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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study.

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ABSTRACT

Objectives: Recent studies in referred populations of superficial venous thrombosis (SVT) patients report risks of venous thrombo-embolic (VTE) sequela (deep vein thrombosis or pulmonary embolism) to be 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 sequela.

Design: A retrospective cohort study, using International Classification of Primary Care coding (K94.02) combined with automated free-text searching (using 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 ~240,000 patients enlisted with general practitioners within the Utrecht General Practitioner Network between 2010 and 2016.

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. Descriptive statistics were used to compare SVT patients with and without VTE-sequela.

Results: A total of 2,008 SVT cases were identified, i.e. a SVT incidence rate of 1.39 (95% CI 1.33 to 1.46) per 1000 person-years follow-up. VTE sequela 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 (RR 2.19; 95% 1.04 to 4.60) or in those with absence of varicose veins at baseline (RR 0.57, 95% CI 0.35 to 0.91).

Conclusion: The incidence rate of SVT in primary care is 1.39 per 1000 person-years. The risks of VTE sequela was relatively low at 4.1%, with the highest risk in cancer patients and in those who experience a SVT in the absence of varicose veins.

Article summary:

Strengths and limitations:

- Superficial venous thrombosis (SVT) is associated with an increased risk of deep vein thrombosis (DVT) or pulmonary embolism (PE).
- Recent studies in referred populations indicated that these risks are substantial (~25%) thereby warranting anticoagulant treatment, yet large-scale population-based studies in primary care are sparse.

- In our largescale population-based study (n=2,008 SVT patients), the incidence rate of SVT is around 1.4 new cases per 1000 person-years of follow-up.
- As opposed to studies in referred populations, the cumulative incidence of DVT and/or PE during 3 months of follow-up is relatively low at 4.1% with the highest risk in SVT patients with an active malignancy, and in those who experience a SVT in the absence of varicose veins.
- 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 SVT location (notably involvement of saphenofemoral junction).

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 – i.e. 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 thrombo-embolic (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 (e.g. fondaparinux) or orally (e.g. rivaroxaban) – has been evaluated in randomized trials, with beneficial effects on reducing the risk of thrombo-embolic sequela.[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 case-mix between referred and non-selected SVT patients 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 thrombo-embolic risks in non-selected SVT patients and identification of subgroups of SVT patients at highest risk is needed to facilitate evidence-based anticoagulant treatment decisions for patients with SVT.

The objectives of this study were to quantify (i) the incidence rate of SVT in the community, and (ii) the short-term thrombo-embolic risks in these non-selected SVT patients – both in terms of concurrent presence and propagation to DVT or PE. Finally, (iii) 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 with approximately 240,000 citizens enlisted. The practice centers contributing to the database represent the average Dutch urban population.[11] The general practitioners (GPs) working in the centers 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 an average period of 10 years. In the Netherlands, all citizens are registered with a general practitioner, 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 to 2016 to detect new diagnoses of SVT. The EMRs were automatically scrutinized 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 i) such findings were not clearly reported leading to uncertainty of the SVT diagnosis; and/or ii) SVT was only considered in differential diagnosis but finally 'ruled-out' (not managed accordingly) by the GP; and/or iii) 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 a 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 i) 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 ii) clinically, if in the free text initiation of low molecular weight heparin combined with a vitamin K antagonist was described (which we considered the consequence of a DVT or PE diagnosis).

Each patient was followed by scrutinizing all subsequent patient contacts in the 3 months following the SVT diagnosis, using manual free text searching. The following outcomes were collected: i) subsequent management, consisting of either a) watchful waiting with or without supportive measures like topical treatment or stockings, or b) low-molecular weight heparin; and ii) 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 three 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 SVT patients currently diagnosed in a community-dwelling setting. Nevertheless, with an estimated incidence rate for SVT of around 1.5 per 1000 person-years of follow-up (albeit 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 2,160 SVT patients.

Statistical analyses

The incidence rate of SVT was expressed as the number of SVT events per 1000 person-years of follow-up, and a 95% confidence interval was calculated. Next, we calculated the 3-month cumulative incidence of VTE sequela using our above-described definitions. 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 a relative risk (plus a corresponding 95% confidence interval). P-values were calculated to compare both groups, using appropriate statistical techniques. Based upon previous studies in the field, the following baseline patient characteristics were assessed: age (dichotomized 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. All data were analyzed using SPSS V.21.0 (SPSS, Chicago, Illinois, USA).

Ethics statement

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

RESULTS

In total we identified 2,008 patients with SVT during the six year period, corresponding with a SVT incidence rate of 1.39 (95% CI 1.33 to 1.46) per 1000 person-years (see Figure 1). The mean age of all SVT patients was 56 years, and 66% were female. Fifty-one patients (prevalence of 2.5%; 95% CI 1.9% to 3.3%) had a VTE at inclusion, whereas in the remaining 1,957 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 (median time of 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 to SVT patients without VTE events, only absence of varicose veins and presence of an active malignancy were more common in SVT patients with VTE sequela (see Table 1). Low molecular weight heparin was provided in the minority of patients (n=146, 7.3%). In most patients, a watchful waiting approach was applied, with or without stockings or topical treatment (Table 2).

DISCUSSION

In this large community-based cohort study, the observed SVT incidence rate was around 1.4 cases per 1000 person-years. Most patients (>90%) were treated conservatively, thus without the initiation of anticoagulant treatment. The risk of (subsequent) VTE sequela was relatively low at around 5% during 3 months of follow-up, and in the majority of those patients (~60%), VTE sequela 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 sequela (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 SVT patient with than in those without VTE sequela.

Comparison with existing literature

The true incidence rate of SVT in a community care setting has long been unknown. Recently, Frappe and co-workers 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 incidence rate 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 upon hospital confirmed SVT diagnoses and thereby depending on the willingness of primary care physicians to refer *all* (suspected) SVT patients to the hospital. This is likely to lead to an underestimation of the true incidence rate 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%, i.e. much higher than in our study. We therefore believe that the findings of our study (1.39 SVT cases per 1000 person-years) more truly reflect the incidence rate of SVT in the community care setting.

Our findings indicate a lower risk of VTE sequela as compared to the available observational evidence suggesting that VTE risk may be as high as 25%. These studies however likely reflect (highly) selected samples of SVT patients with inclusion into these datasets based upon referral and thus a selection on SVT severity.[1–4] Interestingly, if we compare our findings with the VTE risks in the placebo group in the (by far) largest SVT trial up to date (CALISTO) – comparing fondaparinux 2.5 mg once daily with placebo – we observe rather similar findings. The composite of VTE related risks (i.e. 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, i.e. 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.

Although our findings of a lower cumulative VTE incidence in community-care based SVT patients (as compared to the available secondary-care based studies), our findings of a higher VTE risk in cancer patients 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 Thromboflebitis 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 SVT patients.[2] Similarly, in the Multiple Environmental and Genetic Assessment (MEGA) VTE case-control study, the overall odds of VTE after SVT was 5.5-fold (95% 4.4 to 6.8) increased, whereas in patients with a strong thrombo-embolic risk factor – notably including malignancy – this increase was 34.9-fold

(95% CI 19.1 to 63.8).[12] Finally, Baggen and co-workers found in a systematic review including six studies (total number of SVT patients n=1,938) that in 5 of these 6 studies absence of varicose veins was associated with a higher prevalence of concurrent DVT at the time of SVT diagnosis (prevalence range 33% to 44% versus 3% to 23%, in patients without and with varicose veins respectively).[13]

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 its VTE sequela during 3 months of follow-up. However, for full appreciation the following limitations need to addressed.

Firstly, 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 sequela. 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 as compared to 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 SVT patients at increased subsequent VTE risk, such as those with a specific extent or location of SVT. It is for instance widely appreciated that SVT cases with SFJ involvement are more prone to progress to DVT.[1] However, an advantage of the retrospective nature of our study is that by design we were more likely able to capture all SVT cases, regardless of referral decisions to secondary care. This enabled us to (finally) truly estimate the incidence rate 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 (i.e. 7.3%) were managed with anticoagulant treatment. Albeit still a minority, this obviously will lower the risk of VTE sequela 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 sequela. Nevertheless, these 3 months of follow-up is in accordance with previous studies in the field. Moreover, our analyses clearly indicate that in fact the risk of VTE is highest in the first month after SVT diagnosis.

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 sequela 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 randomized trial on SVT management – the CALISTO trial – fondaparinux prescribed for 45 days reduced the risk of VTE sequela with a relative risk reduction of 0.15 (95% CI 0.04 to 0.50) as compared to 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, albeit in a relatively small study (certainly when compared to the CALISTO trial).[5] Importantly though, as mentioned earlier, our observed risk of VTE sequela of around 4% is actually more or less comparable to the risk of VTE sequela in the placebo group from the CALISTO trial. Thus, this may indicate that indeed we do need to treat SVT patients with anticoagulants, given the substantial risk reduction on VTE sequela of around 85% while on anticoagulants with no apparent increase in major bleeding risk. However, we need to appreciate that most SVT patients actually carry a very low risk of VTE sequela. Hence, the absolute benefit that patients will get from anticoagulant treatment surely will be greater in those at a higher risk of VTE sequela.[14] Stratified approaches, i.e. separating those at higher risk of VTE from the low-risk population, may be the next step in order to optimize cost-effectiveness and the benefit-harm relation from anticoagulants. Ideally, therefore, further risk stratification of SVT patients (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 randomized controlled trials on anticoagulant treatment in SVT.[15]

Conclusions

In this largest community based cohort study to date, we observed an incidence rate for SVT of around 1.4 new cases per 1000 person-years. The risks of subsequent VTE sequela was relatively low at 4.1%, and these risks likely are highest in the first month after SVT diagnosis and occur more often in cancer patients and in those who experience a SVT in the absence of varicose veins. Future studies are warranted to risk-stratify SVT patients in order to tailor anticoagulant treatment to those at highest risk of VTE.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors: The original idea behind this study arose in discussions between GJG, AWH and DF. SC and GJG performed data collection and data analysis and prepared a first version of the manuscript, with further intellectual input from FHR, AWH and DF. Dr. G-J Geersing (the manuscript's guarantor) affirms 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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Data sharing: Patient level data and statistical codes are available from the corresponding author upon request, but the decision to share data may need approval from the steering board from the Utrecht General Practitioner Network. Participant consent was not obtained but the presented data are anonymised and risk of identification is very low.

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Table 1: Characteristics of included SVT patients

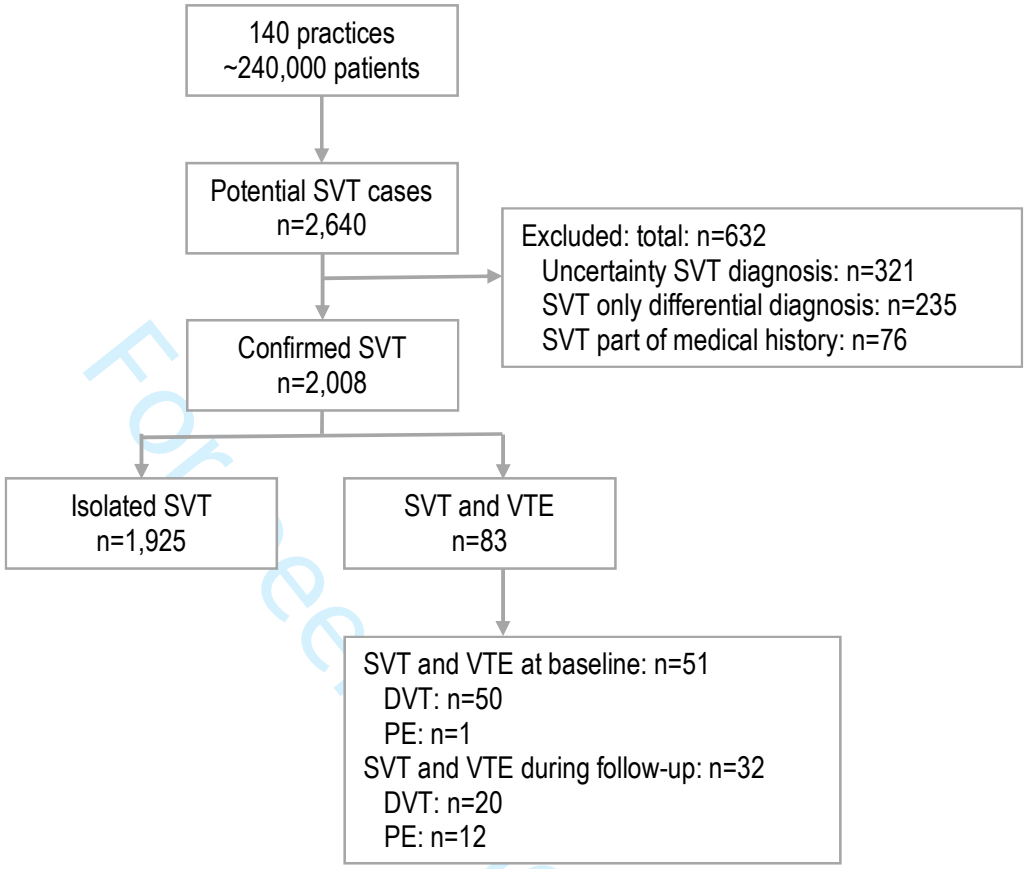
Item	*Isolated SVT n/N (%)*	*SVT with VTE sequela n/N (%)*	*RR (95% CI)*	*p-value*
Age				
Mean age	56.3 years	56.2 years	N.A.	p=0.947
Proportion > 75 yrs	371/1925 (19.3%)	13/83 (15.7%)	0.78 (0.44 to 1.40)	p=0.413
Females	1271/1925 (66.0%)	52/83 (62.7%)	0.87 (0.56 to 1.34)	p=0.525
Active malignancy	74/1925 (3.8%)	7/83 (8.4%)	2.19 (1.04 to 4.60)	p=0.037
Pregnancy	82/1925 (4.3%)	1/83 (1.2%)	0.28 (0.04 to 2.01)	p=0.171
Varicose veins	760/1925 (39.5%)	22/83 (26,5%)	0.57 (0.35 to 0.91)	p=0.018

SVT = superficial venous thrombosis; VTE = venous thrombo-embolism; CI = confidence interval

Table 2: Provided treatment strategies in SVT patients 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%)

Figure 1: Flowchart of included patients



STROBE checklist for: "*Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study.*"

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4,5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	4,5
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,6, Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6, Tab 1,2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	5,6

Outcome data	15	Report numbers of outcome events or summary measures over time	5,6, Tab 1,2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tab 1
		(*b*) Report category boundaries when continuous variables were categorized	5,6, Tab 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6, Tab 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	6,7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7,8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study.

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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study.

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ABSTRACT

Objectives: Recent studies in referred populations of superficial venous thrombosis (SVT) patients report risks of venous thrombo-embolic (VTE) sequela (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-sequela.

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 SVT patients with and without VTE-sequela.

Results: A total of 2,008 SVT cases were identified, i.e. a 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 sequela 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 sequela was relatively low at 4.1%, with the highest risk in cancer patients and in those who experience a SVT in the absence of varicose veins.

Article summary:

Strengths and limitations:

- Superficial venous thrombosis (SVT) is associated with an increased risk of deep vein thrombosis (DVT) or pulmonary embolism (PE).

- Recent studies in referred populations indicated that these risks are substantial (~25%) thereby warranting anticoagulant treatment, yet large-scale population-based studies in primary care are sparse.
- In our largescale population-based study (n=2,008 SVT patients), the incidence rate of SVT is around 1.3 new cases per 1000 person-years of follow-up.
- As opposed to studies in referred populations, the cumulative incidence of DVT and/or PE during 3 months of follow-up is relatively low at 4.1% with the highest risk in SVT patients with an active malignancy, and in those who experience a SVT in the absence of varicose veins.
- 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 SVT location (notably involvement of saphenofemoral junction).

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 – i.e. 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 thrombo-embolic (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 (e.g. fondaparinux) or orally (e.g. rivaroxaban) – has been evaluated in randomized trials, with beneficial effects on reducing the risk of thrombo-embolic sequela.[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 case-mix between referred and non-selected SVT patients 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 thrombo-embolic risks in non-selected SVT patients and identification of subgroups of SVT patients at highest risk is needed to facilitate evidence-based anticoagulant treatment decisions for patients with SVT.

The objectives of this study were to quantify (i) the incidence rate of SVT in the community, and (ii) the short-term thrombo-embolic risks in these non-selected SVT patients – both in terms of concurrent presence and propagation to DVT or PE. Finally, (iii) 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 centers contributing to the database represent the average Dutch urban population.[11] The general practitioners (GPs) working in the centers 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 an average period of 10 years. In the Netherlands, all citizens are registered with a general practitioner, 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 to 2016 to detect new diagnoses of SVT, i.e. 1,534,845 person-years follow-up. The EMRs were automatically scrutinized 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 i) such findings were not clearly reported leading to uncertainty of the SVT diagnosis; and/or ii) SVT was only considered in differential diagnosis but finally 'ruled-out' (not

managed accordingly) by the GP; and/or iii) 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 a 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 i) 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 ii) clinically, if in the free text initiation of low molecular weight heparin combined with a vitamin K antagonist was described (which we considered the consequence of a DVT or PE diagnosis).

Each patient was followed by scrutinizing all subsequent patient contacts in the 3 months following the SVT diagnosis, using manual free text searching. The following outcomes were collected: i) subsequent management, consisting of either a) watchful waiting with or without supportive measures like topical treatment or stockings, or b) low-molecular weight heparin; and ii) 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 three 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 SVT patients currently diagnosed in a community-dwelling setting. Nevertheless, with an estimated incidence rate for SVT of around 1.5 per 1000 person-years of follow-up (albeit 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 2,160 SVT patients.

Statistical analyses

The incidence rate of SVT was expressed as the number of SVT events per 1000 person-years of follow-up, and a 95% confidence interval was calculated. We stratified these analyses for different age categories and gender. Next, we calculated the 3-month cumulative incidence of VTE sequela 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 odds ratio (plus a corresponding 95% confidence interval). Based upon previous studies in the field, the following five baseline patient characteristics were assessed: age (dichotomized

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. These five covariates were assessed into the logistic model both univariately as multivariately, thus without a selection of covariates into the multivariate model based upon p-values. All data were analyzed using SPSS V.21.0 (SPSS, Chicago, Illinois, USA).

Ethics statement

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

RESULTS

In total we identified 2,008 patients with SVT during the six year period, corresponding with a SVT incidence rate of 1.31 (95% CI 1.25 to 1.37) per 1000 person-years (see Figure 1). The mean age of all SVT patients was 56 years, and 66% were female. In males, the IR was slightly lower as compared to females, i.e. 1.16 (95% CI 1.01 to 1.24) versus 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 1,957 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 to SVT patients without VTE events, only absence of varicose veins and presence of an active malignancy were associated with VTE sequela during 3 months of follow-up in SVT patients (see Table 1). Low molecular weight heparin 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 incidence rate was around 1.3 cases per 1000 person-years. IR's were higher in females 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 sequela was relatively low at around 4% during 3 months of follow-up, and in the majority of those patients (~60%), VTE sequela 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 sequela (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 SVT patient with than in those without VTE sequela.

Comparison with existing literature

The true incidence rate of SVT in a community care setting has long been unknown. Recently, Frappe and co-workers 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 incidence rate 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 upon hospital confirmed SVT diagnoses and thereby depending on the willingness of primary care physicians to refer *all* (suspected) SVT patients to the hospital. This is likely to lead to an underestimation of the true incidence rate 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%, i.e. 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 incidence rate of SVT in the community care setting.

Our findings indicate a lower risk of VTE sequela as compared to the available observational evidence suggesting that VTE risk may be as high as 25%. These studies however likely reflect (highly) selected samples of SVT patients with inclusion into these datasets based upon referral and thus a selection on SVT severity.[1–4] Likely, our sample of SVT patients 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 (CALISTO) – comparing fondaparinux 2.5

mg once daily with placebo – we observe rather similar findings. The composite of VTE related risks (i.e. 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, i.e. 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.

Although our findings of a lower cumulative VTE incidence in community-care based SVT patients (as compared to the available secondary-care based studies), our findings of a higher VTE risk in cancer patients 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 Thromboflebitis 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 SVT patients.[2] Similarly, in the Multiple Environmental and Genetic Assessment (MEGA) VTE case-control study, the overall odds of VTE after SVT was 5.5-fold (95% 4.4 to 6.8) increased, whereas in patients with a strong thrombo-embolic risk factor – notably including malignancy – this increase was 34.9-fold (95% CI 19.1 to 63.8).[13] Finally, Baggen and co-workers found in a systematic review including six studies (total number of SVT patients n=1,938) that in 5 of these 6 studies absence of varicose veins was associated with a higher prevalence of concurrent DVT at the time of SVT diagnosis (prevalence range 33% to 44% versus 3% to 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 its VTE sequela during 3 months of follow-up. However, for full appreciation the following limitations need to addressed.

Firstly, 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 sequela. 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 as compared to 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 SVT patients 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 upon our definition was the patients' first lifetime event, as we cannot completely rely that this is routinely reported in medical files. However, an advantage of the retrospective nature of our study is that by design we were more likely able to capture all SVT cases, regardless of referral decisions to secondary care. This enabled us to (finally) truly estimate the incidence rate 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 (i.e. 7.3%) were managed with anticoagulant treatment. Albeit still a minority, this obviously will lower the risk of VTE sequela 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 sequela. Nevertheless, these 3 months of follow-up is in accordance with previous studies in the field, importantly as the risk of subsequent VTE sequela 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, e.g. 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 upon clinical grounds as reported by participating GPs within the Utrecht General Practitioner Network. Finally, also the identification of subsequent VTE sequela was based on signs and symptoms first, with only confirmation in those with suggestive symptoms during 3 months of follow-up. Albeit 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, e.g. for quantifying patient and doctor delay when diagnosing pulmonary embolism.[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 sequela 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 randomized trial on SVT management – the CALISTO trial – fondaparinux prescribed for 45 days reduced the risk of VTE sequela with a relative risk reduction of 0.15 (95% CI 0.04 to 0.50) as compared to 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, albeit in a relatively small study (certainly when compared to the CALISTO trial).[5] Importantly though, as mentioned earlier, our observed risk of VTE sequela of around 4% is actually more or less comparable to the risk of VTE sequela 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 SVT patients with anticoagulants, given the substantial risk reduction on VTE sequela of around 85% while on anticoagulants with no apparent increase in major bleeding risk. However, we need to appreciate that most SVT patients actually carry a very low risk of VTE sequela. 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 sequela.[17] Stratified approaches, i.e. separating those at higher risk of VTE from the low-risk population, may be the next step in order to optimize cost-effectiveness and the benefit-harm relation from anticoagulants. Ideally, therefore, further risk stratification of SVT patients (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 randomized controlled trials on anticoagulant treatment in SVT.[18]

Conclusions

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

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors: The original idea behind this study arose in discussions between GJG, AWH and DF. SC and GJG performed data collection and data analysis and prepared a first version of the manuscript, with further intellectual input from FHR, AWH and DF. Dr. G-J Geersing (the manuscript's guarantor) affirms 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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Data sharing: Patient level data and statistical codes are available from the corresponding author upon request, but the decision to share data may need approval from the steering board from the Utrecht General Practitioner Network. Participant consent was not obtained but the presented data are anonymised and risk of identification is very low.

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Table 1: Characteristics of included SVT patients

Item	*Isolated SVT* *n/N (%)*	*SVT with VTE sequela* *n/N (%)*	*Odds Ratio (95% CI)*	
			Univariate	Multivariate
Age				
Mean age	56.3 years	56.2 years	N.A.	N.A.
Proportion > 75 yrs	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)

SVT = superficial venous thrombosis; VTE = venous thrombo-embolism; CI = confidence interval

Table 2: Provided treatment strategies in SVT patients 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%)

Figure 1: Flowchart of included patients.

Figure 1 legend:

SVT: superficial venous thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thrombo-embolism

Figure 2: Incidence Rate of SVT according to age.

Figure 2 legend:

SVT: superficial venous thrombosis; IR: incidence rate; CI: confidence interval

Figure 1: Flowchart of included patients

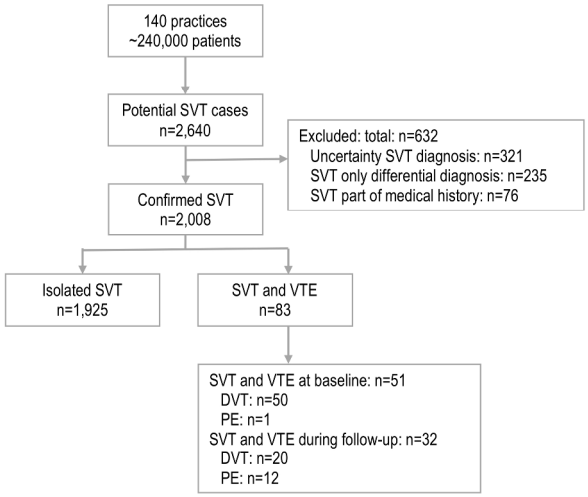

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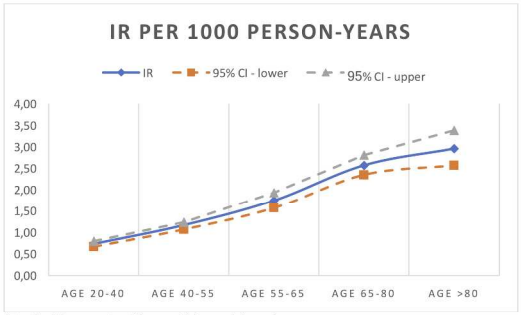
Figure 2: Incidence Rate of SVT according to age.



IR = incidence rate; CI = confidence interval

296x419mm (300 x 300 DPI)

STROBE checklist for: "*Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study.*"

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4,5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	4,5
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,6, Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6, Tab 1,2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	5,6

Outcome data	15	Report numbers of outcome events or summary measures over time	5,6, Tab 1,2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tab 1
		(*b*) Report category boundaries when continuous variables were categorized	5,6, Tab 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6, Tab 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	6,7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7,8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study performed with routine healthcare data from the Netherlands.

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Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study performed with routine healthcare data from the Netherlands.

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ABSTRACT

Objectives: Recent studies in referred populations of superficial venous thrombosis (SVT) patients report risks of venous thrombo-embolic (VTE) sequela (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-sequela.

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 SVT patients with and without VTE-sequela.

Results: A total of 2,008 SVT cases were identified, i.e. a 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 sequela 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 sequela was relatively low at 4.1%, with the highest risk in cancer patients and in those who experience a SVT in the absence of varicose veins.

Article summary:

Strengths and limitations:

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- 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 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 SVT patients that appear in research performed in secondary care are sicker or more likely to have an increased risk of thrombo-embolic sequela. Thereby, our findings may reflect the burden of SVT in terms of thrombo-embolic 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 – i.e. 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 thrombo-embolic (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 (e.g. fondaparinux) or orally (e.g. rivaroxaban) – has been evaluated in randomized trials, with beneficial effects on reducing the risk of thrombo-embolic sequela.[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 case-mix between referred and non-selected SVT patients 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 thrombo-embolic risks in non-selected SVT patients and identification of subgroups of SVT patients at highest risk is needed to facilitate evidence-based anticoagulant treatment decisions for patients with SVT.

The objectives of this study were to quantify (i) the incidence rate of SVT in the community, and (ii) the short-term thrombo-embolic risks in these non-selected SVT patients – both in terms of concurrent presence and propagation to DVT or PE. Finally, (iii) 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 centers contributing to the database represent the average Dutch urban population.[11] The general practitioners (GPs) working in the centers 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 an average period of 10 years. In the Netherlands, all citizens are registered with a general practitioner, 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 to 2016 to detect new diagnoses of SVT, i.e. 1,534,845 person-years follow-up. The EMRs were automatically scrutinized 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 i) such findings were not clearly reported leading to uncertainty of the SVT diagnosis; and/or ii) SVT was only considered in differential diagnosis but finally 'ruled-out' (not managed accordingly) by the GP; and/or iii) 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 a 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 i) 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 ii) clinically, if in the free text initiation of low molecular weight heparin combined with a vitamin K antagonist was described (which we considered the consequence of a DVT or PE diagnosis).

Each patient was followed by scrutinizing all subsequent patient contacts in the 3 months following the SVT diagnosis, using manual free text searching. The following outcomes were collected: i) subsequent management, consisting of either a) watchful waiting with or without supportive measures like topical treatment or stockings, or b) low-molecular weight heparin; and ii) 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 three 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 SVT patients currently diagnosed in a community-dwelling setting. Nevertheless, with an estimated incidence rate for SVT of around 1.5 per 1000 person-years of follow-up (albeit 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 2,160 SVT patients.

Statistical analyses

The incidence rate of SVT was expressed as the number of SVT events per 1000 person-years of follow-up, and a 95% confidence interval was calculated. We stratified these analyses for different age categories and gender. Next, we calculated the 3-month cumulative incidence of VTE sequela 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 odds ratio (plus a corresponding 95% confidence interval). Based upon previous studies in the field, the following five baseline patient characteristics were assessed: age (dichotomized 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. These five covariates were assessed into the logistic model both univariately as

multivariately, thus without a selection of covariates into the multivariate model based upon p-values. All data were analyzed using SPSS V.21.0 (SPSS, Chicago, Illinois, USA).

Ethics statement

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

RESULTS

In total we identified 2,008 patients with SVT during the six year period, corresponding with a SVT incidence rate of 1.31 (95% CI 1.25 to 1.37) per 1000 person-years (see Figure 1). The mean age of all SVT patients was 56 years, and 66% were female. In males, the IR was slightly lower as compared to females, i.e. 1.16 (95% CI 1.01 to 1.24) versus 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 1,957 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 to SVT patients without VTE events, only absence of varicose veins and presence of an active malignancy were associated with VTE sequela during 3 months of follow-up in SVT patients (see Table 1). Low molecular weight heparin 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 incidence rate was around 1.3 cases per 1000 person-years. IR's were higher in females 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 sequela was relatively low at around 4% during 3 months of

follow-up, and in the majority of those patients (~60%), VTE sequela 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 sequela (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 SVT patient with than in those without VTE sequela.

Comparison with existing literature

The true incidence rate of SVT in a community care setting has long been unknown. Recently, Frappe and co-workers 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 incidence rate 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 upon hospital confirmed SVT diagnoses and thereby depending on the willingness of primary care physicians to refer *all* (suspected) SVT patients to the hospital. This is likely to lead to an underestimation of the true incidence rate 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%, i.e. 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 incidence rate of SVT in the community care setting.

Our findings indicate a lower risk of VTE sequela as compared to the available observational evidence suggesting that VTE risk may be as high as 25%. These studies however likely reflect (highly) selected samples of SVT patients with inclusion into these datasets based upon referral and thus a selection on SVT severity.[1–4] Likely, our sample of SVT patients 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 (CALISTO) – comparing fondaparinux 2.5 mg once daily with placebo – we observe rather similar findings. The composite of VTE related risks (i.e. 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,

i.e. 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 to the available secondary-care based studies, we observed a lower cumulative VTE incidence in community-care based SVT patients. Yet, our findings of a higher VTE risk in cancer patients 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 Thromboflebitis 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 SVT patients.[2] Similarly, in the Multiple Environmental and Genetic Assessment (MEGA) VTE case-control study, the overall odds of VTE after SVT was 5.5-fold (95% 4.4 to 6.8) increased, whereas in patients with a strong thrombo-embolic risk factor – notably including malignancy – this increase was 34.9-fold (95% CI 19.1 to 63.8).[13] Finally, Baggen and co-workers found in a systematic review including six studies (total number of SVT patients n=1,938) that in 5 of these 6 studies absence of varicose veins was associated with a higher prevalence of concurrent DVT at the time of SVT diagnosis (prevalence range 33% to 44% versus 3% to 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 its VTE sequela during 3 months of follow-up. However, for full appreciation the following limitations need to addressed.

Firstly, 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 sequela. 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 as compared to 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 SVT

patients 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 upon 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 center 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 incidence rate 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 (i.e. 7.3%) were managed with anticoagulant treatment. Albeit still a minority, this obviously will lower the risk of VTE sequela 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 sequela. Nevertheless, these 3 months of follow-up is in accordance with previous studies in the field, importantly as the risk of subsequent VTE sequela 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, e.g. 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 upon clinical grounds as reported by participating GPs within the Utrecht General Practitioner Network. Finally, also the identification of subsequent VTE sequela was based on signs and symptoms first, with only confirmation in those with suggestive

symptoms during 3 months of follow-up. Albeit 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, e.g. for quantifying patient and doctor delay when diagnosing pulmonary embolism.[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 sequela 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 randomized trial on SVT management – the CALISTO trial – fondaparinux prescribed for 45 days reduced the risk of VTE sequela with a relative risk reduction of 0.15 (95% CI 0.04 to 0.50) as compared to 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, albeit in a relatively small study (certainly when compared to the CALISTO trial).[5] Importantly though, as mentioned earlier, our observed risk of VTE sequela of around 4% is actually more or less comparable to the risk of VTE sequela 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 SVT patients with anticoagulants, given the substantial risk reduction on VTE sequela of around 85% while on anticoagulants with no apparent increase in major bleeding risk. However, we need to appreciate that most SVT patients actually carry a very low risk of VTE sequela. 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 sequela.[17] Stratified approaches, i.e. separating those at higher risk of VTE from the low-risk population, may be the next step in order to optimize cost-effectiveness and the benefit-harm relation from anticoagulants. Ideally, therefore, further risk stratification of SVT patients (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 randomized controlled trials on anticoagulant treatment in SVT.[18]

Conclusions

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

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors: The original idea behind this study arose in discussions between GJG, AWH and DF. SC and GJG performed data collection and data analysis and prepared a first version of the manuscript, with further intellectual input from FHR, AWH and DF. Dr. G-J Geersing (the manuscript's guarantor) affirms 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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Data sharing: Patient level data and statistical codes are available from the corresponding author upon request, but the decision to share data may need approval from the steering board from the Utrecht General Practitioner Network. Participant consent was not obtained but the presented data are anonymised and risk of identification is very low.

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Table 1: Characteristics of included SVT patients

Item	*Isolated SVT n/N (%)*	*SVT with VTE sequela n/N (%)*	*Odds Ratio (95% CI)*	
			Univariate	Multivariate
Age				
Mean age	56.3 years	56.2 years	N.A.	N.A.
Proportion > 75 yrs	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)

SVT = superficial venous thrombosis; VTE = venous thrombo-embolism; CI = confidence interval

Table 2: Provided treatment strategies in SVT patients 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%)

Figure 1: Flowchart of included patients.

Figure 1 legend:

SVT: superficial venous thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thrombo-embolism

Figure 2: Incidence Rate of SVT according to age.

Figure 2 legend:

SVT: superficial venous thrombosis; IR: incidence rate; CI: confidence interval

Figure 1: Flowchart of included patients

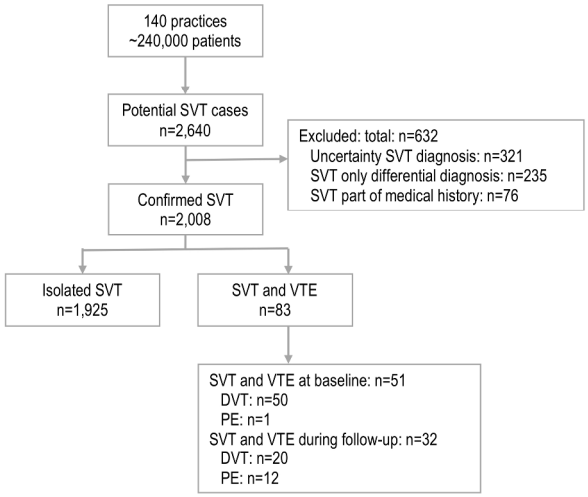

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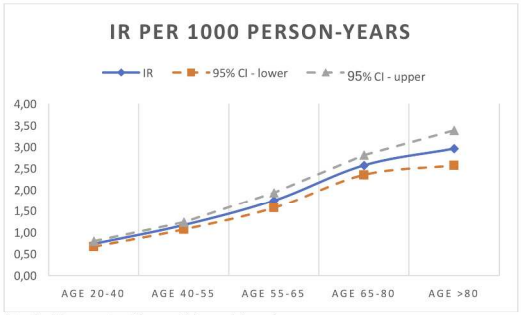
Figure 2: Incidence Rate of SVT according to age.



IR = incidence rate; CI = confidence interval

296x419mm (300 x 300 DPI)

STROBE checklist for: "*Incidence of superficial venous thrombosis in primary care and risk of subsequent venous thrombo-embolic sequela; a retrospective cohort study performed with routine healthcare data from the Netherlands.*"

	Item No	Recommendation	On page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	4,5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	4,5
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, Tab 1,2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	6

Outcome data	15	Report numbers of outcome events or summary measures over time	6, Tab 1,2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tab 1
		(*b*) Report category boundaries when continuous variables were categorized	6, Tab 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6, Tab 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	6,7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11