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Early complication rates among patients treated for upper extremity thrombosis: A meta-analysis and systematic review

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Submitted

ABSTRACT

The rates of recurrent venous thromboembolism (VTE) and bleeding episodes in patients with upper extremity deep vein thrombosis (UEDVT) receiving anticoagulant therapy are unknown. These point estimates are important to assess the risks and benefits of anticoagulation and to help counsel patients with UEDVT.

The aim of this meta-analysis is to summarize the risk of recurrent VTE (UEDVT, pulmonary embolism (PE) and fatal PE), major and fatal bleeding rates in patients with UEDVT undergoing the first 3 months of anticoagulation therapy.

The data sources used were PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, through 20 December 2011.

Two reviewers independently extracted data onto standardized forms.

During the initial three months of anticoagulation, the rates of recurrent UEDVT is 1.7% (95% CI, 0.9-2.6%), 1.6% (95% CI, 1.0 – 2.4%) for PE, and 2.3% (95% CI, 1.2-3.8%) for major bleeding. The rate of fatal PE and fatal bleeding is 0.5% (95% CI, 0.2-1.0%) and 0.87% (95% CI, 0.39-1.54%) respectively. The overall mortality is 13.1% (8.3-19.0%).

The rate of recurrent VTE on anticoagulant therapy for patients with UEDVT is similar to patients with a lower extremity proximal deep vein thrombosis (DVT); however the (fatal) bleeding rates are higher. These results might suggest a less aggressive treatment strategy for patients with UEDVT compared to patients with lower extremity DVT.

INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) accounts for 4-11% of all thromboses in the deep veins.[1, 1-7] Major risk factors are malignancy and the presence of a central venous catheter (CVC).[2-4, 6, 8] Increased use of CVCs and cardiac pacemakers in inpatient and outpatient populations in recent years has coincided with increased rates of UEDVT.[2-4, 8-10] With an aging population and cancer diagnoses on the rise, it can be expected that this trend will continue.

Not treating an UEDVT could lead to a potential fatal pulmonary embolism (PE), while anticoagulant treatment could have a major and even fatal bleeding as a consequence. Current guidelines advise to treat patients with an UEDVT similarly to patients with a lower extremity thrombosis [11], i.e. a minimum duration of treatment of 3 months. However, the risk of recurrent venous thromboembolism (VTE) and major bleeding episodes of patients with UEDVT receiving anticoagulation have not been well characterized. Upper extremity deep vein thrombosis is commonly thought to be associated with a lower incidence of concomitant PE compared to lower extremity deep vein thrombosis (DVT).[1,2,4,8,12] Furthermore, the mortality of patients with UEDVT is most commonly associated with their underlying disease (e.g. metastatic cancer) rather than a fatal embolism.

Therefore, the risk of recurrent VTE and major bleeding during anticoagulant therapy are important for balancing the risk and benefits of anticoagulation therapy in patients with UEDVT. Although many studies have evaluated the rate of recurrent VTE and major bleeding episodes in patients with lower extremity DVT and/or PE with point estimates around 3% for recurrent VTE and 1.6% for all bleedings during 3 months of anticoagulant therapy, these point estimates remain unknown for patients with UEDVT receiving anticoagulant therapy.[13]

We sought to summarize the risk of recurrent VTE and major bleeding in patients with UEDVT by conducting a systematic review of the literature.

METHODS

Patients, Data sources, and Searches

We conducted a systematic literature search with the help of a medical librarian to identify potential studies on MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials using an OVID interface. Full articles, letters, and conference proceedings (International Society of Thrombosis and Haemostasis and American Society of Hematology) published until 20 December 2011 were eligible for this analysis. We also hand-searched publications of potential relevant journals and reviewed references of included studies and narrative reviews for additional potential studies. We included studies which were

written in English, French, Italian, Spanish, Dutch and German. We attempted to contact authors to obtain missing information.

Study selection

We reviewed all abstracts by using a structured questionnaire to aid our literature search. We reviewed potentially relevant articles in full length to ensure that they satisfied 4 criteria: 1) prospective enrollment of consecutive patients with objectively confirmed symptomatic UEDVT. The diagnosis UEDVT had to be defined as an incompressible venous segment on ultrasonography examination or a filling defect on contrast venography, CT venography or Magnetic Resonance imaging; 2) all recurrent events during follow-up needed to be symptomatic and objective; 3) patients had to have received treatment for at least 3 months with anticoagulant therapy. Qualifying therapy would be thrombolytic therapy; UEDVT treated with at least 5 days of intravenous (IV) or subcutaneous (SC) heparin followed by oral anticoagulant therapy with a target International Normalized Ratio

2-3 or an oral or SC direct thrombin inhibitor or a Xa inhibitor (e.g. rivaroxaban), or use of low molecular weight heparin (LWMH) as monotherapy for at least three months; 4) one or more primary outcomes (recurrent UEDVT and major bleeding) or secondary outcomes (recurrent PE, recurrent fatal PE, fatal bleeding or overall mortality) were reported.

We excluded studies if patients were selected, if asymptomatic UEDVT and PE were included in outcome measures, or if studies solely enrolled patients with effort thrombosis or Paget Schroetter syndrome or if studies did not report any of the primary or secondary outcome measures of our systematic review.

Outcome measures

Primary outcomes were recurrent VTE (diagnosed by contrast venography, ultrasonography,CT scanning, MR imaging, ventilation/perfusion scan, pulmonary angiography or autopsy) and major bleeding events during the initial three months of anticoagulation.

Recurrent UEDVT is defined as a new incompressible venous segment on ultrasonographya new filling defect on contrast venography or CT scanning or defects consistent with a new UEDVT on MR imaging. Major bleeding was defined as per the individual studies'definitions.

Secondary outcomes were PE, fatal PE and fatal bleeding during the initial three months of anticoagulation. Recurrent PE was defined as a new filling defect on CT scanning or a new mismatch defect on ventilation/perfusion scanning. Fatal PE was defined as a high clinical suspicion that the patient died of PE or as PE diagnosed by new imaging prior to death or during autopsy. Fatal bleeding was considered when the bleeding

contributed to death. Furthermore the overall mortality rate (i.e. from any cause) was assessed.

Data Extraction and Quality Assessment

Two reviewers (MT and MC) independently assessed eligibility of articles identified in the initial search strategy for inclusion in the review. They discussed the articles deemed potentially eligible; independently extracted data (baseline characteristics, definition of outcomes, numbers of events) by using a standardized data abstraction form; and assessed the methodological quality of the studies (using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials and the Newcastle–Ottawa Quality Assessment scale for observational studies).

We considered the diagnosis recurrent UEDVT and/or PE during follow-up adequate if the study mentioned that the diagnostic test was compared to previous imaging or when the events were adjudicated by independent investigators. We deemed that fatal PE was adequately diagnosed if the study described that autopsy reports, imaging reports prior to death or adjudication by independent investigators were used. A third party (MH) adjudicated discrepancies between the reviewers.

Data Synthesis and Analysis

To estimate the weighted rates and 95% CI for the review's primary outcome, we identified the reported numbers of objectively confirmed recurrent VTE and major bleedings during 3 months of anticoagulant therapy after the UEDVT in all included studies. Individual study rates were transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion.[14] We then calculated a pooled proportion as the back-transform of the weighted mean of the transformed proportions, using a random effects model.[15] The weighting of outcomes accounts for differences in sample size and between the individual studies. Analyses were performed using StatsDirect software version 2.7.9 (StatsDirect Ltd, Cheshire, UK). Outcomes were allocated according to the intention-to-treat principle.

We originally planned to analyze the primary and secondary outcomes in the following 4 subgroups; 1) the different treatment strategies (i.e. LMWH monotherapy, a combination of LMWH and warfarin and thrombolytic therapy); 2) patients with malignancy; 3) patients with central venous catheters; 4) patients with distal UEDVT compared to proximal UEDVT.

The I^2 statistic was used to estimate total variation among the pooled estimates across studies. An I^2 value less than 25% was considered low-level heterogeneity, 25% to 50% was moderate-level, and greater than 50% was high-level.[16]

RESULTS

We identified 1506 citations in our literature search (appendix I), and 11 were deemed eligible (see figure 1). Baseline characteristics of the included studies are reported in Table 1. All studies were prospective cohort studies; no randomized controlled trials were available for inclusion.

Most studies treated patients with a combination of heparin and vitamin K antagonist. One study only enrolled patients with a central venous catheter and two studies enrolled solely patients with a malignancy. Four out of eleven of the studies inadequately reported how the recurrent UEDVT and/or PE were diagnosed by the predefined criteria. All studies inadequately described how the diagnosis of fatal PE was established, since no description of an autopsy report was given.

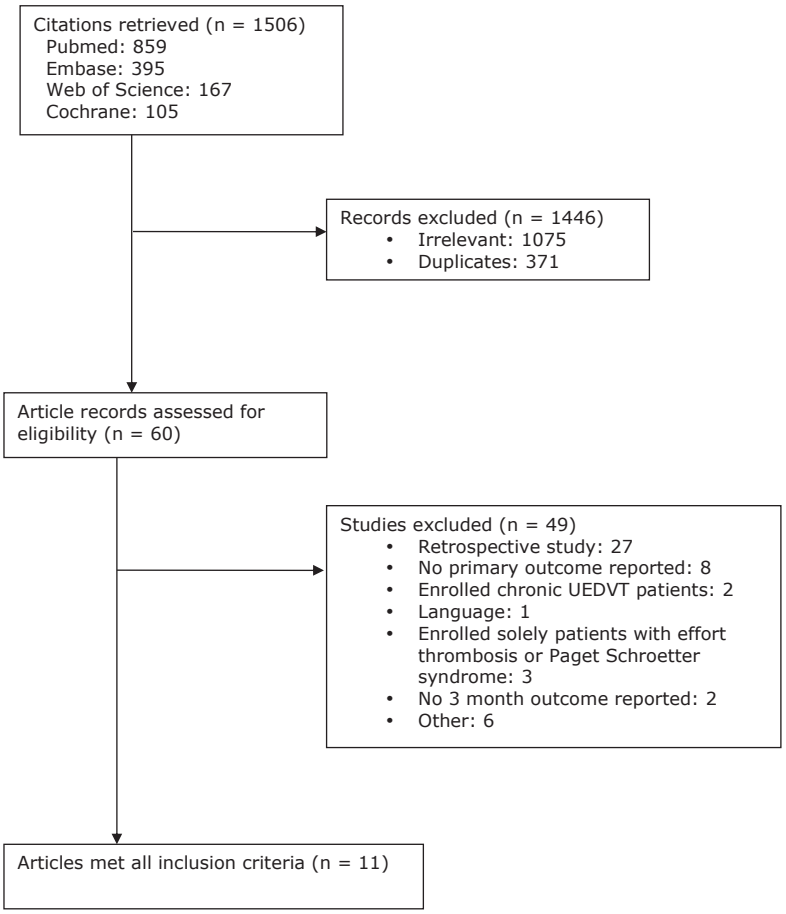

Figure 1. Study flow diagram

Table 1. Baseline characteristics and outcomes of studies of treatment of UEDVT.

Study, year	Treatment (n)	Duration on treatment (months)	CVC n (%)	Malignancy n (%)	Recurrent UEDVT	Recurrent PE	Fatal PE	Methods used to diagnose recurrences	Methods used to diagnose fatal PE	Major bleeding	Fatal bleeding
Rathbun, 2011[19]	Dalteparin + VKA (n = 28) vs. Dalteparin (n = 39)	3	52 (79)	31 (47)	0	0	0	Adequate	Inadequate	1	0
Isma, 2010 [3]	LMWH, VKA, UFH, thrombolysis (n = 63)	3-6	6 (9.5)	19 (30)	0	0	0	Inadequate	Inadequate	NR	NR
Lechner, 2008[20]	VKA (n = 50)	≥ 3	NR	0 (0)	1	0	0	Adequate	Inadequate	NR	NR
Munoz, 2008[1]	LMWH + VKA (n = 512)	3	228 (45)	196 (38)	12	9	1	Adequate	Inadequate	11	3
Kovacs, 2007[21]	Dalteparin + VKA (n = 74)	3	74 (100)	74 (100)	0	0	0	Adequate	Inadequate	3	1
Monreal, 2006[22]	LMWH (n = 147); LMWH + VKA (n = 37)	3	104 (53)	196 (100)	6	6	1	Adequate	Inadequate	8	3
Karabay, 2004[23]	LMWH + VKA; in case of malignancy: LMWH (n=36)	4.7 Mo	23 (64)	6 (17)	0	0	0	Inadequate	Inadequate	NR	NR
Savage, 1999[24]	Dalteparin + VKA (n=46)	3	16 (35)	34 (74)	1	0	0	Adequate	Inadequate	1	0
Prandoni, 1997[6]	IV UFH + VKA (n = 27)	≥ 3	8 (30)	6 (22)	0	0	0	Adequate	Inadequate	NR	NR
Monreal, 1994[25]	IV UFH (8 days) + VKA (n = 85)	NR*	86 (99)	27 (32)	0	3	2	Inadequate	Inadequate	0	0
Wilson, 1990[26]	Streptokinase + UFH iv + Coumadin (n = 7)	NR*	NR	NR	0	0	0	Inadequate	Inadequate	0	0

N: number; CVC: central venous catheter; UEDVT: upper extremity deep vein thrombosis; PE: pulmonary embolism; VKA: vitamin K antagonists; LMWH: low molecular weight heparin; UFH: unfractionated heparin; NR not reported; *the extracted numbers were within the first 3 months of anticoagulant therapy

Table 2. Rates of recurrent UEDVT and (fatal) PE.

	Recurrent UEDVT	PE	Fatal PE	Major bleeding	Fatal bleeding	Overall mortality
Number of patients (n)	1162	1162	1162	986	986	894
Rate of events during 3 months follow-up (%, 95% CI)	1.7% (0.9 – 2.6%)	1.6% (1.0 – 2.4%)	0.5% (0.2 – 1.0%)	2.3% (1.2 – 3.8%)	0.87% (0.39-1.54%)	13% (8.3 – 19%)

UEDVT: upper extremity deep vein thrombosis; PE: pulmonary embolism; n: number; CI: confidence interval

A total of 1162 patients with confirmed UEDVT were included in the analyses. Table 2 gives an overview of the results. All patients received anticoagulation therapy on the basis of the UEDVT diagnosis (i.e. no patients were left untreated). During the first 3 months of anticoagulant therapy, the rate of recurrent UEDVT was 1.7% (95% CI, 0.9-2.6 ;I^2 = 7.6%). The forest plot is shown in figure 2. The rate of recurrent PE and of recurrent fatal PE was 1.6% (95% CI, 1.0-2.4; I^2 = 0%) and 0.5% (95% CI,0.2-1.0; I^2= 0%) respectively.

The rate of major bleeding was 2.3% (95% CI,1.2-3.8; I^2 = 27.9%) during the first 3 months of anticoagulant therapy and its fatal bleeding rate was 0.87% (95% CI, 0.39-1.54; I^2= 0%). The overall mortality in the first 3 months was 13.1% (95% CI, 8.3-19.0; I^2: 76.2%).

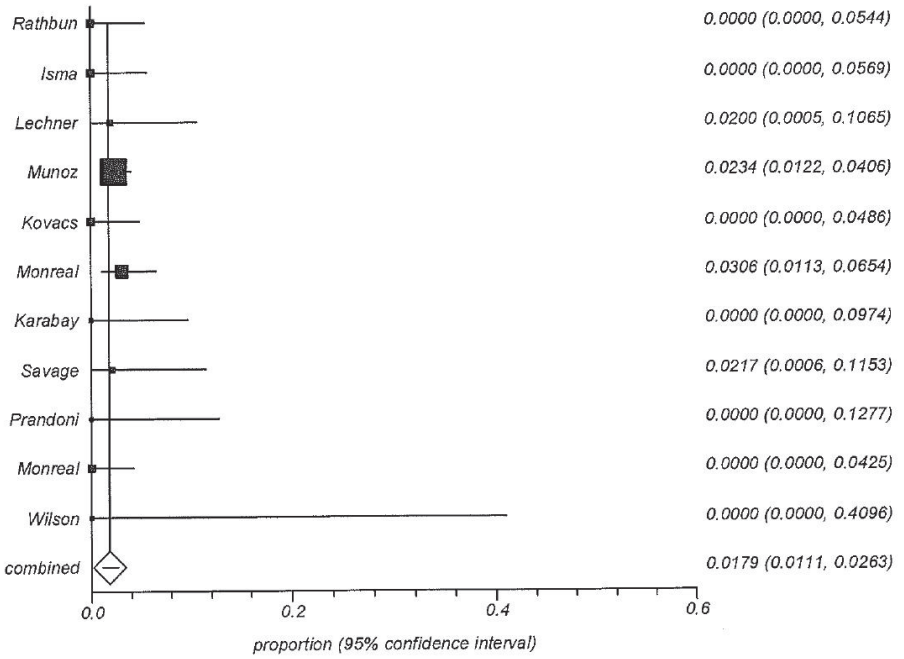

Figure 2. Forest plot of recurrent UEDVT outcome with fixed effects model

We could not perform any of the pre-planned sensitivity analyses due to the small number of included studies. The funnel plots of included studies were not indicative of publication bias. The quality of the observational studies is reported appendix II. All studies had adequate representativeness, assessment of outcome measures and follow-up.

DISCUSSION

The results of this meta-analysis shows that the VTE recurrence rates on anticoagulant therapy for patients with UEDVT is similar to patients with a lower extremity proximal DVT. However the risk of major bleeding and its associated case fatality is higher.

A recent systematic review of the literature assessing the case fatality rates of recurrent VTE in patients with lower limb DVT reported a 3-month risk of recurrent VTE and PE of 3.2% (95% CI, 2.4-4.1) and 1.3% (95% CI, 1.0-1.2) respectively.[17] In our systematic review, we estimated that the recurrence rate of UEDVT was 1.7% (95% CI, 0.9-2.6), while the risk of PE was 1.6% (95% CI, 1.0-2.4). The rate of major and fatal bleeding episodes during the initial 3-months of anticoagulation for lower extremity DVT or PE has been reported to be 1.6% (95% CI, 1.2-2.1) and 0.2% (95% CI, 0.1-0.3) respectively. We found a comparable rate of major bleedings (2.3% (95% CI, 1.2-3.8%) but fatal bleeding episodes were higher in the UEDVT population (0.87% (95% CI, 0.4-1.5%)). A potential cause for this discrepancy may be the high proportion of patients with cancer and other co-morbidities among patients with UEDVT compared to lower extremity DVT and PE patients. Cancer patients receiving anticoagulation are known to have a heightened risk of major bleeding and associated fatal bleeding episodes compared to non-cancer patients with VTE.[18] Another hypothesis could be that the definitions used for major and fatal bleedings were different in the studies included in this systematic review than in the studies which evaluated the recurrence and bleeding rates of patients with lower extremity DVT and PE. The cause of the observed higher fatal bleeding rate should be evaluated in future studies, however our meta-analysis suggests that patients with UEDVT might benefit of less aggressive treatment than patients with lower extremity DVT and PE.

In addition to the intensity of anticoagulation, the optimal duration of anticoagulant treatment of patients with UEDVT is still uncertain. Current guidelines advise to treat patients with UEDVT for at least three months with anticoagulant therapy, which is similar to the treatment of patients with lower extremity DVT and/or PE.[11] However randomized controlled treatment trials are lacking and are urgently needed to evaluate this very clinical relevant issue.

This study is the first systematic review including estimates on the recurrence and bleeding rates of patients with UEDVT, which are based on a larger sample size than

all the individual studies and consequently provides narrower confidence intervals. Additionally the heterogeneity between all studies was low for the primary outcomes of recurrence and major bleeding. Finally our study only took clinical relevant symptomatic VTE in account, because we excluded studies that included patients who had asymptomatic VTE found during screening examinations.

It is important to note the limitations of the systematic review. First, the quality of the studies was limited. Not all studies adequately reported recurrences and the definition of a major bleeding was heterogeneous throughout the studies. Furthermore the observed heterogeneity of overall mortality was high; this is probably due to different proportions of patients with malignancies who were enrolled in the component studies. Third, not all studies consistently reported long-term follow-up after stopping anticoagulant therapy and therefore we couldn't pool this data for this systematic review. Finally patient level data would be needed to establish recurrence and bleeding rates in specific patient populations. Risk factors (for example, malignancy, presence of central venous catheter) might influence recurrence and bleeding rates, but without patient-level data, this could not be explored.

In conclusion, our study shows that the estimates of recurrent (fatal) UEDVT and major bleeding in patients with UEDVT in the first three months of anticoagulant therapy are similar as patients with a lower extremity and/or PE. However, the fatal bleeding rate is higher. This might warrant a less aggressive therapy strategy in patients with UEDVT than proposed in current guidelines. There is an urgent need for randomized therapy studies in patients with UEDVT.

REFERENCES

1. Munoz FJ, Mismetti P, Poggio R et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest 2008;133:143-148.
2. Bernardi E, Pesavento R, Prandoni P. Upper extremity deep venous thrombosis. Semin Thromb Hemost 2006;32:729-736.
3. Isma N, Svensson PJ, Gottsater A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmo thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. Thromb Res 2010;125:e335-e338.
4. Joffe HV, Kucher N, Tapson VF, Goldhaber SZ. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation 2004;110:1605-1611.
5. Martinelli I, Cattaneo M, Panzeri D, Taioli E, Mannucci PM. Risk factors for deep venous thrombosis of the upper extremities. Ann Intern Med 1997;126:707-711.
6. Prandoni P, Polistena P, Bernardi E et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997;157:57-62.
7. Spencer FA, Emery C, Lessard D, Goldberg RJ. Upper extremity deep vein thrombosis: a community-based perspective. Am J Med 2007;120:678-684.
8. Constans J, Salmi LR, Sevestre-Pietri MA et al. A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost 2008;99:202-207.
9. Rooden CJ, Tesselaar ME, Osanto S, Rosendaal FR, Huisman MV. Deep vein thrombosis associated with central venous catheters - a review. J Thromb Haemost 2005;3:2409-2419.
10. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 2003;21:3665-3675.
11. Proceedings of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: evidence-based guidelines. Chest 2004;126:172S-696S.
12. Jones MA, Lee DY, Segall JA et al. Characterizing resolution of catheter-associated upper extremity deep venous thrombosis. J Vasc Surg 2010;51:108-113.
13. Carrier M, Rodger MA, Wells PS, Righini M, Le GG. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. J Thromb Haemost 2011;9:1119-1125.
14. Miller JJ. The inverse of the Freeman-Turkey double arcsine transformation. American statistician 1978;32:138.
15. Laird NM, Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess Health Care 1990;6:5-30.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
17. Carrier M, Le GG, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010;152:578-589.
18. Prandoni P, Lensing AW, Piccioli A et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-3488.
19. Rathbun SW, Stoner JA, Whitsett TL. Treatment of upper-extremity deep vein thrombosis. J Thromb Haemost 2011;9:1924-1930.

20. Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S, Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. J Thromb Haemost 2008;6:1269-1274.
21. Kovacs MJ, Kahn SR, Rodger M et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost 2007;5:1650-1653.
22. Monreal M, Munoz FJ, Rosa V et al. Upper extremity DVT in oncological patients: analysis of risk factors. Data from the RIETE registry. Exp Oncol 2006;28:245-247.
23. Karabay O, Yetkin U, Onol H. Upper extremity deep vein thrombosis: clinical and treatment characteristics. J Int Med Res 2004;32:429-435.
24. Savage KJ, Wells PS, Schulz V et al. Outpatient use of low molecular weight heparin (Dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost 1999;82:1008-1010.
25. Monreal M, Raventos A, Lerma R et al. Pulmonary embolism in patients with upper extremity DVT associated to venous central lines—a prospective study. Thromb Haemost 1994;72:548-550.
26. Wilson JJ, Zahn CA, Newman H. Fibrinolytic therapy for idiopathic subclavian-axillary vein thrombosis. Am J Surg 1990;159:208-210.

Appendix I. Search strategy

((("venous thrombosis"[tiab] OR "Venous Thrombosis"[mesh:noexp] OR "Budd-Chiari Syndrome"[mesh] OR "Postthrombotic Syndrome"[mesh] OR "Budd-Chiari Syndrome"[tiab] OR "Postthrombotic Syndrome"[tiab] OR "Venous Thromboses"[tiab] OR "Vein Thrombosis"[tiab] OR "Vein Thromboses"[tiab]) AND ("Upper Extremity"[mesh:noexp] OR "Arm"[mesh] OR "Axilla"[mesh] OR "Elbow"[mesh] OR "Forearm"[mesh] OR "Shoulder"[mesh] OR "Arm"[tiab] OR Arms[ti] OR "Axilla"[tiab] OR "Elbow"[tiab] OR "Forearm"[tiab] OR "Shoulder"[tiab] OR "Upper Extremity"[tiab] OR "Upper Extremities"[tiab] OR "jugular vein"[tiab] OR "jugular veins"[tiab] OR "jugular venous"[tiab] OR "jugular veins"[mesh] OR "Axillary Vein"[mesh] OR "Brachiocephalic Veins"[mesh] OR "Subclavian Vein"[mesh] OR "Axillary Vein"[tiab] OR "Brachiocephalic Vein"[tiab] OR "Subclavian Vein"[tiab] OR "Axillary Veins"[tiab] OR "Brachiocephalic Veins"[tiab] OR "Subclavian Veins"[tiab])) OR "Upper Extremity Deep Vein Thrombosis"[mesh] OR CAUEDVT[tw] OR UEDVT[tw]) AND (prognosis OR "prognosis"[mesh] OR prognostic OR survival OR "Survival analysis"[mesh] OR recurrence OR "Recurrence"[mesh] OR bleeding OR hemorrhage OR haemorrhage OR "hemorrhage"[mesh] OR "clinical course")

Appendix II. Quality of included studies using the Newcastle – Ottawa quality scale for cohort studies.

	Selection				**Comparability**	**Outcome**		
Study	Representativeness of exposed cohort	Representativeness of non exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Comparability of cohorts	Assessment of Outcome	Was follow-up long enough?	Adequacy of follow-up
Rathbun, 2011[19]	*	*	*	*	**	*	*	*
Isma, 2010[3]	*	NA	*	*	NA	*	*	*
Lechner, 2008[20]	*	*	*	*	**	*	*	*
Munoz, 2008[1]	*	NA	*	*	NA	*	*	*
Kovacs, 2007[21]	*	*	*	*	**	*	*	*
Monreal, 2006[22]	*	NA	*	*	NA	*	*	*
Karabay, 2004[23]	*	NA	*	*	NA	*	*	*
Savage, 1999[24]	*	NA	*	*	NA	*	*	*
Prandoni, 1997[6]	*	*	*	*	*	*	*	*
Monreal, 1994[25]	*	NA	*	*	NA	*	*	*
Wilson, 1990[26]	*	NA	*	*	NA	*	*	*

*A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability; NA: not applicable