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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thromboembolic sequelae: a retrospective cohort study performed with routine healthcare data from the Netherlands

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ABSTRACT

Objectives Recent studies in referred populations of patients with superficial venous thrombosis (SVT) report risks of venous thromboembolic (VTE) sequelae (deep vein thrombosis or pulmonary embolism) as high as 25%. Likely, these estimates are lower in non-referred patients, but large-scale population-based studies are lacking. We aimed to estimate the incidence rate of SVT in primary care and quantify its risk of VTE sequelae.

Design A retrospective cohort study, using International Classification of Primary Care coding (K94.02) combined with free text searching (synonyms for SVT) to capture all SVT events. All patients were followed up for 3 months using manual free text searching.

Setting Primary care.

Participants All patients enlisted with general practitioners within the Utrecht General Practitioner Network between 2010 and 2016 (1 534 845 person-years follow-up).

Main outcome measures The incidence rate of SVT was expressed as the number of SVT events per 1000 person-years of follow-up and the 3-month cumulative incidence of VTE events was calculated. Logistic regression analysis was used to compare patients with SVT with and without VTE sequelae.

Results A total of 2008 SVT cases were identified, that is, an SVT incidence rate of 1.31 (95% CI 1.25 to 1.37) per 1000 person-years follow-up, with higher rates notably with increasing age. VTE sequelae occurred in 83 patients; 51 at the time of SVT diagnosis and 32 patients during follow-up (total cumulative incidence of 4.1%; 95% CI 3.3% to 5.1%), and were more frequent in those with an active malignancy (OR 2.19; 95% 0.97 to 4.95) and less frequent in those with varicose veins at baseline (OR 0.57, 95% CI 0.34 to 0.94).

Conclusion We found an incidence rate of SVT in primary care of 1.31 per 1000 person-years. The risks of VTE sequelae was relatively low at 4.1%, with the highest risk in patients with cancer and in those who experience an SVT in the absence of varicose veins.

Strengths and limitations of this study

- A limitation of this study is its retrospective nature, and thus the inability to fully adjust for provided anticoagulant treatment (although provided in a minority of patients) as well as lack of detailed information regarding superficial venous thrombosis (SVT) location (notably involvement of saphenofemoral junction) or imaging confirmation of (length of) SVT in all study patients.
- A potential advantage of our study is that—by addressing this research question in primary care—we bypassed the effect that patients with SVT that appear in research performed in secondary care are sicker or more likely to have an increased risk of thromboembolic sequelae.
- Thereby, our findings may reflect the burden of SVT in terms of thromboembolic risk more as present in the community care setting.

INTRODUCTION

Superficial thrombophlebitis—or superficial venous thrombosis (SVT)—is a local non-infectious inflammation of a superficial vein, caused by a thrombus. The diagnosis is usually based on clinical signs and symptoms—that is, a red, tender, swollen and palpable area along the course of a superficial vein—with confirmation on leg ultrasonography where needed. It has generally been regarded as a relatively benign and self-limiting disease. Recently, however, there is a growing attention to its associated venous thromboembolic (VTE) risk such as deep vein thrombosis (DVT) or pulmonary embolism (PE). For instance, a recent systematic review reported a weighted mean prevalence of concurrent DVT of 18.1% (95% CI 13.9% to 23.3%) and

6.9% (95% CI 3.9% to 11.8%) for concurrent PE at SVT diagnosis.[1] Also, the risk of propagation to DVT or PE in the 3 months following SVT diagnosis may be substantial, with reported estimates of at least 15%.[2–4] Not surprisingly, treatment with anticoagulation—either parentally (eg, fondaparinux) or orally (eg, rivaroxaban)—has been evaluated in randomised trials, with beneficial effects on reducing the risk of thromboembolic sequelae.[5 6]

Most studies on SVT risk and management, however, have been performed in selected, referred populations in a secondary healthcare setting. The limited number of studies performed in non-selected populations report a much lower risk of around 2.5% for propagation to DVT or PE after SVT diagnosis.[7 8] Differences in casemix between referred and non-selected patients with SVT are likely to contribute to these conflicting findings. In fact, in the aforementioned review of Di Minno *et al*, DVT presence at the time of SVT diagnosis ranged from 3.1% to 65.6% with higher prevalence in selected or referred populations.[9 10] Studies performed in non-selected patients were few, relatively small (including less then 200 patients) or reported little if any information on patient characteristics or prescribed treatment. Nevertheless, many (if not most) patients with SVT are first assessed and managed in primary or community care. Only a small selection, most likely the more severe cases, is referred to secondary care. Given that most current studies were performed in highly selected patient samples, the actual incidence of SVT in a community care setting remains unknown. Knowledge on thromboembolic risks in non-selected patients with SVT and identification of subgroups of patients with SVT at highest risk is needed to facilitate evidence-based anticoagulant treatment decisions for patients with SVT.

The objectives of this study were to quantify (1) the incidence rate (IR) of SVT in the community, (2) the short-term thromboembolic risks in these non-selected patients with SVT—both in terms of concurrent presence and propagation to DVT or PE. Finally, (3) we aimed to identify patient subgroups with the highest risk of VTE.

METHODS

Setting and participants

This study was conducted using healthcare data from the Utrecht General Practitioner Network database. This database contains anonymous routine healthcare data extracted from the electronic medical record (EMR) of 140 general practices in Utrecht and vicinity. The practice centres contributing to the database represent the average Dutch urban population.[11] The general practitioners (GPs) working in the centres are trained in correct disease coding (using the codes from the International Classification of Primary Care, ICPC) and have experience in EMR use and coding for

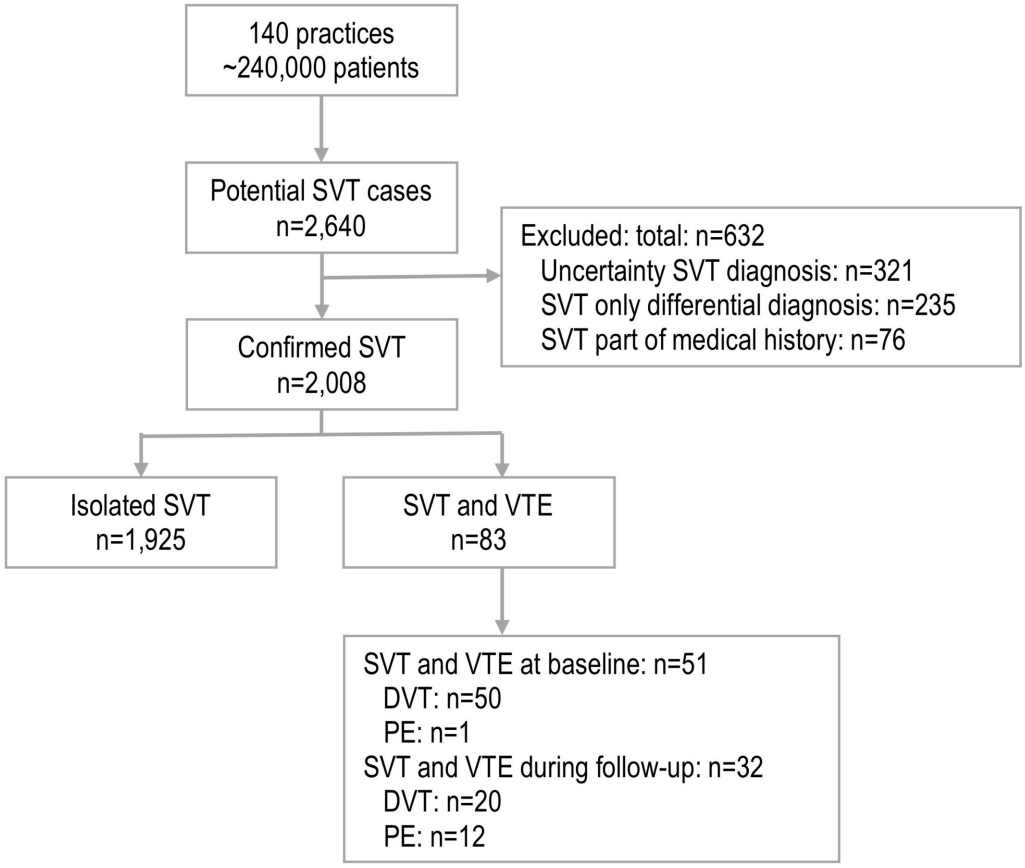

Figure 1 Flow chart of included patients. DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

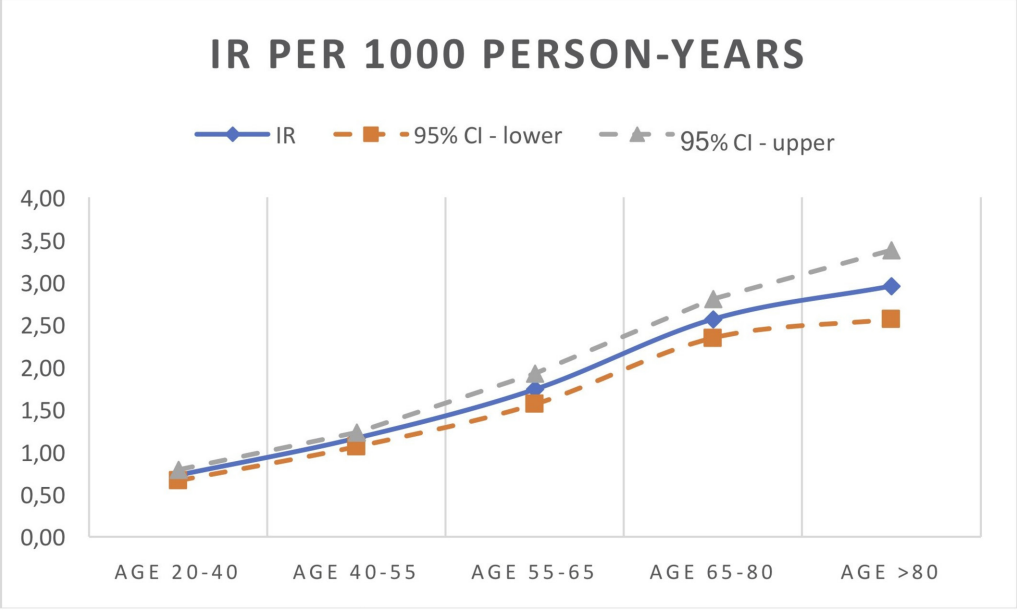

Figure 2 Incidence rate of superficial venous thrombosis according to age. IR, incidence rate.

an average period of 10 years. In the Netherlands, all citizens are registered with a GP, irrespective of cooperative care from a medical specialist, including patients living in a home for the elderly, but with the exception of those living in a nursing home or hospice. This study population is therefore a representative and complete sample of people from the community.

Study design and assessment of SVT and VTE

Using this database, all patient contacts with their GP were retrieved for the period 2010–2016 to detect new diagnoses of SVT, that is, 1 534 845 person-years follow-up. The EMRs were automatically scrutinised for the ICPC code of SVT (K94.02) in addition to automated 'free text searching' in all patient contacts using a variety of synonyms for SVT. SVT was deemed present if the GP clearly described signs and symptoms related to a new SVT diagnosis (typically red, tender, swollen and palpable area along the course of a superficial vein with or without a confirmation of the ICPC code K94.02). Patients were excluded if (1) such findings were not clearly reported leading to uncertainty of the SVT diagnosis; (2) SVT was only considered in differential diagnosis but finally 'ruled-out' (not managed accordingly) by the GP and/or (3) SVT was part of a patients' medical history rather than related to current and new complaints. Next, in all patients with a confirmed SVT diagnosis using our definitions, the following baseline characteristics were collected: age, gender, a history of cardiac and pulmonary diseases, diabetes, and the presence or absence of active malignancy, varicose veins or pregnancy at the time of the clinical assessment.

After confirmation of an SVT diagnosis (as described above), we first assessed the presence (or absence) of concurrent DVT or PE at the time of SVT diagnosis, with concurrent presence defined as (1) the presence of imaging findings suggestive for DVT or PE at the same consultation, or within 7 days following SVT diagnosis, reported in the free text and/or (2) clinically, if in the free text initiation of low-molecular-weight heparin (LMWH) combined with a vitamin K antagonist was described (which we considered the consequence of a DVT or PE diagnosis).

Each patient was followed by scrutinising all subsequent patient contacts in the 3 months following the SVT diagnosis, using manual free text searching. The following outcomes were collected: (1) subsequent management, consisting of either (a) watchful waiting with or without supportive measures like topical treatment or stockings or (b) LMWH and (2) the occurrence of propagation to DVT or PE (same definitions as for DVT/PE presence at SVT diagnosis). If in the EMR propagation to DVT and/or PE was never mentioned or considered during these 3 months of follow-up, we deemed such propagation as absent. As such, there was (strictly speaking) no missing data as we deemed DVT and/or PE absent in case it was not recorded in the EMR.

Sample size considerations

Given the retrospective nature of this study, no formal statistical sample size calculation was performed prior to the start of this study. Instead, the aim of this study was to capture and describe all patients with SVT currently diagnosed in a community-dwelling setting. Nevertheless, with an estimated IR for SVT of around 1.5 per 1000 person-years of follow-up (although highly uncertain prior to the initiation of this study), we anticipated to include around 360 SVTs per year (~240 000 person-years of follow-up annually), leading to a possible total number of around 2160 patients with SVT.

Table 1 Characteristics of included patients with SVT

Item	Isolated SVT n/N (%)	SVT with VTE sequelae n/N (%)	OR (95% CI) Univariate	OR (95% CI) Multivariate
Age				
Mean age	56.3 years	56.2 years	NA	NA
Proportion >75 years	371/1925 (19.3%)	13/83 (15.7%)	0.78 (0.43 to 1.42)	0.76 (0.41 to 1.40)
Females	1271/1925 (66.0%)	52/83 (62.7%)	0.86 (0.55 to 1.36)	0.99 (0.62 to 1.57)
Active malignancy	74/1925 (3.8%)	7/83 (8.4%)	2.30 (1.03 to 5.17)	2.19 (0.97 to 4.95)
Pregnancy	82/1925 (4.3%)	1/83 (1.2%)	0.27 (0.04 to 1.99)	0.28 (0.04 to 2.05)
Varicose veins	760/1925 (39.5%)	22/83 (26.5%)	0.55 (0.34 to 0.91)	0.57 (0.34 to 0.94)

NA, not applicable; SVT, superficial venous thrombosis; VTE, venous thromboembolism.

Statistical analyses

The IR of SVT was expressed as the number of SVT events per 1000 person-years of follow-up, and a 95% CI was calculated. We stratified these analyses for different age categories and gender. Next, we calculated the 3-month cumulative incidence of VTE sequelae using our above-described definitions. As an explorative analysis, using logistic regression, we compared SVT with and without DVT and/or PE sequelae either at the time of SVT diagnosis or during 3 months follow-up, including an OR (plus a corresponding 95% CI). Based on previous studies in the field, the following five baseline patient characteristics were assessed: age (dichotomised at 75 years), gender, active malignancy (defined as an active treatment provided within the 3 months prior to SVT diagnosis or malignancy with metastasis leading to palliative care), varicose veins and pregnancy. The predictive capacity of these five covariates for the occurence of VTE sequelae was assessed into the logistic model both univariately as multivariately, thus without a selection of covariates into the multivariate model based on p values. All data were analysed using SPSS V.21.0 (SPSS).

Ethics statement

The study received a waiver for formal reviewing. As such, according to Dutch law, no explicit informed consent was required as data reducible to the patients were only available at the GP practices and were made anonymous for data evaluation and analysis by the researchers.

Patient involvement

Given the retrospective nature of this study, no patients were involved during this study.

Table 2 Provided treatment strategies in patients with superficial venous thrombosis in primary care

Item	n/N (%)
Low molecular weight heparin	146/2008 (7.3%)
Stockings	516/2008 (25.7%)
Topical treatment	240/2008 (12.0%)

RESULTS

In total, we identified 2008 patients with SVT during the 6-year period, corresponding with an SVT IR of 1.31 (95% CI 1.25 to 1.37) per 1000 person-years (see figure 1). The mean age of all patients with SVT was 56 years, and 66% were female. In males, the IR was slightly lower as compared with females, that is, 1.16 (95% CI 1.01 to 1.24) vs 1.67 (95% CI 1.58 to 1.76). We observed an increasing IR with increasing age, ranging from 0.73 (95% CI 0.66 to 0.79) in patients below 40 years of age to 2.95 (95% CI 2.56 to 3.38) in patients above 80 years of age (see figure 2). Fifty-one patients (prevalence of 2.5%; 95% CI 1.9% to 3.3%) had a VTE (50 DVT and 1 PE) at inclusion, whereas in the remaining 1957 patients free of VTE after 1 week 32 patients (incidence of 1.6%; 95% CI 1.2% to 2.3%) experienced propagation to VTE within 3 months of follow-up (20 DVT and 12 PE; median time to propagation was 36 days). Thus, in total, VTE events were observed in 83 patients, leading to a cumulative incidence of 4.1% (95% CI 3.3% to 5.1%).

As compared with patients with SVT without VTE events, only absence of varicose veins and presence of an active malignancy were associated with VTE sequelae during 3 months of follow-up in patients with SVT (see table 1). LMWH was provided in the minority of patients (n=146, 7.3%). In most patients, a watchful waiting approach—which could include over-the-counter pain medication—was applied, with or without stockings or topical treatment (table 2).

DISCUSSION

In this large community-based cohort study, the observed SVT IR was around 1.3 cases per 1000 person-years. IR's were higher in women and more notably increased with increasing age, with the highest rate of nearly 3 cases per 1000 person-years in elderly patients above 80 years of age. Most patients (>90%) were treated conservatively, thus without the initiation of anticoagulant treatment. The risk of (subsequent) VTE sequelae was relatively low at around 4% during 3 months of follow-up, and in the majority of those patients (~60%), VTE sequelae

occurred either directly at the time of SVT diagnosis or within 7 days. In the remainder of patients in whom propagation after 7 days was present, this occurred at a median follow-up of 36 days, indicating that in fact the risks of VTE sequelae (either concurrent presence or propagation) are predominantly present in the first month after SVT diagnosis. Active malignancy and absence of varicose veins were significantly more common in patient with SVT with than in those without VTE sequelae.

Comparison with existing literature

The true IR of SVT in a community care setting has long been unknown. Recently, Frappé *et al* published the results from the STEPH study.[9] They used a rigorous approach, inviting all primary care physicians and vascular surgeons in the Saint-Etienne region (catchment area 265 687 adults) to refer (between November 2011 and November 2012) all suspected SVT cases for compression ultrasonography. Their analyses included 171 confirmed SVT cases in that year, leading to an IR of 0.64 SVT cases per 1000 person-years (95% CI 0.55 to 0.74), thus around half the rate of our current study. Their analyses, were, however, still based on hospital-confirmed SVT diagnoses and thereby depending on the willingness of primary care physicians to refer all (suspected) patients with SVT to the hospital. This is likely to lead to an underestimation of the true IR in the community, as likely primary care physicians (only) refer the more severe SVT cases to the hospital. There is indeed a suggestion in their data that this is what happened: the median age was 68 years and over 80% had varicose veins, whereas these numbers were 56 years and less than 40% in our study. Similarly, the proportion of patients with concurrent DVT at the time of SVT diagnosis was 24.6%, that is, much higher than in our study. We, therefore, believe that the findings of our study (1.31 SVT cases per 1000 person-years) more truly reflect the IR of SVT in the community care setting.

Our findings indicate a lower risk of VTE sequelae as compared with the available observational evidence suggesting that VTE risk may be as high as 25%. These studies, however, likely reflect (highly) selected samples of patients with SVT with inclusion into these datasets based on referral and thus a selection on SVT severity.[1–4] Likely, our sample of patients with SVT more reflects findings from a non-referred, community based and thus less severe population of SVT cases. This phenomenon is called the 'iatrotropic stimulus' and essentially underpins the need to perform research in a primary care setting, in order to test if replication of observations made in referred, more severe populations whether or not hold in primary care medicine.[12] Interestingly, if we compare our findings with the VTE risks in the placebo group in the (by far) largest SVT trial up to date (Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO))—comparing fondaparinux 2.5 mg once daily with placebo—we observe rather similar findings. The composite of VTE-related risks (ie, death, symptomatic DVT or PE, symptomatic propagation to the saphenofemoral junction (SFJ), or symptomatic recurrent SVT) occurred in 88 out of 1500 (placebo) patients during 47 days of follow-up, that is, 5.9%.[6] This proportion is only slightly higher than our finding of 4.1%, which might be explained by the inclusion of SFJ involvement into their primary outcome which we obviously, due to the retrospective nature of our study, were unable to include. In addition, some of our patients (7.3%) were treated with LMWH, and thus likely experience a lower risk of such events.

Compared with the available secondary care-based studies, we observed a lower cumulative VTE incidence in community care-based patients with SVT. Yet, our findings of a higher VTE risk in patients with cancer with SVT and a lower risk in patients with concurrent varicose veins are largely in accordance with existing literature. For instance, one of the largest secondary care-based study in this field (the Prospective Observational Superficial Thrombophlebitis study, n=844), also found a history of cancer and absence of varicose veins to be associated with a higher risk of VTE propagation in patients with SVT.[2] Similarly, in the Multiple Environmental and Genetic Assessment VTE case–control study, the overall odds of VTE after SVT was 5.5-fold (95% CI 4.4 to 6.8) increased, whereas in patients with a strong thromboembolic risk factor—notably including malignancy—this increase was 34.9-fold (95% CI 19.1 to 63.8).[13] Finally, Baggen *et al* found in a systematic review including six studies (total number of SVT patients, n=1938) that in five of these six studies absence of varicose veins was associated with a higher prevalence of concurrent DVT at the time of SVT diagnosis (prevalence range 33%–44% vs 3%–23%, in patients without and with varicose veins, respectively).[14] Nevertheless, although largely in accordance with existing literature, we would like to stress that our observations from the underlying logistic models (as presented in table 1) should be regarded as an exploratory analysis, simply due to the fact that our retrospective design prevents us from assessing the predictive importance of all relevant variables.

Strengths and limitations

Strengths of our study include a large community, primary care-based cohort using a rigorous approach of 'free text' searching in order to capture all SVT cases as well as its VTE sequelae during 3 months of follow-up. However, for full appreciation the following limitations need to addressed.

First, we used a retrospective design. Thus, inherently to this design, there always is a risk of not capturing all SVT events and their subsequent VTE sequelae. The previously referenced recent systematic review on VTE presence at the time of SVT diagnosis indeed reported a lower weighted mean DVT prevalence of 10.0% (95% CI 5.6% to 17.2%) in the retrospective studies compared with the overall mean weighted prevalence of 18.1% (95% CI 13.9% to 23.3%). This indeed may indicate that a retrospective design may underestimate VTE risk.

These retrospective studies also differed from prospective studies in the type of patients included. For instance, inpatients (who are at highest VTE risk) were not included in the retrospective studies, whereas they were included in 6 out of the 14 prospective studies. Also, having a retrospective design limited us in identifying some subgroups of patients with SVT at increased subsequent VTE risk, such as those with a specific extent or location of SVT, those with a history of VTE or specific other sites of SVT such as Mondor disease or upper limb SVT. It is for instance widely appreciated that SVT cases with SFJ involvement are more prone to progress to DVT.[1] Nor were we able to ascertain if a confirmed SVT diagnosis based on our definition was the patients' first lifetime event, as we cannot completely rely that this is routinely reported in medical files. However, a potential advantage of the retrospective nature of our study performed in primary care is that (by design) we were more likely able to capture all SVT cases. Studies performed in a secondary care setting may dependent on the willingness of primary care physicians to refer patients to a vascular centre in order to include them in their dataset. This effect—called the 'iatrotropic stimulus' or 'interiatric referral'—affects the likelihood that patients appear in a specific setting in which the research questions is addressed.[12] By performing our research in primary care, we consequently were able to (finally) truly estimate the IR of SVT in the community.

Second, an important aspect of our study is that due to the observational aspect of our study part of the patients (ie, 7.3%) were managed with anticoagulant treatment. Although still a minority, this obviously will lower the risk of VTE sequelae after SVT diagnosis, thus possibly underestimating our estimates for VTE risk.

Third, we only manually extracted follow-up information of 3 months after SVT diagnosis. Likely, a longer follow-up period would have yielded more VTE sequelae. Nevertheless, these 3 months of follow-up is in accordance with previous studies in the field, importantly as the risk of subsequent VTE sequelae is highest in these first 3 months.[8] Moreover, indeed, our analyses clearly conform that in fact the risk of VTE is highest in the first month after SVT diagnosis. Moreover, given the retrospective nature of our study, patients were not routinely contacted at 3 months to ascertain if a VTE event occurred. As such, we cannot completely rule-out the possibility that not all VTE outcome events are captured as we had to rely on information as reported within the electronic medical files. Thus, this could lead to an underestimation of the proportion of patients with a VTE outcome, for example, if a patient with a VTE outcome directly went to the hospital without a consultation with the GP first. However, in the Netherlands, all patients are registered with a GP and all hospital discharge information is routinely collected and reported within Utrecht General Practitioner Network. Hence, we expect that this underestimation likely is negligibly small.

Fourth, this was a practice-based study in a primary healthcare setting, and as such not all patients underwent formal confirmation of the SVT diagnosis using ultrasonography. On a similar level, the presence or absence of varicose veins was based on clinical grounds as reported by participating GPs within the Utrecht General Practitioner Network. Finally, also the identification of subsequent VTE sequelae was based on signs and symptoms first, with only confirmation in those with suggestive symptoms during 3 months of follow-up. Although following clinical practice and patient management, all this may result in some form of misclassification of events and patient characteristics. However, participating GPs within our network are experienced in classifying patient contacts as accurate as possible for research purposes for an average period of 10 years, and we successfully used this database for thrombosis research, for example, for quantifying patient and doctor delay when diagnosing PE.[15]

Implications for clinical practice and future studies

When a patient is diagnosed with SVT in a primary care setting, logically, the next important question will be: do we need to anticoagulant this patient in order to prevent subsequent VTE sequelae and how is this risk reduction weighted against the inherent risk of bleeds related to this treatment? This answer will obviously not be answered by our observational retrospective study. In the largest placebo-controlled randomised trial on SVT management—the CALISTO trial—fondaparinux prescribed for 45 days reduced the risk of VTE sequelae with a relative risk reduction of 0.15 (95% CI 0.04 to 0.50) as compared with placebo, without an increase in the risk of major bleeding complications (only 0.1% in both groups).[6] More recently, the direct oral factor Xa inhibitor rivaroxaban was shown to be non-inferior to fondaparinux, although in a relatively small study (certainly when compared with the CALISTO trial).[5] Importantly though, as mentioned earlier, our observed risk of VTE sequelae of around 4% is actually more or less comparable to the risk of VTE sequelae in the placebo group from the CALISTO trial. Also, the latest guideline on VTE prophylaxis in surgical patients recommends anticoagulant prophylaxis in those at intermediate (~3%) or high risk (~6%), depending on bleeding risk.[16] Thus, this may indicate that indeed we do need to treat patients with SVT with anticoagulants, given the substantial risk reduction on VTE sequelae of around 85% while on anticoagulants with no apparent increase in major bleeding risk. However, we need to appreciate that most patients with SVT actually carry a very low risk of VTE sequelae. Similarly, we surely do not consider anticoagulant treatment in patients suspected of DVT, where the overall prevalence of DVT at 3 months is around 10%. Hence, the absolute benefit that patients will get from anticoagulant treatment likely will be greater in those at a higher risk of VTE sequelae.[17] Stratified approaches, that is, separating those at higher risk of VTE from the low-risk population, may be the next step in order to optimise cost-effectiveness and the benefit–harm relation from anticoagulants. Ideally, therefore, further risk stratification of patients with SVT (both in terms of VTE

risk and bleeding risk on anticoagulant treatment) is important and similar, large, population-based studies like ours (where we identified a cancer diagnosis and absence of varicose veins as VTE risk indicators) are required to guide treatment decisions in daily practice. In addition to this—which is in agreement with the latest guidance from Cochrane—other outcomes like quality of life and costs then should also be assessed, preferably in randomised controlled trials on anticoagulant treatment in SVT.[18]

CONCLUSIONS

In this largest community-based cohort study to date, we observed an IR for SVT of around 1.3 new cases per 1000 person-years. The risk of subsequent VTE sequelae was relatively low at 4.1%, and these risks likely are highest in the first month after SVT diagnosis and occur more often in patients with cancer and in those who experience an SVT in the absence of varicose veins. Future studies are warranted to risk-stratify patients with SVT in order to tailor anticoagulant treatment to those at highest risk of VTE.

Contributors The original idea behind this study arose in discussions between G-JG, AWH and DAF. SC and G-JG performed data collection and data analysis, and prepared a first version of the manuscript, with further intellectual input from FR, AWH and DAF. G-JG (the manuscript's guarantor) affirmed that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study was assessed by the local Institutional Ethics Review Board of the UMC Utrecht.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Patient-level data and statistical codes are available from the corresponding author on request, but the decision to share data may need approval from the steering board from the Utrecht General Practitioner Network.

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