STATINS AND RISK OF VENOUS THROMBOEMBOLISM

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DISCLOSURES

- The project was funded by Aarhus University, Department of Clinical Epidemiology

- No relationships to disclose

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STATINS HAVE PLEIOTROPIC EFFECTS

- Lipid-lowering
- Anti-inflammatory
- Anti-thrombotic

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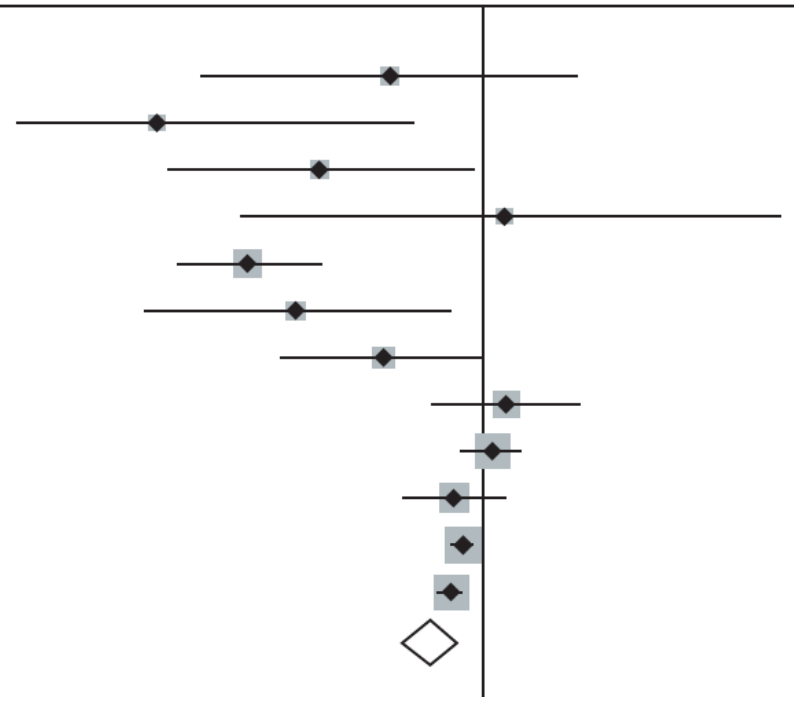
JUPITER TRIAL: 40% REDUCED RISK

	Rosuvastatin (N=8901)		Placebo (N=8901)		
Venous thromboembolism	*no. of patients*	*no. of events/ 100 person-yr*	*no. of patients*	*no. of events/ 100 person-yr*	**Hazard Ratio (95% CI)**
Total	34	0.18	60	0.32	0.57 (0.37–0.86)
Unprovoked	19	0.10	31	0.17	0.61 (0.35–1.09)
Provoked	15	0.08	29	0.16	0.52 (0.28–0.96)
Pulmonary embolism	17	0.09	22	0.12	0.77 (0.41–1.45)
Deep-vein thrombosis only	17	0.09	38	0.20	0.45 (0.25–0.79)

Glynn, *et al* N Engl J Med 2009

META-ANALYSIS: 25% REDUCED RISK

Author, year of publication	Participants	Cases	RR (95% CI)
Venous thromboembolism			
Harbi, 2013	798	6	0·63 (0·25–1·57)
Resh, 2011	289	20	0·20 (0·10–0·70)
Herrington, 2002	2763	41	0·44 (0·21–0·94)
Yang, 2002	504	72	1·10 (0·30–4·30)
Khemasuwan, 2011	1100	107	0·31 (0·22–0·44)
Lotsch, 2014	1434	107	0·39 (0·16–0·92)
Lassilia, 2014	7925	136	0·60 (0·36–1·00)
Shai, 2014	1746	175	1·10 (0·76–1·58)
Smeeth, 2009	729529	6199	1·02 (0·88–1·18)
Huerta, 2007	16550	6550	0·85 (0·66–1·09)
Hippisley-Cox, 2010	2004692	12199	0·89 (0·84–0·93)
Fournier, 2014	255067	23505	0·83 (0·78–0·87)
Subtotal	**3022397**	**49117**	**0·75 (0·65–0·87)**



Kunutsor, *et al* Lancet Haematol 2017

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LIMITATIONS OF PREVIOUS STUDIES

- Healthy users

- Prevalent users
  - Survival bias
  - Adherence bias
  - Complicates confounding control

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STUDY OBJECTIVE

To examine the effect of initiating statins on the risk of venous thromboembolism (VTE)

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STUDY DESIGN & DATA SOURCES

- Nationwide, matched cohort study in Denmark
- Unique 10-digit identifier allows accurate linkage
- Danish National Health Service Prescription Database
  - all redeemed prescriptions since 2004
- Danish National Patient Registry
  - all hospital contacts since 1977

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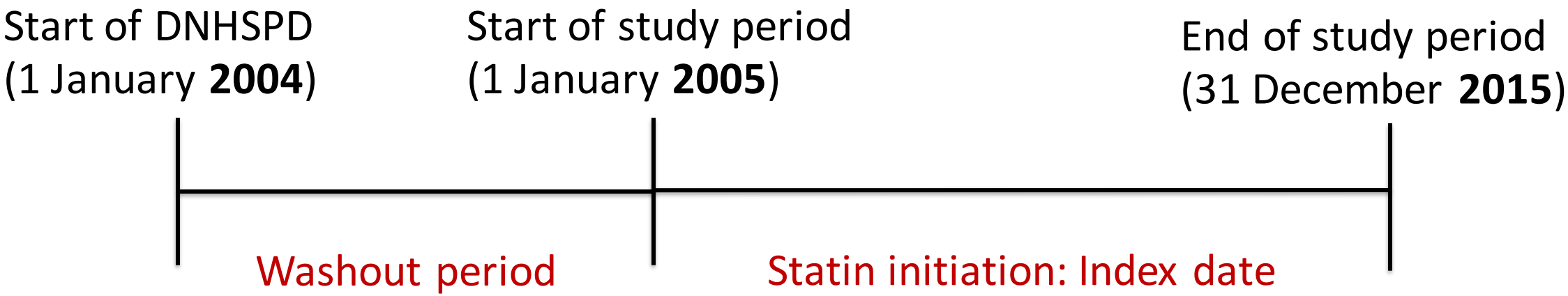
STUDY POPULATION, 2005–2015

New-user design



Exclusion criteria: previous VTE, MI, ischemic stroke

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STUDY POPULATION, 2005–2015

Statin cohort

- Matching factors
  - Sex
  - Age
  - Calendar year
- 3:1 ratio

General population

Matched comparison cohort

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OUTCOMES

Primary outcomes

- First-time VTE
  - All
  - Provoked
  - Unprovoked

Positive control outcomes

- First-time myocardial infarction
- First-time ischemic stroke

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BASELINE CHARACTERISTICS

	Statin cohort N = 601,011	Comparison cohort N = 1,803,033
Men	49.2%	49.2%
Women	50.8%	50.8%
Median age	62 years	62 years

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BASELINE CHARACTERISTICS

Statin users have a higher burden of cardiovascular disease

	Statin cohort **N = 601,011**	**Comparison cohort** **N = 1,803,033**
Heart failure	2.1%	0.9%
Diabetes	4.4%	2.7%
Obesity	4.5%	2.0%
Hypertension	14.7%	6.8%
Atrial fibrillation	4.3%	2.6%
Antipsychotics	5.6%	4.1%
Antithrombotics	19.5%	8.8%

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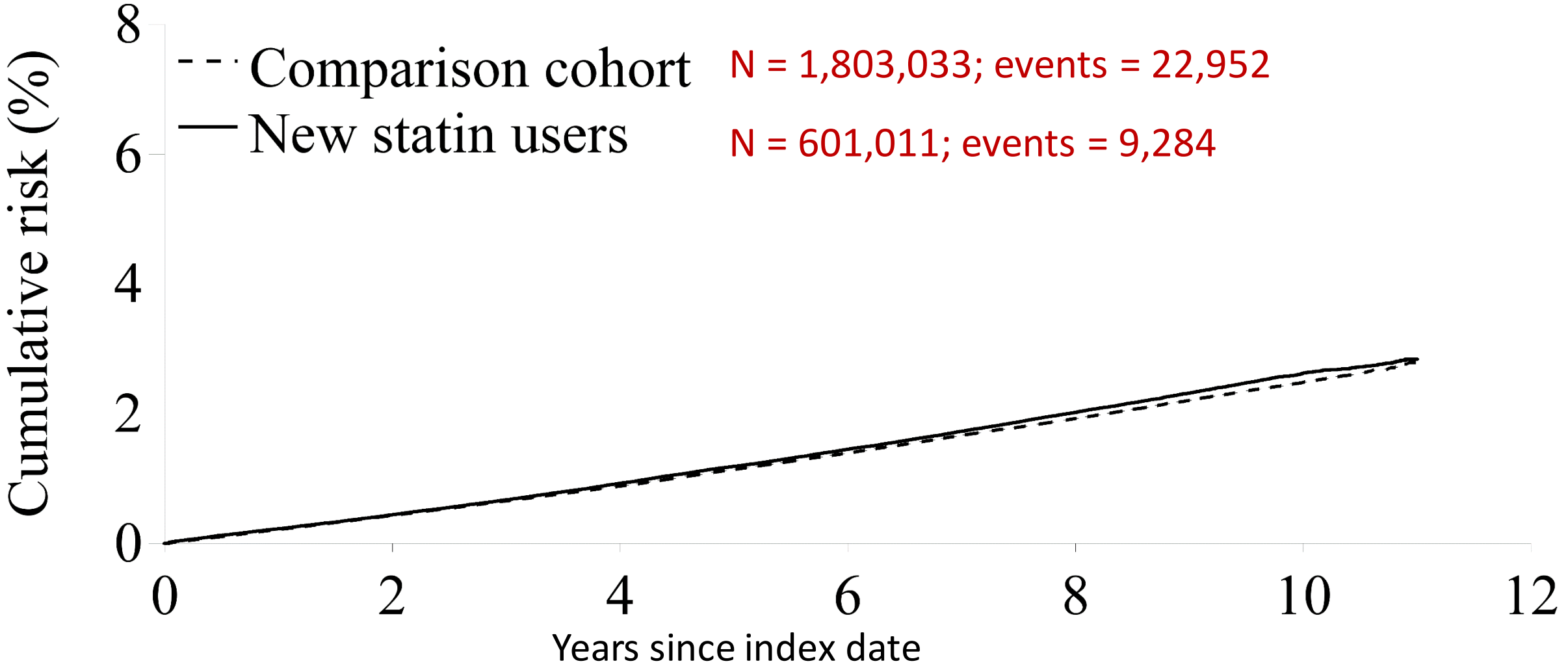
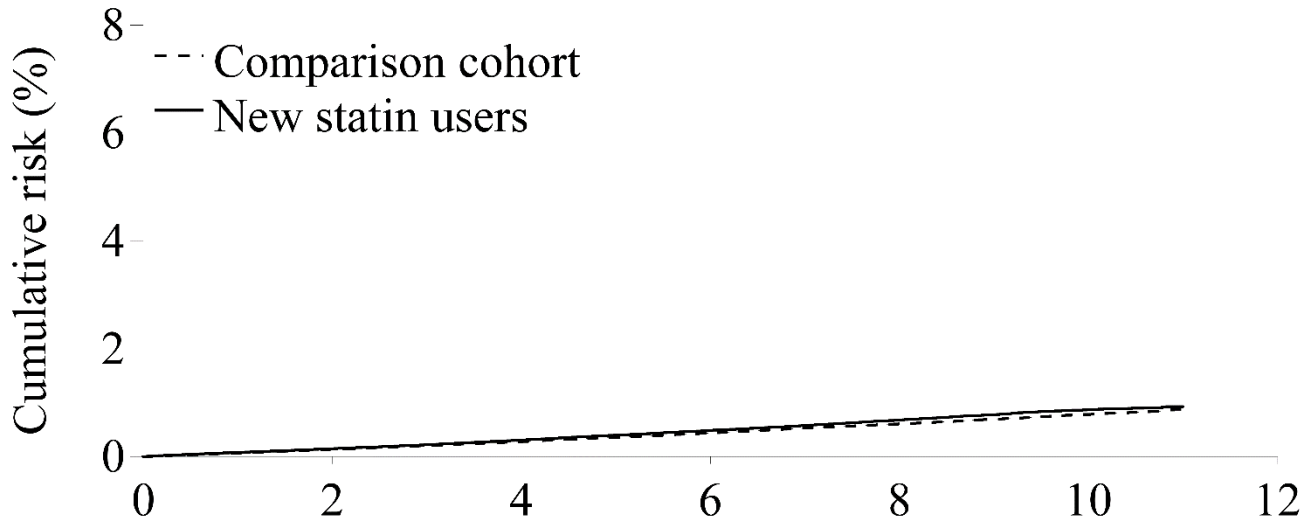
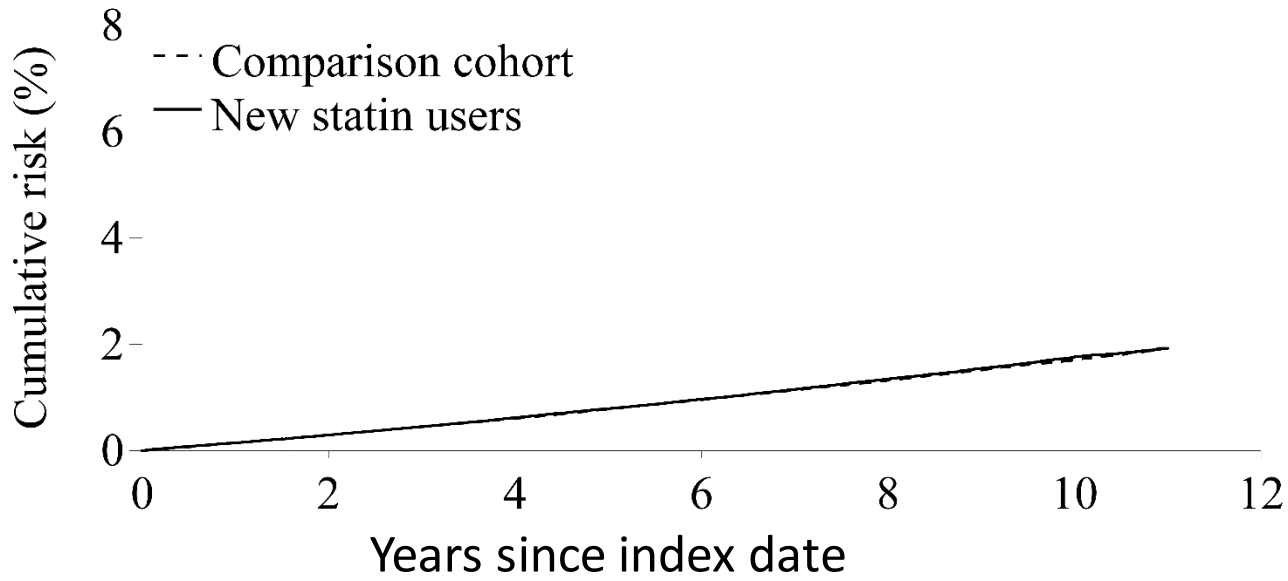
Venous thromboembolism



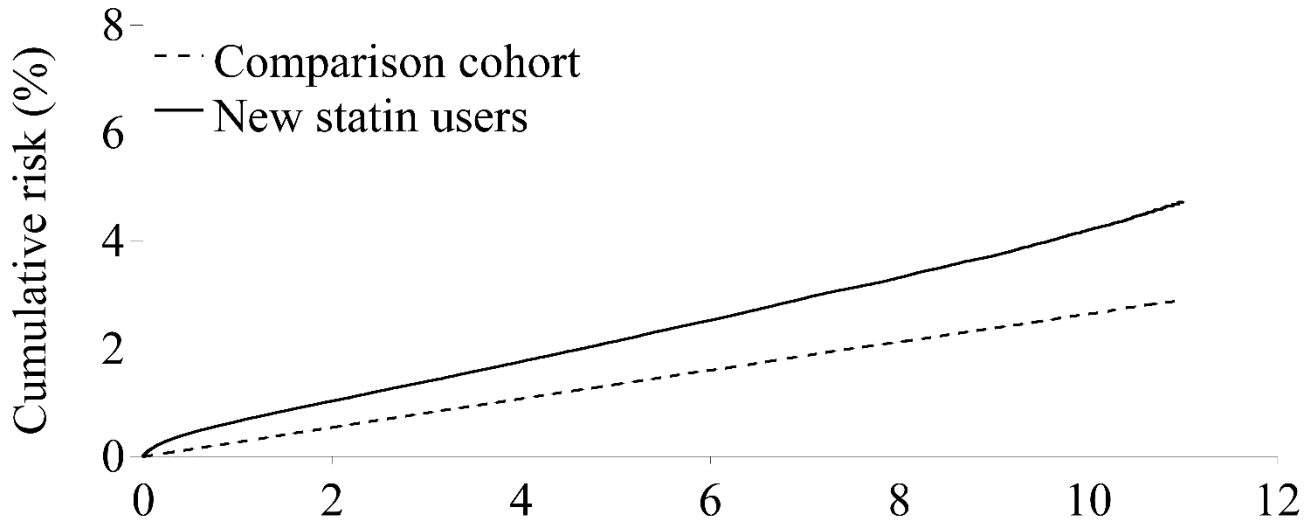
Provoked venous thromboembolism



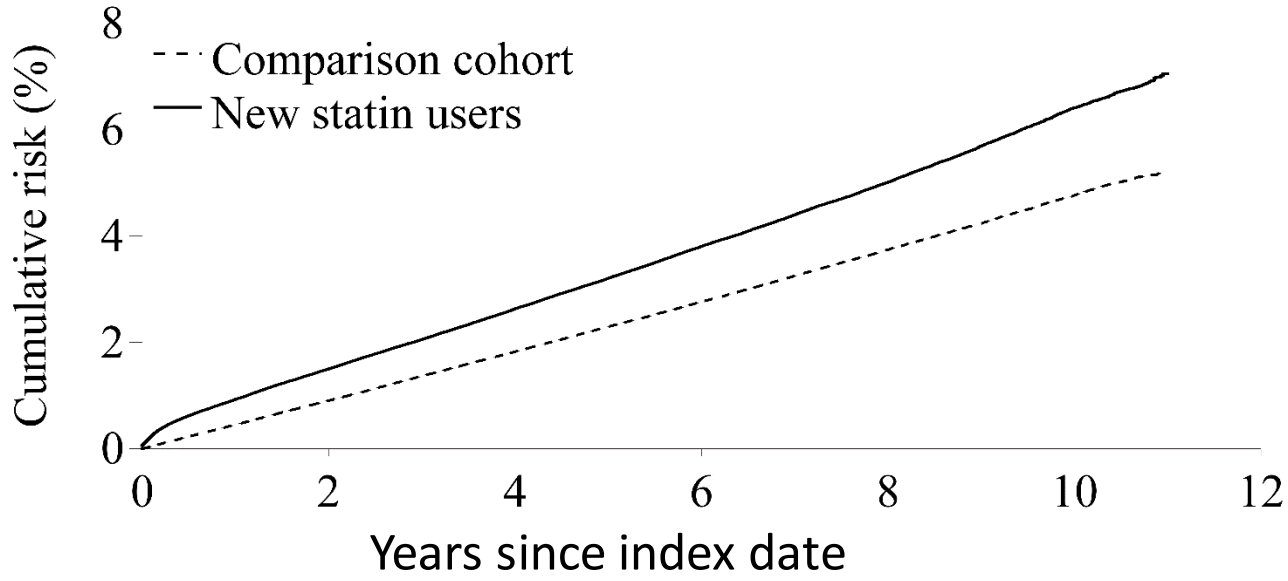
Unprovoked venous thromboembolism



Myocardial infarction



Ischemic stroke



REDUCED RISK AFTER ADJUSTMENT

	Hazard ratios (95% CI)	
	Unadjusted	Adjusted*
VTE	1.01 (0.99–1.04)	0.95 (0.92–0.97)
Unprovoked VTE	0.99 (0.96–1.02)	0.92 (0.89–0.95)
Provoked VTE	1.07 (1.02–1.12)	1.02 (0.97–1.07)

*Controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, cancer, CKD, liver disease, PHRT, antipsychotics, antithrombotics.

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REDUCED RISK AFTER ADJUSTMENT

	Hazard ratios (95% CI)	
	Unadjusted	Adjusted*
Myocardial infarction	1.60 (1.57–1.63)	1.44 (1.40–1.47)
Ischemic stroke	1.36 (1.34–1.38)	1.20 (1.18–1.23)

*Controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, cancer, CKD, liver disease, PHRT, antipsychotics, antithrombotics.

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RESULTS IN SUBGROUPS

- The beneficial statin effects were more pronounced
  - among men than women
  - with increasing age
  - among patients with ≥2 cardiovascular risk factors

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RESULTS IN SUBGROUPS

- The beneficial statin effects were similar
  - between low-potency & high-potency statins
  - for deep vein thrombosis & pulmonary embolism

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SENSITIVITY ANALYSES

- The associations were more pronounced when
  - restricted to VTEs confirmed with ultrasound or CT scan

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CONCLUSIONS

- Slightly reduced risk of VTE (particularly unprovoked VTE) among statin initiators compared with non-users
- Ultrasound/CT verification – associations amplified
- Associations similar for DVT/PE and between statins of different potency
- No "healthy-user" effect

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EVENTS AND RISKS (0-11 YEARS)

	Statin initiators N=601,011		General population cohort members N=1,803,033	
	Events	Risk, % (95% CI)	Events	Risk, % (95% CI)
VTE	9,284	2.84 (2.75–2.93)	22,952	2.79 (2.71–2.86)
Unprovoked VTE	6,196	1.92 (1.84–2.01)	15,761	1.92 (1.86–1.98)
Provoked VTE	3,088	0.93 (0.88–0.98)	7,191	0.88 (0.84–0.92)

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EVENTS AND RISKS (0-11 YEARS)

	Statin initiators N=601,011		General population cohort members N=1,803,033	
	Events	Risk, % (95% CI)	Events	Risk, % (95% CI)
Myocardial infarction	15,880	4.72 (4.57–4.86)	26,014	2.89 (2.83–2.96)
Ischemic stroke	23,911	7.05 (6.89–7.22)	45,524	4.84 (4.75–4.92)

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HAZARD RATIOS (0-1 YEARS)

	Hazard ratios (95% CI)	
	Unadjusted	Adjusted*
VTE	1.05 (0.99–1.12)	0.99 (0.93–1.06)
Unprovoked VTE	1.00 (0.92–1.08)	0.93 (0.86–1.01)
Provoked VTE	1.17 (1.05–1.30)	1.18 (1.04–1.33)

*Controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, cancer, CKD, liver disease, PHRT, antipsychotics, antithrombotics.

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BY SEX (0-11 YEARS)

	Hazard ratios (95% CI)	
VTE	Unadjusted	Adjusted*
Men	0.99 (0.95–1.02)	0.92 (0.89–0.96)
Women	1.04 (1.00–1.07)	0.97 (0.94–1.01)

*Controlled for matching factors and adjusted for heart failure, diabetes, obesity, hypertension, atrial fibrillation, cancer, CKD, liver disease, PHRT, antipsychotics, antithrombotics.

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BY AGE (0-11 YEARS)

	Hazard ratios (95% CI)	
VTE	Unadjusted	Adjusted*
0–40 years	1.79 (1.49–2.16)	1.51 (1.21–1.88)
41–50 years	1.30 (1.19–1.43)	1.11 (0.99–1.23)
51–60 years	1.10 (1.04–1.17)	0.98 (0.92–1.04)
61–70 years	0.93 (0.89–0.97)	0.87 (0.83–0.91)
>70 years	0.97 (0.93–1.01)	0.94 (0.90–0.98)

*Controlled for matching factors and adjusted for the categorical covariables.

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BY POTENCY (0-11 YEARS)

	Hazard ratios (95% CI)	
VTE	Unadjusted	Adjusted*
Low potency	1.01 (0.99–1.04)	0.95 (0.92–0.97)
High potency	1.00 (0.87–1.15)	0.93 (0.80–1.08)

*Controlled for matching factors and adjusted for the categorical covariables.

Low potency: simvastatin, lovastatin, pravastatin, and fluvastatin
High potency: rosuvastatin, atorvastatin

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BY CV RISK FACTORS (0-11 YEARS)

	Hazard ratios (95% CI)	
VTE	Unadjusted	Adjusted*
0	1.02 (0.98–1.05)	0.95 (0.92–0.98)
1	0.75 (0.71–0.78)	0.91 (0.86–0.95)
≥2	0.73 (0.68–0.78)	0.85 (0.78–0.91)

*Controlled for matching factors and adjusted for the categorical covariables.

Cardiovascular risk factors: heart failure, diabetes, obesity, hypertension, atrial fibrillation, cancer, chronic kidney disease, and liver disease

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BY VTE TYPE (0-11 YEARS)

	Hazard ratios (95% CI)	
VTE	Unadjusted	Adjusted*
DVT	1.01 (0.98–1.05)	0.94 (0.90–0.97)
PE	1.01 (0.98–1.05)	0.96 (0.92–0.99)

*Controlled for matching factors and adjusted for the categorical covariables.

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SENSITIVITY ANALYSES

1. Statin initiators **censored** at first encountered event

	Adjusted hazard ratios (95% CI)*	
	Sensitivity analysis	Main analysis
VTE	0.93 (0.91–0.96)	0.95 (0.92–0.97)
Unprovoked VTE	0.88 (0.85–0.91)	0.92 (0.89–0.95)
Provoked VTE	0.97 (0.92–1.02)	1.02 (0.97–1.07)

*Controlled for matching factors and adjusted for the categorical covariables.

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SENSITIVITY ANALYSES

2. General population cohort members **not censored** at statin initiation

	Adjusted hazard ratios (95% CI)*	
	Sensitivity analysis	Main analysis
VTE	0.95 (0.93–0.98)	0.95 (0.92–0.97)
Unprovoked VTE	0.93 (0.90–0.96)	0.92 (0.89–0.95)
Provoked VTE	1.02 (0.97–1.06)	1.02 (0.97–1.07)

*Controlled for matching factors and adjusted for the categorical covariables.

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SENSITIVITY ANALYSES

3. Statin initiators **censored** at last statin redemption

	Adjusted hazard ratios (95% CI)*	
	Main analysis	Sensitivity analysis
VTE	0.95 (0.92–0.97)	0.85 (0.80–0.91)
Unprovoked VTE	0.92 (0.89–0.95)	0.85 (0.79–0.92)
Provoked VTE	1.02 (0.97–1.07)	0.89 (0.79–0.99)

*Controlled for matching factors and adjusted for the categorical covariables.

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SENSITIVITY ANALYSES

4. Restricted to VTEs diagnosed with **ultrasound or CT scan**

	Adjusted hazard ratios (95% CI)*	
	Main analysis	Sensitivity analysis
VTE	0.95 (0.92–0.97)	0.89 (0.86–0.92)

*Controlled for matching factors and adjusted for the categorical covariables.

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COVARIABLES

- Heart failure
- Diabetes
- Obesity
- Hypertension
- Atrial fibrillation
- Cancer
- Chronic kidney disease
- Liver disease
- Postmenopausal hormone replacement therapy
- Antipsychotics
- Antithrombotics

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CLINICAL RELEVANCE

We lack clinical detail and cannot provide firm clinical recommendations

Could be considered for as primary thromboprophylaxis for people at high risk of VTE

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STATISTICAL ANALYSES

Follow-up:

Both cohorts followed until

- VTE
- Myocardial infarction
- Ischemic stroke
- Death (censoring)
- Emigration (censoring)
- Study end (censoring)

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PROPENSITY SCORE BASED MODEL

Better control of confounding by indication?

Particularly useful when assessing rare outcomes

Would likely yield similar estimates

Stürmer *et al* J Clin Epidemiol 2006

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MATCHING PROCEDURE

We matched in a 3:1 ratio, with replacement (initially 5:1 but too many repeat subjects)

Matching without replacement can lead to immortal time bias

Heide-Jørgensen *et al* Clin Epidemiol 2018

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VTE DIAGNOSIS

In Denmark, VTE diagnosis is based on ultrasound scan

In our dataset, 69% of VTEs had a ultrasound or computed tomography performed

The rest? Lack of registration and outcome misclassification.

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STRENGTHS

Size, long-term

Population-based design

New-user design

No loss to follow-up

Redeemed statin prescriptions

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LIMITATIONS

Lack of randomization

Residual and unmeasured confounding

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CONCLUSIONS

Growing, convincing evidence that statins reduce risk of venous thromboembolism

Small effect

Do statins have a role in primary prevention of venous thromboembolism?

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