

# BMJ Open General practitioner use of D-dimer in suspected venous thromboembolism: historical cohort study in one geographical region in the Netherlands

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## ABSTRACT

**Objectives** To investigate how many general practitioner (GP)-referred venous thromboembolic events (VTEs) are diagnosed during 1 year in one geographical region and to investigate the (urgent) referral pathway of VTE diagnoses, including the role of laboratory D-dimer testing.

**Design** Historical cohort study.

**Setting** GP patients of 47 general practices in a demarcated geographical region of 161 503 inhabitants in the Netherlands.

**Participants** We analysed all 895 primary care patients in whom either the GP determined a D-dimer value or who had a diagnostic work-up for suspected VTE in a non-academic hospital during 2015.

**Primary and secondary outcome measures** The primary outcomes of this study were the total number of VTEs per year and the diagnostic pathways—including the role of GP determined D-dimer testing—of patients urgently referred to secondary care for suspected VTE. Additionally, we explored the use of an age-adjusted D-dimer cut-off.

**Results** The annual VTE incidence was 0.9 per 1000 inhabitants. GPs annually ordered 5.1 D-dimer tests per 1000 inhabitants. Of 470 urgently GP-referred patients, 31.3% had a VTE. Of those urgently referred based on clinical assessment only (without D-dimer testing), 73.8% (96/130) had a VTE; based on clinical assessment and laboratory D-dimer testing yielded 15.0% (51/340) VTE. Applying age-adjusted D-dimer cut-offs to all patients aged 50 years or older resulted in a reduction of positive D-dimer results from 97.9% to 79.4%, without missing any VTE.

**Conclusions** Although D-dimer testing contributes to the diagnostic work-up of VTE, GPs have a high detection rate for VTE in patients who they urgently refer to secondary care based on clinical assessment only.

## INTRODUCTION

The annual incidence of venous thromboembolic events (VTEs)—deep vein thrombosis (DVT) and pulmonary embolism (PE)—in high-income countries is approximately 70–270 per 100 000 people.<sup>1–3</sup> It is vital to quickly recognise a VTE and initiate

## Strengths and limitations of this study

- This is the first study that explored the actual use of D-dimer tests in venous thromboembolic events suspected patients in general practice and the diagnostic pathways of deep vein thrombosis and pulmonary embolism in one demarcated geographical region during 1 year.
- We carefully investigated the patient flow of all general practitioner-referred patients and investigated the D-dimer use in all primary care patients in this region.
- We were unable to create a clear overview of the non-referred patients and to reliably determine some aspects of the consultation and patient history from the medical records.

treatment, in order to prevent further morbidity, disability or death.<sup>3–4</sup> However, diagnosing VTEs is a challenge in general practice, as symptoms may be non-specific and the clinical presentation can vary strongly.<sup>5–6</sup>

In the current diagnostic pathways for suspected VTE, it is recommended that general practitioners (GPs) combine clinical decision rules with a D-dimer test in patients with a low clinical pretest probability for VTE.<sup>6–10</sup> A low Wells score combined with a D-dimer value below 500 µg/L can safely exclude a VTE. Furthermore, using an age-adjusted D-dimer cut-off in patients ≥50 years seems to be safe.<sup>11–18</sup> Currently, GPs in the Netherlands have access to D-dimer through routine laboratory tests with results available within a few hours. Using a point-of-care test (POCT) might speed up the diagnosis and inform the decision to refer to secondary care, as the results can immediately support clinical decision-making during the consultation. Many GPs would like to use a D-dimer POCT, although GPs express concerns

about the reliability of POCTs in general.<sup>5 19</sup> Moreover, user-friendliness of existing D-dimer POCTs varies.<sup>20</sup>

The actual use of routine laboratory D-dimer testing by GPs has not been investigated and might provide useful insights in how GPs currently test and refer VTE suspected patients (both low-risk and high-risk patients) and may inform possible future D-dimer POCT implementation. The primary aim of this study is to assess how many GP-referred VTEs are diagnosed during 1 year in one geographical region and to investigate the (urgent) referral pathway of VTE diagnoses, including the role of laboratory D-dimer testing. Moreover, we want to evaluate the possible effect of implementing an age-adjusted D-dimer cut-off.

## METHOD

### Study design and setting

This is a historical cohort study (2015) in a demarcated geographical area in the Netherlands served by one non-academic hospital and primary care being provided by 47 general practices (83 GPs) to 161 503 inhabitants. Patients are primarily referred to this hospital and GPs in this area order laboratory tests via one local diagnostic primary care centre 'MCC Omnes Centre for Diagnostics and Innovation'.

### Patient selection

We analysed all patients who were diagnostically worked-up for suspected VTE in hospital or in whom the GP determined a D-dimer value in the year 2015. The cohort was constructed based on data from two sources: the medical registration archives of the hospital and the diagnostic testing database of the local diagnostic centre. From the hospital medical registration archives we selected all patients with a diagnosis-treatment code for DVT and/or PE in the study period. From the diagnostic testing database of the local diagnostic centre we selected all patients of whom the GP requested at least one D-dimer test in the study period. We excluded patients who were registered with a GP working outside the postal code area of the study region or who were not referred by a GP, for example, patients who were already admitted to hospital or were translocated from another hospital. Self-referrals and referrals from nursing home physicians were included and analysed as referrals from primary care.

Combining the two data sources resulted in three populations available for the analyses: patients urgently referred to hospital, patients non-urgently referred to hospital and patients in whom the GP determined a D-dimer but were not referred to hospital. Urgent referrals were defined as referral within 7 days. All referred patients could be divided into patients referred for suspected VTE based on GP clinical assessment only (hence without D-dimer) and patients referred for suspected VTE based on GP clinical assessment and D-dimer testing.

### Data extraction and outcomes

For all urgently referred patients, data were extracted from digital clinical medical records by one researcher

(EM) through accessing each patient record and recording data on the final diagnosis, diagnostic work-up and medical history of patients on a prespecified case record form. In case of doubt, patients were discussed with another researcher (AS). When more than one D-dimer test was performed or more than one diagnosis-treatment code was assigned in referred patients, we evaluated the clinically most relevant event, with the highest suspicion of a PE or DVT. In case a patient had more than one VTE in 2015 this was noted. Diagnoses reported in discharge letters were noted as exactly as possible and subsequently pooled into groups. The number of GP-requested D-dimer tests and D-dimer results in non-referred patients was extracted from the diagnostic testing database of the local diagnostic centre. All data were collected from October to December 2016.

The primary outcomes of this study were the total number of DVTs and PEs per year and diagnostic pathways of patients urgently referred to secondary care for suspected VTE (referred based on clinical assessment only or based on clinical assessment and D-dimer). Therefore, we registered the total number of GP-requested D-dimer tests, the D-dimer values, the time between D-dimer testing and the hospital visit, the final diagnoses after referral and patient characteristics. For the D-dimer value we used a cut-off of 500 µg/L. Additionally, we explored the use of an age-adjusted D-dimer cut-off, defined as age  $\times$  10 within patients  $\geq$ 50 years.<sup>13–16</sup>

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Data Editor V.23. Analyses consisted primarily of descriptive analyses to describe the study population, patient flow and D-dimer values, using frequencies, averages, medians or percentages. The total population size of 161 503 inhabitants was calculated by adding the number of patients of all included general practices, based on list sizes of practices provided by MCC Omnes. The incidence rate was calculated by dividing the total number of VTEs by the total population size.

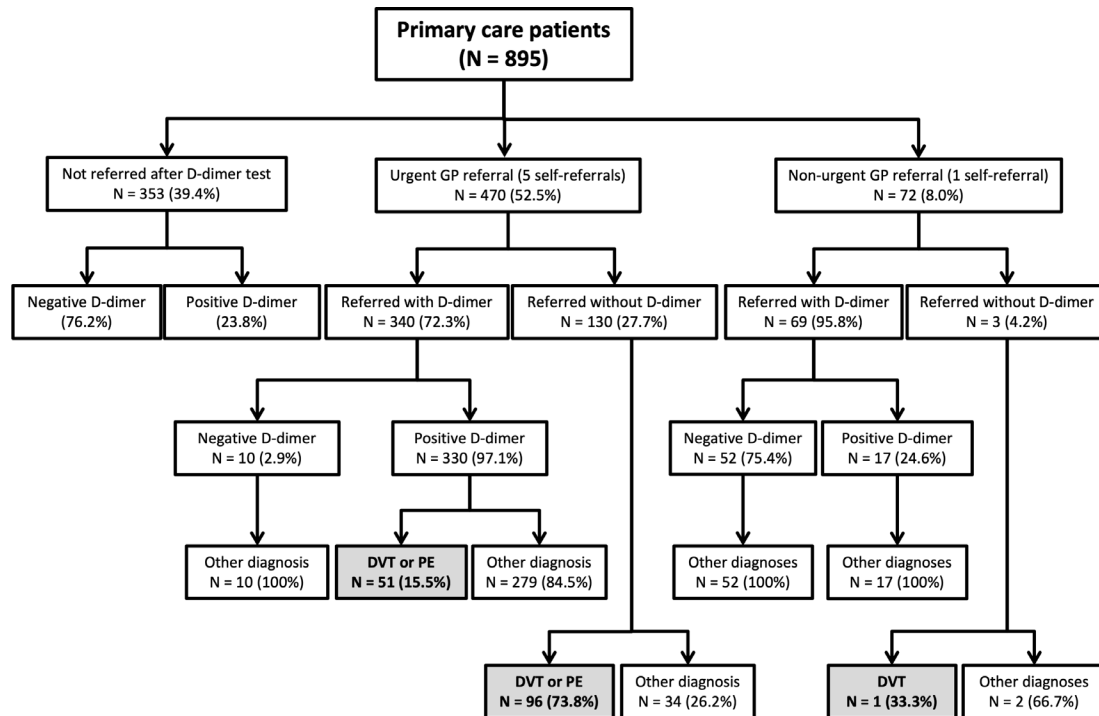
### Patient and public involvement

No patients or public were involved in the design and execution this study.

## RESULTS

### Patient characteristics and VTE incidence

Figure 1 illustrates the patient flow of all included patients. We included 895 primary care patients, of which 148 were diagnosed with VTE in a total population of 161 503 inhabitants. Three (2.0%) patients had more than one VTE during 2015. The annual incidence of GP-referred VTE was 0.9 per 1000 inhabitants. GPs requested 821 D-dimer tests; two times in 34 patients and three times in 5 patients. An average of 5.1 D-dimer tests per 1000 inhabitants were performed by GPs.



**Figure 1** Patient flow and GP use of D-dimer test. In this figure only one D-dimer test and one clinical event per patient is shown. When more than one D-dimer test was performed or more than one diagnosis-treatment code was assigned in referred patients, we evaluated the clinically most relevant event, with the highest suspicion of a PE or DVT. DVT, deep vein thrombosis; GP, general practitioner; PE, pulmonary embolism.

### Referral pathways

Four hundred and seventy (52.5%) patients were urgently referred to secondary care, 72 patients (8.0%) were referred non-urgently and 353 patients (39.4%) were not referred to secondary care (figure 1). Of all non-urgently referred patients, one self-referred patient was diagnosed with a DVT. About a quarter (23.8%) of patients not referred to secondary care had a positive D-dimer, with a median D-dimer value of 648.5 (501–3386).

### Urgently referred patients

A total of 470 patients were urgently referred to secondary care for suspected VTE, which is 52.5% of all patients in this cohort. On average, these patients were 63 years old, and 38.9% were male (table 1).

### Urgently referred patients based on clinical assessment and D-dimer

The majority of urgently referred patients (n=340, 72.3%) were referred based on the GP's clinical assessment plus a D-dimer test (table 1). Of these patients 330 (97.1%) had a positive test (>500 µg/L), with a median D-dimer of 1072 µg/L (502–22,863) (table 2). In 51 of these 340 patients a VTE was diagnosed (15.0%), of which 19 (37.3%) patients had a PE, 21 (41.2%) a DVT and 11 (21.6%) a PE and DVT. No VTE was found among the 10 patients with a normal D-dimer test. Three hundred and twenty two patients (94.7%) were seen within 1 day after a D-dimer test was requested; average time between D-dimer test and hospital visit was 0.62 days.

### Urgently referred patients based on clinical assessment only

One hundred and thirty (27.7%) patients were urgently referred to secondary care based on clinical assessment only, hence without a D-dimer test. Of these, 96 (73.8%) were diagnosed with a VTE; 28 (29.2%) patients with a PE, 45 (46.9%) with a DVT and 23 (24.0%) patients had a combined diagnoses of PE and DVT.

### VTE and alternative diagnoses in urgently referred patients

Hence in total, of all 470 urgently referred patients (both based on clinical assessment only and clinical assessment plus D-dimer) 147 (31.3%) were diagnosed with a VTE (table 3). Frequent alternative diagnoses were musculo-skeletal disorders (14.9%), respiratory tract infections or other pulmonary disorders (11.3%) and oedema, and other vascular disorders (10.2%) (table 3).

### Applying age-adjusted D-dimer cut-off in urgently referred patients

Among urgently referred patients with a D-dimer test, 287 patients were ≥50 years. Using a cut-off of 500 µg/L, 281 (97.9%) patients had a positive D-dimer value. Applying an age-adjusted D-dimer cut-off value to this group would leave 228 (79.4%) patients with a positive D-dimer value; a reduction of 18.5%. No VTE would have been missed.

## DISCUSSION

### Main findings

In this historical cohort study in a well-defined geographical area, we found an annual incidence of 0.9 VTE per

**Table 1** Patient characteristics of urgently referred patients (n=470)

Patient characteristics and D-dimer use	
Mean age, years (range)	63 (18–95)
Gender, male (%)	183 (38.9)
Number of GP determined D-dimer tests (%)	340 (72.3)
Number of positive D-dimer tests, >500 µg/L (%)	330 (97.1)
Median of D-dimer tests, µg/L (range)	1041.5 (256–22 863)
Use of medication when referred to hospital	
Oral anticoagulation* (%)	11 (2.3)
Platelet aggregation inhibitor (%)	45 (9.6)
Medical history when referred to hospital	
Pregnancy* (%)	5 (1.1)
Previous DVT/PE (%)	100 (21.3)
Malignancy* (%)	36 (7.7)
Diabetes mellitus (%)	61 (13.0)
Cardiac disorders* (%)	96 (20.4)
Previous CVA/TIA (%)	34 (7.2)
Hypertension (%)	135 (28.7)
COPD (%)	38 (8.1)
Renal insufficiency (%)	16 (3.4)

\*Use of anticoagulants consisted of coumarin derivatives, heparins and direct oral anticoagulants; malignancy was defined as active malignancy, malignancy treated within past 6 months or palliation; pregnancy as current pregnancy or postpartum period (6 weeks postpartum); cardiac history included any cardiac disorder, for example, atrial fibrillation, myocardial infarction and bundle branch block. COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischaemic attack.

1000 inhabitants. GPs requested annually 5.1 D-dimer test per 1000 inhabitants. Of all urgently referred patients to secondary care, 31.3% was diagnosed with a VTE. Of those urgently referred based on clinical assessment only, 73.8% had a VTE, while in those referred based on clinical assessment and D-dimer 15.5% had a VTE. The use of an age-adjusted D-dimer cut-off could have resulted in a reduction of 18.5% of positive D-dimer tests (97.9% to 79.4%) in the group of urgently referred patients  $\geq 50$  years, without missing any DVT or PE.

### Strengths and limitations

This is the first study that explored the actual use of D-dimer tests in general practice and the diagnostic pathway of DVT and PE in one demarcated geographical region during 1 year. We not only carefully investigated the patient flow of all GP-referred patients, we also investigated the D-dimer use in all primary care patients in this region.

Unfortunately, we were unable to create a clear overview of the non-referred patients, as we did not have patient's permission to access GPs' patient records. We can only speculate as

**Table 2** GP determined D-dimer values of all urgently referred patients with a positive D-dimer value (>500 µg/L) (n=330)\*

Diagnoses	Median D-dimer value (range, µg/L)
All urgently referred patients (n=330)	1072 (502–22 863)
VTE (n=51)	3321 (982–21 345)
PE (n=19)	1799 (1113–20 492)
DVT (n=21)	4449 (1223–16 782)
Combination of PE and DVT (n=11)	5718 (982–21 345)
Alternative diagnosis (n=279)	928 (502–22 863)

\*Of all urgently referred patients (n=470), 340 were referred based on GP clinical assessment and D-dimer and 10 of those were negative (<500 µg/L).

DVT, deep vein thrombosis; GP, general practitioner; PE, pulmonary embolism; VTE, venous thromboembolic events.



**Table 3** Final diagnoses in patients urgently referred (within 7 days) to secondary care (n=470), based on hospital medical records.

Final diagnoses	No of patients (%)
VTE	147 (31.3)
PE	47 (10.0)
DVT	66 (14.0)
Combination PE and DVT	34 (7.2)
Musculoskeletal disorders	70 (14.9)
Respiratory tract infections or other pulmonary disorders	53 (11.3)
Pneumonia	12 (2.6)
Oedema and other vascular disorders*	48 (10.2)
(Skin)Infections of leg	20 (4.3)
Erysipelas/cellulitis	18 (3.8)
Thrombophlebitis	28 (6.0)
Baker's cyst	20 (4.3)
Cardiac disorders	10 (2.1)
Other diagnoses	13 (2.8)
Unclear diagnosis/no diagnosis	47 (10.0)
More than one differential diagnosis	14 (3.0)

\*Including one mesenteric vein thrombosis. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolic events.

to what reasons GPs had to not refer patients with a positive D-dimer test, for example, GPs may have used age-adjusted D-dimer cut-off values or reconsidered the appropriateness of performing the test in that particular patient, the patient may have refused to go into hospital or was sent to another hospital outside of the study region, or the patient might have died before arrival into hospital. This may have led to a slight underestimation of the number of VTEs in the study population. We tried to reduce this chance by selecting a specific demarcated geographical region where almost all GPs refer their patients to one hospital and where all GPs do all diagnostic tests in one diagnostic centre. We assume the number of potentially missed VTE cases will be less than approximately 10 cases (<7%), assuming the percentage of VTE in this group will not be higher than in referred patients with a positive D-dimer. We were unable to reliably determine some aspects of the consultation and patient history in the medical records, for example, components of the Wells score were missing in discharge letters of many patients and some aspects of the medical history might have been underestimated as these are not always fully reported in the records. Moreover, the final diagnosis was determined based on medical records instead of a uniform predefined assessment or adjudication committee. Some minor selection bias may have occurred as we only evaluated the most clinically suspected event in each patient.

#### Comparison with existing literature and recommendation in GP guidelines

We found an annual incidence of approximately one VTE per 1000 person-years at risk, which is comparable

with incidence rates in other studies.<sup>1–3</sup> In this study we found that of all urgently referred patients based on clinical assessment only, almost 75% of patients indeed had a VTE. This suggests that GP's judgement in high-risk patients is remarkably good, which supports the current recommendation in the Dutch national guidelines that requesting a D-dimer test in these high-risk patients is not advisable and will only delay referral to secondary care.<sup>6–10</sup> Of those urgently referred after D-dimer testing, 15.5% of patients was diagnosed with a VTE.

Nonetheless, it is important to note that, although almost 85% of patients urgently referred to secondary care with a positive D-dimer test did not have a VTE, a significant portion of these patients may still have had another clinically relevant diagnosis for which referral may have been wise or needed. A study by Erkens *et al*,<sup>21</sup> found that 28.9% of patients suspected of a PE but in whom a PE was eventually ruled-out received another clinically relevant diagnoses; a positive Wells rule or a positive D-dimer test were positively associated with a higher probability of another clinically relevant disease.<sup>21</sup>

Applying the age-adjusted D-dimer cut-off to our primary care population again shows that VTE can be safely ruled out with the age-adjusted cut-off value in patients  $\geq 50$  years and may reduce the referral rate in patients aged 50 years and older by 18.5%.<sup>13–18</sup>

#### Implications for research and/or practice

Looking at the patient flow, we can see that the D-dimer test contributes significantly to the diagnostic work-up of VTE, but two-thirds of patients diagnosed with a VTE were found after clinical assessment only. We may speculate, although we did not have access to GP medical records, that these were patients with a high probability of VTE as estimated by the consulting GP and these patients were rightfully directly referred, in line with recommendations in the GP guidelines. Taking into account that a GP will infrequently use a D-dimer test in daily practice and the finding that GPs have a high detection rate for highly suspicious VTE, one might argue that replacing the laboratory D-dimer test by a D-dimer POCT is not directly necessary. Moreover, a D-dimer POCT may be used more often in patients without a clear or evidence-based indication, which will most likely—especially in the case of a non-specific test—lead to an increase in referrals to secondary care due to false positive tests. The closer proximity to a D-dimer POCT may also lead to a lower threshold for testing in high probability patients, which is not recommended by guidelines and may lead to a delay in referral.<sup>6–9</sup> This effect of non-evidence-based testing (for other indications) has previously been seen with the introduction of the CRP POCT.<sup>22–24</sup> Excessive test use and a possible increase in referrals in turn may lead to an increased number of patients being anticoagulated inappropriately, due to an increased number of false positive cases with leg ultrasonography and an increased number of overdiagnosis in patients with clinically insignificant subsegmental PEs.<sup>25 26</sup> Furthermore, the low frequency of test use and potential excessive use of a

D-dimer POCT also raises questions with regards to training and cost-effectiveness of such a POCT. Additionally, the use of D-dimer POCTs in routine clinical practice is insufficiently evaluated (in randomised studies) and qualitative and semi-quantitative test results pose additional challenges in interpretation. However, if a D-dimer POCT were to be implemented, careful monitoring is essential to assess its effect on the diagnostic work-up of patients with suspected VTE and the referral rate to secondary care.

## Conclusion

Although D-dimer testing contributes to the diagnostic work-up of VTE, GPs have a high detection rate for VTE in patients they urgently refer to secondary care based on clinical assessment only.

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**Contributors** AS, EM, G-JD, MK and JC created the research protocol and EM extracted data from digital clinical medical records and in case of doubt discussed patients with AS. AS, EM and JC performed the data analyses and these results were discussed with G-JD, HS and MK. AS and EM drafted the first manuscript and AS and JC revised the manuscript. AS, EM, G-JD, HS, MK, and JC all contributed to the decisions about how to present the data, organise and edit the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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