The increased risk of arterial cardiovascular disease after venous thrombosis is determined by common etiologic factors

Short title: Etiology of CVD after VT

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KEY POINTS

- Patients with venous thrombosis have an increased risk of subsequent arterial cardiovascular disease compared with control subjects.

- The increased risk of arterial cardiovascular disease in these patients can be explained by etiologic factors leading to both diseases.
ABSTRACT

Patients with venous thrombosis (VT) have an increased risk of subsequent arterial cardiovascular disease (CVD), but the underlying pathophysiology is unclear.

Using data from the MEGA follow-up study, 4480 patients with VT, 2926 partner controls and 2638 random digit dialing (RDD) controls were followed between 1999-2008. Incidence rates and hazard ratios (HR) with 95% confidence intervals (95%CI) of CVD (defined as myocardial infarction or ischemic stroke) were calculated for patients versus controls. Measurable confounders (age, sex, BMI, smoking, chronic disease, malignancy, genetic thrombophilia and procoagulant markers) were adjusted for when comparing patients with RDD controls. Unmeasured lifestyle-related factors were additionally considered by comparing patients with their partners. Over a median follow up time of 5 years, 124 CVD events occurred. Incidence of CVD per 1000 person years was 3.2 (95%CI, 2.5-4.0) in patients, 2.2 (95%CI, 1.5-3.0) in partners and 1.6 (95%CI, 0.9-2.6) in RDD controls. Crude HR was 2.2 (95%CI, 1.2-3.8) in patients compared with RDD controls and 1.5 (95%CI, 1.0-2.3) compared with partners. After adjustment for all abovementioned confounders, these risks attenuated to: 1.8 (95%CI, 0.8-4.2) and 1.3 (95%CI, 0.7-2.5). In conclusion, individuals with VT had an increased risk of CVD. This could be explained by common etiologic factors.
INTRODUCTION

Venous thrombosis and arterial cardiovascular disease have traditionally been seen as two separate diseases, each with their own risk factors and pathophysiological mechanisms. In the past decade, this notion has been contested. In 2003 it was shown that patients admitted to hospital with unprovoked venous thrombosis had a higher prevalence of atherosclerosis than age- and sex-matched hospital controls. A large population-based study in Denmark also found individuals with venous thrombosis to be at a 2-fold increased risk of arterial cardiovascular disease compared with controls. These findings have since been confirmed for individuals with unprovoked venous thrombotic events.

Whether venous thrombosis is causally associated with arterial cardiovascular disease is under debate. Two prospective population-based cohort studies, the ARIC (Atherosclerosis Risk in Communities) and the CHS (Cardiovascular Health Study), failed to confirm the earlier found association between atherosclerosis and venous thrombosis. Furthermore, the increased risk of arterial cardiovascular disease after venous thrombosis could be confounded by shared risk factors. Age, sex, an increased body mass index (BMI), smoking, chronic disease, malignancy and (genetic) thrombophilia have all been found to increase the risk of both venous thrombosis and arterial cardiovascular disease. However, either, due to a lack of information on classical cardiovascular risk factors (apart from age and sex) or due to a broad definition of arterial cardiovascular disease (e.g. including otherwise unexplained death, angina, transient ischemic attack and angioplasty), no study has yet provided estimates of the risk of myocardial infarction and ischemic stroke after venous thrombosis adjusted for shared risk factors. Also, other health determinants that may affect both the risk of venous thrombosis and arterial
cardiovascular disease, such as socioeconomic status, diet and alcohol consumption have not previously been taken into account.\textsuperscript{12-15}

In a large prospective cohort study (n >10 000), we aimed to assess the risk of arterial cardiovascular disease in venous thrombosis patients compared with two separate control groups without a history of venous thrombosis: random digit dialing controls and partners of patients. When comparing patients with random digit dialing controls, we adjusted for the measurable confounders age, sex, BMI, smoking, chronic disease, malignancy and thrombophilia by multivariate analysis. By comparing patients with their partners, some unmeasured health determinants were additionally taken into account, as partners generally share a similar lifestyle and socioeconomic status.\textsuperscript{16}
METHODS

Study design

Between March 1999 and September 2004, consecutive patients aged 18-70 years with a first deep vein thrombosis or pulmonary embolism were included in the Multiple Environmental and Genetic Assessment of risk factors (MEGA) study from six anticoagulation clinics. In the Netherlands, anticoagulation clinics are regionally organized and all patients with venous thrombosis living in a certain area are monitored by the same clinic, regardless of the hospital they are admitted to or the physician who starts the treatment. Eighty-six percent of eligible patients were willing to participate in the MEGA study. Partners of patients were invited to participate as controls if they were aged 18-70 and had no history of venous thrombosis. From January 2002 to September 2004, additional controls were recruited by random digit dialing (RDD). All participants provided informed consent in accordance with the Declaration of Helsinki. The MEGA study was approved by the medical ethics committee of the Leiden University Medical Center and has been described in detail elsewhere.17,18

Data collection

Participants completed a detailed questionnaire on risk factors for venous thrombosis. Items covered in the questionnaire included surgery, pregnancy, plaster cast immobilization and hospitalization in the three months before the index date, oral contraception or postmenopausal hormone therapy use in the month before the index date, chronic disease (defined as liver disease, kidney disease, rheumatoid arthritis or multiple sclerosis) and malignancy in the five years before the index date. The index date
was defined as the date of diagnosis of venous thrombosis for patients and their partners and the date of completing the questionnaire for RDD controls. Self-reported information was also obtained on weight, height and smoking status. BMI was calculated by dividing weight (in kg) by height squared (m²).

At least three months after discontinuation of anticoagulation, or during anticoagulant therapy in patients who continued this for over one year, patients and controls visited the anticoagulation clinic for an interview and a blood sample to obtain DNA. The blood samples were used to assess levels of coagulation factors, and the presence or absence of common genetic risk factors. All assays were performed in automated machines by laboratory technicians who were unaware of the case-control status of the samples. A detailed description of the assays can be found elsewhere.19-23

Follow-up
Between February 2007 and May 2009, the vital status of all MEGA participants was acquired from the Dutch population register, as has been described previously.24 For participants who had died, both primary and secondary causes of death were retrieved from the national registry of death certificates. Causes of death were encoded according to the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM). In 2011, participants of the MEGA study were linked to the Dutch Hospital Data registry to identify individuals with an arterial cardiovascular event. This registry has provided nationwide electronic coverage of data on all hospital admissions since 1995. Data are collected in virtually all general and university hospitals and most specialized clinics. For each hospital admission, information on the date of admission and
discharge, diagnoses and surgical procedures is available. These diagnoses are encoded according to ICD-9-CM. A previous study comparing a random sample of the hospital admissions in the Dutch Hospital Data registry to information from hospital records showed that 99% of the personal, admission, and discharge data and 84% of principal diagnoses were correctly encoded.\textsuperscript{25} The percentage of correctly encoded myocardial infarctions has since been found to be almost 100%.\textsuperscript{26} Participants of the MEGA study were linked to this registry through date of birth, sex and postal code. Individuals with information leading to more than one person (e.g. twins or individuals with the same date of birth in the same postal area) or to nobody at all (immigrants, visitors) were excluded. Of the 11 253 MEGA participants, 10 178 (4539 patients, 2967 partners and 2672 RDD controls) could be uniquely linked to the registry.

After linkage to the Dutch Hospital Data registry, all MEGA participants with an acute arterial cardiovascular event were identified. Acute arterial cardiovascular disease was defined as myocardial infarction (ICD-9-CM codes 4100-4109, ICD-10-CM code I21) or ischemic stroke (ICD-9-CM codes 433, 4330-4333, 4338, 4339, 434, 4340, 4341 and 4349, ICD-10-CM code I63, I64). We specifically chose to include these two cardiovascular diseases only as patients with myocardial infarction or ischemic stroke will always have been hospitalized due to the disease severity, and were therefore definitely captured by the Dutch Hospital Data registry (in contrast to, for example, transient ischemic attacks). Individuals with arterial cardiovascular disease diagnosed between 1995 and the index date, and individuals for whom either the date of inclusion in the study or the date of diagnosis was unknown, were excluded.
Statistical analysis

We estimated the absolute risk of incident arterial cardiovascular disease in venous thrombosis patients versus controls by dividing the number of arterial cardiovascular events by the observation time. The observation time was defined as the time between the index date and the end of follow-up. Follow-up ended on the date of a first arterial cardiovascular event, the date of recurrent venous thrombosis, the date of death or the date on which the vital status was retrieved (between February 2007 and May 2009), whichever came first. The 95% confidence intervals (95% CIs) around the incidence rates were based on a Poisson distribution.

Kaplan-Meier curves were used to plot the survival for patients versus controls (Figure 1). As we observed that the Kaplan-Meier curves crossed around 1 year of follow-up, the assumption for proportional hazards was not met over the entire observation period. Patients with acute venous thrombosis are treated with oral anticoagulant therapy (i.e. vitamin K antagonists) for at least some time to prevent a recurrent event. However, vitamin K antagonists are also highly effective for the prevention of arterial cardiovascular disease and their use could explain this finding. We therefore used an extended Cox regression model to compare the risk of arterial cardiovascular disease in patients and controls, and included anticoagulant therapy for treatment of acute venous thrombosis as a time-dependent covariate.

The effect of measured confounders was taken into account through adjustments for age (categorical: deciles), sex, BMI (categorical: <25 kg/m², 25-30 kg/m², >30 kg/m²), smoking history, chronic disease, malignancy, genetic thrombophilia (factor V
Leiden, prothrombin G20210A and blood group non-O) and procoagulant markers (fibrinogen, factor VIII and C-reactive protein). As the distribution of C-reactive protein was skewed to the left, the log transformation of this variable was used. Fibrinogen and factor VIII were normally distributed and were added as continuous variables. Other cardiovascular risk factors (i.e. diabetes mellitus, hyperlipidemia) were not considered as these have not been found to be associated with venous thrombosis. Unmeasured lifestyle-related confounders were additionally taken into account by comparing patients with the partner controls, as partners generally share the patients’ lifestyle.

Patients with deep vein thrombosis and pulmonary embolism were studied separately. In addition, we analyzed myocardial infarction and ischemic stroke separately. Participants with ischemic stroke were excluded from the analysis of myocardial infarction and vice versa. Two participants (one patient and one partner control) experienced both myocardial infarction and ischemic stroke. They were included in both analyses with follow up time ending on the date of the event of interest.

It has been suggested that the risk of arterial cardiovascular disease is higher after an unprovoked venous thrombosis than after a provoked venous thrombosis. Therefore, we also analyzed individuals with unprovoked and provoked venous thrombosis separately. In addition, since the many provoking risk factors have varying levels of severity, the relation between arterial and venous disease was considered separately for subjects who reported exogenous hormone use (defined as oral contraception or postmenopausal hormone therapy), pregnancy, surgery, hospitalization and malignancy at the time of their venous event.
The diagnosis of a fatal arterial cardiovascular event may not always have been classified by objective methods. To explore whether fatal arterial cardiovascular events influenced our results, we performed a sensitivity analysis where fatal arterial cardiovascular events were censored.

Our study hypothesis and alternative explanations, as they are discussed above, are graphically summarized in the Supplemental Figure 1. All statistical analyses were performed with SPSS for Windows, release 14.0 (SPSS Inc, Chicago, Ill).
RESULTS
In total, 11,253 individuals were included in the MEGA study (Figure 2). Of these individuals, 1075 could not be linked to the Dutch Hospital Data registry. Of the 10,178 individuals remaining, 107 individuals were excluded as their arterial event occurred before the index date and 27 were excluded as either their index date or the date of diagnosis of arterial cardiovascular disease or recurrent venous thrombosis was unknown. 4480 patients, 2926 partner controls and 2638 RDD controls were available for analysis. Their clinical characteristics at enrollment are depicted in Table 1. In all groups there were slightly more women than men. RDD controls were slightly younger (46 years, range 18-70) than patients and their partners (both 49 years, range 18-70). Mean follow up time was 5.5 years in patients, 5.6 years in partner controls and 3.9 years in RDD controls. During follow-up 557 (12%) patients, 76 (3%) partner controls and 46 (2%) RDD controls died. Arterial cardiovascular disease was the cause of death in 24 patients, 6 partner controls and 1 RDD control.

In the patients, 72 arterial cardiovascular events occurred over a follow-up time of 22,423 person years, which led to an incidence rate of 3.2 per 1000 person years (95% CI, 2.5-4.0) (Table 2). The incidence rate of arterial cardiovascular disease was similar after a deep vein thrombosis: 3.4 per 1000 person years (95% CI, 2.5-4.5) and after a pulmonary embolism: 3.0 per 1000 person years (95% CI, 2.0-4.3). The incidence rate of myocardial infarction was higher, 2.4 per 1000 person years (95% CI, 1.8-3.2), than the incidence rate of ischemic stroke, 0.9 per 1000 person years (95% CI, 0.5-1.3). RDD controls had 16 arterial cardiovascular events over a follow-up time of 10,166 person years, corresponding to an incidence rate of 1.6 per 1000 person years (95% CI, 0.9-2.6).
Partner controls had 36 arterial cardiovascular events over 16,402 person years yielding an incidence rate of 2.2 per 1000 person years (95% CI, 1.5-3.0).

The hazard ratio of arterial cardiovascular disease during anticoagulation therapy was 0.6 (95% CI, 0.3-1.7) for patients compared with RDD controls and 0.7 (95% CI, 0.3-1.8) for patients compared with partner controls. The anticoagulation adjusted hazard ratio for arterial events compared with RDD controls was 2.2 (95% CI, 1.2-3.8). This risk estimate was not affected by adjustments for age, sex, BMI and smoking: 2.3 (95% CI, 1.2-4.3) or by additional adjustments for chronic disease and malignancy: 2.2 (95% CI, 1.2-4.2). When compared with partner controls, the hazard ratio of arterial cardiovascular disease adjusted for anticoagulation therapy was 1.5 (95% CI, 1.0-2.3). Again, adjustments for age, sex, BMI and smoking, 1.6 (95% CI, 1.0-2.4), and additional adjustment for chronic disease and malignancy, 1.5 (95% CI, 1.0-2.4), did not influence the risk estimate. The analysis restricted to patients with unprovoked venous thrombosis, and the analyses for the various provoking risk factors, revealed results that pointed into the same direction, except for patients who were pregnant (Table 3). The sensitivity analysis in which fatal arterial cardiovascular events were censored resulted in slightly lower relative risk estimates: 1.7 (95% CI, 0.8-3.4) compared with RDD controls and 1.3 (95% CI, 0.8-2.2) compared with partner controls (Table 4).

In a final analysis, we recalculated the risk of arterial cardiovascular disease in patients compared with controls, this time including genetic thrombophilia, procoagulant markers, or both, as covariates (Table 5). Further adjusting the above risk estimates for factor V Leiden, prothrombin G20210A and blood group non-O yielded risk estimates of 1.8 (95% CI, 0.9-3.6) compared with RDD controls and 1.4 (95% CI, 0.9-2.3) compared
with partner controls. Replacing the genetic factors with fibrinogen, factor VIII and C-reactive protein yielded similar results: 1.9 (95%CI, 0.8-4.4) and 1.4 (95%CI, 0.7-2.6), respectively. These results were virtually the same in a sensitivity analysis in which individuals who had been using anticoagulant therapy at the blood draw (n=271) were excluded, with hazard ratios of 1.8 (95%CI, 0.7-4.6) and 1.4 (95%CI, 0.7-2.6). Finally, after full adjustment for age, sex, BMI, smoking, chronic disease, malignancy, genetic thrombophilia and procoagulant markers, the risk estimates were: 1.8 (95%CI, 0.8-4.2) compared with RDD controls and 1.3 (95%CI, 0.7-2.5) compared with partner controls. Results were not different when continuous variables were used as categorical variable in the model rather than as continuous variables.
DISCUSSION

In this study, we found patients with venous thrombosis to have a 2.2-fold (95% CI, 1.2-3.8) increased risk of arterial cardiovascular disease compared with control subjects without venous thrombosis. This risk estimate was lowered (hazard ratio 1.5, 95% CI 1.0-2.3) when unmeasured lifestyle-related confounders were taken into account by comparing patients with their partners. After measured confounders (age, sex, BMI, smoking, malignancy, chronic disease, genetic thrombophilia and procoagulant markers) were additionally considered, the risk estimate was no longer increased in patients compared with partner controls (hazard ratio 1.3 (95% CI, 0.7-2.5). Thus, from our results, it seems that the relationship between venous thrombosis and subsequent arterial cardiovascular disease is not causal, but can be explained by common etiologic factors.

Our overall results are in line with findings of previous studies that showed patients with venous thrombosis to have an increased risk of subsequent arterial cardiovascular disease. In addition, the absolute risk of arterial cardiovascular disease after venous thrombosis found in our study (3.2 per 1000 person years) was the same as the absolute risk estimate previously shown by a systematic review: 3.2 per 1000 person years.\(^5\) However, to our knowledge, this is the first study to view the relationship between venous thrombosis and arterial cardiovascular disease whilst adjusting for both measured and unmeasured shared risk factors. Unlike most control groups, partners generally share the patients’ lifestyle. They are therefore likely to have a similar socioeconomic status, diet and level of alcohol consumption or other unknown factors which may affect the risk of both venous thrombosis and arterial cardiovascular disease.\(^12-15\) The fact that our fully adjusted risk estimates were no longer increased when patients were compared with their
partners, indicates that venous thrombosis and arterial cardiovascular disease are associated with the same risk factors, but are not causally related.

Two previous studies found a higher risk of arterial cardiovascular disease in the first year after venous thrombosis than in the years thereafter. However, in our study we found the opposite. A possible explanation for this difference could be that all of the patients who are included in the MEGA study had to survive long enough for a first visit to the anticoagulation clinic. Therefore, individuals who died shortly after the venous thrombotic event were not included in our study. If the cause of death in those individuals was arterial cardiovascular disease, we would have missed it. However, it is not likely that this can explain the discrepancy, as the largest published study on this issue by Sørensen et al did not include cardiovascular deaths in the analysis. Another explanation could be that the risk of arterial cardiovascular disease in the first year of follow-up is in fact lower. Indeed, a study performed by a different research group in our hospital (with an identical treatment program for venous thrombosis) also found that the absolute risk of arterial cardiovascular disease after venous thrombosis was low in the first year of follow-up. This can be understood since most patients with venous thrombosis are prescribed anticoagulant therapy to prevent a recurrent event. Considering that anticoagulant therapy is highly effective for the primary and secondary prevention of arterial cardiovascular disease, an increased risk in the first year after venous thrombosis seems unlikely, unless anticoagulation therapy was only given for a very short period. Furthermore, unlike our study, the results of Sørensen et al were partly driven by hemorrhagic stroke. As hemorrhagic stroke is a common complication of anticoagulant treatment, including this as a type of arterial cardiovascular disease would
overestimate the number of events in the first year after venous thrombosis. In the study of Van Schouwenburg et al., a broad definition of arterial cardiovascular disease was used which included sub acute ischemic heart disease and angioplasty. As patients are often admitted to hospital for a short time after venous thrombosis and closely monitored thereafter, it is possible that increased medicalization can explain the high number of arterial cardiovascular diagnoses made in the first year after venous thrombosis onset. This too would explain the difference in our findings compared with the study from Van Schouwenburg et al., as we only used hard endpoints.

The results of the analyses in which the outcomes myocardial infarction and ischemic stroke were analyzed separately seemed to yield different risk estimates according to whether the patient had experienced a deep vein thrombosis or a pulmonary embolism (Table 2). However, as numbers were small and confidence intervals were wide, these differential findings should be interpreted with caution.

As this is an observational study in which blood samples were collected after the venous thrombotic event, one could argue that levels of procoagulant markers in our study may have been affected by acute phase reactions. For instance, it may be possible that the venous event itself may have led to increases in procoagulant markers and subsequently increased the risk of arterial cardiovascular disease. However, we consider it unlikely that the effect of procoagulant markers was a result of venous thrombosis, as a previous study has shown that CRP, factor VIII and fibrinogen levels normalize within 3 months after the acute venous thrombotic event. In our study, procoagulant markers were obtained at least 3 months after the end of anticoagulant therapy, or, in case of long-term treatment with vitamin K antagonists, 1 year after venous thrombotic event onset.
By this time the effect of the acute-phase reaction will have worn off. Furthermore, our results were not affected by individuals using anticoagulant therapy at the blood draw, as a sensitivity analysis in which these individuals were excluded yielded similar results as our overall analysis.

Strengths of our study are that data were collected in the same manner for all participants and all venous thrombotic events were objectively diagnosed. It was therefore possible to compare the risk of arterial cardiovascular disease in patients versus all controls and versus the two control groups separately. Furthermore, the two control groups made it possible to take both measured and unmeasured lifestyle factors into account for the first time. A possible limitation of our study is the fact that arterial cardiovascular events were not objectively confirmed, but obtained from the Dutch Hospital Data registry. However, a previous study showed that the percentage of correctly encoded myocardial infarctions in this registry was almost 100%. In addition, although the exact percentage of correctly encoded ischemic strokes is unknown, it is unlikely that any misclassification in this diagnosis would have occurred differently in patients and controls. Another limitation is that numbers of arterial cardiovascular events in some subgroups were small. However, from the upper limits of the confidence intervals, it seems that, even if numbers had been larger, it is unlikely that risk estimates would have been much higher. In addition, as the MEGA study is one of the largest of its kind, the low numbers indicate that arterial cardiovascular disease after venous thrombosis is not a common occurrence, at least in this age group. In our study we did not have information on medication use during the follow up period. Patients with venous thrombosis can nowadays be treated with aspirin or statin to prevent a recurrent event.
As these medications are also effective against cardiovascular diseases, the risk of arterial cardiovascular disease could have been underestimated in our study. However, as the protective effect of aspirin and statin on recurrent venous thrombosis has only been discovered in recent years, whereas the patients in our study experienced a first venous thrombosis between 1999-2004, it is unlikely that patients would have received more aspirin or statin than control subjects. Nevertheless, we cannot rule out a slight underestimation of our risk estimates, as some patients could have been prescribed cardioprotective drugs more often than controls through increased medical attention following venous thrombosis. Finally, information on clinical characteristics and procoagulant markers was only obtained once. It is possible that characteristics such as weight and smoking status, and levels of procoagulant markers could have changed over time. This may explain why the fully adjusted risk estimate did not reach 1.0 (residual confounding). Future studies with multiple measurements could be useful to investigate this further.

In conclusion, we found individuals with venous thrombosis to have an increased risk of subsequent arterial cardiovascular disease. This could be explained by the presence of common etiologic factors.
ACKNOWLEDGEMENTS

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AUTHORSHIP

REJR performed the statistical analyses and drafted the manuscript. WML designed the analyses and revised the manuscript. LEF collected the data and revised the manuscript. FRR was responsible for the MEGA study concept and design and revision of the manuscript. SCC designed the analyses and revised the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

All authors declare no conflicts of interest.
Reference List


findings of the national conference on cardiovascular disease prevention. 


<table>
<thead>
<tr>
<th>Tabel 1. Clinical Characteristics</th>
<th>Patients (n=4480)</th>
<th>Partner Controls (n=2926)</th>
<th>RDD Controls (n=2638)</th>
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* Provoking risk factors include surgery, malignancy, immobilization, hormone use and pregnancy

RDD denotes random digit dialing, BMI denotes body mass index
Some data were missing for some participants in some subgroups
Continuous variables denoted as mean (range), categorical variables as number (%)
Table 2. Risk of arterial cardiovascular disease in patients with venous thrombosis

<table>
<thead>
<tr>
<th>Event of interest: overall arterial cardiovascular disease</th>
<th>Number of individuals</th>
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<th>No. of events</th>
<th>Incidence rate per 1000py (95%CI)</th>
<th>Adjusted HR* (95%CI)</th>
<th>Adjusted HR† (95%CI)</th>
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<table>
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<th>No. of events</th>
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<th>Adjusted HR* (95%CI)</th>
<th>Adjusted HR† (95%CI)</th>
<th>Adjusted HR‡ (95%CI)</th>
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<td>22363</td>
<td>54</td>
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<td>2.8 (1.2-6.3)</td>
<td>2.7 (1.2-6.1)</td>
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<td>2626</td>
<td>12993</td>
<td>35</td>
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<td>3.3 (1.6-7.0)</td>
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<td>9370</td>
<td>19</td>
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<tr>
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<td>22363</td>
<td>54</td>
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<td>1.6 (1.0-2.8)</td>
<td>1.6 (1.0-2.7)</td>
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<td>1.3 (0.7-2.6)</td>
<td>1.3 (0.6-2.5)</td>
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<th>No. of events</th>
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<th>Adjusted HR† (95%CI)</th>
<th>Adjusted HR‡ (95%CI)</th>
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RDD denotes random digit dialing, DVT: deep vein thrombosis, PE: pulmonary embolism, HR: hazard ratio, py: person years
* Adjusted for anticoagulaton therapy
† Adjusted for anticoagulation therapy, age, sex, BMI and smoking
‡ Adjusted for anticoagulation therapy, age, sex, BMI, smoking, chronic disease (defined as liver disease, kidney disease, multiple sclerosis or rheumatoid arthritis), malignancy
Table 3. Risk of arterial cardiovascular disease in patients with provoked and unprovoked venous thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Number of individuals</th>
<th>Obs years</th>
<th>No. Of events</th>
<th>Incidence rate per 1000py (95%CI)</th>
<th>Adjusted HR* (95%CI)</th>
<th>Adjusted HR† (95%CI)</th>
<th>Adjusted HR‡ (95%CI)</th>
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<td>10166</td>
<td>16</td>
<td>1.6 (0.9-2.6)</td>
<td>Reference</td>
<td>Reference</td>
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</tr>
<tr>
<td>Patients with unprovoked VT</td>
<td>2006</td>
<td>10022</td>
<td>36</td>
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<td>2.6 (1.4-4.9)</td>
<td>1.8 (0.9-3.7)</td>
<td>1.8 (0.9-3.6)</td>
</tr>
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<td>Patients with VT provoked by:</td>
<td>2474</td>
<td>12401</td>
<td>36</td>
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<td>2.0 (1.1-3.9)</td>
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<td>2.6 (1.2-5.4)</td>
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<td>OC or HRT use§</td>
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<td>6960</td>
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<td>935</td>
<td>0</td>
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<td>NA</td>
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<tr>
<td>Surgery‖</td>
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<td>3716</td>
<td>18</td>
<td>4.8 (2.9-7.7)</td>
<td>3.5 (1.6-7.4)</td>
<td>2.8 (1.2-6.4)</td>
<td>2.5 (1.1-6.0)</td>
</tr>
<tr>
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<td>3890</td>
<td>13</td>
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<td>2.3 (1.0-5.4)</td>
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<tr>
<td>Malignancy**</td>
<td>422</td>
<td>1255</td>
<td>8</td>
<td>6.4 (2.8-12.6)</td>
<td>4.3 (1.6-12.1)</td>
<td>2.1 (0.7-7.0)</td>
<td>2.0 (0.6-6.7)</td>
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<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Patients with unprovoked VT</td>
<td>2006</td>
<td>10022</td>
<td>36</td>
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<td>OC or HRT use§</td>
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<td>6960</td>
<td>9</td>
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<tr>
<td>Pregnancy</td>
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<td>163</td>
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<td>Surgery‖</td>
<td>731</td>
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</table>

RDD denotes random digit dialing, OC: oral contraception, HRT: hormone replacement therapy, HR: hazard ratio, py: person years

* Adjusted for anticoagulation therapy
† Adjusted for anticoagulation therapy, age, sex, BMI and smoking
‡ Adjusted for anticoagulant therapy, age, sex, BMI, smoking, chronic disease (defined as liver disease, kidney disease, multiple sclerosis or rheumatoid arthritis) and malignancy, where applicable
§ In the year before the index date
‖ In the three months before the index date
** In the five years before the index date
<table>
<thead>
<tr>
<th></th>
<th>Number of individuals</th>
<th>Obs years</th>
<th>No. Of events</th>
<th>Incidence rate per 1000py (95%CI)</th>
<th>Adjusted HR* (95%CI)</th>
<th>Adjusted HR† (95%CI)</th>
<th>Adjusted HR‡ (95%CI)</th>
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<td>1.3 (0.8-2.2)</td>
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RDD denotes random digit dialing, HR: hazard ratio, py: person years
* Adjusted for anticoagulant therapy
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RDD denotes random digit dialing, DVT: deep vein thrombosis, PE: pulmonary embolism, HR: hazard ratio, py: person years

* Adjusted for anticoagulation therapy, age, sex, BMI, smoking, chronic disease (defined as liver disease, kidney disease, multiple sclerosis or rheumatoid arthritis), malignancy
† Adjusted for anticoagulation therapy, age, sex, BMI, smoking, chronic disease, malignancy, factor V Leiden, prothrombin G20210A and blood group non-O
‡ Adjusted for anticoagulation therapy, age, sex, BMI, smoking, chronic disease, malignancy, factor VIII, fibrinogen and CRP
§ Fully adjusted for all abovementioned factors
Figure 1. Cumulative incidence of arterial cardiovascular disease in venous thrombosis patients, their partners and RDD controls

CVD denotes arterial cardiovascular disease, RDD denotes random digit dialing.
Figure 2. Flow chart of number of individuals included

MEGA participants
N=11253

Not uniquely identified
N=1075

Linked to national registry
N=10178

CVD before VT
n=107

Remaining
N=10071

No follow up time
N=27

Participants
N=10044

Patients
N=4480

Partner Controls
N=2926

RDD Controls
N=2638

CVD: arterial cardiovascular disease, RDD: random digit dialing, VT: venous thrombosis
The increased risk of arterial cardiovascular disease after venous thrombosis is determined by common etiologic factors