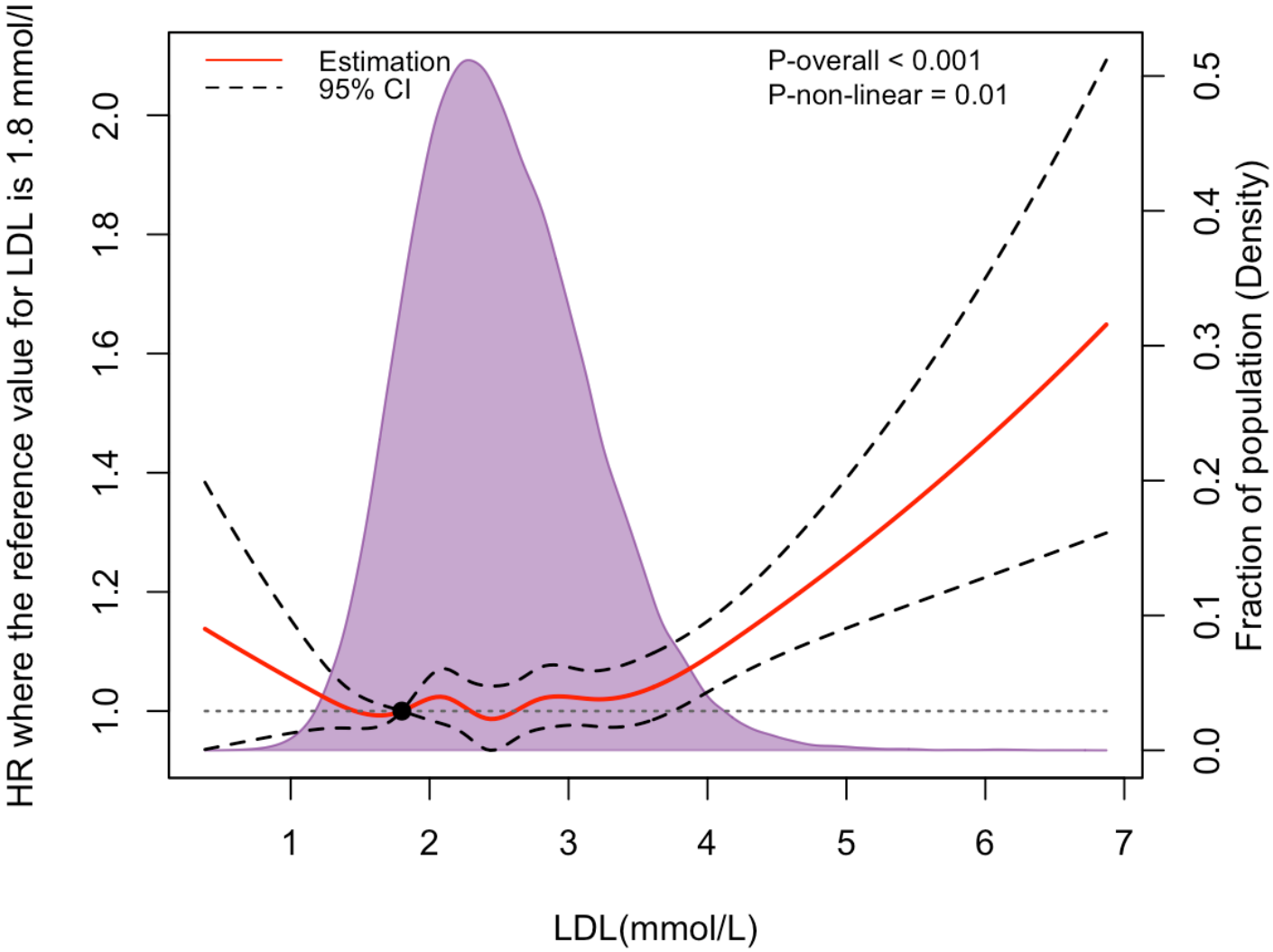
†A multivariable adjusted model further accounted for the following prognostic covariates: age at index date, sex, smoking, CHA_2DS_2-VASc score, comorbidities, including diabetes, hypertension, ischemic stroke, transient ischaemic attack, coronary artery disease, chronic kidney disease, peripheral vascular disease, venous thromboembolism, 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.

Figure S1. Flow chart of study cohort selection.



Abbreviation: AF, atrial fibrillation; HF, heart failure.

Figure S2. Restricted cubic spline for the association between LDL and incident heart failure.



Abbreviation: LDL, low-density lipoprotein.