

Common alternative diagnoses in general practice when deep venous thrombosis is excluded

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ABSTRACT

Background: In patients initially suspected of deep venous thrombosis (DVT) the diagnosis can be confirmed in approximately 10 to 30% of cases. For the majority of patients this means that eventually an alternative diagnosis is assigned.

Objective: To assess the frequency distribution of alternative diagnoses and subsequent management of patients in primary care after initial exclusion of DVT. In addition, assess the value of ultrasound examination for the allocation of alternative diagnoses.

Methods: Data were recorded by general practitioners alongside a diagnostic study in primary care in the Netherlands (AMUSE). Additional data were retrieved from a three-month follow-up questionnaire. A descriptive analysis was performed using these combined data.

Results: The most prevalent diagnoses were muscle rupture (18.5%), chronic venous insufficiency (CVI) (14.6%), erysipelas/cellulitis (12.6%) and superficial venous thrombosis (SVT) (10.9%). Alternative diagnoses were based mainly on physical examination; ultrasound examination (US) did not improve the diagnostic yield for the allocation of alternative diagnoses. In about 30% of all cases, a wait and see approach was used (27 to 41%). During the three-month follow-up nine patients were diagnosed with venous thromboembolic disease, three of which occurred in patients with the working diagnosis of SVT ($p=0.026$).

Conclusions: We found that after exclusion of DVT in general practice a wait and see policy in the primary care

setting is uneventful for almost one third of patients, but with the alternative diagnosis of SVT, patients may require closer surveillance since we found a significant association with thrombosis in these patients.

KEYWORDS

Deep venous thrombosis, alternative diagnoses, general practice

INTRODUCTION

The clinical diagnosis of deep venous thrombosis (DVT) is challenging. Unilateral complaints such as painful swelling of the leg, with or without accompanying redness, are common symptoms of many conditions besides DVT. This may explain why only a small proportion of patients who are clinically suspected of having a DVT and who are subsequently evaluated by ultrasound examination do actually have the condition, with rates ranging between 10 to 30% for different populations.¹⁻⁴ Therefore an alternative diagnosis is eventually assigned for the majority of patients. In order to study the distribution of alternative diagnoses in patients in whom DVT was excluded, we gathered data alongside a diagnostic management study in general practice.⁵ We assessed the frequencies of alternative

diagnoses that were allocated and assessed which signs and/or symptoms are used to arrive at the different alternative diagnoses. In addition we looked at the associated disease management in these patients.

It has been suggested that the reduction of the number of ultrasound examinations by the use of a clinical decision rule in combination with a D-dimer assay and subsequent avoidance of objective testing in 30 to 50% of patients who present with complaints suspected of DVT is undesirable since these examinations could be helpful to establish an alternative diagnosis in the absence of DVT.⁶

Therefore, our study aims were to assess the frequency of common alternative diagnoses and associated disease management, to describe the signs and symptoms that were used to establish the different alternative diagnoses, and to explore the additional value of ultrasound examination for the allocation of alternative diagnoses.

METHODS

We studied the alternative diagnoses and the management of patients suspected of DVT in primary care, after DVT was ruled out based on a clinical decision strategy. From March 2005 till January 2007 data were collected alongside the 'Amsterdam Maastricht Utrecht Study on venous thrombo-Embolism' (AMUSE), a diagnostic management study in primary care.⁵ We performed a descriptive analysis using these data. Briefly, the AMUSE study is a management study conducted in primary care in three regions of the Netherlands, involving 1028 consecutive patients with complaints suspect for DVT. In AMUSE the safety and efficiency of the use of a clinical decision rule including a point of care D-dimer assay to exclude DVT in primary care was evaluated. Patients who scored above a predefined threshold were referred for ultrasound; patients below the threshold were not referred.⁷ Following the initial presentation, all patients were evaluated at day 7±2 by the general practitioner. For the present descriptive study, data on clinical status that were collected at this one-week follow-up visit during the management study and data derived from a questionnaire on health problems that were experienced during a period of three months after the initial presentation were analysed.

Data collection

The variables for the analysis were derived from a systematic case record form (CRF) filled out by the general practitioner at the second patient visit, after one week. The following items were recorded: leg complaints, onset of complaints, medical history, risk factors for venous thrombosis, medication use, findings at physical examination, ultrasound result (if ultrasound was

conducted), result of clinical decision rule, most likely diagnosis (working diagnosis) and the therapy that was instituted.

In addition, variables were derived from questionnaires that were sent out to all patients three months after inclusion. The questionnaires comprised questions on leg complaints, office visits in general practice and/or visits to hospital-based specialists for leg problems, as well as questions on initiated therapy for these problems. All patients who did not respond (30%) were contacted. On suspicion of a (recurrent) thromboembolic event, based on the questionnaires, additional medical information was retrieved from the medical records of the treating physician.

Venous thromboembolism

Of the 1028 eligible patients available for analysis, 127 patients were diagnosed with DVT at presentation. During three months of follow-up venous thromboembolism furthermore occurred in 11 patients who were initially not diagnosed with DVT (1.1%). In total 138 patients were documented to have thrombotic disease. During the entire follow-up period ten patients died (seven were non-VTE deaths) and three patients were lost to follow-up.

Of the 1028 patients analysed, 1002 were initially assessed according to the AMUSE protocol.⁵ The diagnostic clinical decision rule according to the AMUSE protocol used the following dichotomous variables: male gender, use of hormonal contraceptives, active malignancy in the past six months, surgery in the previous month, absence of leg trauma, distension of collateral veins, difference in calf circumference ≥ 3 cm, and D-dimer (Simplify®) abnormal.⁷ Twenty-six patients were not assessed in accordance with the AMUSE protocol; they all underwent ultrasound assessment. All adverse outcome events during follow-up were assessed by an independent adjudication committee.

Alternative diagnoses

We analysed the prevalence of different alternative diagnoses as recorded by the general practitioners during the one-week follow-up visit, thus after results of the ultrasound examinations were known for referred patients. The general practitioner could choose from a list of ten possible alternative diagnoses to be recorded on the CRF: deep vein thrombosis (DVT), erysipelas /cellulitis, chronic venous insufficiency (CVI), lymphoedema, superficial venous thrombosis (SVT), mycosis, muscle rupture/haematoma, Baker's (popliteal) cyst, ankle arthritis and pelvic tumour. The general practitioners were asked to record the most likely diagnosis, in their opinion. If this diagnosis was not among these ten pre-specified diagnoses, they could record the preferred diagnosis as open text. The diagnosis of DVT could be assigned when the patient had a documented DVT

on ultrasound one week earlier or when the diagnosis of DVT was still the most likely diagnosis at that point in time, according to the general practitioner.

Statistical analysis

We first assessed the frequency of DVT and the frequencies of all alternative diagnoses in our study population. Then, for each of the four most frequent alternative (i.e. non-DVT) diagnoses, the presence of signs and symptoms was described and the association of signs and symptoms with each diagnosis was estimated. Similarly, known risk factors for thrombosis, data on ultrasound examination, therapeutic strategies and referral and follow-up practices were analysed for frequency and their respective association with each alternative diagnosis. Associations were described as odds ratios and their 95% confidence intervals and were calculated comparing persons with a specific diagnosis (erysipelas/cellulitis, muscle rupture/haematoma, CVI, SVT, DVT, respectively) with all of those without that particular diagnosis, using univariate logistic regression and tested using the Chi-square test for categorical variables (SPSS 17.0 for Windows). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Common alternative diagnoses

At the one-week follow-up visit, 669/1028 CRFs (65.1%) contained a specific diagnosis. No specific diagnosis was stated on the remaining 359/1028 CRFs (34.9%). At the time of the follow-up visit 129/1028 patients had already been diagnosed with DVT. For 57/129 of these patients no diagnosis was stated on the CRF, leaving 302/1028 (29%) of patients without an alternative diagnosis at week 1. Although 29% of cases did not have a diagnosis stated at the one-week visit, all but three of the 1028 patients were followed up. Among the diagnoses given, the four most prevalent alternative diagnoses to DVT were muscle rupture/haematoma (18.5%), CVI (14.6%), erysipelas/cellulitis (12.6%), and SVT (10.9%). The other alternative diagnoses mentioned were each present in less than 6% (lymphoedema (5.5%), Baker's (popliteal) cyst (4.5%), pelvic tumour (0.6%), ankle arthritis (1.8%), and mycosis (0%). Fifteen percent of the general practitioners described an alternative diagnosis other than the ten diagnostic options mentioned in the CRF. The added alternatives were mainly described as: muscle complaints, lower back hernia, known oedema and gonarthrosis.

Table 1. Signs and symptoms for each alternative diagnosis besides DVT

| Disease | Erysipelas/cellulitis N = 84 | | Muscle rupture/ hematoma N = 124 | | CVI N = 98 | | SVT N = 73 | | DVT N = 138 | |
|----------------------------|---------------------------------|----------------------------------|--|---------------------------------|---------------|--------------------------------|---------------|-------------------------------|----------------|-------------------------------|
| | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) |
| <i>Signs, symptoms</i> | | | | | | | | | | |
| Right side | 38(49) | | 56(49) | | 48(53) | | 49 | | 56(42) | |
| Pain | 76(92) | | 113(92) | <0.05 OR=2.1 (1.04-4.03) | 71(76) | <0.01 OR=0.4 (0.25-0.7) | 69(95) | <0.05 OR=3.1 (1.1-8.3) | 118(86) | |
| Swelling | 80(96) | <0.001 OR=8.6 (2.8-26.1) | 86(69) | <0.01 OR=0.6 (0.36-0.86) | 80(84) | | 51(70) | | 126(91) | <0.001 OR=3.4 (1.9-6.2) |
| Swelling entire leg | 15(19) | | 18(15) | <0.05 OR=0.2 (0.09-0.29) | 30(32) | 0.01 OR=1.9 (1.2-3.03) | 9(13) | 0.05 OR=0.5 (0.24-1.0) | 48(35) | <0.001 OR=2.1 (1.5-3.2) |
| Painful palpation vein | 39(48) | | 67(57) | | 49(47) | | 57(80) | <0.001 OR=3.7 (2.0-6.7) | 69(53) | |
| Redness | 76(91) | <0.001 OR=21.3 (10.2-44.3) | 15(12) | <0.001 OR=0.6 (0.34-0.99) | 30(33) | | 37(51) | <0.05 OR=1.8 (1.1-2.8) | 53(40) | |
| Collateral vein dilatation | 10(26) | | 11(9) | | 20(21) | | 19(26) | | 29(21) | <0.05 OR=1.7 (1.1-2.6) |
| Acute onset | 48(61) | | 71(59) | | 34(38) | <0.01 OR=0.5 (0.34-0.86) | 40(56) | | 76(57) | |

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05. Then, odds ratios and 95% confidence intervals are included as well (n = 669).

Muscle rupture/haematoma was the only diagnosis that was seen equally frequently in men and women, whereas the other alternative diagnoses occurred significantly more often in women ($p \leq 0.05$).

Association with signs and symptoms

Table 1 shows the distribution of signs and symptoms for each of the four most frequent alternative diagnoses and DVT respectively. 'Pain' and 'swelling' were common findings in all four most frequent alternative diagnoses. For most of the alternative diagnoses the onset of complaints was acute. An exception was the non-acute onset of CVI in a majority (61.8%) of cases: OR 0.5 (0.34 to 0.86). Compared with the other alternative diagnoses, CVI also presented more often with 'swelling of the entire leg'. 'Redness' was the most distinctive feature of erysipelas: OR 21.3 (10.2 to 44.3) and was present in 91% of these patients. In contrast, 'redness' as well as 'swelling' was more often absent in

muscle rupture/haematoma. 'Painful palpation of the vein' was observed to be discriminatory for SVT: OR 3.7 (1.1 to 8.3).

Association with risk factors for thrombosis

The distribution of classic risk factors for venous thromboembolism of each alternative diagnosis was compared with the distribution of these risk factors in patients with confirmed DVT (table 2). Muscle rupture/haematoma was negatively associated with most risk factors for thrombosis. In contrast, positive associations with previous SVT (OR 2.9 (1.7 to 5.1)), and previous DVT (OR 5.2 (2.8 to 9.5)) were observed for SVT. CVI showed positive associations with active malignancy (OR 2.4 (1.6 to 3.8)) and malignancy not active (OR 2.1 (1.0 to 4.4)).

Therapeutic strategies

The instituted therapy as recorded in the CRF at week 1 was analysed for the four most prevalent alternative

Table 2. Risk factors for each alternative diagnosis besides DVT

| Disease | Erysipelas/cellulitis N = 84 | | Muscle rupture/ hematoma N = 124 | | CVI N = 98 | | SVT N = 73 | | DVT N = 138 | |
|-----------------------|---------------------------------|------------------------------|--|--------------------------------|---------------|-------------------------------|---------------|-------------------------------|----------------|-------------------------------|
| | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) | N (%) | P OR (95% CI) |
| <i>Risk factors</i> | | | | | | | | | | |
| Malignancy active | 2(2) | | 2(2) | <0.05 OR=0.25 (0.1-0.9) | 10(10) | <0.05 OR=2.4 (1.6-3.8) | 4(6) | | 15(11) | <0.01 OR=2.6 (1.4-4.9) |
| Malignancy not active | 4(5) | | 4(3) | | 10(10) | <0.05 OR=2.1 (1.0-4.4) | 5(7) | | 14(10) | <0.05 OR=1.9 (1.0-3.4) |
| Age > 70 yr | 28(35) | | 22(19) | 0.001 OR=0.4 (0.27-0.7) | 42(44) | <0.01 OR=2 (1.3-3.1) | 27(38) | | 39(29) | |
| Previous DVT | 5(7) | <0.05 OR=0.3 (0.1-0.8) | 13(15) | | 19 (20) | | 22(31) | 0.001 OR=2.9 (1.7-5.1) | 30(22) | <0.05 OR=1.6 (1.1-2.6) |
| Previous SVT | 8(10) | | 4(3) | <0.05 OR=0.3 (0.12-0.8) | 7(7) | | 19(26) | <0.001 OR=5.2 (2.8-9.5) | 9(7) | |
| Recent surgery | 3(4) | | 4(3) | <0.05 OR=0.4 (0.1-0.98) | 11(11) | | 3(4) | | 11(8) | |
| Travel | 6(8) | | 13(11) | | 7(7) | | 8(11) | | 20(15) | <0.05 OR=1.9 (1.1-3.3) |
| Trauma absent | 59(70) | | 77(62) | <0.01 OR=0.5 (0.34-0.8) | 77(79) | | 58(79) | | 109(79) | |
| Male gender | 37(44) | | 56(45) | | 30(31) | <0.05 OR=0.7 (0.4-1.1) | 19(26) | <0.05 OR=0.5 (0.3-0.9) | 69(50) | <0.001 OR=1.9 (1.3-2.7) |
| Varicositas | 24(29) | | 27(22) | <0.001 OR=0.4 (0.27-0.7) | 51(55) | <0.001 OR=2.4 (1.6-3.8) | 47(67) | <0.001 OR=4.2 (2.5-7.1) | 44(33) | |

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05. Then, odds ratios and 95% confidence intervals are included as well (n = 669).

diagnoses. The preprinted therapeutic options on the CRF that the general practitioner could choose from were: antibiotic therapy, pain reduction (NSAIDs), antithrombotic therapy (LMWH and coumarins), compression therapy, physiotherapy or no therapy (observant).

In almost 30% of cases, a wait and see approach was used and no therapy was instituted (27 to 41%). For the diagnosis of muscle rupture/haematoma a wait and see policy was significantly more often followed than for the other alternatives. In contrast, for the diagnosis of erysipelas/cellulitis no immediate action was undertaken in only 7% of the cases; in 70% antibiotic therapy was instituted, which was combined with compression therapy in a third of the cases (35%).

For CVI, compression therapy was the most common form of therapy (33%) when therapy was stipulated, and furthermore diuretics (10%) as well as NSAIDs (7%) were prescribed. In the treatment of SVT, compression therapy was observed to be the main therapeutic feature (40%). The four additional forms of therapy were NSAIDs, LMWH, coumarins and antibiotics (19%, 12%, 7% and 6% respectively).

Referral and follow-up

The majority of patients with an alternative diagnosis were followed up in general practice. Patients were referred for further evaluation and therapy in secondary care in 15 to 20% of cases. Of the patients with the diagnosis of muscle rupture/haematoma and CVI 10% and 9%, respectively, were referred to the surgical department for evaluation. Patients with the diagnosis of SVT and erysipelas were most commonly referred to a dermatologist (9 to 11%).

On average, patients visited their general practitioner in the follow-up of leg complaints two to three times (mean 2.4, SD 3.7) over the course of three months.

For most alternative diagnoses the maximum number of visits was six.

Additional value of ultrasound examination

Ultrasound examination was only performed in patients with either a high clinical score and/or a positive result on D-dimer testing. The avoidance of ultrasound examinations in 50% of patients suspected of DVT did not, however, impact the prevalence of the most common alternative diagnoses. The same distribution was found for SVT and erysipelas irrespective of ultrasound examination: SVT without ultrasound in 9.2% (32/349) vs 12.8% (41/320) with ultrasound, $p=0.13$; erysipelas without ultrasound in 12.6% (44/349) vs 12.5% (40/320) with ultrasound, $p=0.97$. Both the diagnosis of muscle rupture and CVI were more frequent in patients who did not undergo ultrasound examination 24.6% (86/349) vs 11.9% (38/320), $p<0.0001$ and 16.9 (59/349) vs 12.2% (39/320), $p=0.09$, respectively. For the less frequently observed alternative diagnoses, arthritis of the ankle

was significantly more often diagnosed in patients not undergoing ultrasound: 3.3% (11/341) vs 0.3% (1/327), $p=0.004$. Also lymphoedema was significantly more often diagnosed in patients who did not have an ultrasound examination: 7.2% (24/309) vs 3.6% (12/321), $p=0.04$. This was also the case for the diagnosis of Baker's cyst: 32.7% (86/263) vs 11.9% (38/320), $p<0.001$.

Thrombotic events in relation to alternative diagnosis

During the three months follow-up period 11 patients (1.1%) who were not diagnosed with DVT at presentation (7 in the low-score group, 4 in the high-score group) were diagnosed with venous thromboembolic disease, one of which was fatal. Two of these 11 patients were diagnosed with DVT within two days after presentation; the alternative diagnoses of the remaining nine patients were SVT (3), muscle rupture (1), lymphoedema (1) and other (1). For three patients, two in the low-score group and one in the high-score group, no alternative diagnosis was stated; these patients were eventually diagnosed with pulmonary embolism.

DISCUSSION

The alternative diagnoses given were based mainly on clinical features. No specific diagnosis was stated in 29% of patients; this percentage of patients without a diagnosis is in accordance with a report from secondary care, where all patients underwent ultrasound and no diagnosis was affirmed in 24% of patients.⁶ The use of a clinical decision rule and the associated 50% reduction of ultrasound examinations, therefore, are not likely accountable for the lack of allocated alternative diagnoses. Ultrasound did not improve the diagnostic yield; none of the alternative diagnoses were more prevalent among patients who did have ultrasound examination. After the exclusion of DVT a wait and see policy in the primary care setting was sufficient in one third of the patients. However, patients diagnosed as SVT may require closer surveillance because, of the patients who were diagnosed with DVT during the follow-up period of three months, three out of six were diagnosed as SVT. Although the analyses were not pre-specified it is statistically unusual ($p=0.026$) that of the nine missed venous thromboembolic events, three occurred in patients with the working diagnosis of SVT. None of these patients were treated with anticoagulant medication. The omission of treatment could very well be influenced by lack of information on the extent of the thrombus into the (deep) venous system. SVT has been reported in association with DVT in several instances, a review of cases of SVT in primary care showed that DVT occurred in 2.7% of all SVT patients as compared with 0.2% in the controls: $OR=10.2$

(2.0-51.6).^{8,9} A recently published retrospective evaluation of therapeutic management and clinical outcome of SVT in a secondary care facility¹⁰ also showed that SVT may be prone to venous thromboembolism. By using a clinical decision rule in combination with D-dimer testing the extra information retrieved from D-dimer testing may also guide the decision process towards the allocation of an alternative diagnosis. SVT was both significantly associated with a positive result on D-dimer testing and with a more prothrombotic profile.

Some limitations of this study have to be mentioned. First, all alternative diagnoses in our cohort were working diagnoses; no objective diagnostic testing was performed to confirm these diagnoses. For most diagnoses, however, no gold standard diagnostic tests are available or routinely used if available; in our opinion, this study is therefore a good representation of current practice. Second, for 29% of patients no alternative diagnosis was stated; all of these patients, however, had a follow-up without incident.

In conclusion: We found that the reduction in the number of ultrasound examinations does not influence the diagnostic yield and that after exclusion of DVT based on a decision strategy a wait and see policy in the primary care setting is uneventful for almost one third of patients. Patients with the diagnosis of SVT may require closer surveillance since we found a significant association with thrombosis in these patients.

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REFERENCES

1. Cogo A, Lensing AWA, Koopman MMW, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis.: prospective cohort study. *BMJ*. 1998;316:17-20.
2. Lensing AW, Prandoni P, Prins MH, Buller HR. Deep-vein thrombosis. *Lancet*. 1999;353:479-85.
3. Ten Cate-Hoek AJ, Prins MH. Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism: a systematic review. *J Thromb Haemost*. 2005;3:2465-70.
4. Wells PS, Owen C, Doucette S, et al. Does this patient have deep vein thrombosis? *JAMA*. 2006;295:199-207.
5. Buller HR, ten Cate-Hoek AJ, Hoes AW, et al. Safely Ruling Out Deep Venous Thrombosis in Primary Care. *Ann Intern Med*. 2009;150:229-35.
6. Blättler W, Martinez I, Blättler IK. Diagnosis of deep venous thrombosis and alternative diseases in symptomatic outpatients. *Eur J Intern Med*. 2004;15:305-11.
7. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost*. 2005;94:200-5.
8. Di Nisio M, Wichers IM, Middeldorp S. Treatment of superficial venous thrombosis of the leg (review). *The Cochrane Library* 2008, issue 1.
9. van Weert H, Dolan G, Wichers I, et al. Spontaneous superficial venous thrombophlebitis: Does it increase risk for thromboembolism? A historic follow-up study in primary care. *J Fam Pract*. 2006;55:52-7.
10. Wichers IM, Haighton M, Büller HR, Middeldorp S. A retrospective analysis of patients treated for superficial vein thrombosis. *Neth J Med*. 2008;66:423-7.