TITLE PAGE

Full title: Effectiveness of statins as primary prevention in people with gout: a population-based cohort study.

Maria Garcia-Gil[a], Marc Comas-Cufí[a], Rafel Ramos[a,b,c], Ruth Martí[a,d], Lia Alves-Cabratosa[a], Dídac Parramon[a], Daniel Prieto-Alhambra[e,f], Jose Miguel Baena-Díez[g,h,i], Betlem Salvador-González[g,h,j], Roberto Elosua[g,k], Irene R. Dégano[g,k], Jaume Marrugat[g,k], María Grau[g,k,l]

a. Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Catalonia, Spain; ISV Research Group, Research Unit in Primary Care.

b. Primary Care, Primary Care Services, Girona, Catalan Institute of Health (ICS), Catalonia, Spain.

c. Department of Medical Sciences, School of Medicine, University of Girona, Spain.

d. Biomedical Research Institute, Girona (IdIBGi), ICS, Catalonia, Spain.

e. Musculoskeletal Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom.

f. GREMPAL (Grup de Recerca en Malalties Prevalents de l'Aparell Locomotor) Research Group, IDIAP Jordi Gol and CIBERFes. Universitat Autònoma de Barcelona and Instituto Carlos III, Barcelona, Spain.

g. REgistre Gironí del Cor Research Group (REGICOR) and Cardiovascular, Epidemiology and Genetics Research Group (EGEC), Hospital del Mar Medical Research Institute (IMIM), Barcelona, Catalonia, Spain.

h. Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Catalunya, Spain. MACAP Renal Research Group. Research Unit in Primary Care.

i. La Marina Primary Care Centre. Catalan Institute of Health (ICS), Barcelona, Spain.

j. Florida Sud Primary Care Centre, Primary Care Services, Costa Ponent. Catalan Institute of Health, Catalunya, Spain

k. CIBER Cardiovascular Diseases (CIBERCV), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.

l. Universitat de Barcelona, Catalonia, Spain.

Corresponding author: Dr. Rafel Ramos. Research Unit, Family Medicine, Girona.

Jordi Gol Institute for Primary Care Research (IDIAP Jordi Gol) and Primary Care Services, Girona. Catalan Institute of Health (ICS), Catalonia, Spain.

Address: Carrer Maluquer Salvador, 11. 17003 Girona. SPAIN

Telephone: 34 972 212670; FAX: 34 972 214100;E-Mail: ramos.girona.ics@gencat.cat

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ABSTRACT

Background: Cardiovascular guidelines do not give firm recommendations on statin therapy in patients with gout because evidence is lacking.

Aim: To analyse the effectiveness of statin therapy in primary prevention of coronary heart disease, ischemic stroke and all-cause mortality in a population with gout.

Methods: A retrospective cohort study (July 2006-December 2017) based on SIDIAP^{Q}, a research-quality database of electronic medical records, included primary care patients (aged 35-85 years) without previous CVD. Participants were categorized as non-users or new-users of statins (defined as receiving statins for the first time during the study period). Index date was first statin invoicing for new-users and randomly assigned to non-users. The groups were compared for the incidence of coronary heart disease (CHD), ischemic stroke (IS) and all-cause mortality, using Cox proportional hazards modelling adjusted for propensity score.

Results: Between July 2006 and December 2008, 8,018 individuals were included; 736 (9.1%) were new users of statins. Median follow-up was 9.8 years. Crude incidence of CHD was 8.16 (95%CI: 6.25-10.65) and 6.56 (95%CI: 5.85-7.36) events per 1000 person-years in new-users and non-users, respectively. Hazard ratios were 0.84 (95%CI: 0.60-1.19) for CHD, 0.68 (0.44-1.05) for IS and 0.87 (0.67-1.12) for all-cause mortality. Hazard for diabetes was 1.27 (0.99-1.63).

Conclusions: Statin therapy was not associated with a clinically significant decrease in CHD. Despite higher risk of CVD in gout populations compared to general population, patients with gout from a primary prevention population with a low-to-intermediate incidence of CHD should be evaluated according to their cardiovascular risk assessment, life-style recommendations and preferences, in line with recent EULAR recommendations.

INTRODUCTION

Gout is the most frequent inflammatory arthritis. Both the prevalence and incidence of gout are higher in men than in women and are rising in developed countries (1), and it is associated with increased cardiovascular mortality and morbidity (2)(3)(4) and cardiovascular risk factors such as hypertension (5), chronic kidney disease (CKD) (6) and metabolic syndrome (7). The coexistence of gout with these diseases suggests commonalities in the inflammatory pathogenic mechanisms related to the atherogenic process (8)(9) and in disease-related treatment mechanisms such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (10), which have also been associated with an increase of cardiovascular risk (11).

In 2016, the European League Against Rheumatism (EULAR) task force recommended treatment of gout flares. Colchicine, NSAIDS and corticoids are the first line therapies of the acute episodes because of their anti-inflammatory effects and urate-lowering drugs are the first choice at the new-onset of this disease (12). In addition to the active treatment of the disease, identification of cardiovascular risk factors and active cardiovascular risk management were particularly recommended. However, no specific recommendations on statin therapy were made. Moreover, local cardiovascular guidelines do not give firm recommendations in patients because evidence is lacking. The potential benefits of statins in relation to their pleiotropic effect has not been evaluated in individuals with gout; most studies involving statins have focused on other inflammatory arthritis (13)(14), with no studies on their effectiveness in primary prevention of cardiovascular diseases (CVD) in these patients. Evidence from electronic medical records data can be useful in cardiovascular risk management decision-making and in evaluating treatment effectiveness in clinical settings.

The present study aimed to analyse the effectiveness of statin therapy in primary prevention of coronary heart disease, ischemic stroke and all-cause mortality in a population with gout.

METHODS AND MATERIALS

Study design and data source

Retrospective population-based cohort study using a research-quality set of anonymised longitudinal patient records from the Information System for the Development of Research in Primary Care (SIDIAP^{Q}) (15), which contains anonymised longitudinal data on approximately 2 million patients, attended by 1,365 GPs, and has been used in numerous epidemiological studies (16)(17)(18)(19). The full database contains records for ~6 million people (80% of the Catalan population, constituting 10.2% of Spain's population).

The information recorded includes demographic and lifestyle factors relevant to primary care settings (body mass index [BMI], smoking status, alcohol use); clinical diagnoses, outcomes and events, coded by International Classification of Diseases, 10th revision (ICD-10); referrals and hospital discharges (coded by ICD-9); laboratory tests; and prescribed medications dispensed by community pharmacies. Ethics approval for observational research using SIDIAP^{Q} data was obtained from our local ethics committee.

Study population

All patients aged 35 to 85 years with an active gout code diagnosis (ICD-10 codes M10) were eligible for study inclusion. Exclusion criteria included active diagnostic codes at baseline for cancer, dementia, paralysis, organ transplant, dialysis or institutionalized care, missing data for MEDEA deprivation index score (20), and previous history of symptomatic peripheral arterial disease (PAD), coronary heart disease (CHD), ischemic (IS) or haemorrhagic stroke, revascularization, heart failure or cardiac therapy (Anatomical

Therapeutic Chemical Classification code C01), or cholesterol-lowering drugs other than statins taken between July 2006 and December 2008.

Study enrolment

Patients were enrolled from July 2006 to December 2008 and censored at the date of transfer out from SIDIAP^{Q} or the end of follow-up, December 31, 2017.

Statin exposure

To prevent survivor bias and covariate measurement bias among users of statins (simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin, pitavastatin), only new users were selected and their first date statins were dispensed was set as index date; those same dates were then randomly assigned to included non-users. Individuals with fewer than two invoices for statins during the enrolment period were excluded.

Main analyses were performed considering statin exposure as new-users *versus* non-users. In descriptive analysis, we classified patients' exposure to statins according to the drug's cholesterol reduction capacity, as follows: low, <30%; moderate, 30-40%; and high, >40% (21).

Outcomes

The SIDIAP^{Q} codes for CVD, previously validated for research use (19), were identified in both primary care (ICD-10) and hospital discharge records (ICD-9). Primary outcomes were CHD (a composite of AMI and angina), IS and all-cause mortality recorded during follow-up.

Adverse effects

Liver toxicity and myopathy occurring within 12 months of initiating statins therapy were attributed to the treatment. New-onset diabetes, cancer and haemorrhagic stroke diagnosed at least 12 months after the first date statins were dispensed was also considered as associated to statin exposure (22).

Baseline covariates

Baseline period was defined as 1 year before the index date. The following covariates that may have influenced prescription decisions and study outcomes were considered: age, sex, deprivation index developed for Spain by the MEDEA study (20), systolic and diastolic blood pressure (SBP, DBP) (mmHg) and dichotomous (yes/no) variables for high-risk alcohol intake, smoking, diabetes or record of antidiabetic drug use, hypertension or record of antihypertensive drug use, dyslipidaemia, and BMI>30 kg/m^2. Laboratory results were considered for fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Comorbidities were noted (yes/no): atrial fibrillation, CKD, chronic obstructive pulmonary disease (COPD), asthma, benign neoplasms, hypo- and hyperthyroidism. Finally, the number of GP visits in the 12 months before index date and other drug uses were recorded: antiplatelets, anti-inflammatory drugs, gout treatments, psychoanaleptics and psycholeptics. Ten-year CHD risk was calculated using the Framingham function adapted and validated in the Spanish population by the REGICOR study in the population aged 35-74 years (23).

Statistical analysis

Results are expressed as percentages for categorical variables and otherwise as mean (standard deviation, SD) or median [quartiles]. Multiple imputations by chained equations (24) were used to replace missing baseline values for total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, SBP, DBP and BMI (weight and height), as detailed in the supplementary file.

Due to non-random treatment allocation, a propensity score (PS) for statin treatment was calculated, using a logistic model based on potential confounding covariates (contained in supplementary file). Baseline characteristics before and after PS adjustment were compared using standardised differences, with values <0.10 indicating well-balanced variables. Variables not balanced between users and non-users of statins were further

included in the models. Multivariate analysis was restricted to individuals with a common PS range for non-users and new-users. Supplementary Table 1 shows the baseline characteristics of the individuals out of the common range. Ten PS and 10 hazard ratio (HR) values were calculated in each imputed dataset. Pooled HR was then calculated according to Rubin (24) with quadratic PS as covariate.

Proportionality of hazards assumption was tested by calculating the median of the chi-square tests of the models fitted for the 10 imputed datasets. Five-year number needed to treat (NNT) for one additional patient to survive was also calculated. A sensitivity analysis compared complete-case with multiple imputation results (supplementary file). We analyzed the data using a simulated "intention to treat" scenario where subsequent treatment of the exposed and unexposed patients is assumed to be the same as defined in the baseline. Competing risk analysis was performed to discard survival bias (supplementary file). Statistical analysis used R-software version 3.4.3 (25).

RESULTS

Baseline characteristics

During the enrolment period, 8,018 patients met inclusion criteria and 736 (9.1%) were new users of statins. Losses to follow-up were 106 (1.3%), all of them due to transfer out of the SIDIAP^{Q} database. The study flow chart is detailed in Figure 1. Median follow-up was 9.8 years (9.1, 1st quartile; 10.5, 3rd quartile).

Missing data for incomplete variables and a comparison of the complete-case and imputed datasets are shown in Supplementary Table 2. Overall, mean values for incomplete variables were lower after multiple imputations.

Women constituted 8% of the study population and the mean age was 59.0 (11.6) years. Diabetes was present in nearly 12% of participants, hypertension in 49%, smoking in 30%, and dyslipidaemia in 30%; nonetheless, mean (SD) estimated 10-year CHD risk was low, at

4.1 (2.5). Median medication possession ratio (# days of statin supplied in 6 consecutive months / 183 days) was 77% [1st quartile, 46%; 3rd quartile, 100%].

Baseline characteristics for new-users and non-users and standardised differences before and after adjusting for PS are presented in Table 1. More than 80% of new users were treated with a statin of moderate LDL-reduction capacity.

Supplementary Table 3 shows the results in the complete dataset. Overall, the population with complete data was older, with a worse cardiovascular risk profile.

Outcomes and effectiveness of statins

For 2006-2017, overall crude incidence per 1,000 person-years at risk (PYAR) of CHD, IS and all-cause mortality were 6.43 (95%CI 5.85-7.01), 5.51 (95%CI 4.97-6.04) and 13.17 (95%CI 12.35-13.98), respectively. Crude incidence, adjusted hazard ratios and 5-year NNTs for all primary outcomes by statin use in people within the PS common range (n=7,186) are shown in Table 2.

Crude incidence of CHD was higher in statin users than in non-users. Statin treatment decreased CHD risk by 16% although the null hypothesis could not be rejected [adjusted HR: 0.84 (0.60-1.19)]. The 5-year NNT for CHD was 248. There was also no significant risk reduction in IS and all-cause mortality. Further adjustment for variables not balanced after PS adjustment did not change the results.

Supplementary Table 4 shows the results in the complete dataset. CHD crude incidence was higher in statin users whereas IS and all-cause mortality incidences were lower, compared to non-users. Adjusted HRs were similar compared to the imputed dataset..

Adverse Events

Unadjusted incidence of cancer and diabetes was higher in new users of statin than in non-users. The increase in diabetes risk showed a weak evidence against the null hypothesis [1.27 (0.99-1.63)]. There was no increase in cancer and the small sample size of the haemorrhagic stroke led to a very imprecise effect size. Supplementary Table 4 shows similar adverse event results in the complete dataset.

The sensitivity analysis that considered death as competing risk showed similar results (Supplementary Table 5). Supplementary Table 6 shows the results of the proportionality of hazards assumption.

DISCUSSION

Summary

To our knowledge, this is the first study to analyse the real-world clinical effectiveness of statins in reducing CHD, IS and all-cause mortality among individuals diagnosed of gout and free of clinical CVD. Statin therapy decreased CHD, IS and all-cause mortality risk by 16%, 32%, and 13%, respectively, although this effect was not significant. The 5-year NNT's ranged from 248 to 145. New users of statins had a clinically significant higher incidence of diabetes. No excess risk of cancer was recorded during follow-up.

Comparison with existing literature

In our study, the higher rate of CHD incidence observed in the gout population, compared to that estimated by the risk equation, supports the consideration that these patients are at higher risk of coronary events than the general population (2)(3)(4). Despite this higher incidence rate, it remained close to 6.5% in statin non-users and 8.0% in statin users at 10 years, considered an intermediate level of coronary risk (18).

Most studies on efficacy of statins in primary prevention have focused on CHD risk in the general population, reporting similar results in high and intermediate coronary risk populations, defined as a 10-year coronary risk greater than 10% and 7.5%, respectively (26)(27). Our population may be comparable to that of the studies focusing on intermediate coronary risk, but has clinical characteristics that make it difficult to compare the effects of statin therapy with general population results. The effect size of our results was in accordance with the intermediate-risk studies in terms of effectiveness; however, in our gout population statin treatment could have limited net benefit due to the large 5-year NNT: 248 to prevent one event (18).

The magnitude of statin effectiveness in preventing IS was lower than that of studies in general population (18)(28). The limited number of IS events observed in our sample likely

influenced effect size in our results. The mechanism by which statins may be effective in reducing the incidence of CVD diseases in gout populations is not well understood. On one hand, statins and some acute gout treatments might have a joint effect. Colchicine could be associated with a reduced risk of CVD events (29)(30)(31) whereas NSAIDS seemed to be related with an increased risk of AMI (11). On another hand, urate-lowering therapies, allopurinol in particular, was found to be associated with an improvement in flow mediated dilation (32) and a reduced risk of CVD events (33)(34)(35). Uncertainty prevails regarding the final joint effect of anti-inflammatory gout therapies and statins on CVD incidence but this interaction could explain the possible differences in effectiveness between the general population and our study population with gout .

In addition, further research is needed on how dyslipidaemia and hyperuricaemia mechanisms affect stroke risk, particularly in populations with gout (36). No studies have evaluated the association between statin use and IS in these populations.

In our study, gout and anti-inflammatory treatments were well balanced between new users and non-users of statins, so their potential confounding effect was minimised although we cannot rule out some residual confounding

Studies in general populations have inspired debate about statins' effectiveness in reducing all-cause mortality (27)(37)(38), despite agreement on their moderate success (~10%, similar to our findings) in reducing relative risk. A recent study showed a greater decrease in overall mortality in a gout population, particularly in the subgroup analyses of individuals without previous cardiovascular disease. However, the healthier characteristics of the sample, compared to general population, did not preclude a bias effect (39).

We observed no increased risk of cancer or haemorrhagic stroke among new users of statins, which is consistent with the literature in general population (40)(41); a longer

follow-up might be needed to detect an association between statin use and these adverse effects. There are no studies in the population with gout.

Finally, statin treatment increased the risk of diabetes about 27%, in line with previous results (42). This is a clinically significant result because there is also evidence that gout is associated with an increased risk of diabetes (43)(44).

Strengths and limitations

The large sample of individuals, drawn from a high-quality, internally validated database of electronic medical records that provides high external validity and clinical data from patients often excluded from trials (e.g., women, older patients, individuals with diabetes), is a main strength of our study

Several general limitations are inherent to observational studies using medical records.
First, we cannot discard some risk of misclassification but the presence of cardiovascular risk factors and outcomes were previously validated in SIDIAP (45) and data on statin exposures were obtained from official pharmacy invoicing records of the National Health Service. About 60% of the study population was taking gout treatment, which reinforces the accuracy of the diagnoses, although some degree of misclassification cannot be completely ruled out.
Second, residual confounding is a possibility, especially by indication. To avoid frailty bias, we excluded individuals with cancer, dementia, paralysis, organ transplant, in dialysis or institutionalized. We used a new-users design to minimize potential effect of statins on confounding factors, then adjusted for PS. In addition, non-clinical factors that may influence prescription patterns and treatment adherence were not measured. These include doctor perception of a patient's risk profile, prescriber experiences, unreported side effects and patient perceptions of risk and willingness to take the drug (46).
Third, missing data can influence results. To avoid selection bias, we imputed the missing values for continuous variables instead of excluding those records. The characteristics of

the study population met plausibility for the missing-at-random assumption for all imputed variables except for the MEDEA deprivation index, in which its missing mechanism was completely at random; thus, exclusion of participants with missing values for this variable did not imply selection bias.

Fourth, cause of death is not available in the SIDIAP[Q] database, which precluded analysis of statins' effect on CVD mortality.

Fifth, acute liver diseases and myopathy could not be compared between new users and non-users due to the low number of events, particularly in statin users. This underreporting could lead to non-differential misclassification and reduce statistical power, biasing results towards the null hypothesis. In addition, we could not draw conclusions about the effect of statins on haemorrhagic stroke due to the width of the 95% CI.

Sixth, the present analysis did not consider variables such as degree of inflammation, uricemia levels or elapsed time between gout diagnosis and the incidence of cardiovascular events or death. Therefore, we were not able to evaluate uricemia levels and the degree of gout activity.

Finally, changes in the patterns of statins use, such as the increase in their prescription for primary prevention (47)(48) and the use of high-potency statins (49)(50) were unlikely to have influenced the results of our study. Spanish blood lipid national and local guidelines advise no systematic prescription of statins and the overall management of the cardiovascular risk and, when recommended, statins of low and moderate statins should be the first choice (51)(52).

CONCLUSION

Statins were not associated with a decrease in CHD in a gout population at 10-year low-to-intermediate coronary risk. Diabetes risk was increased. No significant adverse effects

were found. The high 5-year NNT to prevent one CHD event raises questions about recommending statin treatment in this population.

In addition, despite the higher risk of CVD in gout populations compared to general population, patients with gout from a population with a low-to-intermediate incidence of CHD should not be systematically considered at high risk and should be evaluated according to their cardiovascular risk assessment, life-style recommendations and preferences, in line with the recent EULAR recommendations.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due confidenciality policy of SIDIAP database but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable

Ethical approval

Ethics approval for observational research using SIDIAPQ data was obtained from our local ethics committee.

Conflict of Interest Statement

None declared. Drs Ramos and Garcia-Gil reported collaboration in projects funded by AstraZeneca, AMGEN and Novonordisk through IDIAP Jordi Gol. Dr Garcia-Gil has received speaker fees from Novartis. DPA's research group has received research grants from Servier, Amgen and UCB; speaker fees from Amgen; and consultancy fees from UCB Biopharma. These projects are unrelated to the present work.

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Figure 1. Flowchart of participant selection.

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Table 1. Baseline characteristics of the total population before and after adjusting for propensity score (PS).

			Before	After
Variables	Statin non-users (n=7,282)	Statin new-users (n=736)	SDiff*	SDiff*
Age, mean (SD) years	58.76 (11.72)	61.93 (9.97)	-0.29	0.12
Sex (% women)	8.12	10.05	0.07	0.24
High-risk alcohol intake (%)**	9.74	10.78	-0.03	0.07
Smokers (%)	30.73	31.66	-0.02	0.20
Diabetes (%)	10.67	29.76	-0.49	0.04
Hypertension (%)	47.01	69.57	-0.47	0.13
Dyslipidaemia (%)	26.15	72.28	-1.04	0.09
Obesity (%)	48.81	55.46	-0.13	0.05
Chronic kidney disease (%)	3.76	6.52	-0.13	0.03
Blood pressure				
Systolic, mean (SD), mm Hg	135.54 (16.36)	138.26 (16.27)	-0.17	0.03
Diastolic, mean (SD), mm Hg	80.35 (10.22)	80.78 (10.49)	-0.04	0.08
Glucose, mean (SD), mmol/L	5.64 (1.33)	6.32 (1.94)	-0.41	0.06
Total cholesterol, mean (SD),	5.35	6.43	-1.03	0.38

mmol/L	(0.93)	(1.15)		
LDL cholesterol, mean (SD),	3.28	4.14	-0.93	0.37
mmol/L	(0.83)	(1.01)		
HDL cholesterol, mean (SD),	1.29	1.29	0.01	0.05
mmol/L	(0.33)	(0.32)		
Serum triglycerides, mmol/L	1.76	2.24	-0.39	0.05
	(1.05)	(1.40)		
Medication (%)				
Antidiabetics	5.16	18.89	-0.43	0.04
Aspirin (%)	3.65	14.54	-0.39	0.08
Diuretic	10.79	21.20	-0.29	0.02
ß-blocker	7.81	12.91	-0.17	0.06
ACE inhibitor/ARB	27.03	49.59	-0.48	0.05
Calcium channel blocker	7.46	12.36	-0.16	0.17
Psycholeptics	11.38	17.39	-0.17	0.07
Psychoanaleptics	5.69	8.56	-0.11	0.14
Anti-inflammatory drugs	25.68	38.32	-0.27	0.01
Gout drugs	59.10	67.53	-0.18	0.08
Statin by LDL-reduction				
capacity No (%)				
Low (<30%)	-	4.08	-	-
Moderate (30-40%)	-	81.25	-	-
High (>40%)	-	14.67	-	-
10-year CHD risk, mean (SD)	3.97	5.20	-0.44	0.02
	(2.52)	(2.97)		
Comorbidities (%)				

Atrial fibrillation	1.22	1.49	-0.02	0.02
COPD	7.84	7.07	0.03	0.02
Benign neoplasms	7.73	7.61	0.00	0.07
Hypothyroidism	1.69	1.77	-0.01	0.14
Hyperthyroidism	0.36	0.27	0.02	0.11
Number of visits, mean (SD)	4.12 (4.88)	5.70 (5.02)	-0.32	0.08
MEDEA index, mean (SD)	0.75 (0.89)	0.74 (0.86)	0.01	0.09

*SDiff, standardised differences; 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

**High-risk alcohol intake: >28 UBE units for men and >17 UBE units for women. 1 UBE unit = 10 g alcohol

Table 2. Adjusted hazard ratios (HR) of incident cardiovascular events, mortality, adverse effects and the 5-year number needed to treat (NNT) to prevent one event by use of statins. Incidence per 1000 person/years. Median follow-up: 9.8 years. Individuals within the PS common range (n=7,186)

	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	390	6.56 (5.85-7.36)	54	8.16 (6.25-10.65)	0.84 (0.60-1.19)	248
Ischemic stroke	349	5.82 (5.20-6.52)	30	4.45 (3.10-6.37)	0.68 (0.44-1.05)	145
All-cause mortality	825	13.48 (12.55-14.48)	86	12.41 (10.04-15.34)	0.87 (0.67-1.12)	202
Adverse effects						
Cancer	1048	20.72 (19.27-22.29)	129	22.51 (18.92-26.77)	0.97 (0.78-1.21)	--
Type 2 diabetes	883	20.36 (18.92-21.91)	109	28.77 (23.84-34.73)	1.27 (0.99-1.63)	--
Haemorrhagic stroke	84	1.54 (1.23-1.92)	5	0.86 (0.35-2.11)	0.41 (0.16-1.17)	--
Acute liver disease	9	1.44 (0.74-2.80)	1	-	-	--
Myopathy	3	-	0	-	-	--

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	