IN FOCUS

HMG-CoA reductase inhibitors, other lipid-lowering medication, antiplatelet therapy, and the risk of venous thrombosis

A. S. RAMCHARAN,* K. J. VAN STRALEN,* J. D. SNOEP,* A. K. MANTEL-TEEUWISSE,†
F. R. ROSENDAAL*‡ and C. J. M. DOGGEN*

*Department of Clinical Epidemiology, Leiden University Medical Centre; †Division of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University; and ‡Thrombosis and Haemostasis Research Centre, Leiden University Medical Centre, the Netherlands

Summary. *Background:* Statins [3-hydroxymethyl-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors] and antiplatelet therapy reduce the risk of atherosclerotic disease. Besides a reduction of lipid levels, statins might also have antithrombotic and anti-inflammatory properties, and antiplatelet therapy reduces clot formation. We have studied the risk of venous thrombosis with use of statins, other lipid-lowering medication, and antiplatelet therapy. *Materials and methods:* Patients with a first episode of deep vein thrombosis in the leg or pulmonary embolism between March 1999 and September 2004 were included in a large population-based case–control study (MEGA study). Control subjects were partners of patients (53%) or recruited via a random-digit-dialing method (47%). Participants reported different all-medication use in a questionnaire. *Results:* Of 4538 patients, 154 used statins (3.3%), as did 354 of 5914 control subjects (5.7%). The use of statins [odds ratio (OR) 0.45; 95% confidence interval (CI) 0.36–0.56] but not other lipid-lowering medications (OR 1.22; 95% CI 0.62–2.43), was associated with a reduced venous thrombosis risk as compared with individuals who did not use any lipid-lowering medication, after adjustment for age, sex, body mass index, atherosclerotic disease, antiplatelet therapy and use of vitamin K antagonists. Different types and various durations of statin therapy were all associated with a decreased venous thrombosis risk. Antiplatelet therapy also reduced

venous thrombosis risk (OR 0.56; 95% CI 0.42–0.74). However, sensitivity analyses suggested that this effect is most likely explained by a so-called 'healthy user effect'. Simultaneous use of medication most strongly reduced venous thrombosis risk. *Conclusion:* These results suggest that the use of various types of statins is associated with a reduced risk of venous thrombosis, whereas antiplatelet therapy and other lipid-lowering medications are not.

Keywords: aspirin, statins, venous thrombosis.

Correspondence: Frits R. Rosendaal, Department of Clinical Epidemiology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands.
Tel.: +31 71 526 4037; fax: +31 74 526 6994.
E-mail: f.r.rosendaal@lumc.nl

Introduction

Several clinical trials have demonstrated that 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins prevent and reduce mortality and morbidity among patients with cardiovascular disease [1–3]. It has been suggested that the therapeutic benefits of statins are due not only to their plasma low-density lipoprotein cholesterol-lowering effect, but also to antithrombotic and anti-inflammatory properties [4–11].

These so-called pleiotropic effects of statins may reduce the risk for venous thrombosis, through inactivation of factor V, FXIII and prothrombin. Both cohort and case–control studies have shown risk reductions for venous thrombosis of between 22% and 58% with statin therapy[12–15]. However, previous studies were small with respect to number of venous thrombotic events that occurred, and the effects of various types and duration of statin therapy have only been studied to a limited extent [4,9,11–15].

The use of antiplatelet therapy has been extensively studied in the context of arterial thrombosis, and is a cornerstone in the prevention of atherosclerotic disease [16]. As platelets play a role in the development of venous thrombi, it has been

hypothesized that antiplatelet therapy may have a preventive effect on venous thrombosis as well. In various studies, risk reductions for venous thrombosis of between 5% and 50% have been reported [17].

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study) is a large population-based case–control study including over 4000 patients with venous thrombosis. We studied the effects of various types of statins, other lipid-lowering and antiplatelet therapy and vitamin K antagonists in detail. Furthermore, we studied combinations of these therapies as well as duration of therapy, and we performed various subgroup and sensitivity analyses.

Materials and methods

Subjects and data collection

Patients aged 18–70 years, with a first episode of deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) between March 1999 and September 2004, were recruited for inclusion in the MEGA study from six anticoagulation clinics in the Netherlands. Exclusion criteria were severe psychiatric disease and lack of knowledge of Dutch. Among 6331 eligible patients, 276 died before participating, 82 were in the end stage of disease, and 917 refused to participate. Some patients ($n = 425$) only provided a standardized mini-questionnaire by telephone that did not contain information on medication use. These patients were excluded from the present analyses. Information regarding the diagnostic procedure was obtained via hospital records and family physicians. Patients in whom the diagnosis was considered probable or definite were included, as has been described previously [18]. Patients who were treated for a venous thrombosis but nevertheless had a negative diagnostic procedure ($n = 93$) were excluded, resulting in a total of 4538 patients.

Control subjects were partners of patients ($n = 3126$, 53%) or obtained via a random-digit-dialing (RDD) method ($n = 2788$, 47%); they were all aged 18–70 years. The RDD control subjects were recruited from the same geographical area as the patients, and were frequency matched to the patients on age and sex. The same exclusion criteria were applied for control subjects as for patients, resulting in 5914 participating control subjects [18]. Participants gave written informed consent. This study was approved by the Ethics Committee of the Leiden University Medical Centre, Leiden, the Netherlands.

Participants were asked to fill in a standardized questionnaire within a few weeks after inclusion in the study. The index date was defined as the date of venous thrombosis event for the patients, and the date of completing the questionnaire for the control subjects. The questionnaire provided information on atherosclerotic and other diseases, weight, height, the use of medication, and risk factors for venous thrombosis, such as surgery and malignancies in the period prior to the index date. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Atherosclerotic disease was defined as

current angina pectoris or a history of a transient ischemic attack, stroke or myocardial infarction.

The use of medications in the 12 months before the index date was self-reported in the questionnaire. Month and year of start and end of therapy were asked for each type of medication. Both brand names and active components were reported. Current users were those individuals who used their medication at the time of the venous thrombosis (patients) or at the time of filling in the questionnaire (control subjects). Duration of medication use was calculated in months. Participants who did not provide the start date of use were excluded from the analysis for duration of treatment. Discharge letters of patients who did not provide a date of use were used to confirm medication use at the time of the thrombosis. Patients who started to use medication after the index date were considered to be non-users. If no end date was reported, participants were considered to have used the medication at the time of the index date. Lipid-lowering medication exposure was divided into two groups: statin therapy (HMG-CoA reductase inhibitors, simvastatin, pravastatin, atorvastatin, rosuvastatin, or fluvastatin), and other lipid-lowering therapy (colestipol, colestyramin, acipimox, bezafibrate, ciprofibrate, or gemfibrozil). Use of oral antiplatelet therapy (acetylsalicylic acid or aspirin, calcium carbasalate, clopidogrel, or dipyridamole) and use of vitamin K antagonists (coumarins) before the index date were also extracted from the questionnaire and discharge letters. When patients did not report the date of vitamin K antagonist use, it was assumed that vitamin K use started after the thrombosis. These patients were considered to be non-users.

Statistical analyses

To determine whether exposure to the different types of medications was associated with a risk reduction for venous thrombosis as compared with individuals who did not use any of these therapies, odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated as estimates of relative risk. Adjustment for potential confounding effects, such as age, sex, BMI and atherosclerotic disease, and use of other therapies, was performed by unconditional logistic regression.

Two sensitivity analyses were performed. The aim of the first sensitivity analysis was to rule out a healthy user effect, as individuals seeking preventive medication may differ in health status from those who do not. In this analysis, we only included statin or antiplatelet medication users with a clear indication for therapy, that is, atherosclerotic disease (relatively sick participants), and compared these users to those who did not use statin or antiplatelet medication (non-users) without atherosclerotic disease (relatively healthy participants).

A second sensitivity analysis was performed in very healthy individuals without any comorbidities, that is, no malignancy, diabetes, thyroid, kidney or lung diseases, rheumatoid arthritis and multiple sclerosis or atherosclerotic disease, as a previous report could not find a beneficial effect of statin therapy among patients with these diseases [19]. SPSS version 12.0.1 for

Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Characteristics of the 4538 patients and 5914 control subjects are shown in Table 1. No differences were found for age and sex between patients and control subjects. Patients had a slightly higher BMI, and more often had atherosclerotic disease as compared with control subjects.

Within the control group, statin and antiplatelet users were more often male (55.6%) than non-users (45.4%), and most statin and antiplatelet drug users were over 50 years of age (87.5%). In this age group, current statin and antiplatelet drug users were more often obese (BMI > 30 kg m^{-2}, 22.9% vs. 15.0%), and more often had atherosclerotic disease (35.2% vs. 1.8%) and diabetes (17.3% vs. 4.3%), but malignancy (9.6% vs. 7.8%) and surgery (10.8% vs. 8.2%) were as frequent in users as in non-users. Statin users more often had diabetes, and were more often obese as compared with antiplatelet drug users; however, the latter group more often had atherosclerotic disease.

Lipid-lowering medication

Of the patients, 154 currently used statins (3.3%), as did 354 of the control subjects (5.7%) (Table 2). Median duration of statin therapy among patients was 25.0 months (range 2–313), and that among control subjects was 29.5 months (range 2–265). Current use of statins was associated with a 45% reduced risk of venous thrombosis (OR 0.55; 95% CI 0.46–0.67) as compared to non-use (Table 2). Adjustment for age, sex, BMI, atherosclerotic disease and the use of antiplatelet therapy or vitamin K antagonists led to a more pronounced protective effect of statins (OR$_{adj}$ 0.45; 95% CI 0.36–0.56). Further adjustment for malignancy, diabetes and surgery did not result in a different estimate (OR$_{adj}$ 0.46; 95% CI 0.37–0.58). Current use of other lipid-lowering medications was not associated with a reduced risk of venous thrombosis (OR 0.88; 95% CI 0.46–1.71); OR fully adjusted for age, sex, BMI, atherosclerotic disease, statin, antiplatelet therapy or vitamin K antagonists was 1.22 (95% CI 0.62–2.43).

All types of statins were associated with a similarly reduced risk of venous thrombosis (Table 3). Use of pravastatin showed a more beneficial effect than simvastatin use (OR$_{adj}$ pravastatin as compared with simvastatin 0.59; 95% CI 0.31–1.11). Overall duration of statin therapy did not affect thrombosis risk, with ORs of 0.50 (95% CI 0.27–0.91) for those who started statins in the 2–6 months before the index date and 0.49 (95% CI 0.37–0.66) for those who had used statins for at least 2 years (test for trend P = 0.36). The risk reduction associated with statin therapy among men (OR$_{adj}$ 0.38; 95% CI 0.29–0.51) was slightly more pronounced than the risk reduction in women (OR$_{adj}$ 0.47; 95% CI 0.34–0.65). Similarly, the risk among those over 60 years of age (OR$_{adj}$ 0.32; 95% CI 0.23–0.45) was more pronounced than the risk reduction in those below 60 years of age (OR$_{adj}$ 0.53; 95% CI 0.40–0.71). Among those without atherosclerotic disease (OR$_{adj}$ 0.41; 95% CI 0.32–0.53) or any comorbidities (OR$_{adj}$ 0.43; 95% CI 0.29–0.65), risk reductions were similar. The risk reduction for PE with statin therapy was slightly less (OR$_{adj}$ 0.56; 95% CI 0.43–0.75) than the risk reduction for DVT (OR$_{adj}$ 0.31; 95% CI 0.23–0.42). When we contrasted patients with each of the two control groups separately, current statin therapy was associated with reduced risks for both comparisons: RDD controls, OR$_{adj}$ 0.35 (95% CI 0.27–0.44); and partner controls, OR$_{adj}$ 0.47 (95% CI 0.37–0.60). Among those with artherosclerotic disease, the risk reduction with statins was 0.47 (95% CI 0.31–0.71).

Antiplatelet therapy

Among the patients, 119 currently used antiplatelet therapy (2.3%), as did 203 of the control subjects (3.4%) (Table 2). Nearly all of them were treated with aspirin (97%). Current antiplatelet therapy use was associated with a 23% reduced risk of venous thrombosis (OR 0.76; 95% CI 0.60–0.95) as compared to non-use. Adjustment for age, sex, BMI, atherosclerotic disease, statin therapy, other lipid-lowering medication or vitamin K antagonists led to a slightly stronger protective effect of antiplatelet therapy (OR$_{fully\ adj}$ 0.56; 95% CI 0.42–0.74). Further adjustment for malignancy, diabetes and surgery did not result in a different estimate. ORs were lower in men (OR$_{adj}$ 0.49; 95% CI 0.34–0.70) than in women (OR$_{adj}$ 0.60; 95% CI 0.38–0.95), and for PE (OR$_{adj}$ 0.51; 95% CI 0.35–0.74) than for DVT (OR$_{adj}$ 0.61; 95% CI 0.43–0.87). Among those with atherosclerotic disease, the risk reduction with aspirin was 0.40 (95% CI 0.26–0.60).

Table 1 Characteristics of patients and control subjects, all at the time of the thrombosis or the index date

	Patients (*n* = 4538)	Controls (*n* = 5914)
Age [years; median (5th–95th percentile)]	49.6 (25.7–67.8)	48.3 (25.7–66.8)
Sex [women; *n* (%)]	2461 (54.2)	3181 (53.8)
BMI [kg m^{-2}; median (5th–95th percentile)]	26.2 (19.9–36.6)	25.0 (19.6–33.5)
Atherosclerotic disease, *n* (%)	230 (5.1)	200 (3.4)
Self-reported medication use, *n* (%)	2925 (64.5)	2941 (49.7)
Malignancies, *n* (%)	572 (12.6)	275 (4.6)
Diabetes, *n* (%)	183 (4.0)	198 (3.3)
Surgery, *n* (%)	1069 (23.6)	472 (8.0)
DVT, *n* (%)	2670 (58.9)	–
PE, *n* (%)	1583 (35.0)	–
DVT + PE, *n* (%)	285 (6.1)	–

BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2 Association of statin, other lipid-lowering or antiplatelet therapy or vitamin K antagonists and the risk of venous thrombosis

Lipid-lowering medication	Patients ($n = 4538$)	Controls ($n = 5914$)	OR (95% CI)	OR (95% CI)*	OR (95% CI)[†]	OR (95% CI)[‡]
Statins						
Non-users	4384	5560	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Users	154	354	0.55 (0.46–0.67)	0.50 (0.42–0.62)	0.41 (0.33–0.51)	0.45 (0.36–0.56)
Other lipid-lowering medication						
Non-users	4523	5892	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Users	15	22	0.88 (0.46–1.71)	0.90 (0.46–1.74)	0.84 (0.43–1.64)	1.22 (0.62–2.43)
Oral antiplatelet therapy						
Non-users	4419	5711	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Users	119	203	0.76 (0.60–0.95)	0.70 (0.56–0.89)	0.49 (0.37–0.65)	0.56 (0.42–0.74)
Vitamin K antagonists						
Non-users	4527	5880	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Users	11	34	0.42 (0.21–0.83)	0.41 (0.21–0.81)	0.37 (0.19–0.74)	0.46 (0.23–0.92)

CI, confidence interval; OR, odds ratio. *ORs adjusted for age, sex and body mass index (BMI) (kg m^{-2}). [†]ORs adjusted for age, sex, BMI (kg m^{-2}) and atherosclerotic disease. [‡]ORs adjusted for age, sex, BMI (kg m^{-2}), atherosclerotic disease, and the other medications.

Vitamin K antagonists

Vitamin K antagonists were seldom used prior to the index date. Their use was associated with a more than 50% reduced risk of venous thrombosis (OR adjusted for age, sex, BMI, atherosclerotic disease, statin therapy, other lipid-lowering medication or antiplatelet therapy 0.46; 95% CI 0.23–0.92). Further adjustments did not result in a different risk estimate.

Combinations of therapy

Statin therapy, other lipid-lowering medication, antiplatelet therapy and vitamin K antagonists were often prescribed simultaneously. When adjusted for age, sex and BMI, use of statin therapy only (OR 0.58; 95% CI 0.46–0.73) and vitamin K antagonists only (OR 0.56; 95% CI 0.24–1.30) were both associated with a reduced risk of venous thrombosis as compared to those who did not use statin, vitamin K antagonists, other lipid-lowering medication or antiplatelet therapy. Other lipid-lowering medication (OR$_{adj}$ 1.41; 95% CI 0.51–3.90) and antiplatelet therapy (OR$_{adj}$ 0.96; 95% CI 0.71–1.29) were not associated with a decreased thrombosis risk (Table 4). After adjustment for atherosclerotic disease, risks were further reduced. Other lipid-lowering medication use remained associated with a higher risk of venous thrombosis. Simultaneous use of therapy was associ-

Table 3 Association of different types of statin therapy and the risk of venous thrombosis

	Patients[†]	Controls	OR (95% CI)*	OR (95% CI)
Non-users	4384	5560	1 (reference)	
Type of statin				
Simvastatin	69	144	0.51 (0.38–0.69)	1 (reference)
Atorvastatin	61	136	0.48 (0.35–0.65)	0.88 (0.57–1.35)
Pravastatin	18	53	0.34 (0.20–0.65)	0.59 (0.31–1.11)
Rosuvastatin	3	11	0.33 (0.09–1.21)	0.45 (0.12–1.77)
Fluvastatin	7	10	0.81 (0.31–2.14)	1.51 (0.54–4.27)

CI, confidence interval; OR, odds ratio. *ORs adjusted for age, sex, body mass index (kg m^{-2}) and atherosclerotic disease. [†]Four patients used more than one type of statin.

ated with the largest reduction in risk for both combinations of statin with antiplatelet therapy (OR$_{adj}$ 0.38; 95% CI 0.25–0.57), and statin therapy with vitamin K antagonists (OR$_{adj}$ 0.21; 95% CI 0.06–0.74).

Sensitivity analyses

Two sensitivity analyses were performed to rule out a possible 'healthy user effect'. First, relatively sick participants with atherosclerotic disease who used statins had a lower risk of venous thrombosis than relatively healthy participants who were non-users without atherosclerotic disease (OR$_{adj}$ 0.53; 95% CI 0.43–0.65). However, antiplatelet therapy did not reduce venous thrombosis risk in this high-risk population with a clear indication for therapy (OR 0.90; 95% CI 0.65–1.24). Second, in very healthy participants without diseases, statin therapy use was still associated with a reduced risk (OR$_{adj}$ 0.44; 95% CI 0.29–0.67), which again was not the case for antiplatelet therapy (OR$_{adj}$ 0.95; 95% CI 0.50–1.77).

Discussion

Individuals who used statin therapy or vitamin K antagonists were found to have an almost 60% reduced risk of venous thrombosis. This risk reduction was similar in users of all different types of statins. Other lipid-lowering therapy did not reduce the risk of venous thrombosis. Antiplatelet therapy seemed to reduce the risk of venous thrombosis, but this effect was largely explained by a so-called healthy user effect, which will be discussed below.

Lipid-lowering medication

Our results confirm the results of previous studies suggesting similar reductions in venous thrombosis risk with statin therapy [12–15]. In the HERS study, the use of statins was associated with a 50% reduced risk of venous thrombosis [12], and in a Canadian cohort study, the risk reduction was 22% as compared to non-users [13]. One drawback of these studies was

Table 4 Combination of statin, antiplatelet and vitamin K antagonists and the risk of venous thrombosis

Medication	Patients	Controls	OR (95% CI)*	OR (95% CI)[†]
Non-users	4281	5434	1 (reference)	1 (reference)
Only one therapy				
Statin therapy only	115	226	0.58 (0.46–0.73)	0.49 (0.39–0.62)
Other lipid-lowering therapy only	8	7	1.41 (0.51–3.90)	1.44 (0.52–4.00)
Oral antiplatelet therapy only	85	101	0.96 (0.71–1.29)	0.62 (0.45–0.87)
Oral vitamin K antagonists only	8	18	0.56 (0.24–1.30)	0.49 (0.21–1.15)
Simultaneous use				
Statin therapy and other lipid-lowering therapy	4	10	0.52 (0.16–1.17)	0.46 (0.14–1.53)
Statin therapy and oral antiplatelet therapy	31	96	0.38 (0.25–0.57)	0.21 (0.13–0.32)
Statin therapy and vitamin K antagonists	3	16	0.21 (0.06–0.74)	0.14 (0.04–0.47)
Other lipid-lowering therapy and antiplatelet therapy	2	0	Could not be estimated	
Statin therapy, other lipid-lowering therapy and oral antiplatelet therapy	1	5	0.23 (0.03–1.96)	0.12 (0.01–1.08)

CI, confidence interval; OR, odds ratio. None of the participants used a combination of oral vitamin K antagonists and antiplatelet therapy. *ORs adjusted for age, sex and body mass index (BMI) (kg m^{-2}). [†]ORs adjusted for age, sex, BMI (kg m^{-2}) and atherosclerotic disease.

that they included a selective population; in HERS, only postmenopausal women with coronary disease were included, whereas the Canadian cohort study included a rather healthy (no malignancy or cardiovascular disease) population of over 65 years of age. One study even suggested that statin therapy only would decrease the risk of provoked thrombosis, but not of idiopathic thrombosis [19]. Similar risk reductions (58%) for venous thrombosis with statin therapy were observed in two other case–control studies [14,15].

As our study was large, we could study the effects of statins in more detail. One previous study [15] showed that only simvastatin reduced the risk of venous thrombosis, and there was even a suggestion of an increased risk of venous thrombosis for those using pravastatin. We showed that all different types of statins seemed to reduce the risk of venous thrombosis. Pravastatin appeared to be slightly more beneficial than simvastatin. We did not find an association between the duration of statin therapy and the risk of venous thrombosis. Short-term and long-term statin therapy equally reduced the risk of venous thrombosis, suggesting an immediate effect of statins. Unfortunately, we did not have any information regarding the dose of medication. One study showed that high-dose statin therapy seemed to be more beneficial than low-dose statin therapy [15].

We have not found any suggestion of a possible protective effect of the use of other lipid-lowering medications, thereby confirming the results of other studies [14,15] and even a randomized controlled trial on the effects of fenofibrate [20]. Nevertheless, an earlier study showed that high triglyceride levels are associated with an increased risk of venous thrombosis [21], suggesting that lipid-lowering might decrease venous thrombosis risk. Furthermore, another study has shown that fibrates decrease the levels of fibrinogen, whereas statins do not [22]. Therefore, we do not have an explanation for this increased risk, besides a possible sharing of risk factors between those receiving other lipid-lowering medications and those with a high risk of venous thrombosis. The number of individuals treated with fibrates in our study was low, as statin therapy is the first recommended therapy in the Netherlands.

Antiplatelet therapy

Previous studies have shown that the use of antiplatelet therapy is associated with a 22% risk reduction for recurrent athero-sclerotic disease [16]. Conversely, aspirin has been shown to be less effective in preventing first atherosclerotic disease (risk reductions of 12–14%) [17]. A review showed that in patients with a high risk of venous thrombosis, such as surgery patients, the use of antiplatelet therapy is associated with a reduction of the risk of venous thrombosis of approximately 30% [23]. Regarding first unprovoked venous thrombotic events, a relatively small case–control study revealed risk reductions of up to 50% associated with antiplatelet therapy [24]. However, in a long-lasting randomized controlled trial among apparently healthy women, the risk of venous thrombosis was only slightly attenuated by low-dose aspirin [25]. Our population-based study confirms these results. We also showed that antiplatelet therapy seemed to be effective among a high-risk group (only those with arterial thrombosis) but not in those with a low risk. Furthermore, sensitivity analyses seem to suggest that the effect may be introduced by confounding by a so-called healthy user effect; that is, those who choose to use aspirin for primary prevention are healthy, health-conscious individuals.

When different studies are compared, case–control studies seem to show a larger beneficial effect of statins than was found in cohort studies. Cohort studies have the drawback that they usually assess indicators at baseline, long before the occurrence of the disease, resulting in a possible dilution of the effect when individuals have stopped or started therapy during follow-up. Case–control studies have the benefit of gathering information about medication use just prior to the thrombo-sis. As there is a time lag in cohort studies between assessment of medication use and the event, case–control studies might be better for showing the association between medication use and the risk of venous thrombosis. Case–control studies have the drawback of recall bias. In our study, medication use was assessed via self-report, and we did not have the possibility of confirming medication use via pharmacy records. Therefore, patients might have recalled their medication differently from

control subjects. However, in the Netherlands, statins and low-dose aspirin require a doctor's prescription, and we expect that both patients and control subjects reported use of these specific medications. Therefore, we do not believe that misclassification, if present, would have had a large impact. Furthermore, if patients had reported their treatment more accurately than the control subjects, this would have resulted in an underestimation of the real effect of statins and antiplatelet therapy.

Atherosclerotic disease has been described as a potential risk factor for venous thrombosis [26–28]. A debate as to whether they share the same risk factors or whether having atherosclerotic disease is a risk factor itself is still ongoing [29]. If atherosclerotic disease is indeed a risk factor, this might distort the association between statins, antiplatelet therapy and venous thrombosis, which is the reason why we adjusted for atherosclerotic disease. The simultaneous use of comedications may also influence the risk. After adjustments, the beneficial effect of statins, therapy with antiplatelet drugs or vitamin K antagonists was not affected by the use of other medications. Simultaneous use of oral vitamin K antagonists and statins showed the largest reduction in risk.

It has been suggested that the beneficial effect of statins and antiplatelet therapy other than on atherosclerotic disease may be explained by the so-called 'healthy user effect' [30–33]. This effect would occur when those with a risk profile leading to a reduced risk of thrombosis would preferentially seek treatment with statins or antiplatelet therapy. Furthermore, patients regularly using statins or antiplatelet therapy for preventive reasons may have a healthier lifestyle and may be more compliant users of medications, factors that are known to lead to overoptimistic estimates of effects [33]. We found no indication of a healthy user effect for statin therapy, as users were less healthy than non-users, being more often obese and more often having diabetes. Furthermore, we performed a sensitivity analysis comparing the risk in unhealthy users of statin therapy (only those with atherosclerotic disease) with that in healthy non-users. As the risk of venous thrombosis was still decreased, this contradicts a possible healthy user effect for statin therapy. We did find indications that the healthy user effect may explain the effect of antiplatelet therapy, as the sensitivity analyses largely removed the effect of antiplatelet therapy on the risk of venous thrombosis.

In conclusion, our data suggest a protective effect of statin therapy regarding the risk of venous thrombosis, independent of age, sex, BMI and atherosclerotic disease and the use of comedication. Although antiplatelet therapy also seemed to reduce venous thrombosis risk, this effect might be largely explained by a healthy user effect.

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Disclosure of Conflict of Interests

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