Validation of the imputation process.

In the pre-multiple imputation stage, we checked for normality, extreme values and outliers in continuous variables, correlations and collinearity among variables with missing data and variables that may be included in multiple imputation. Variables related to missing data and/or to the value of missing data were identified. Based on these results, we assumed that the missingness mechanism was at random for each of the variables to be imputed and was related with different subsets of the variables included in the imputation models (i.e., that it was possible to estimate their missing values as conditioned by the values of other observed variables).

The following variables were included in the imputation models: age, MEDEA index score, smoking, diabetes, hypertension, acute and chronic kidney disease, dyslipidaemia, acute and chronic liver disease, atrial fibrillation, asthma, hyper- and hypothyroidism, myopathy, benign neoplasms, sleep apnoea syndrome, obesity, valvular heart diseases, antihypertensive agents, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin-aldosterone system, hypoglycaemic agents, statins, antiplatelet agents, analgesics, anti-inflammatory and antirheumatic agents, systemic corticosteroids, sex hormones, weight, height, and the natural logarithm (ln) of the following variables: systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and glucose. We also included incident cardiovascular disease and time to incident cardiovascular disease or time to censoring.

We used the natural logarithmic transformation of the indicated continuous variables included in the imputation models to improve normality of distribution and to avoid the unlikely possibility of imputing any negative numbers. After imputation, variables were transformed back to the original scale.

We assumed the interaction between sex and coronary risk and performed this analysis in men and women separately.

Propensity score analysis

A logistic model based on potential confounding covariates was used to calculate a propensity score (PS) for statin therapy. An *a priori* method was used to select variables to be included in the models.

The variables were selected based on their association with the statin exposure or the outcomes. A mixed approach was used; variables were chosen according to the previous clinical knowledge of relationships between the exposure and the outcome and their statistical significance in the models. Quadratic PS was included in the models as a covariate (*see: Austin, P. C. (2008). Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiology and Drug Safety, 17(12), 1202–1217. http://doi.org/10.1002/pds.1673*

Austin, P. C. (2009). The Relative Ability of Different Propensity Score Methods to Balance Measured Covariates Between Treated and Untreated Subjects in Observational Studies, (416), 1–17. http://doi.org/10.1177/0272989X09341755).

Linearity of all continuous variables was tested by the inclusion of polynomial terms in the models. A quadratic polynomial term was included for age. Collinearity was also tested and no variance inflation factor exceeded 4.

The analysis was restricted to individuals with a common PS range. Adjusted models included 7,186 individuals out of 8,018 (89,6% of the initial sample). Of those excluded, 818 were non-statin users (98.3%) and 14 statin users (1.7%).

Supplementary Table 1. Baseline characteristics of individuals out of the common range.

Variables	n=832
Age, mean (SD) years	52.56 (12.13)
Women (%)	7.94%
Smokers (%)	31.88
Diabetes (%)	2.32
Hypertension (%)	20.06
Dyslipidaemia (%)	2.32
Obesity (%)	41.99
Chronic kidney disease (%)	1.19
Blood pressure	
Systolic, mean (SD), mm Hg	132. 26 (16.37)
Diastolic, mean (SD), mm Hg	80.13 (10.28)
Glucose, mean (SD), mmol/L	5.33 (1.43)
Total cholesterol, mean (SD), mmol/L	4.47 (0.78)
LDL cholesterol, mean (SD), mmol/L	2.54 (0.64)
HDL cholesterol, mean (SD), mmol/L	1.29 (0.36)
Serum triglycerides, mmol/L	1.49 (0.89)
Medication (%)	
Antidiabetics	1.19
Aspirin (%)	1.05
Diuretic	2.42
ß-blocker	2.93
ACE inhibitor/ARB	6.50
Calcium channel blocker	2.51
Psycholeptics	6.24
Psychoanaleptics	3.50
Anti-inflammatory drugs	13.36
Gout drugs	42.72%
10-year CHD risk, mean (SD)	2.80 (1.93)
Comorbidities (%)	
Atrial fibrillation	0.60
COPD	7.10
Benign neoplasms	7.41
Hypothyroidism	1.98
Hyperthyroidism	0.19
Number of visits, mean (SD)	1.90 (3.57)
MEDEA index, mean (SD)	0.81 (0.94)

LDL, low-density lipoprotein; HDL, high-density lipoprotein;
ACE, angiotensin-converting enzyme;
ARB, angiotensin II receptor (AT-II) blockers;
CHD, coronary heart disease;
COPD, chronic obstructive pulmonary disease

Supplementary Table 2. Missing values (%) for the imputed variables within entire population and mean values for the imputed variables in the complete and imputed datasets.

	Missing (%)	Complete (n=1,575)	Imputed (n=8,018)
SBP (mmHg)	3,798 (47.37)	138.14 (15.39)	135. 79 (16.37)
DBP (mmHg)	3,859 (48.13)	79.91 (9.80)	80.39 (10.25)
Total cholesterol (mmol/L)	4,012 (50.04)	5.46 (1.01)	5.45 (1.00)
HDL cholesterol (mmol/L)	4,840 (60.36)	1.28 (0.31)	1.29 (0.33)
LDL cholesterol (mmol/L)	4,910 (61.24)	3.40 (0.86)	3.36 (0.88)
Triglycerides (mmol/L)	4,633 (57.78)	1.72 (0.92)	1.80 (1.10)
Glucose (mmol/L)	3,964 (49.44)	6.18 (1.84)	5.70 (1.41)
BMI	5,190 (64.73)	30.64 (4.52)	29.78 (4.46)
10-year CHD risk (mean)	5,946 (74.16)	5.39 (3.07)	4.08 (2.59)

SBP/DBP: systolic/diastolic blood pressure·

Supplementary Table 3. Baseline characteristics of the total population before and after adjusting for propensity score. Complete dataset.

			Before	After
Variables	Statin non-users	Statin new-users	SDiff*	SDiff*
	n= 1,271	n = 304		
Age, mean (SD) years	64.08 (10.90)	63.97 (9.61)	0.01	0.12
Sex (% women)	11.96	11.84	0.00	0.16
High-risk alcohol intake (%)	7.71	11.59	-0.13	0.02
Smokers (%)	25.49	32.24	-0.15	0.09
Diabetes (%)	27.07	45.39	-0.39	0.11
Hypertension (%)	75.92	80.59	-0.11	0.09
Dyslipidaemia (%)	33.99	75.00	-0.90	0.24
Obesity (%)	55.55	56.91	-0.03	0.05
Chronic kidney disease (%)	6.37	7.24	-0.03	0.03
Blood pressure				
Systolic, mean (SD), mm Hg	137.89 (15.42)	139.19 (15.28)	-0.09	0.04
Diastolic, mean (SD), mm Hg	79.81 (9.79)	80.36 (9.79)	-0.06	0.09
Glucose, mean (SD), mmol/L	6.06 (1.77)	6.70 (2.03)	-0.33	0.09

Total cholesterol, mean (SD), mmol/L	5.27 (0.86)	6.27 (1.16)	-0.98	0.34
LDL cholesterol, mean (SD), mmol/L	3.25 (0.75)	4.03 (0.97)	-0.91	0.31
HDL cholesterol, mean (SD), mmol/L	1.29 (0.31)	1.26 (0.29)	0.10	0.11
Serum triglycerides, mmol/L	1.62 (0.80)	2.15 (1.23)	-0.51	0.03
Medication (%)				
Aspirin (%)	7.08	20.07	-0.39	0.18
Diuretic	20.46	25.33	-0.12	0.15
ß-blocker	12.51	16.45	-0.11	0.11
ACE inhibitor/ARB	51.85	59.54	-0.16	0.09
Calcium channel blocker	14.40	13.16	0.04	0.29
Psycholeptics	15.66	19.08	-0.09	0.05
Psychoanaleptics	7.00	7.57	-0.02	0.11
Anti-inflammatory drugs	31.39	37.50	-0.13	0.09
Gout therapy	66.25	68.09	-0.04	0.05
Antidiabetic therapy	15.18	29.61	-0.35	0.05
Statin by LDL-reduction capacity (%)				
Low (<30%)	-	4.61	-	-
Moderate (30-40%)	-	81.91	-	-
High (>40%)	-	13.49	-	-
10-year CHD risk, mean (SD)	5.23 (3.03)	5.99 (3.17)	-0.24	0.07
Comorbidities (%)				

Atrial fibrillation	2.68	1.97	0.05	0.15
COPD	11.80	8.55	0.11	0.08
Benign neoplasms	9.60	9.21	0.01	0.10
Hypothyroidism	2.28	1.64	0.05	0.12
Hyperthyroidism	0.55	0.66	-0.01	0.47
Number of visits, mean (SD)	5.50 (5.24)	5.95 (5.31)	-0.08	0.15
MEDEA index, mean (SD)	0.71 (0.84)	0.76 (0.89)	-0.05	0.04

*SDiff: standardised differences

Supplementary Table 4. Adjusted hazard ratios (HR) of incident cardiovascular events, all-cause mortality, adverse effects, and 5-year number needed to treat (NNT) to prevent one event by statin use. Incidence per 1000 person/years. Complete dataset. Individuals within the PS common range (n=1,521)

	Statin non-users		Statin new-users			
	Events	Crude incidence (95%CI)	Events	Crude incidence (95%CI)	Adjusted HR (95%CI)	5-year NNT
Outcomes of interest						
Coronary heart disease	77	6.78 (5.26-8.29)	23	8.94 (5.29-12.59)	0.73 (0.42-1.26)	
Ischemic stroke	88	7.70 (6.09-9.31)	12	4.55 (1.98-7.13)	0.59 (0.30-1.17)	
All-cause mortality	182	15.56 (13.30-17.82)	38	14.13 (9.64-18.62)	1.00 (0.67-1.50)	-
Adverse effects						
Cancer	236	24.83 (21.66-28.00)	56	25.64 (18.92-32.35)	1.28 (0.91-1.80)	-
Type 2 diabetes	159	23.96 (20.23-27.68)	33	27.30 (17.99-36.62)	1.20 (0.76-1.90)	-
Haemorrhagic stroke	19	1.83 (1-01-2.65)	2	-	-	-
Acute liver disease	2	-	0	-	-	-
Myopathy	1	-	0	-	-	-

Supplementary Table 5. Adjusted hazard ratios (HR) of incident cardiovascular events, all-cause mortality, and 5-year number needed to treat (NNT) to prevent one event by statin use, including death as competing risk

	Adjusted HR (95%CI)	5-year NNT
Death as competing risk		
Coronary heart disease	0.85 (0.60-1.20)	263
Ischemic stroke	0.69 (0.45-1.05)	150

Supplementary Table 6. Proportionality of hazards assumption (p-values)

	Final model	Death as competing risk
Outcomes of interest		
Coronary heart disease	0.632	0.684
Ischemic stroke	0.052	0.022
All-cause mortality	0.262	-
Adverse effects		
Cancer	0.138	
Type 2 diabetes	0.405	
Haemorrhagic stroke	0.380	