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Statin use associates with a reduced incidence of venous thromboembolism – A population-based cohort study

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Abstract

Objectives: Venous thromboembolism (VTE) continues to be a frequent, medical emergency demanding condition to reach the diagnosis and initiate anticoagulation therapy. The use of statins is reported, in addition to reducing the incidence of arterial thrombosis, also to decrease both the incidence and reoccurrence of VTE. The aim of our study is to explore the association between statin usage and the incidence of new VTE at the population level during a 10-year follow-up.

Design: Population based historic cohort

Setting: The Health 2000 survey was based on a nationally representative sample.

Participants: 8028 individuals aged 30 years or over in Finland.

Primary and secondary outcome measures: The primary end-point event was the first ever hospitalization due to one of the following causes: pulmonary embolism (ICD10 I26), cerebral venous nonpyogenic thrombosis (I63.6), phlebitis and thrombophlebitis of superficial vessels of lower extremities (180.0-180.9).

Results: The preselected explanatory variables applied to Poisson regression model were statin usage (no/yes) during follow-up (2000-2011) and several baseline data (age, sex ; usage of blood glucose lowering drug, vitamin K antagonists, and anti-platelet agents). We observed 136 VTE events, the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years. Current statin usage did not associate with the incidence of VTE according to the univariate model (RR 0.93, 0.56-1.52), but when adjusted with baseline variables (age, sex, medications) the RR declined to 0.60 (0.36-1.00, p= 0.04).

Conclusions: Statin use offers protection against first ever VTE event and appears as a primary prevention tool in patients without anticoagulation or anti-platelet medication.

Strengths of this study

- population based, no selection bias in start of follow-up
- long and complete follow-up information

Limitations of this study

- limited number of background variables
- the comprehensive use of prescribed drugs in this study, could not be verified with certainty

Introduction

Venous thromboembolism (VTE) continues to be a frequent condition which demands medical emergency attention to reach the diagnosis and initiate anticoagulation therapy. The mortality during a few months after VTE varies between 5-20%, and the patients often have other co-morbidities, such as cardiovascular disease and cancer. The yearly incidence of VTE is 1-2/1000 inhabitants in western societies. Nowadays, the traditional heparin and vitamin K antagonist (VKA) therapy followed with the course of temporal (3-6 months) or permanent VKA can be opted with novel oral anticoagulants[1].

The decision of either continuing the anticoagulation for a few months or permanently depends on the acquired or inherited risk factor profile of the patient. This includes age above 60 years and concomitant illness, including cancer and inflammatory diseases as well as obesity, hormonal remedies and family history or severe thrombophilias (such as homozygosity of factor V Leiden or prothrombin mutation, double defects, antiphospholipid antibody syndrome), subjecting the

patient to recurrent VTE. Despite the clinical evaluation the recurrence rate of VTE continues to be 15-20% after an idiopathic event and around 5% after a provoked thrombosis[1]. Bleeding tendency needs to be regularly weighted also against the risk of thrombosis recurrence, while maintaining the anticoagulation.

The use of statins has been reported to reduce the incidence of not only the arterial thrombosis, but also interesting data on the decline of both the incidence and reoccurrence of VTE have emerged. Retrospective observational and case-control studies as well as experimental evidence refer to the possibility that statins exert an antithrombotic effect also in the venous system. A recent meta-analysis reported the association of VTE and a 20-36% protection with statin use [2]. A primary prevention trial of VTE with rosuvastatin in a randomized placebo-controlled design showed a 48% reduction in the incidence of VTE[3]. Moreover, statin treatment alleviated the risk of recurrent pulmonary embolism by 50% whether the patient used long-term vitamin K antagonist treatment or had stopped anticoagulation, as reported by a Dutch population-based study with initially hospitalized patients[4]. Finally, statins decrease the occurrence of venous thromboembolism even in patients with cancer[5].

Statins reduce the procoagulant activity of platelet membranes and downplay the signaling via LDL receptors, which are engaged with the platelet activation[6]. Statins also enhance fibrinolysis by reducing the plasminogen activator inhibitor-1 and triglyceride concentration. Also, other pleiotropic and anti-inflammatory mechanisms, including dampened tissue factor expression by monocytes, have been described which can attenuate the risk of thrombosis.

The aim of the study is to explore the association between statin usage and incidence of the first ever VTE in Finland. Our study utilizes a nationally representative sample of 8028 persons aged

>30 years [7] of The Health 2000 Survey and a prospective observational pharmaco-epidemiological design.

Material and methods

Study population

The Health 2000 survey was based on a nationally representative sample of 8028 individuals aged 30 years or over in Finland. To ensure that sample is representative of the Finnish population, a two-stage stratified cluster sampling procedure was used. The baseline data collection from study subjects took place between September 2000 and June 2001, and consisted of an interview and a comprehensive health examination. Of the study sample 6986 subjects (87 %) were interviewed at their home or in an institution, 6354 subjects (79 %) took part in a comprehensive health examination and 416 subjects (5%) were examined at their home. The Health 2000 study was approved by the Ethics Committees of the National Public Health Institute (since 2009 the National Institute for Health and Welfare) and the Hospital District of Helsinki and Uusimaa, and the participants gave written informed consent[7].

Follow-up time and end-points

The primary end-point event of this study was the first hospitalization due one of the following causes: pulmonary embolism (ICD10 I26), cerebral infarction due to cerebral venous nonpyogenic thrombosis (I63.6), phlebitis and thrombophlebitis of superficial vessels of lower extremities (180.0-180.9). The information about end-points was obtained from National Hospital Discharge Register that covers all hospitalizations in Finland starting from 1969. The 10-year follow-up was started at the beginning of Health 2000 Study and was

stopped at death, end of year 2011, or end-point, whichever occurred first. The data about deaths were obtained from the Statistics Finland. There were 103 individuals with recorder primary end-point before the start of follow-up compatible with the general prevalence of the disease, and these subjects were excluded from the study population. Thus, the size of study population in the start of follow-up was 7925.

Laboratory measurements

Venous blood samples were drawn from the antecubital vein after a minimum of 4 h fasting. HDL cholesterol, total cholesterol, triglyceride and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL; Olympus System Reagent, Hamburg, Germany for total cholesterol, triglycerides and glucose) with a clinical chemistry analyser (Olympus, AU400, Hamburg, Germany)[8]. C-reactive protein (CRP) concentrations were determined by a chemiluminescent immunometric assay (Immulite, Diagnostic Products, Los Angeles, CA)[8]. LDL cholesterol was calculated with the Friedewald formula. Plasma insulin and homocysteine concentrations were determined with microparticle enzyme immunoassay (Abbott Laboratories, Dainabot, Tokyo, Japan)[9,10]. S-25(OH)D concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN, USA)[11].

Drug information

The data about the prescribed and purchased drugs were obtained from registers of the Social Insurance Institution. We had records of the following drugs classified by Anatomical Therapeutic Chemical (ATC) code[12]: statins (C10AA), blood glucose lowering drugs, excluding insulins (A10B), insulin (A10A), VKA (B01AA) , and antiplatelet agents, excluding heparin (B01AC) and over the counter acetylsalicylic acid. Regarding statins the data included all prescribed statins purchased during the follow-up period in 2000 – 2006 and 2008.

Because there were no data available regarding the drug amounts purchased for years 2007, and 2009-2011, we calculated the mean amount of purchase based on available years and adapted it for the whole follow-up period. Time dependent variable for the current statin usage was determined for each individual with the prescription data using R language package Epi[13]. The follow-up time of each individual with statin exposure was cut into 6-month periods and the statin usage in each period was determined. For other drugs we had only the number of prescriptions at the baseline year 2000, which was used to construct a dichotomic variable of drug usage at baseline (no/yes).

Statistical modeling

We applied the Poisson regression model using end-point event as a dependent variable, length of the follow-up as an offset variable, and statin usage (no/yes) during each time period as time-varying explanatory variable. The following variables were used as time-invariant variables measured at baseline: age (30-40, 40-50, 50-60, 60-70, over 70), sex (male/female), blood glucose lowering drug usage, excluding insulins (no/yes), insulin usage (no/yes), vitamin K antagonists usage (no/yes) , antiplatelet agents (no/yes) , blood glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), CRP (mg/L), vitamin D3 (nmol/L), homocysteine (μmol/L), and insulin (mU/L). The values of the laboratory measurements were transformed to categorical variables defined by tertiles. We also estimated the inverse probability weights (IPW) to fit marginal structural models[14]. IPW were estimated using age and sex in the numerator, and age, sex, blood glucose lowering drugs other than insulin usage, VKA usage, and use of antiplatelet agent in the denominator.

Results

The size of the study population was 7925, including 3589 males and 4336 females (Table 1). We observed 136 VTE events during the follow-up with the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years during the mean follow-up time 10 years (Table 2). There were 64 events with the diagnosis pulmonary embolism (ICD-10 I26), one with sinus thrombosis (I636) and 71 with deep vein thrombosis (180.0-180.9).

All together there were 67,532 statin prescriptions, and 2083 individuals (26% of population) had at least one prescription. Simvastatin (ATC code C10AA01) with 54% of prescriptions and atorvastatin (C10AA05) with 23% represented the most frequent active lipid-lowering substances. Current statin usage that comprised 14% of all cumulated person-years, did not associate with the incidence of VTE according to the univariate model Rate Ratio (RR) 0.93 (0.56-1.52)(Table 2). The use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), but insulin usage did not show any association. Using any antithrombotic drugs associated with higher incidence (RR 4.55, 2.70-7.66).

Addition of more explanatory variables in the model substantially altered the association between the statin usage and incidence (Table 3). Adjusting for sex, age, baseline oral antidiabetic, insulin, and use of antithrombotics (Model II) reduced the RR to 0.60 (0.36-1.00). Using IPW for the structural model (Model III) decreased the RR further to 0.58 (0.35-0.96). Adjusting for the baseline laboratory measurements also decreased slightly the estimate for statin effect, e.g. adjusting for CRP gave RR 0.43 (0.23- 0.81). However, because of the missing laboratory measurements we do not report these results in further detail, e.g. for CRP there

were several (1694) missing values.(Table 2). Increased levels of LDL associated with an increasing incidence of VTE, the same occurred with homocysteine.

In addition, we looked for the possible interactions between statin usage and age, sex, blood glucose lowering drugs usage (excluding use of insulin), VKA and platelet aggregation inhibitors. Interaction for sex and statin usage was significant (χ^2=6.310, df=1, p=0.012). Interestingly, it turned out that the incidence of VTE among the statin group for males was quite low (RR 0.22, 0.06-0.65), but for females such an association was not obvious (RR 0.75, 0.41-1.38), upon comparing the statin usage without its usage (Table 4.).

Discussion

To our knowledge, this is the first report studying association between statin usage and VTE that utilizes a nationally representative population sample. Our results during the 11 years of prospective follow-up on the incidence of VTE are in line with the recent meta-analysis[15], which showed the risk reduction of 0.89 (0.78-1.01) for VTE among statin users. The JUPITER study, the largest meta-analysis of trials, including 465 events, showed 36% reduction in VTE (RR 0·64, 0·39–1·06, p=0·08)[16]. Our study addressed the new incidence of VTE, as the patients who previously had suffered from VTE (136/8028) were excluded from study population. The prospective nature and large population-based design of pharmaco-epidemiology are the strengths of our study.

In this freely living Finnish population sample we could demonstrate that statin use is associated with a reduction of the incidence of VTE, including both deep vein thrombosis of the lower extremities, pulmonary embolism and one case of cerebrovascular sinus thrombosis. This adds to the confirmation that statins exert anticoagulant activity[2–5].

Furthermore, it supports the idea that statin therapy could be implemented to the patients with the risk of VTE.

We observed that use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), which refers to that insulin-resistant patients carry a high risk of VTE, and the oral antidiabetic drugs do not seem to alleviate this risk, while insulin may do so[17]. The positive association between antithrombotic drugs and VTE is quite probably due to confounding by indication[18], and also the co-occurrence of cardiovascular disease and VTE has been noted in several studies[19]. The limitation of our study relies on the fact that over-the counter aspirin use is not controlled. This is significant, as aspirin has been recently shown to inhibit the reoccurrence of idiopathic VTE[20].

Men seemed to respond to statin use more favourably than females, indicating a plausible hormonal regulation of the effect of statins. In women we did not control for hormonal replacement therapy, which may be a confounding remedy, known to be a risk factor for VTE[21,22] The well-known age-association in increasing the incidence of DVT and PE was evidenced also among our patients. Also, the overall incidence of VTE in Finland is compatible with what has been reported internationally. The protective association with incidence of VTE among highest third tertile of HDL-LDL ratio, lowest homocysteine and CRP support earlier results of these surrogate laboratory markers.

Several limitations must be kept in mind when evaluating results from any observational study based on record linkage of drug information. Firstly, the comprehensive use of prescribed drugs in this study, could not be verified with certainty, and may be subject to misclassification. The prescription data do not contain information on drugs used in nursing

homes, therefore, the misclassification of exposure is more likely among the older patient groups. Secondly, although model based adjustments using regression and IPW were applied, it is always possible that residual confounding factors could influence the results. E.g. statin usage may depend on variables that are not included in the statistical models; or the statistical models used in the analysis do not properly adjust for the confounding factors. The importance of adjusting for possible confounding effects is reflected by the large difference between estimates obtained from the uni- and multivariate models. On the other hand, the results based on three models with different pattern of covariates and modeling technique remained nearly unchanged regarding the effect of current statin usage (Table 3). This compatibility increases the credibility of the results. Also, the hospital records that are nationally gathered may suffer from inconsistencies. Recently, these were evaluated in a separate study which validated this form of data collection in PE, but not in DVT[23].

In conclusion, statin use offers protection against first ever VTE event. The elevated LDL cholesterol, CRP and homocysteine, as reported earlier also associate with the risk of new VTE. Statins appears as a primary prevention tool in patients with a high risk of VTE, exerting its best effect in male population.

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RL, AJ and JP have no relevant disclosures to declare. JH has had previous research agreements with Janssen-Cilag, Novartis, Orion Pharma, Abbott, Novo Nordisk Farma, Pfizer, Sanofi-Aventis, Astellas, and Takeda.

Contributorship Statement

All authors have substantial contributions to the conception and design of the work and acquisition of the data. JH did analyses, all authors contributed to interpretation of data for the work

JH drafted the work, other authors revised it critically for important intellectual content.

All authors have approved the final version of the work to be published.

All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

None

Data Sharing Statement

No additional data available

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Tables

Table 1 Baseline characteristics of study population

Categorical variables and usage of drugs at baseline			
Sex	male	3589	45%
	female	4336	55%
Blood glucose lowering drug	no	7637	96%
	yes	288	4%
Insulin	no	7787	98%
	yes	138	2%
Antithrombotic agent	no	7582	96%
	yes	343	4%
Antiplatelet agent	no	7764	98%
	yes	161	2%
Vitamin K antagonists	no	7732	98%
	yes	193	2%

Continuous variables at baseline LDL cholesterol (mmol/L)						
	1st Qu.	**Median**	**Mean**	**3rd Qu.**	**SD**	**Missing**
Age	42.0	52.0	54.7	66.0	16.1	100
Blood glucose (mmol/L)	5.0	5.3	5.6	5.7	1.3	1275
Total cholesterol (mmol/L)	5.1	5.9	5.9	6.6	1.1	1275
HDL cholesterol (mmol/L)	1.1	1.3	1.3	1.6	0.4	1275
LDL cholesterol (mmol/L)	3.1	3.8	3.8	4.5	1.2	1276
Triglycerides (mmol/L)	1.0	1.3	1.6	1.9	1.1	1275
Ratio HDL/Chol	18.0	22.0	23.0	28.0	7.4	1275
CRP (mg/L)	0.3	0.8	2.3	2.0	6.3	1694
Vitamin D3 (nmol/L)	33.0	43.0	44.9	55.0	16.9	1825
Homocysteine (µmol/L)	9.2	11.0	12.0	13.5	5.1	1825
Insulin (mU/L)	5.0	7.0	9.6	11.0	30.3	1627

Table 2. Incidence of end-point events. RR (rate ratios) with 95% confidence intervals (CI) based on univariate Poisson regression model. Laboratory measurements in tertiles "[a,b)" means that interval a-b is closed left and open right. The data on variables are collected at baseline.

Variable	P-years (1000)	Events	Incidence (1/1000)	95% CI		RR	95% CI	
Current statin usage								
no	67.78	118	1.74	1.44	2.09			
yes	11.17	18	1.61	0.95	2.55	0.93	0.56	1.52
Sex								
male	36.02	53	1.47	1.1	1.93			
female	42.93	83	1.93	1.54	2.4	1.31	0.93	1.85
Age								
(0,40]	19.92	10	0.50	0.24	0.92			
(40,50]	20.22	15	0.74	0.41	1.22	1.48	0.66	3.29
(50,60]	17.11	24	1.40	0.90	2.09	2.79	1.34	5.84
(60,70]	11.05	28	2.53	1.68	3.66	5.05	2.45	10.39
(70,Inf]	10.65	59	5.54	4.22	7.15	11.04	5.65	21.58
Insulin usage at baseline								
no	77.83	133	1.71	1.43	2.03			
yes	1.12	3	2.68	0.55	7.83	1.57	0.50	4.92
Blood glucose lowering drug								
no	76.71	124	1.62	1.34	1.93			
yes	2.24	12	5.37	2.77	9.37	3.32	1.84	6.00
Antithrombotic agent usage								
no	76.7	120	1.56	1.30	1.87			
yes	2.25	16	7.11	4.06	11.55	4.55	2.70	7.66
Antiplatelet agents usage								
no	77.87	126	1.62	1.35	1.93			
yes	1.08	10	9.27	4.44	17.05	5.73	3.01	10.91
Vitamin K antagonists usage								
no	77.7	128	1.65	1.37	1.96			
yes	1.25	8	6.42	2.77	12.66	3.90	1.91	7.97
Blood glucose (mmol/L)								
[2.4,5.1]	24.79	36	1.45	1.02	2.01			
(5.1,5.6]	23.93	31	1.30	0.88	1.84	0.89	0.55	1.44
(5.6,26.7]	18.69	48	2.57	1.89	3.40	1.77	1.15	2.72
Total cholesterol (mmol/L)								
[1.9,5.4]	23.71	36	1.52	1.06	2.10			
(5.4,6.3]	21.33	33	1.55	1.06	1.02	0.64	1.63	1.02
(6.3,11.7]	22.38	46	2.06	1.50	1.35	0.88	2.09	1.35
HDL cholesterol (mmol/L)								
[0.23,1.13]	22.39	45	2.01	1.46				

(1.13,1.45]	22.45	33	1.47	1.01	0.73	0.47	1.15	0.73
(1.45,3.41]	22.57	37	1.64	1.15	0.82	0.53	1.26	0.82
LDL cholesterol (mmol/L								
[0,3.3]	22.56	34	1.51	1.04				
(3.3,4.2]	22.79	38	1.67	1.18	1.11	0.70	1.76	1.11
(4.2,8.8]	22.06	43	1.95	1.41	1.29	0.82	2.03	1.29
Triglycerides (mmol/L)								
[0.4,1.1]	26.16	30	1.15	0.77				
(1.1,1.7]	21.84	45	2.06	1.50	1.80	1.13	2.85	1.80
(1.7,16.6]	19.42	40	2.06	1.47	1.80	1.12	2.88	1.80
Ratio HDL/Chol								
[3,19]	23.92	48	2.01	1.48				
(19,25.7]	20.58	34	1.65	1.14	0.82	0.53	1.28	0.82
(25.7,56]	22.91	33	1.44	0.99	0.72	0.46	1.12	0.72
C-reactive protein (mg/L)								
[0,0.39]	22.26	22	0.99	0.62				
(0.39,1.41]	21.62	42	1.94	1.40	1.97	1.17	3.29	1.97
(1.41,191]	20.53	40	1.95	1.39	1.97	1.17	3.32	1.97
Vitamin D3 (nmol/L)								
[5,36]	20.55	35	1.70	1.19	2.37			
(36,50]	21.42	31	1.45	0.98	2.06	0.85	0.52	1.38
(50,134]	21.15	37	1.75	1.23	2.41	1.03	0.65	1.63
Homocysteine (µmol/L)								
[3.7,9.7]	22.15	18	0.81	0.48	1.29			
(9.7,12.5]	21.82	32	1.47	1.00	2.07	1.80	1.01	3.22
(12.5,111]	19.16	53	2.77	2.07	3.62	3.40	1.99	5.81
Insulin (mU/L)								
[1,5]	22.72	26	1.14	0.75	1.68			
(5,9]	22.67	45	1.99	1.45	2.66	1.73	1.07	2.81
(9,2200]	19.64	33	1.68	1.16	2.36	1.47	0.88	2.00

Table 3. Rate ratios (RR) with 95% confidence intervals (CI) of three Poisson regression models. Model I included only statin, age and sex as covariates. Models II and III included also Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates. Inverse Probability Weights (IPW) Model III is based on stabilized weights for statin usage. In IPW model age and sex were in numerator, and age, sex, baseline oral antidiabetics, baseline insulin, and baseline anticoagulant usage were in denominator.

		Model I			Model II			Model III		
		RR (95% CI)			RR (95% CI)			RR, IPW (95% CI)		
Statin	no	(reference)			(reference)			(reference)		
	current	**0.64**	0.38	1.05	**0.60**	0.36	1.00	**0.58**	0.35	0.96
Age	under 40	(reference)			(reference)			(reference)		
	(40,50]	1.52	0.68	3.38	1.51	0.68	3.37	1.53	0.68	3.43
	(50,60]	2.99	1.42	6.26	2.91	1.39	6.10	3.20	1.53	6.70
	(60,70]	5.66	2.73	11.75	5.31	2.55	11.05	5.36	2.55	11.24
	(70,Inf]	11.68	5.94	22.95	9.92	4.99	19.74	9.93	4.95	19.92
Sex	male	(reference)			(reference)			(reference)		
	female	1.02	0.72	1.45	1.02	0.72	1.46	0.99	0.70	1.41
Blood glucose lowering drug	no				(reference)			(reference)		
	yes				1.89	0.98	3.63	1.63	0.86	3.11
Insulin usage	no				(reference)			(reference)		
	yes				0.72	0.21	2.45	0.72	0.25	2.13
Vitamin K antagonists	no				(reference)			(reference)		
	yes				1.46	0.69	3.07	1.38	0.68	2.80
Antiplatelet agents	no				(reference)			(reference)		
	yes				2.33	1.20	4.53	2.60	1.42	4.76

Table 4. Statin usage and sex, interaction model. Model included age, Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates.

	P-years	Events	Incidence (95% CI)			RR (95% CI)		
no statin/male	30.57	50	1.64	1.21	2.16	(reference)		
statin/male	5.45	3	0.55	0.11	1.61	0.20	0.06	0.65
no statin/female	37.21	68	1.83	1.42	2.32	0.87	0.60	1.27
statin/female	5.72	15	2.62	1.47	4.33	0.75	0.41	1.38

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Statin use associates with a reduced incidence of venous thromboembolism – A population-based cohort study**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses Done
Methods		
Study design	4	Present key elements of study design early in the paper Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Done
		~~(*b*) For matched studies, give matching criteria and number of exposed and unexposed~~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Done
Bias	9	Describe any efforts to address potential sources of bias Done
Study size	10	Explain how the study size was arrived at Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done
		(*b*) Describe any methods used to examine subgroups and interactions Done
		(*c*) Explain how missing data were addressed Done
		(*d*) If applicable, explain how loss to follow-up was addressed Done
		(*e*) Describe any sensitivity analyses Done

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Done**
		(b) Give reasons for non-participation at each stage **Done**
		(c) Consider use of a flow diagram Not included, presented in previous papers
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Done
		(b) Indicate number of participants with missing data for each variable of interest Done
		(c) Summarise follow-up time (eg, average and total amount) Done
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Done,95% Ci given, interaction test with p-value and X2 test.
		(*b*) Report category boundaries when continuous variables were categorized Done
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not done because of brevity. Easy to do if needed with data in tables.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done
Discussion		
Key results	18	Summarise key results with reference to study objectives Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done
Generalisability	21	Discuss the generalisability (external validity) of the study results Done. This is population based study.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Details give, not extra funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association of statin use with a reduced incidence of venous thromboembolism – A population-based cohort study

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Statin use associates with a reduced incidence of venous thromboembolism – A population-based cohort study

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Abstract

Objectives: Venous thromboembolism (VTE) continues to be a frequent, medical emergency demanding condition to reach the diagnosis and initiate anticoagulation therapy. The use of statins is reported, in addition to reducing the incidence of arterial thrombosis, also to decrease both the incidence and reoccurrence of VTE. The aim of our study was to explore the association between statin usage and the incidence of new VTE at the population level during a 10-year follow-up.

Design: Population based historic cohort

Setting: The Health 2000 survey was based on a nationally representative sample.

Participants: 8028 individuals aged 30 years or over in Finland.

Primary and secondary outcome measures: The primary end-point event was the first ever hospitalization due to one of the following causes: pulmonary embolism (ICD10 I26), cerebral venous nonpyogenic thrombosis (I63.6), and venous thrombosis (I80.0-189).

Results: The preselected explanatory variables applied to Poisson regression model were statin usage (no/yes) during follow-up (2000-2011) and several baseline data (age, sex; usage of blood glucose lowering drug, vitamin K antagonists, and anti-platelet agents). We observed 136 VTE events, the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years. Current statin usage did not associate with the incidence of VTE according to the univariate model (RR 0.93, 0.56-1.52), but when adjusted with baseline variables (age, sex, medications) the RR declined to 0.60 (0.36-1.00, p= 0.04).

Conclusions: Statin use offers protection against first ever VTE event and appears as a primary prevention tool in patients without anticoagulation or anti-platelet medication.

Strengths of this study

- population based, no selection bias in start of follow-up
- long and complete follow-up information

Limitations of this study

- limited number of background variables and incidence events
- the comprehensive use of prescribed drugs in this study, could not be verified with certainty

Introduction

Venous thromboembolism (VTE) continues to be a frequent condition which demands medical emergency attention to reach the diagnosis and initiate anticoagulation therapy. The mortality during a few months after VTE varies between 5-20%, and the patients often have other co-morbidities, such as cardiovascular disease and cancer. The yearly incidence of VTE is 1-2/1000 inhabitants in western societies. Nowadays, the traditional heparin and vitamin K antagonist (VKA) therapy followed with the course of temporal (3-6 months) or permanent VKA can be opted with novel oral anticoagulants[1].

The decision of either continuing the anticoagulation for a few months or permanently depends on the acquired or inherited risk factor profile of the patient. This includes age above 60 years and concomitant illness, including cancer and inflammatory diseases as well as obesity, hormonal remedies and family history or severe thrombophilias (such as homozygosity of factor V Leiden or prothrombin mutation, double defects, antiphospholipid antibody syndrome), subjecting the patient to recurrent VTE. Despite the clinical evaluation the recurrence rate of VTE continues to

be 15-20% after an idiopathic event and around 5% after a provoked thrombosis[1]. Bleeding tendency needs to be regularly weighted also against the risk of thrombosis recurrence, while maintaining the anticoagulation.

The use of statins has been reported to reduce the incidence of not only the arterial thrombosis, but also interesting data on the decline of both the incidence and reoccurrence of VTE have emerged. Retrospective observational and case-control studies as well as experimental evidence refer to the possibility that statins exert an antithrombotic effect also in the venous system. A recent meta-analysis reported the association of VTE and a 20-36% protection with statin use[2]. A primary prevention trial of VTE with rosuvastatin in a randomized placebo-controlled design showed a 48% reduction in the incidence of VTE[3]. Moreover, statin treatment alleviated the risk of recurrent pulmonary embolism by 50% whether the patient used long-term vitamin K antagonist treatment or had stopped anticoagulation, as reported by a Dutch population-based study with initially hospitalized patients[4]. Finally, statins decrease the occurrence of venous thromboembolism even in patients with cancer[5].

Statins reduce the procoagulant activity of platelet membranes and downplay the signaling via LDL receptors, which are engaged with the platelet activation[6]. Statins also enhance fibrinolysis by reducing the plasminogen activator inhibitor-1 and triglyceride concentration. Also, other pleiotropic and anti-inflammatory mechanisms, including dampened tissue factor expression by monocytes, have been described which can attenuate the risk of thrombosis.

The aim of the study was to explore the association between statin usage and incidence of the first ever VTE in Finland. Our study utilizes a nationally representative sample of 8028 persons

aged >30 years [7] of The Health 2000 Survey and a prospective observational pharmaco-epidemiological design.

Material and methods

Study population

The Health 2000 survey was based on a nationally representative sample of 8028 individuals aged 30 years or over in Finland. To ensure that sample is representative of the Finnish population, a two-stage stratified cluster sampling procedure was used. The baseline data collection from study subjects took place between September 2000 and June 2001, and consisted of an interview and a comprehensive health examination. Of the study sample 6986 subjects (87 %) were interviewed at their home or in an institution, 6354 subjects (79 %) took part in a comprehensive health examination and 416 subjects (5%) were examined at their home. The Health 2000 study was approved by the Ethics Committees of the National Public Health Institute (since 2009 the National Institute for Health and Welfare) and the Hospital District of Helsinki and Uusimaa, and the participants gave written informed consent[7].

Follow-up time and end-points

The primary end-point event of this study was the first hospitalization due one of the following causes: pulmonary embolism (ICD10 I26), cerebral infarction due to cerebral venous nonpyogenic thrombosis (I63.6), deep vein thrombosis, including thrombophlebitis of lower extremities (I80.0-I80.9). The information about end-points was obtained from National Hospital Discharge Register that covers all hospitalizations in Finland starting from 1969. The 10-year follow-up was started at the beginning of Health 2000 Study and was

stopped at death, end of year 2011, or end-point, whichever occurred first. The data about deaths were obtained from the Statistics Finland. There were 103 individuals with recorder primary end-point before the start of follow-up compatible with the general prevalence of the disease, and these subjects were excluded from the study population. Thus, the size of study population in the start of follow-up was 7925.

Laboratory measurements

Venous blood samples were drawn from the antecubital vein after a minimum of 4 h fasting. HDL cholesterol, total cholesterol, triglyceride and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL; Olympus System Reagent, Hamburg, Germany for total cholesterol, triglycerides and glucose) with a clinical chemistry analyser (Olympus, AU400, Hamburg, Germany)[8]. C-reactive protein (CRP) concentrations were determined by a chemiluminescent immunometric assay (Immulite, Diagnostic Products, Los Angeles, CA)[8]. LDL cholesterol was calculated with the Friedewald formula. Plasma insulin and homocysteine concentrations were determined with microparticle enzyme immunoassay (Abbott Laboratories, Dainabot, Tokyo, Japan)[9,10]. S-25(OH)D concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN, USA)[11].

Drug information

The data about the prescribed and purchased drugs were obtained from registers of the Social Insurance Institution. We had records of the following drugs classified by Anatomical Therapeutic Chemical (ATC) code[12]: statins (C10AA), blood glucose lowering drugs, excluding insulins (A10B), insulin (A10A), VKA (B01AA) , and antiplatelet agents, excluding heparin (B01AC) and over the counter acetylsalicylic acid. Regarding statins the data included all prescribed statins purchased during the follow-up period in 2000 – 2006 and 2008.

Because there were no data available regarding the drug amounts purchased for years 2007, and 2009-2011, we calculated the mean amount of purchase based on available years and adapted it for the whole follow-up period. Time dependent variable for the current statin usage was determined for each individual with the prescription data using R language package Epi[13]. The follow-up time of each individual with statin exposure was cut into 6-month periods and the statin usage in each period was determined. For other drugs we had only the number of prescriptions at the baseline year 2000, which was used to construct a dichotomic variable of drug usage at baseline (no/yes).

Statistical modeling

We applied the Poisson regression model using end-point event as a dependent variable, length of the follow-up as an offset variable, and statin usage (no/yes) during each time period as time-varying explanatory variable. The following variables were used as time-invariant variables measured at baseline: age (30-40, 40-50, 50-60, 60-70, over 70), sex (male/female), blood glucose lowering drug usage, excluding insulins (no/yes), insulin usage (no/yes), vitamin K antagonists usage (no/yes) , antiplatelet agents (no/yes) , blood glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), CRP (mg/L), vitamin D3 (nmol/L), homocysteine (µmol/L), and insulin (mU/L). The values of the laboratory measurements were transformed to categorical variables defined by tertiles. We also estimated the inverse probability weights (IPW) to fit marginal structural models[14]. IPW were estimated using age and sex in the numerator, and age, sex, blood glucose lowering drugs other than insulin usage, VKA usage, and use of antiplatelet agent in the denominator. In order to check survivor bias we carried out

modeling without subjects with prevalent statin use in start of follow-up (N=460 excluded) [15].

Results

The size of the study population was 7925, including 3589 males and 4336 females (Table 1). We observed 136 VTE events during the follow-up with the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years during the mean follow-up time 10 years (Table 2). There were 64 events with the diagnosis pulmonary embolism (ICD-10 I26), one with sinus thrombosis (I636) and 71 with deep vein thrombosis (I80.0-I80.9).

All together there were 67,532 statin prescriptions, and 2083 individuals (26% of population) had at least one prescription. Simvastatin (ATC code C10AA01) with 54% of prescriptions and atorvastatin (C10AA05) with 23% represented the most frequent active lipid-lowering substances. Current statin usage that comprised 14% of all cumulated person-years, did not associate with the incidence of VTE according to the univariate model Rate Ratio (RR) 0.93 (0.56-1.52)(Table 2). The use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), but insulin usage did not show any association. Using any antithrombotic drugs associated with higher incidence (RR 4.55, 2.70-7.66).

Addition of more explanatory variables in the model substantially altered the association between the statin usage and incidence (Table 3). Adjusting for sex, age, baseline oral antidiabetic, insulin, and use of antithrombotics (Model II) reduced the RR to 0.60 (0.36-1.00). Using IPW for the structural model (Model III) decreased the RR further to 0.58 (0.35-0.96).

Adjusting for the baseline laboratory measurements also decreased slightly the estimate for statin effect, e.g. adjusting for CRP gave RR 0.43 (0.23- 0.81). However, because of the missing laboratory measurements we do not report these results in further detail, e.g. for CRP there were several (1694) missing values. (Table 2). Increased levels of LDL associated with an increasing incidence of VTE, the same occurred with homocysteine.

In addition, we looked for the possible interactions between statin usage and age, sex, blood glucose lowering drugs usage (excluding use of insulin), VKA and platelet aggregation inhibitors. Interaction for sex and statin usage was significant (χ^2=6.310, df=1, p=0.012). Interestingly, it turned out that the incidence of VTE among the statin group for males was quite low (RR 0.22, 0.06-0.65), but for females such an association was not obvious (RR 0.75, 0.41-1.38), upon comparing the statin usage without its usage (Table 4.).

In sensitivity analyses without prevalent statin users there was 115 cases in non-statin group and 10 cases in statin group; unadjusted RR was 0.82 (0.43- 1.56) and adjusted 0.63 (0.33- 1.21).

Discussion

To our knowledge, this is the first report studying association between statin usage and VTE that utilizes a nationally representative population sample. Our results during the 11 years of prospective follow-up on the incidence of VTE are in line with the recent meta-analysis[16], which showed the risk reduction of 0.89 (0.78-1.01) for VTE among statin users. The JUPITER study, the largest randomized trial, including 465 events, showed 36% reduction in VTE (RR 0·64, 0·39–1·06, p=0·08)[3,16]. Our study addressed the new incidence of VTE, as the patients who previously had suffered from VTE (136/8028) were excluded from study

population. The prospective nature and large population-based design of pharmaco-epidemiology are the strengths of our study.

In this freely living Finnish population sample we could demonstrate that statin use is associated with a reduction of the incidence of VTE, including both deep vein thrombosis of the lower extremities, pulmonary embolism and one case of cerebrovascular sinus thrombosis. This adds to the confirmation that statins exert anticoagulant activity[2–5]. Furthermore, it supports the idea that statin therapy could be implemented to the patients with the risk of VTE.

We observed that use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), which refers to that insulin-resistant patients carry a high risk of VTE, and the oral antidiabetic drugs do not seem to alleviate this risk, while insulin may do so[18]. The positive association between antithrombotic drugs and VTE is quite probably due to confounding by indication[19], and also the co-occurrence of cardiovascular disease and VTE has been noted in several studies[20]. The limitation of our study relies on the fact that over-the counter aspirin use is not controlled. This is significant, as aspirin has been recently shown to inhibit the reoccurrence of idiopathic VTE[21].

Men seemed to respond to statin use more favourably than females, indicating a plausible hormonal regulation of the effect of statins. In women we did not control for hormonal replacement therapy, which may be a confounding remedy, known to be a risk factor for VTE[22,23] The well-known age-association in increasing the incidence of DVT and PE was evidenced also among our patients. Also, the overall incidence of VTE in Finland is compatible with what has been reported internationally. The protective association with incidence of VTE

among highest third tertile of HDL-LDL ratio, lowest homocysteine and CRP support earlier results of these surrogate laboratory markers.

Several limitations must be kept in mind when evaluating results from any observational study based on record linkage of drug information. Firstly, the comprehensive use of prescribed drugs in this study, could not be verified with certainty, and may be subject to misclassification. The prescription data do not contain information on drugs used in nursing homes, therefore, the misclassification of exposure is more likely among the older patient groups. Secondly, although model based adjustments using regression and IPW were applied, it is always possible that residual confounding factors could influence the results. E.g. statin usage may depend on variables that are not included in the statistical models; or the statistical models used in the analysis do not properly adjust for the confounding factors. The importance of adjusting for possible confounding effects is reflected by the large difference between estimates obtained from the uni- and multivariate models. On the other hand, the results based on the three models with different pattern of covariates and modeling technique remained nearly unchanged regarding the effect of current statin usage (Table 3). This compatibility increases the credibility of the results, albeit the actual incidences are relatively low in numbers due to the natural incidence of 1-2 cases/1000 inhabitants annually. Also, the hospital records that are nationally gathered may suffer from inconsistencies. Recently, these were evaluated in a separate study which validated this form of data collection in PE, but not in DVT[24]. Thirdly, analyses without prevalent statin showed attenuated, not significant effect, which may be due to lower effect and lower number of cases resulting wider confidence limits.

In conclusion, statin use offers protection against first ever VTE event. The elevated LDL cholesterol, CRP and homocysteine, as reported earlier also associate with the risk of new VTE. Statins appears as a primary prevention tool in patients with a high risk of VTE, exerting its best effect in male population.

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All authors have substantial contributed to conception and design, acquisition of data, and analysis and interpretation of data; RL and JH have drafted the article, and AJ and JP have revised it critically for important intellectual content; all authors have final approved the version to be published. RL, AJ and JP have no relevant disclosures to declare. JH has had previous research agreements with Janssen-Cilag, Novartis, Orion Pharma, Abbott, Novo Nordisk Farma, Pfizer, Sanofi-Aventis, Astellas, and Takeda. This study was funded by University of Helsinki and The National Institute for Health and Welfare, Finland (THL). No data sharing is possible because of data protection.

Contributorship Statement

All authors have substantial contributions to the conception and design of the work and acquisition of the data. JH did analyses, all authors contributed to interpretation of data for the work

JH drafted the work, other authors revised it critically for important intellectual content.

All authors have approved the final version of the work to be published.

All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

None

Data Sharing Statement

No additional data available

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Tables

Table 1 Baseline characteristics of study population

Categorical variables and usage of drugs at baseline			
Sex	male	3589	45%
	female	4336	55%
Blood glucose lowering drug	no	7637	96%
	yes	288	4%
Insulin	no	7787	98%
	yes	138	2%
Antithrombotic agent	no	7582	96%
	yes	343	4%
Antiplatelet agent	no	7764	98%
	yes	161	2%
Vitamin K antagonists	no	7732	98%
	yes	193	2%

Continuous variables at baseline LDL cholesterol (mmol/L)						
	1st Qu.	**Median**	**Mean**	**3rd Qu.**	**SD**	**Missing**
Age	42.0	52.0	54.7	66.0	16.1	100
Blood glucose (mmol/L)	5.0	5.3	5.6	5.7	1.3	1275
Total cholesterol (mmol/L)	5.1	5.9	5.9	6.6	1.1	1275
HDL cholesterol (mmol/L)	1.1	1.3	1.3	1.6	0.4	1275
LDL cholesterol (mmol/L)	3.1	3.8	3.8	4.5	1.2	1276
Triglycerides (mmol/L)	1.0	1.3	1.6	1.9	1.1	1275
Ratio HDL/Chol	18.0	22.0	23.0	28.0	7.4	1275
CRP (mg/L)	0.3	0.8	2.3	2.0	6.3	1694
Vitamin D3 (nmol/L)	33.0	43.0	44.9	55.0	16.9	1825
Homocysteine (µmol/L)	9.2	11.0	12.0	13.5	5.1	1825
Insulin (mU/L)	5.0	7.0	9.6	11.0	30.3	1627

Table 2. Incidence of end-point events. RR (rate ratios) with 95% confidence intervals (CI) based on univariate Poisson regression model. Laboratory measurements in tertiles "[a,b)" means that interval a-b is closed left and open right. The data on variables are collected at baseline.

Variable	P-years (1000)	Events	Incidence (1/1000)	95% CI		RR	95% CI	
Current statin usage								
no	67.78	118	1.74	1.44	2.09			
yes	11.17	18	1.61	0.95	2.55	0.93	0.56	1.52
Sex								
male	36.02	53	1.47	1.1	1.93			
female	42.93	83	1.93	1.54	2.4	1.31	0.93	1.85
Age								
(0,40]	19.92	10	0.50	0.24	0.92			
(40,50]	20.22	15	0.74	0.41	1.22	1.48	0.66	3.29
(50,60]	17.11	24	1.40	0.90	2.09	2.79	1.34	5.84
(60,70]	11.05	28	2.53	1.68	3.66	5.05	2.45	10.39
(70,Inf]	10.65	59	5.54	4.22	7.15	11.04	5.65	21.58
Insulin usage at baseline								
no	77.83	133	1.71	1.43	2.03			
yes	1.12	3	2.68	0.55	7.83	1.57	0.50	4.92
Blood glucose lowering drug								
no	76.71	124	1.62	1.34	1.93			
yes	2.24	12	5.37	2.77	9.37	3.32	1.84	6.00
Antithrombotic agent usage								
no	76.7	120	1.56	1.30	1.87			
yes	2.25	16	7.11	4.06	11.55	4.55	2.70	7.66
Antiplatelet agents usage								
no	77.87	126	1.62	1.35	1.93			
yes	1.08	10	9.27	4.44	17.05	5.73	3.01	10.91
Vitamin K antagonists usage								
no	77.7	128	1.65	1.37	1.96			
yes	1.25	8	6.42	2.77	12.66	3.90	1.91	7.97
Blood glucose (mmol/L)								
[2.4,5.1]	24.79	36	1.45	1.02	2.01			
(5.1,5.6]	23.93	31	1.30	0.88	1.84	0.89	0.55	1.44
(5.6,26.7]	18.69	48	2.57	1.89	3.40	1.77	1.15	2.72
Total cholesterol (mmol/L)								
[1.9,5.4]	23.71	36	1.52	1.06	2.10			
(5.4,6.3]	21.33	33	1.55	1.06	1.02	0.64	1.63	1.02
(6.3,11.7]	22.38	46	2.06	1.50	1.35	0.88	2.09	1.35

HDL cholesterol (mmol/L)								
[0.23,1.13]	22.39	45	2.01	1.46				
(1.13,1.45]	22.45	33	1.47	1.01	0.73	0.47	1.15	0.73
(1.45,3.41]	22.57	37	1.64	1.15	0.82	0.53	1.26	0.82
LDL cholesterol (mmol/L								
[0,3.3]	22.56	34	1.51	1.04				
(3.3,4.2]	22.79	38	1.67	1.18	1.11	0.70	1.76	1.11
(4.2,8.8]	22.06	43	1.95	1.41	1.29	0.82	2.03	1.29
Triglycerides (mmol/L)								
[0.4,1.1]	26.16	30	1.15	0.77				
(1.1,1.7]	21.84	45	2.06	1.50	1.80	1.13	2.85	1.80
(1.7,16.6]	19.42	40	2.06	1.47	1.80	1.12	2.88	1.80
Ratio HDL/Chol								
[3,19]	23.92	48	2.01	1.48				
(19,25.7]	20.58	34	1.65	1.14	0.82	0.53	1.28	0.82
(25.7,56]	22.91	33	1.44	0.99	0.72	0.46	1.12	0.72
C-reactive protein (mg/L)								
[0,0.39]	22.26	22	0.99	0.62				
(0.39,1.41]	21.62	42	1.94	1.40	1.97	1.17	3.29	1.97
(1.41,191]	20.53	40	1.95	1.39	1.97	1.17	3.32	1.97
Vitamin D3 (nmol/L)								
[5,36]	20.55	35	1.70	1.19	2.37			
(36,50]	21.42	31	1.45	0.98	2.06	0.85	0.52	1.38
(50,134]	21.15	37	1.75	1.23	2.41	1.03	0.65	1.63
Homocysteine (µmol/L)								
[3.7,9.7]	22.15	18	0.81	0.48	1.29			
(9.7,12.5]	21.82	32	1.47	1.00	2.07	1.80	1.01	3.22
(12.5,111]	19.16	53	2.77	2.07	3.62	3.40	1.99	5.81
Insulin (mU/L)								
[1,5]	22.72	26	1.14	0.75	1.68			
(5,9]	22.67	45	1.99	1.45	2.66	1.73	1.07	2.81
(9,2200]	19.64	33	1.68	1.16	2.36	1.47	0.88	2.00

Table 3. Rate ratios (RR) with 95% confidence intervals (CI) of three Poisson regression models. Model I included only statin, age and sex as covariates. Models II and III included also Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates. Inverse Probability Weights (IPW) Model III is based on stabilized weights for statin usage. In IPW model age and sex were in numerator, and age, sex, baseline oral antidiabetics, baseline insulin, and baseline anticoagulant usage were in denominator.

		Model I			Model II			Model III		
		RR (95% CI)			RR (95% CI)			RR, IPW (95% CI)		
Statin	no	(reference)			(reference)			(reference)		
	current	**0.64**	0.38	1.05	**0.60**	0.36	1.00	**0.58**	0.35	0.96
Age	under 40	(reference)			(reference)			(reference)		
	(40,50]	1.52	0.68	3.38	1.51	0.68	3.37	1.53	0.68	3.43
	(50,60]	2.99	1.42	6.26	2.91	1.39	6.10	3.20	1.53	6.70
	(60,70]	5.66	2.73	11.75	5.31	2.55	11.05	5.36	2.55	11.24
	(70,Inf]	11.68	5.94	22.95	9.92	4.99	19.74	9.93	4.95	19.92
Sex	male	(reference)			(reference)			(reference)		
	female	1.02	0.72	1.45	1.02	0.72	1.46	0.99	0.70	1.41
Blood glucose lowering drug	no				(reference)			(reference)		
	yes				1.89	0.98	3.63	1.63	0.86	3.11
Insulin usage	no				(reference)			(reference)		
	yes				0.72	0.21	2.45	0.72	0.25	2.13
Vitamin K antagonists	no				(reference)			(reference)		
	yes				1.46	0.69	3.07	1.38	0.68	2.80
Antiplatelet agents	no				(reference)			(reference)		
	yes				2.33	1.20	4.53	2.60	1.42	4.76

Table 4. Statin usage and sex, interaction model. Model included age, Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates.

	P-years	Events	Incidence (95% CI)			RR (95% CI)		
no statin/male	30.57	50	1.64	1.21	2.16	(reference)		
statin/male	5.45	3	0.55	0.11	1.61	0.20	0.06	0.65
no statin/female	37.21	68	1.83	1.42	2.32	0.87	0.60	1.27
statin/female	5.72	15	2.62	1.47	4.33	0.75	0.41	1.38

Statin use associates with a reduced incidence of venous thromboembolism – A population-based cohort study

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Abstract

Objectives: Venous thromboembolism (VTE) continues to be a frequent, medical emergency demanding condition to reach the diagnosis and initiate anticoagulation therapy. The use of statins is reported, in addition to reducing the incidence of arterial thrombosis, also to decrease both the incidence and reoccurrence of VTE. The aim of our study ~~is~~ was to explore the association between statin usage and the incidence of new VTE at the population level during a 10-year follow-up.

Design: Population based historic cohort

Setting: The Health 2000 survey was based on a nationally representative sample.

Participants: 8028 individuals aged 30 years or over in Finland.

Primary and secondary outcome measures: The primary end-point event was the first ever hospitalization due to one of the following causes: pulmonary embolism (ICD10 I26), cerebral venous nonpyogenic thrombosis (I63.6), and venous thrombosis ~~phlebitis and thrombophlebitis of superficial vessels of lower extremities~~ (I~~1~~80.0-~~180.9~~189).

Results: The preselected explanatory variables applied to Poisson regression model were statin usage (no/yes) during follow-up (2000-2011) and several baseline data (age, sex-; usage of blood glucose lowering drug, vitamin K antagonists, and anti-platelet agents). We observed 136 VTE events, the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years. Current statin usage did not associate with the incidence of VTE according to the univariate model (RR 0.93, 0.56-1.52), but when adjusted with baseline variables (age, sex, medications) the RR declined to 0.60 (0.36-1.00, p= 0.04).

Conclusions: Statin use offers protection against first ever VTE event and appears as a primary prevention tool in patients without anticoagulation or anti-platelet medication.

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Strengths of this study

- population based, no selection bias in start of follow-up
- long and complete follow-up information

Limitations of this study

- limited number of background variables and incidence events
-
- the comprehensive use of prescribed drugs in this study, could not be verified with certainty

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Introduction

Venous thromboembolism (VTE) continues to be a frequent condition which demands medical emergency attention to reach the diagnosis and initiate anticoagulation therapy. The mortality during a few months after VTE varies between 5-20%, and the patients often have other co-morbidities, such as cardiovascular disease and cancer. The yearly incidence of VTE is 1-2/1000 inhabitants in western societies. Nowadays, the traditional heparin and vitamin K antagonist (VKA) therapy followed with the course of temporal (3-6 months) or permanent VKA can be opted with novel oral anticoagulants[1].

The decision of either continuing the anticoagulation for a few months or permanently depends on the acquired or inherited risk factor profile of the patient. This includes age above 60 years and concomitant illness, including cancer and inflammatory diseases as well as obesity, hormonal remedies and family history or severe thrombophilias (such as homozygosity of factor V Leiden or

prothrombin mutation, double defects, antiphospholipid antibody syndrome), subjecting the patient to recurrent VTE. Despite the clinical evaluation the recurrence rate of VTE continues to be 15-20% after an idiopathic event and around 5% after a provoked thrombosis[1]. Bleeding tendency needs to be regularly weighted also against the risk of thrombosis recurrence, while maintaining the anticoagulation.

The use of statins has been reported to reduce the incidence of not only the arterial thrombosis, but also interesting data on the decline of both the incidence and reoccurrence of VTE have emerged. Retrospective observational and case-control studies as well as experimental evidence refer to the possibility that statins exert an antithrombotic effect also in the venous system. A recent meta-analysis reported the association of VTE and a 20-36% protection with statin use[2]. A primary prevention trial of VTE with rosuvastatin in a randomized placebo-controlled design showed a 48% reduction in the incidence of VTE[3]. Moreover, statin treatment alleviated the risk of recurrent pulmonary embolism by 50% whether the patient used long-term vitamin K antagonist treatment or had stopped anticoagulation, as reported by a Dutch population-based study with initially hospitalized patients[4]. Finally, statins decrease the occurrence of venous thromboembolism even in patients with cancer[5].

Field Code Changed

Statins reduce the procoagulant activity of platelet membranes and downplay the signaling via LDL receptors, which are engaged with the platelet activation[6]. Statins also enhance fibrinolysis by reducing the plasminogen activator inhibitor-1 and triglyceride concentration. Also, other pleiotropic and anti-inflammatory mechanisms, including dampened tissue factor expression by monocytes, have been described which can attenuate the risk of thrombosis.

The aim of the study was~~is~~ to explore the association between statin usage and incidence of the first ever VTE in Finland. Our study utilizes a nationally representative sample of 8028 persons aged >30 years [7] of The Health 2000 Survey and a prospective observational pharmaco-epidemiological design.

Material and methods

Study population

The Health 2000 survey was based on a nationally representative sample of 8028 individuals aged 30 years or over in Finland. To ensure that sample is representative of the Finnish population, a two-stage stratified cluster sampling procedure was used. The baseline data collection from study subjects took place between September 2000 and June 2001, and consisted of an interview and a comprehensive health examination. Of the study sample 6986 subjects (87 %) were interviewed at their home or in an institution, 6354 subjects (79 %) took part in a comprehensive health examination and 416 subjects (5%) were examined at their home. The Health 2000 study was approved by the Ethics Committees of the National Public Health Institute (since 2009 the National Institute for Health and Welfare) and the Hospital District of Helsinki and Uusimaa, and the participants gave written informed consent[7].

Follow-up time and end-points

The primary end-point event of this study was the first hospitalization due one of the following causes: pulmonary embolism (ICD10 I26), cerebral infarction due to cerebral venous nonpyogenic thrombosis (I63.6), ~~phlebitis and thrombophlebitis of superficial vessels~~deep vein thrombosis, including thrombophlebitis of lower extremities (I~~1~~80.0-180.9).

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The information about end-points was obtained from National Hospital Discharge Register that covers all hospitalizations in Finland starting from 1969. The 10-year follow-up was started at the beginning of Health 2000 Study and was stopped at death, end of year 2011, or end-point, whichever occurred first. The data about deaths were obtained from the Statistics Finland. There were 103 individuals with recorder primary end-point before the start of follow-up compatible with the general prevalence of the disease, and these subjects were excluded from the study population. Thus, the size of study population in the start of follow-up was 7925.

Laboratory measurements

Venous blood samples were drawn from the antecubital vein after a minimum of 4 h fasting. HDL cholesterol, total cholesterol, triglyceride and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL; Olympus System Reagent, Hamburg, Germany for total cholesterol, triglycerides and glucose) with a clinical chemistry analyser (Olympus, AU400, Hamburg, Germany)[8]. C-reactive protein (CRP) concentrations were determined by a chemiluminescent immunometric assay (Immulite, Diagnostic Products, Los Angeles, CA)[8]. LDL cholesterol was calculated with the Friedewald formula. Plasma insulin and homocysteine concentrations were determined with microparticle enzyme immunoassay (Abbott Laboratories, Dainabot, Tokyo, Japan)[9,10]. S-25(OH)D concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN, USA)[11].

Drug information

The data about the prescribed and purchased drugs were obtained from registers of the Social Insurance Institution. We had records of the following drugs classified by Anatomical Therapeutic Chemical (ATC) code[12]: statins (C10AA), blood glucose lowering drugs,

excluding insulins (A10B), insulin (A10A), VKA (B01AA) , and antiplatelet agents, excluding heparin (B01AC) and over the counter acetylsalicylic acid. Regarding statins the data included all prescribed statins purchased during the follow-up period in 2000 – 2006 and 2008. Because there were no data available regarding the drug amounts purchased for years 2007, and 2009-2011, we calculated the mean amount of purchase based on available years and adapted it for the whole follow-up period. Time dependent variable for the current statin usage was determined for each individual with the prescription data using R language package Epi[13]. The follow-up time of each individual with statin exposure was cut into 6-month periods and the statin usage in each period was determined. For other drugs we had only the number of prescriptions at the baseline year 2000, which was used to construct a dichotomic variable of drug usage at baseline (no/yes).

Statistical modeling

We applied the Poisson regression model using end-point event as a dependent variable, length of the follow-up as an offset variable, and statin usage (no/yes) during each time period as time-varying explanatory variable. The following variables were used as time-invariant variables measured at baseline: age (30-40, 40-50, 50-60, 60-70, over 70), sex (male/female), blood glucose lowering drug usage, excluding insulins (no/yes), insulin usage (no/yes), vitamin K antagonists usage (no/yes) , antiplatelet agents (no/yes) , blood glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), CRP (mg/L), vitamin D3 (nmol/L), homocysteine (μmol/L), and insulin (mU/L). The values of the laboratory measurements were transformed to categorical variables defined by tertiles. We also estimated the inverse probability weights (IPW) to fit marginal structural models[14]. IPW were estimated using age and sex in the numerator, and

age, sex, blood glucose lowering drugs other than insulin usage, VKA usage, and use of antiplatelet agent in the denominator. In order to check survivor bias we carried out modeling without subjects with prevalent statin use in start of follow-up (N=460 excluded) [15].

Results

The size of the study population was 7925, including 3589 males and 4336 females (Table 1). We observed 136 VTE events during the follow-up with the incidence of 1.72 (95% CI 1.44-2.04) per 1000 person-years during the mean follow-up time 10 years (Table 2). There were 64 events with the diagnosis pulmonary embolism (ICD-10 I26), one with sinus thrombosis (I636) and 71 with deep vein thrombosis (~~I80~~I80.0-~~I80.9~~I80.9).

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All together there were 67,532 statin prescriptions, and 2083 individuals (26% of population) had at least one prescription. Simvastatin (ATC code C10AA01) with 54% of prescriptions and atorvastatin (C10AA05) with 23% represented the most frequent active lipid-lowering substances. Current statin usage that comprised 14% of all cumulated person-years, did not associate with the incidence of VTE according to the univariate model Rate Ratio (RR) 0.93 (0.56-1.52)(Table 2). The use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), but insulin usage did not show any association. Using any antithrombotic drugs associated with higher incidence (RR 4.55, 2.70-7.66).

Addition of more explanatory variables in the model substantially altered the association between the statin usage and incidence (Table 3). Adjusting for sex, age, baseline oral

antidiabetic, insulin, and use of antithrombotics (Model II) reduced the RR to 0.60 (0.36-1.00). Using IPW for the structural model (Model III) decreased the RR further to 0.58 (0.35-0.96). Adjusting for the baseline laboratory measurements also decreased slightly the estimate for statin effect, e.g. adjusting for CRP gave RR 0.43 (0.23- 0.81). However, because of the missing laboratory measurements we do not report these results in further detail, e.g. for CRP there were several (1694) missing values. (Table 2). Increased levels of LDL associated with an increasing incidence of VTE, the same occurred with homocysteine.

Comment [LR2]: Kannattaisiko tämä paljastaa jo metodeissa ja kertoa jotakin syistä kun jaamasivat noista muista puuttuvista datoista

In addition, we looked for the possible interactions between statin usage and age, sex, blood glucose lowering drugs usage (excluding use of insulin), VKA and platelet aggregation inhibitors. Interaction for sex and statin usage was significant (χ^2=6.310, df=1, p=0.012). Interestingly, it turned out that the incidence of VTE among the statin group for males was quite low (RR 0.22, 0.06-0.65), but for females such an association was not obvious (RR 0.75, 0.41-1.38), upon comparing the statin usage without its usage (Table 4.).

In sensitivity analyses without prevalent statin users there was 115 cases in non-statin group and 10 cases in statin group; unadjusted RR was 0.82 (0.43- 1.56) and adjusted 0.63 (0.33-1.21).

Discussion

To our knowledge, this is the first report studying association between statin usage and VTE that utilizes a nationally representative population sample. Our results during the 11 years of prospective follow-up on the incidence of VTE are in line with the recent meta-analysis[16][~~15~~], which showed the risk reduction of 0.89 (0.78-1.01) for VTE among statin users. The JUPITER study, the largest ~~meta-analysis of trials~~randomized trial, including 465

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events, showed 36% reduction in VTE (RR 0·64, 0·39–1·06, p=0·08)[3,16]. Our study addressed the new incidence of VTE, as the patients who previously had suffered from VTE (136/8028) were excluded from study population. The prospective nature and large population-based design of pharmaco-epidemiology are the strengths of our study.

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In this freely living Finnish population sample we could demonstrate that statin use is associated with a reduction of the incidence of VTE, including both deep vein thrombosis of the lower extremities, pulmonary embolism and one case of cerebrovascular sinus thrombosis. This adds to the confirmation that statins exert anticoagulant activity[2–5]. Furthermore, it supports the idea that statin therapy could be implemented to the patients with the risk of VTE.

We observed that use of oral antidiabetic drugs at the baseline was associated with a three-fold increased incidence (RR 3.32, 1.84-6.00), which refers to that insulin-resistant patients carry a high risk of VTE, and the oral antidiabetic drugs do not seem to alleviate this risk, while insulin may do so[18]~~[17]~~. The positive association between antithrombotic drugs and VTE is quite probably due to confounding by indication[19]~~[18]~~, and also the co-occurrence of cardiovascular disease and VTE has been noted in several studies[20]~~[19]~~. The limitation of our study relies on the fact that over-the counter aspirin use is not controlled. This is significant, as aspirin has been recently shown to inhibit the reoccurrence of idiopathic VTE[21]~~[20]~~.

Men seemed to respond to statin use more favourably than females, indicating a plausible hormonal regulation of the effect of statins. In women we did not control for hormonal replacement therapy, which may be a confounding remedy, known to be a risk factor for

VTE[22,23]~~[21,22]~~ The well-known age-association in increasing the incidence of DVT and PE was evidenced also among our patients. Also, the overall incidence of VTE in Finland is compatible with what has been reported internationally. The protective association with incidence of VTE among highest third tertile of HDL-LDL ratio, lowest homocysteine and CRP support earlier results of these surrogate laboratory markers.

Several limitations must be kept in mind when evaluating results from any observational study based on record linkage of drug information. Firstly, the comprehensive use of prescribed drugs in this study, could not be verified with certainty, and may be subject to misclassification. The prescription data do not contain information on drugs used in nursing homes, therefore, the misclassification of exposure is more likely among the older patient groups. Secondly, although model based adjustments using regression and IPW were applied, it is always possible that residual confounding factors could influence the results. E.g. statin usage may depend on variables that are not included in the statistical models; or the statistical models used in the analysis do not properly adjust for the confounding factors. The importance of adjusting for possible confounding effects is reflected by the large difference between estimates obtained from the uni- and multivariate models. On the other hand, the results based on the three models with different pattern of covariates and modeling technique remained nearly unchanged regarding the effect of current statin usage (Table 3). This compatibility increases the credibility of the results, albeit the actual incidences are relatively low in numbers due to the natural incidence of 1-2 cases/1000 inhabitants annually. Also, the hospital records that are nationally gathered may suffer from inconsistencies. Recently, these were evaluated in a separate study which validated this form of data collection in PE, but not in DVT[24]~~[23]~~. Thirdly, analyses without prevalent statin showed attenuated, not significant

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effect, which may be due to lower effect and lower number of cases resulting wider confidence limits.

In conclusion, statin use offers protection against first ever VTE event. The elevated LDL cholesterol, CRP and homocysteine, as reported earlier also associate with the risk of new VTE. Statins appears as a primary prevention tool in patients with a high risk of VTE, exerting its best effect in male population.

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RL, AJ and JP have no relevant disclosures to declare. JH has had previous research agreements with Janssen-Cilag, Novartis, Orion Pharma, Abbott, Novo Nordisk Farma, Pfizer, Sanofi-Aventis, Astellas, and Takeda.

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Tables

Table 1 Baseline characteristics of study population

Categorical variables and usage of drugs at baseline			
Sex	male	3589	45%
	female	4336	55%
Blood glucose lowering drug	no	7637	96%
	yes	288	4%
Insulin	no	7787	98%
	yes	138	2%
Antithrombotic agent	no	7582	96%
	yes	343	4%
Antiplatelet agent	no	7764	98%
	yes	161	2%
Vitamin K antagonists	no	7732	98%
	yes	193	2%

Continuous variables at baseline LDL cholesterol (mmol/L)						
	1st Qu.	**Median**	**Mean**	**3rd Qu.**	**SD**	**Missing**
Age	42.0	52.0	54.7	66.0	16.1	100
Blood glucose (mmol/L)	5.0	5.3	5.6	5.7	1.3	1275
Total cholesterol (mmol/L)	5.1	5.9	5.9	6.6	1.1	1275
HDL cholesterol (mmol/L)	1.1	1.3	1.3	1.6	0.4	1275
LDL cholesterol (mmol/L)	3.1	3.8	3.8	4.5	1.2	1276
Triglycerides (mmol/L)	1.0	1.3	1.6	1.9	1.1	1275
Ratio HDL/Chol	18.0	22.0	23.0	28.0	7.4	1275
CRP (mg/L)	0.3	0.8	2.3	2.0	6.3	1694
Vitamin D3 (nmol/L)	33.0	43.0	44.9	55.0	16.9	1825
Homocysteine (µmol/L)	9.2	11.0	12.0	13.5	5.1	1825
Insulin (mU/L)	5.0	7.0	9.6	11.0	30.3	1627

Table 2. Incidence of end-point events. RR (rate ratios) with 95% confidence intervals (CI) based on univariate Poisson regression model. Laboratory measurements in tertiles "[a,b)" means that interval a-b is closed left and open right. The data on variables are collected at baseline.

Variable	P-years (1000)	Events	Incidence (1/1000)	95% CI		RR	95% CI	
Current statin usage								
no	67.78	118	1.74	1.44	2.09			
yes	11.17	18	1.61	0.95	2.55	0.93	0.56	1.52
Sex								
male	36.02	53	1.47	1.1	1.93			
female	42.93	83	1.93	1.54	2.4	1.31	0.93	1.85
Age								
(0,40]	19.92	10	0.50	0.24	0.92			
(40,50]	20.22	15	0.74	0.41	1.22	1.48	0.66	3.29
(50,60]	17.11	24	1.40	0.90	2.09	2.79	1.34	5.84
(60,70]	11.05	28	2.53	1.68	3.66	5.05	2.45	10.39
(70,Inf]	10.65	59	5.54	4.22	7.15	11.04	5.65	21.58
Insulin usage at baseline								
no	77.83	133	1.71	1.43	2.03			
yes	1.12	3	2.68	0.55	7.83	1.57	0.50	4.92
Blood glucose lowering drug								
no	76.71	124	1.62	1.34	1.93			
yes	2.24	12	5.37	2.77	9.37	3.32	1.84	6.00
Antithrombotic agent usage								
no	76.7	120	1.56	1.30	1.87			
yes	2.25	16	7.11	4.06	11.55	4.55	2.70	7.66
Antiplatelet agents usage								
no	77.87	126	1.62	1.35	1.93			
yes	1.08	10	9.27	4.44	17.05	5.73	3.01	10.91
Vitamin K antagonists usage								
no	77.7	128	1.65	1.37	1.96			
yes	1.25	8	6.42	2.77	12.66	3.90	1.91	7.97
Blood glucose (mmol/L)								
[2.4,5.1]	24.79	36	1.45	1.02	2.01			
(5.1,5.6]	23.93	31	1.30	0.88	1.84	0.89	0.55	1.44
(5.6,26.7]	18.69	48	2.57	1.89	3.40	1.77	1.15	2.72
Total cholesterol (mmol/L)								
[1.9,5.4]	23.71	36	1.52	1.06	2.10			
(5.4,6.3]	21.33	33	1.55	1.06	1.02	0.64	1.63	1.02
(6.3,11.7]	22.38	46	2.06	1.50	1.35	0.88	2.09	1.35

HDL cholesterol (mmol/L)								
[0.23,1.13]	22.39	45	2.01	1.46				
(1.13,1.45]	22.45	33	1.47	1.01	0.73	0.47	1.15	0.73
(1.45,3.41]	22.57	37	1.64	1.15	0.82	0.53	1.26	0.82
LDL cholesterol (mmol/L								
[0,3.3]	22.56	34	1.51	1.04				
(3.3,4.2]	22.79	38	1.67	1.18	1.11	0.70	1.76	1.11
(4.2,8.8]	22.06	43	1.95	1.41	1.29	0.82	2.03	1.29
Triglycerides (mmol/L)								
[0.4,1.1]	26.16	30	1.15	0.77				
(1.1,1.7]	21.84	45	2.06	1.50	1.80	1.13	2.85	1.80
(1.7,16.6]	19.42	40	2.06	1.47	1.80	1.12	2.88	1.80
Ratio HDL/Chol								
[3,19]	23.92	48	2.01	1.48				
(19,25.7]	20.58	34	1.65	1.14	0.82	0.53	1.28	0.82
(25.7,56]	22.91	33	1.44	0.99	0.72	0.46	1.12	0.72
C-reactive protein (mg/L)								
[0,0.39]	22.26	22	0.99	0.62				
(0.39,1.41]	21.62	42	1.94	1.40	1.97	1.17	3.29	1.97
(1.41,191]	20.53	40	1.95	1.39	1.97	1.17	3.32	1.97
Vitamin D3 (nmol/L)								
[5,36]	20.55	35	1.70	1.19	2.37			
(36,50]	21.42	31	1.45	0.98	2.06	0.85	0.52	1.38
(50,134]	21.15	37	1.75	1.23	2.41	1.03	0.65	1.63
Homocysteine (µmol/L)								
[3.7,9.7]	22.15	18	0.81	0.48	1.29			
(9.7,12.5]	21.82	32	1.47	1.00	2.07	1.80	1.01	3.22
(12.5,111]	19.16	53	2.77	2.07	3.62	3.40	1.99	5.81
Insulin (mU/L)								
[1,5]	22.72	26	1.14	0.75	1.68			
(5,9]	22.67	45	1.99	1.45	2.66	1.73	1.07	2.81
(9,2200]	19.64	33	1.68	1.16	2.36	1.47	0.88	2.00

Table 3. Rate ratios (RR) with 95% confidence intervals (CI) of three Poisson regression models. Model I included only statin, age and sex as covariates. Models II and III included also Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates. Inverse Probability Weights (IPW) Model III is based on stabilized weights for statin usage. In IPW model age and sex were in numerator, and age, sex, baseline oral antidiabetics, baseline insulin, and baseline anticoagulant usage were in denominator.

		Model I			Model II			Model III		
		RR (95% CI)			RR (95% CI)			RR, IPW (95% CI)		
Statin	no	(reference)			(reference)			(reference)		
	current	**0.64**	0.38	1.05	**0.60**	0.36	1.00	**0.58**	0.35	0.96
Age	under 40	(reference)			(reference)			(reference)		
	(40,50]	1.52	0.68	3.38	1.51	0.68	3.37	1.53	0.68	3.43
	(50,60]	2.99	1.42	6.26	2.91	1.39	6.10	3.20	1.53	6.70
	(60,70]	5.66	2.73	11.75	5.31	2.55	11.05	5.36	2.55	11.24
	(70,Inf]	11.68	5.94	22.95	9.92	4.99	19.74	9.93	4.95	19.92
Sex	male	(reference)			(reference)			(reference)		
	female	1.02	0.72	1.45	1.02	0.72	1.46	0.99	0.70	1.41
Blood glucose lowering drug	no				(reference)			(reference)		
	yes				1.89	0.98	3.63	1.63	0.86	3.11
Insulin usage	no				(reference)			(reference)		
	yes				0.72	0.21	2.45	0.72	0.25	2.13
Vitamin K antagonists	no				(reference)			(reference)		
	yes				1.46	0.69	3.07	1.38	0.68	2.80
Antiplatelet agents	no				(reference)			(reference)		
	yes				2.33	1.20	4.53	2.60	1.42	4.76

Table 4. Statin usage and sex, interaction model. Model included age, Blood glucose lowering drug, Insulin usage, Vitamin K antagonists usage, and Antiplatelet agents usage as covariates.

	P-years	Events	Incidence (95% CI)			RR (95% CI)		
no statin/male	30.57	50	1.64	1.21	2.16	(reference)		
statin/male	5.45	3	0.55	0.11	1.61	0.20	0.06	0.65
no statin/female	37.21	68	1.83	1.42	2.32	0.87	0.60	1.27
statin/female	5.72	15	2.62	1.47	4.33	0.75	0.41	1.38

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Statin use associates with a reduced incidence of venous thromboembolism – A population-based cohort study**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses Done
Methods		
Study design	4	Present key elements of study design early in the paper Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Done
		~~(*b*) For matched studies, give matching criteria and number of exposed and unexposed~~
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Done
Bias	9	Describe any efforts to address potential sources of bias Done
Study size	10	Explain how the study size was arrived at Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done
		(*b*) Describe any methods used to examine subgroups and interactions Done
		(*c*) Explain how missing data were addressed Done
		(*d*) If applicable, explain how loss to follow-up was addressed Done
		(*e*) Describe any sensitivity analyses Done

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Done**
		(b) Give reasons for non-participation at each stage **Done**
		(c) Consider use of a flow diagram Not included, presented in previous papers
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Done
		(b) Indicate number of participants with missing data for each variable of interest Done
		(c) Summarise follow-up time (eg, average and total amount) Done
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Done,95% Ci given, interaction test with p-value and X2 test.
		(*b*) Report category boundaries when continuous variables were categorized Done
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not done because of brevity. Easy to do if needed with data in tables.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done
Discussion		
Key results	18	Summarise key results with reference to study objectives Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done
Generalisability	21	Discuss the generalisability (external validity) of the study results Done. This is population based study.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Details give, not extra funding.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.