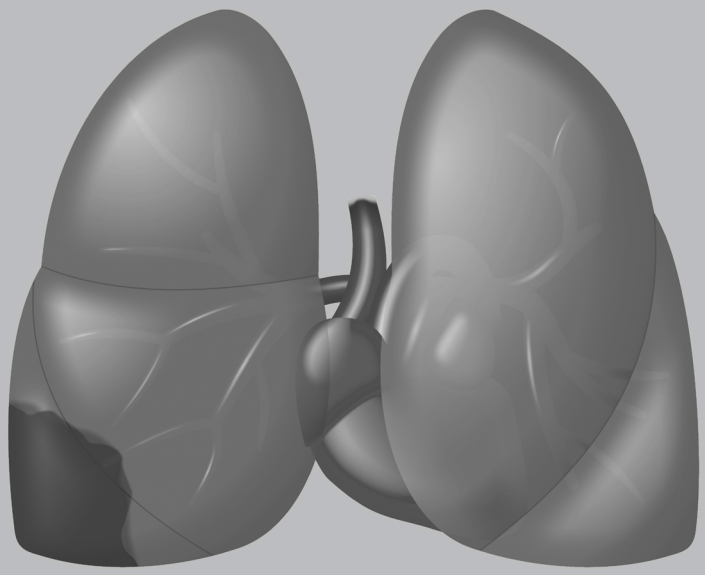
PART II

Recurrent Acute Pulmonary Embolism



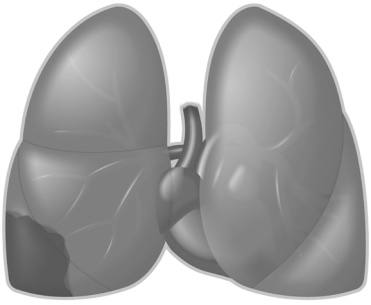
CHAPTER 6

The incidence of recurrent venous thromboembolism in a defined population

I.C.M. Mos*, M. Tan*, M. Klinkenberg, F.J.M. van der Meer and M.V. Huisman

*Equally contributed

Submitted



ABSTRACT

Background

Recurrent venous thromboembolism (VTE) is a common disorder, but the incidence of recurrent VTE within a defined population has never been formally assessed. The aim of this study was to determine the incidence of acute recurrent VTE in a defined population.

Methods

All patients with an objectively confirmed acute recurrent VTE in the selected period, January 2003 until December 2007 who were registered at the Thrombosis Service in the region of Leiden were identified. Medical records of included patients were reviewed for demographic characteristics and risk factors and questionnaires were sent to all potential study patients who were alive. The incidence was stratified by age and sex.

Results

A total of 516 patients were identified with recurrent VTE within the 5 year study period in a defined population of 513.143 inhabitants. The overall incidence of recurrent VTE was found to be 0.22 per 1000 inhabitants per year. The incidence of recurrent deep venous thrombosis, pulmonary embolism and arm vein thrombosis were respectively 0.13, 0.08 and 0.008 per 1000 per year. The incidence was different between men and women; 0.24 per 1000 male inhabitants per year and 0.20 per 1000 female inhabitants per year respectively. The most frequent risk factor associated with recurrent VTE was malignancy (16%).

Conclusions

The incidence of recurrent VTE in a defined urban population is 0.22 per 1000 inhabitants per year.

INTRODUCTION

Venous thromboembolism (VTE) consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE) is a common disorder with an incidence of 1.2-1.8 per 1000 inhabitants per year.[1,2] The reported incidence of DVT varies between 0.48 and 1.6 per 1000 per year[2-4] and 0.2-0.69 per 1000 per year for PE.[2,5] The two-year cumulative incidence of recurrent VTE has been reported to be 17.5% after a first DVT and 17.3% after a first PE.[6,7] Patients with symptomatic VTE have a high risk for recurrent VTE that persist for many years, with a risk of recurrence after 5 years of 20-25%.[8] The risk profile differs between first and recurrent events. Risk factors associated with a higher risk of a recurrent VTE are e.g. male sex and cancer.[9,10] Patients with VTE provoked by surgery, trauma, immobilization, pregnancy or female hormone intake or patients with arm vein thrombosis are at low risk of a recurrent event.[9,10] However, whether patients with a pulmonary embolism have a higher risk of recurrence than patients with DVT is uncertain.[11]

Although studies have reported on the cumulative incidence of recurrent VTE after a first event, no study has specifically assessed the incidence of recurrent VTE in a well defined urban population. The epidemiology in this group of patients is of particular interest because of implications for prevention of morbidity and mortality, and management with consequences of the indication for prolonged anticoagulant therapy. The aim of this study is to determine the incidence of recurrent VTE in a well defined general population (the region of Leiden, The Netherlands) and to assess this incidence according to age and gender.

METHODS

Data sources

For the determination of the incidence of recurrent VTE, all consecutive patients with a confirmed recurrent VTE who received anticoagulation treatment for this recurrent episode in the period January 1st 2003 until December 31st 2007 in the region of Leiden were identified.

In The Netherlands, all patients who have a (recurrent) VTE event are referred to local Thrombosis Services. All potential patients with recurrent VTE were identified from the database of the Thrombosis Services Leiden by the following methods: 1) patients who were registered as 'recurrent VTE' by the treating physician during the study period; 2) patients who were already registered prior to the study period for a VTE event and were registered for a new VTE event (i.e. the recurrent event) the study period; 3) all patients registered as VTE with long term or indefinite treatment were identified and reviewed if they had a prior VTE event.

Medical records of all potential study patients were reviewed and in addition, questionnaires were sent to all patients who were alive at June 1st 2010. A second questionnaire was sent to the non-responders.

A recurrent episode of VTE, i.e. PE, DVT and/or arm vein thrombosis was defined as a recurrent thrombotic event requiring anticoagulant treatment according to the attending physician and proven by compression ultrasonography, CT-scan, ventilation perfusion scintigraphy or contrast venography. Patients who presented with both DVT and PE were classified as having PE. Patients were included in case of an objectively confirmed acute recurrent VTE during the 5 year study period and if they lived in the Leiden district on date of the recurrent VTE episode. The study was approved by the local Review Board.

Data collection

All potential study patients were evaluated in the civil registration system whether they were alive at time of sending the questionnaires and in addition the date of death. Medical records and questionnaires of all patients were reviewed for demographic characteristics, risk factors and information about the recurrent and previous VTE events (e.g. date of VTE events, type, location and duration of oral anticoagulant therapy) and if applicable the cause of death.

Recurrent VTE events were included, independent of the type of previous VTE event (e.g. also PE after a DVT episode). The database was checked for double entry and in case a patient had more recurrent events during the study period only the first episode was considered for inclusion.

Unprovoked VTE was defined in case of the absence of immobilization more than 3 days, surgery or a recent long flight, plaster cast of the lower extremity, active malignancy, pregnancy or postpartum period, use of oral contraceptive or hormone replacement therapy and the presence of a central venous catheter in case of arm vein thrombosis.[12]

Study outcomes and statistical analysis

The primary outcome of the study was the incidence of recurrent VTE (PE, DVT and arm vein thrombosis) in the Leiden region between January 1st 2003 and December 31st 2007. In addition, age and sex-specific incidence rates of recurrent VTE were calculated. Annual incidence rates (per 1000 inhabitants) were calculated as the number of patients with recurrent VTE occurring during the 5-year study period divided by the number of inhabitants of the Leiden District with corresponding 95% confidence intervals (CI). The Thrombosis Service Leiden covers a well described population of 513,143 inhabitants, estimated by the National Institute of Statistics, a national registry in which the age and gender of all inhabitants of the Netherlands are registered. All continuous variables are expressed as mean (standard deviation) and categorical data given in proportions and percentages. Mean values and frequencies were compared using Student's t-test and

Pearson's chi-square test, respectively. Analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, Ill).

RESULTS

Between January 1st 2003 and December 31st 2007, 640 potential patients were identified with recurrent VTE episode in the Leiden region and medical records were reviewed. Among these potential patients, 128 patients (23%) died and questionnaires were sent to the remaining 512 patients. Of these patients 59 declined participation and 67 did not respond after two sent questionnaires.

After review of the questionnaires and medical records of the 640 potential patients, 79 patients were excluded from further analysis because they did not live in the Leiden region at time of the recurrent event or because no recurrent event occurred during the study period. Finally, 561 patients were left for inclusion in the analysis.

Data to calculate the primary endpoint (presence of recurrent DVT, PE or arm vein thrombosis) were available in all 561 patients.

Clinical characteristics of patients with recurrent VTE.

In a total population of 513,143 inhabitants, 561 patients had a recurrent VTE event during 5 years, the total incidence of recurrent VTE was therefore 0.22 per 1000 inhabitants per year. The clinical characteristics of the 561 patients with recurrent VTE are summarized in Table 1. The mean age of the cohort was 59.79 ±16.6 years (range 15-95) with more males (53% versus 47%). In 346 patients (62%) the recurrent event was an isolated DVT, in 195 (35%) a PE (including 13 patients with also DVT of the lower limbs) and in 20 patients (3.6%) an arm vein thrombosis (including one patient with concomitant DVT of the lower extremity). The incidence of recurrent deep venous thrombosis, pulmonary embolism and arm vein thrombosis were therefore 0.13, 0.08 and 0.008 per 1000 inhabitants per year respectively.

The incidence rates increased steadily with age for both sexes (Figure 1). Overall the incidence was different between men and women; for men, 0.24 per 1000 male inhabitants per year (95% CI 0.236-0.244) and 0.20 per 1000 female inhabitants per year (95% CI 0.197 -0.204) for women. Men had higher incidence rates compared to women above 45 years of age (Figure 1). Deep vein thrombosis accounted for the majority (44-69%) of recurrent VTE in all age categories (Figure 2).

Presence of risk factors was known in 431 patients (77%). In these patients the recurrent event was provoked in 35%. The most frequent risk factor associated with recurrent VTE was malignancy (16% of 431), most commonly hematologic (20%), gastrointestinal (15%), breast (15%), lung (15%), gynecological (10%) and prostate (10%) malignancies.

Table 1. Patient characteristics of the 561 included patients.

Characteristic	Value
Male, n (%)	300 (53)
Recurrent event	
Age, mean (SD), y	60 (17)
Deep vein thrombosis	59 (16)
Pulmonary embolism	61 (17)
Arm vein thrombosis	54 (18)
Number of recurrent VTE events (%)	
One recurrent event	447 (80)
Two recurrent events	94 (17)
More than two recurrent events	20 (3.6)
Site of recurrent event	
Deep vein thrombosis, n (%)	346 (62)
Pulmonary embolism, n (%)	195 (35)*
Arm vein thrombosis, n (%)	20 (3.6)**
Years since previous event, mean (SD), y	5.0 (6.5)
Risk factors[#]	
Provoked event, n (%)	152 (35)
- recent surgery, n (%)	31 (20)
- immobilization, n (%)	30 (20)
- estrogen use, n (%)	26 (17)
- pregnancy, n (%)	5 (3.2)
- long flight, n (%)	8 (5.3)
- central venous catheter, n (%)	2 (1.3)
- active malignancy, n (%)	71 (47)
Idiopathic event	279 (65)
Mortality	
1 year after recurrent VTE event, n (%)	55 (9.8)
2 year after recurrent VTE event, n (%)	73 (13)
Previous event	
Age, mean (SD), y	55 (17)
Site of previous event	
Deep vein thrombosis, n (%)	360 (64)
Pulmonary embolism, n (%)	182 (32)***
Arm Vein thrombosis, n (%)	18 (3.2)
Risk factors[±]	
Provoked event, n (%)	128 (33)
Idiopathic event, n (%)	261 (67)

[#] presence of risk factors of the recurrent event known in 431 patients; [±] presence of risk factors of the previous event was known in 389 patients; * including 13 patients with concurrent DVT; ** including one patient with concurrent DVT of the leg; ***including 31 patients with concurrent DVT of the leg. n: number; SD: standard deviation; y: year; VTE: venous thromboembolism.

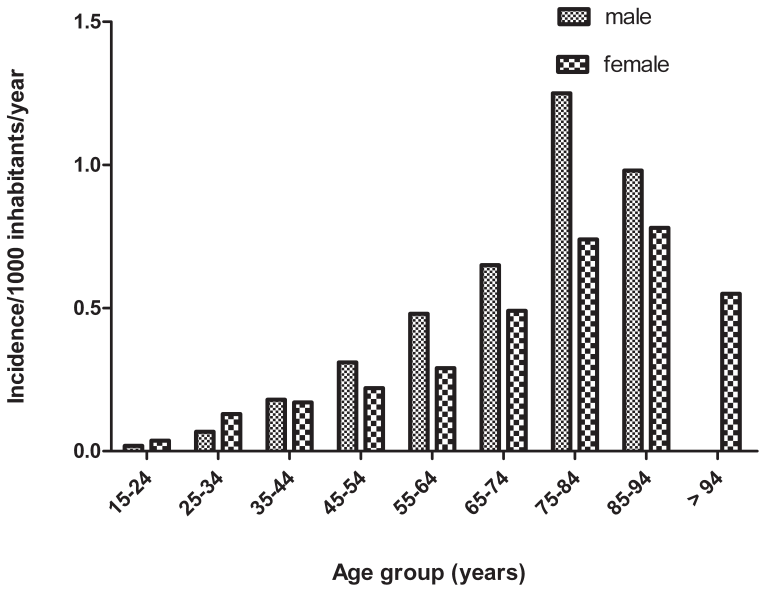


Figure 1. Age distribution stratified by gender (incidence).

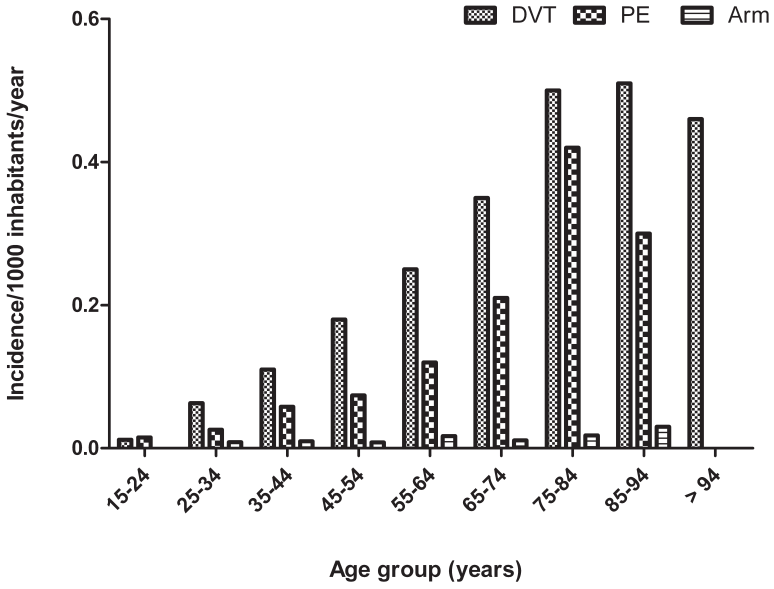


Figure 2. Age distribution stratified by type of recurrent venous thromboembolism (VTE) event (incidence).

The 1 and 2 year mortality rate were 9.8% and 13% respectively. (Table 1). The cause of death was registered by the Thrombosis Service Leiden in 81 patients (63%) None of the known causes of deaths were attributed to venous thromboembolic events, 43 (53%) died of malignancy, 14 (17%) patients due to cardiovascular causes and 3 patients died of a fatal bleeding during anticoagulant therapy.

The majority (80%) of the patients had one recurrent VTE episode, 17% had two recurrent events and 3% of the patients had more than two recurrent events (Table 1). In 38 patients (6.8%), the recurrent VTE event occurred during anticoagulant treatment, 47% of these patients had active malignancy.

Comparison to the previous VTE event

The recurrent VTE events occurred after a mean of 5.0 years (SD 6.5) after the previous VTE event. When stratified into years after the previous VTE event, a strong decline was found with the years, and 43% of the recurrent events occurred within two years (Figure 3). The percentage of patients with an active malignancy was higher during the first two years than after. The type of the previous event did not differ from the recurrent events; 64% had a DVT, 32% PE and 3.2% had arm vein thrombosis.

Data on the presence of risk factors of the previous thrombotic event were available in 389 patients (69%). The percentages of provoked versus idiopathic previous VTE event in these patients, were similar to the recurrent VTE events as well, 33 and 67% respectively.

In patients with a previous DVT, recurrent DVT occurred more often (80%) than PE (19%). The same effect was found after initial PE, the risk for recurrent PE was 69%, while 30% of the patients had a DVT (Figure 4).

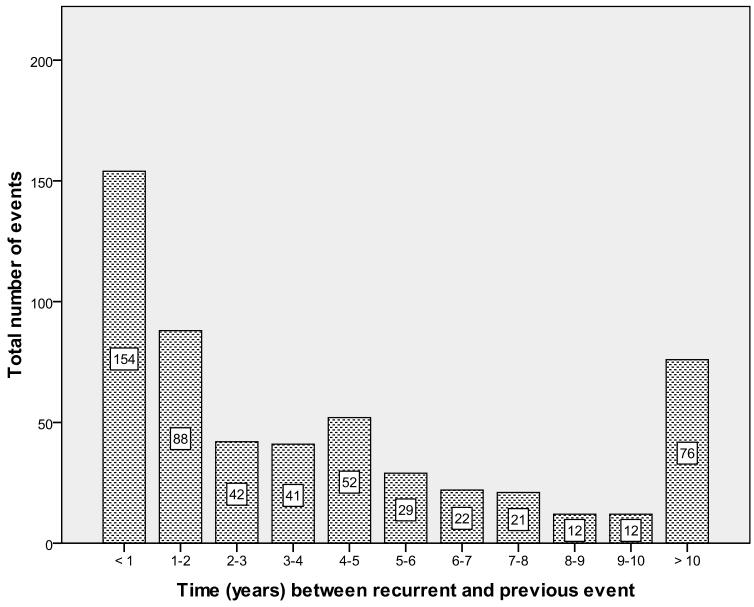


Figure 3. Time between recurrent and previous venous thromboembolism (VTE) event. The graph shows the times (years) between the recurrent and previous event in. The number in each column indicates the total number of events in time period. In 12 patients the time between previous and recurrent event was unknown.

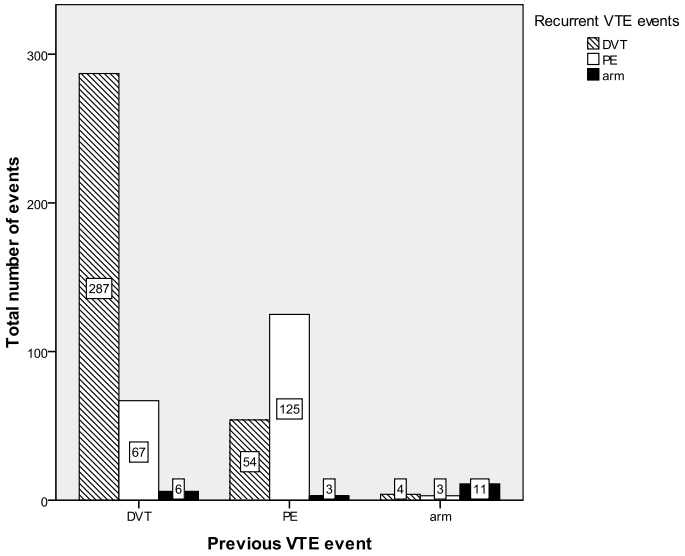


Figure 4. Type of recurrent venous thromboembolism (VTE) event versus type of previous VTE event. The graph shows the type of recurrent VTE event (deep vein thrombosis (DVT), pulmonary embolism (PE) or arm vein thrombosis) versus type of the previous VTE event (DVT, PE, arm vein thrombosis). The number in each column indicates the total number of events in each group. In 1 patient the type of previous event was not known.

DISCUSSION

This study was performed in a well-defined region and showed an overall annual incidence of recurrent VTE of 0.22 per 1000 inhabitants with significant more recurrent events occurring in male patients.

The results of our study are consistent with previous studies showing that the majority of recurrences occur in the first two years after the previous event and the incidence of recurrent DVT was one and half times higher than the incidence of recurrent PE and the incidence of recurrent arm vein thrombosis was rare with an incidence of 0.008 per 1000 inhabitants per year.[13]

We also confirmed earlier findings in that patients with a previous DVT were more likely to have a DVT as a recurrent event than PE, and patients with a previous PE were more likely to develop a recurrent PE.[14] An explanation could be that a residual thrombosis is regarded as a recurrent event. The diagnosis of recurrent VTE is often difficult, because of the presence of persistent thrombotic abnormalities after a first VTE event. In patients with a proximal DVT persistent vein abnormalities are present in 80% and 50% of patients at 3 months and 1 year.[15,16] Therefore, when a patient presents with a suspected recurrent event, it can be difficult to determine whether this represents

new disease or a residual abnormality. Furthermore, residual thrombosis might be a mechanical risk factor, which, by obstructing blood flow, facilitates recurrent thrombosis due to local stasis. However studies showed lower risk of recurrent ipsilateral DVT than contralateral recurrence.[16,17]

In our study we found an incidence rate increasing with age and a significantly higher incidence among men above 45 years of age. Similar as the results in population-based and autopsy studies which have shown that acute VTE occurs predominantly in the middle-aged and elderly people and showing exponential increase with age.[18] An explanation could be that women below 45 years of age are more exposed to risk factors like pregnancy and use of hormonal therapy (i.e. oral contraceptives and hormonal replacement therapy). Nevertheless the absolute recurrence numbers were low at younger age. Furthermore as mentioned in previous studies men have a higher risk for recurrent VTE events than women.[9,10]

This study contained a very large cohort of patients with recurrent VTE and is the first that reports on the absolute incidence of recurrent VTE in a defined population instead of cumulative incidence. This is of importance because patients with recurrent VTE receive prolonged anticoagulation, with associated risks and costs. Absolute incidence numbers reflect the impact of the disorder in the general population without the limitation of duration of follow-up to find recurrent events. The Dutch Thrombosis Service has a well described coverage area and patients with a (recurrent) VTE from the Leiden region are all (with only a few exceptions) registered at the Thrombosis Services. Both patients who received their diagnosis in hospital as patients who were diagnosed by their general practitioner were included in this analysis. Patients who developed a recurrent VTE during anticoagulant treatment were registered again and could therefore not be missed. Furthermore, all included cases were confirmed by objective tests.

This study has some limitations. We performed a retrospective analysis, which can be subject to various biases. Nevertheless, data to calculate our primary endpoint were available in all patients and information of the secondary endpoint, including the presence of risk factors, were available in 77% of the cohort.

Patients who died in the hospital after diagnosis and patients who receive only heparin treatment were not included. During the study period patients with malignancy were treated with oral anticoagulant therapy instead of low molecular weight heparin (LMWH) as is currently recommended in this group of patients. In our study 16% of the patients had a malignancy; this percentage does not indicate that patients with malignancy were missed.

The diagnostic management of recurrent VTE is difficult, because of the non-specific clinical symptoms of recurrent VTE, which could be attributed to chronic symptoms of a previous event and therefore underrecognized. Furthermore imaging of recurrent VTE has limitations. It is difficult to distinguish a residual from an acute new thrombosis

as mentioned above. Criteria for suspected ipsilateral recurrent DVT have been established[19], but these are lacking for patients with suspected recurrent PE or suspected recurrent arm vein thrombosis. Additionally a recent study showed that in 32% of the patients with a suspected ipsilateral recurrent DVT the diagnosis could not be established based on these criteria.[20]

Finally searching for isolated distal DVT was not routinely performed by all radiologists and could therefore have lead to an underestimation of the incidence of DVT. In our study we were not able to distinguish an isolated distal DVT from proximal DVT due to the lack of reported information about the location of DVT. However, the diagnostic value of isolated distal DVT is still a matter of debate.

In conclusion, this study identified an incidence of recurrent VTE of 0.22 per 1000 inhabitants per year with higher incidence in men than women and confirmed that the majority of recurrent events occurred within two years. These factors should be taken into account with risk stratification and knowledge of this figure is important because of the major consequences of prolonged anticoagulant therapy, morbidity and mortality for this group of patients.

REFERENCES

1. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000; 83:657-60.
2. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998 Mar 23;158(6):585-93.
3. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992 Aug;232(2):155-60.
4. Van de Lisdonk EH, Van den Bosch WJHM, Lagro-Janssen ALM. Ziekten in de huisartspraktijk. 4th ed. Maarssen: Elsevier Gezondheidszorg, 2003.
5. Van der Linden MW, Westert GP, De Bakker DH, Schellevis FG. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Bilthoven: RIVM, 2004. Utrecht/Bilthoven: NIVEL/RIVM, 2004.
6. Prandoni P, Lensing AWA, Cogo A, et al. The Long-Term Clinical Course of Acute Deep Venous Thrombosis. Ann of Intern Med. 1996; 125 (1): 1-7
7. Eichinger S, Weltermann A, Minar E, Stain M, Schönauer V, Schneider B, Kyrle PA. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. Arch Intern Med. 2004 Jan 12;164:92-6
8. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet 2010; 376: 2032-9.
9. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350: 2558-63.
10. Christiansen SC, Lijfering WM, Helmerhorst FM, Rosendaal FR, Cannegieter SC. Sex difference in risk of recurrent venous thrombosis and the risk profile for a second event. J Thromb Haemost. 2010;8:2159-68
11. Eichinger S, Kyrle PA. Duration of anticoagulation after initial idiopathic venous thrombosis--the swinging pendulum: risk assessment to predict recurrence. J Thromb Haemost. 2009; 7 Suppl 1: 291-5.
12. Tapson VF. Acute pulmonary embolism. N Engl J Med. 2008;358:1037-52
13. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000 Mar 27;160(6):761-8.
14. Kovacs MJ, Kahn SR, Wells PS, Anderson DA, Chagnon I, LE Gal G, Solymoss S, Crowther M, Perrier A, Ramsay T, Betancourt MT, White RH, Vickars L, Rodger MA. Patients with a first symptomatic unprovoked deep vein thrombosis are at higher risk of recurrent venous thromboembolism than patients with a first unprovoked pulmonary embolism. J Thromb Haemost. 2010; 8:1926-32.
15. Murphy TP, Cronan JJ. Evolution of deep venous thrombosis: a prospective evaluation with US. Radiology 1990;177: 543-8.

16. Piovella F, Crippa L, Barone M et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. Haematologica 2002 May;87(5):515-22

17. Lindmarker P, Schulman S. The risk of ipsilateral versus contralateral recurrent deep vein thrombosis in the leg. The DURAC Trial Study Group. J Intern Med. 2000; 247:601-6.

18. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991;151:933-8.

19. Prandoni P, Cogo A, Bernardi E, Villalta S, Polistena P, Simioni P, Noventa F, Benedetti L, Girolami A. A simple ultrasound approach for detecting of recurrent proximal-vein thrombosis. Circulation 1993; 88: 1730–35.

20. Tan M, Velthuis SI, Westerbeek RE, van Rooden CJ, van der Meer FJ, Huisman MV. High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis. J Thromb Haemost. 2010;8(4):848-50.