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Real-life impact of clinical prediction rules for venous thromboembolism in primary care: a cross-sectional cohort study

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ABSTRACT

Objective Clinical prediction rules (CPRs) followed by D-dimer testing were shown to safely rule out venous thromboembolism (VTE) in about half of all suspected patients in controlled and experienced study settings. Yet, its real-life impact in primary care is unknown. The aim of this study was to determine the real-life impact of CPRs for suspected VTE in primary care.

Design Cross-sectional cohort study.

Setting Primary care in the Netherlands.

Participants Patients with suspected deep venous thrombosis (n=993) and suspected pulmonary embolism (n=484).

Interventions General practitioners received an educational instruction on how to use CPRs in suspected VTE. We did not rectify incorrect application of the CPR in order to mimic daily clinical care.

Main outcome measures Primary outcomes were the diagnostic failure rate, defined as the 3-month incidence of VTE in the non-referred group, and the efficiency, defined as the proportion of non-referred patients in the total study population. Secondary outcomes were determinants for and consequences of *incorrect* application of the CPRs.

Results In 267 of the included 1477 patients, VTE was confirmed. When CPRs were correctly applied, the failure rate was 1.51% (95% CI 0.77 to 2.86), and the efficiency was 58.1% (95% CI 55.2 to 61.0). However, the CPRs were incorrectly applied in 339 patients, which resulted in an increased failure rate of 3.31% (95% CI 1.07 to 8.76) and a decreased efficiency of 35.7% (95% CI 30.6 to 41.1). The presence of concurrent heart failure increased the likelihood of incorrect application (adjusted OR 3.26; 95% CI 1.47 to 7.21).

Conclusions Correct application of CPRs for VTE in primary care is associated with an acceptable low failure rate at a high efficiency. Importantly, in nearly a quarter of patients, the CPRs were incorrectly applied that resulted in a higher failure rate and a considerably lower efficiency.

Strengths and limitations of this study

- ► A large population of 1477 patients was included, resulting in an accurate estimate of the failure rate and efficiency of clinical prediction rules for venous thromboembolism.
- ► The reference standard between referred and non-referred patients suspected of venous thromboembolism differed, which might result in differential verification bias.
- ► The point-of-care test for D-dimer used during the study had too many false-negative results, leading to an increased failure rate for those patients.
- ► A sample size calculation was not performed a priori; however, a number of 268 outcome VTE events allowed robust statistical analyses.

INTRODUCTION

When patients visit their general practitioner (GP) with a red and swollen calf, deep venous thrombosis (DVT) may be considered. In case of shortness of breath or thoracic pain, pulmonary embolism (PE) could be the cause. Together, both conditions are part of the spectrum of venous thromboembolic diseases, which has an incidence of 1–2 per 1000 person-years.[1 2] It is associated with a considerable global impact on morbidity and mortality, with an estimated number of 370 012 VTE-related deaths yearly in Europe.[2] Prompt referral and initiation of treatment in confirmed cases is thus pivotal. However, for both *suspected* DVT and PE, several alternative diagnoses with mimicking and overlapping signs and symptoms exist, hampering the clinical assessment.[3] Perhaps as a consequence, VTE is also one of the most frequently missed diagnoses in daily clinical care.[4 5] Therefore, to optimise the diagnostic work-up of venous thromboembolism (VTE), clinical prediction rules (CPRs) have been developed. Rigorous validation studies in a controlled research environment showed that with the use of these CPRs, referrals to secondary care were safely avoided in almost half of all patients suspected of either DVT or PE.[6 7] Consequently, the use of CPRs in suspected VTE

are recommended in national and international guidelines.[8 9]

However, research on the actual impact of the CPRs when applied in inevitably less 'controlled' day-to-day care is scarce. In fact, to the best of our knowledge, only two prospective studies were published. We previously evaluated the use of the Oudega rule for patients suspected of having DVT. This study showed that in one-third of the patients, the CPR was not correctly applied by GPs, commonly because of applying the CPR to patients for whom the strategy should not have been used or because of inappropriate use of the D-dimer test.[10] Clinical outcomes of such incorrect management by GPs were not reported as a main outcome in that study. The other study from Roy and coworkers[11] evaluated the effects of implementing the Wells rule for patients with suspected PE, showing that an inappropriate diagnostic assessment in suspected PE was also common (43% of all suspected patients). This inappropriate management was independently associated with a higher rate of preventable thromboembolic occurrences during follow-up.[11]

Hence, ample available evidence suggests that incorrect use of CPRs may occur more frequently than desired, possibly (1) increasing the likelihood of thromboembolic occurrences, but (2) perhaps also leading to more unneeded, costly and burdensome referrals. Both are worrying outcomes, and thus it is important to understand better what the real-life effects are of implementing these CPRs in the diagnostic work-up for VTE in primary care. The aim of this study was therefore to evaluate the real-life impact of CPRs for both DVT and PE in daily primary care practice. Our secondary aim was to explore determinants and consequences of incorrect use of these CPRs.

METHODS
Study design
This is (in part) an extension of a previously performed and published diagnostic cohort study that was smaller (619 patients suspected of DVT) and focused on the implementation outcomes (such as feasibility and sustainability) of the Oudega rule for DVT in primary care.[10] In the current study, we report on the real-life impact (ie, the clinical outcomes) of two CPRs (Wells and Oudega rule) in 1017 patients suspected of DVT and 492 patients suspected of PE in primary care.

Participants
From October 2013 until July 2017 patients were recruited from primary care centres in the Netherlands. All patients in whom the GP suspected a diagnosis of DVT or PE (based on clinical symptoms such as calf pain or swelling for DVT, and dyspnoea, coughing or chest pain for PE) were eligible for inclusion. Institutionalised frail elderly patients were not included in this study, given that existing evidence suggests that ruling out VTE in them with a CPR and D-dimer is unsafe.[12 13]

Study procedures
All GPs received an educational instruction on how to manage their patients according to the CPRs recommended in the primary care guidelines.[8] We explained the use of the CPR as well the patient groups in whom the rule should not be used, that is: (1) patients aged <18 years, (2) pregnant or postpartum women, (3) current use of oral anticoagulants (vitamin K antagonist, direct oral anticoagulant or low molecular heparin) and (4) symptoms lasting longer than 30 days. For patients suspected of DVT, the Oudega rule was recommended. This CPR was modified from the original Wells rule and externally validated for the use in primary care given that the original Wells CPR for suspected DVT was shown to be unable to safely rule out DVT in primary care.[6 14 15] The Wells rule for PE has also been validated for use in primary care, and there was no need for modification or updating.[7] Both CPRs combine seven clinical items into a score ranging from 0 to 8 for DVT and from 0 to 12.5 for PE, which classifies patients in an 'unlikely' or a 'likely' risk category of having VTE. In patients with a score of ≤3 points on the DVT CPR, or ≤4 points on the PE CPR, D-dimer had to be determined. If D-dimer was below the threshold of 500 ng/mL, patients were classified as low risk of having VTE, and therefore, VTE was considered to be safely ruled out without the need for additional investigation. Contrary, patients with a score of ≥4 points for DVT, or ≥4.5 points for PE, or with a D-dimer either above 500 ng/mL or a 'positive' result on a qualitative point-of-care test for D-dimer, were classified as 'high risk' of having VTE. In these patients, all following existing guidelines, referral to the hospital for further diagnostic procedures was recommended. Non-referred patients were instructed to schedule a follow-up appointment with their GP in case of worsening or persistent symptoms. Participating GPs filled out a paper case report form, which consisted of questions about patient clinical characteristics, the items of the CPR, the D-dimer result and whether the patient was referred. In this cross-sectional diagnostic study, we used clinical follow-up of 3 months to assess the final diagnosis. Thus, the reference standard in our study was the clinical follow-up in the non-referred patients and further diagnostic procedures in hospital (most often a compression ultrasound of the leg in case of suspected DVT or a CT pulmonary angiography in case of suspected PE) in the referred patients. Importantly, the above described strategy was the preferred and recommended approach, yet–after the short educational instruction—we did not rectify incorrect application of the CPR in order to mimic daily clinical care as much as possible. This thus was an assistive recommendation only, with decisions on referral left at the discretion of participating GPs.

Ethical approval
A waiver for informed consent was provided, as patient information was encrypted for the researchers. We performed this study according to the World Medical Association's Declaration of Helsinki.[16]

Outcomes

The primary outcome of this study was the impact of the everyday use of the CPRs in primary care, denoted as the diagnostic failure rate and efficiency. The failure rate was defined as the proportion of patients with a VTE diagnosis during the 3-month follow-up within the non-referred patients. The efficiency was defined as the proportion of patients not referred to secondary care within the total study population. We first analysed these primary endpoints for the total suspected VTE group, thus regardless of whether the actual CPRs were correctly applied. Subsequently, we repeated these analyses for patients in whom the CPR was correctly or incorrectly used and for patients suspected of having DVT or PE separately. The secondary outcome was incorrect application of the CPRs by GPs. Reasons for incorrect application were defined as (in hierarchical order): (1) the wrong CPR used (ie, the Oudega rule for PE or the Wells PE rule for DVT), (2) applied in inappropriate patients (eg, patients already on anticoagulants, pregnant or postpartum or aged <18 years, see previous), (3) incorrect summation of the CPR points, (4) inappropriate use of the D-dimer test and, finally, (5) deviation from the standard referral recommendation. Each patient could only be counted once for incorrect CPR use, notwithstanding that in some patients multiple items for incorrect CPR use were applicable. Last, we analysed several possible determinants for incorrect application of both CPRs in the total patients suspected of VTE: age in categories (≤50 years, >50 and ≤75 years, and >75 years), sex, heart failure, chronic obstructive pulmonary disease/asthma, active malignancy, recent surgery or immobilisation and (for suspected PE patients, as this was only collected for this subgroup) previous VTE. These determinants were selected as the same set of variables was evaluated in the abovementioned study from Roy and colleagues[11] analysing the appropriateness of the diagnostic management of suspected PE patients to yield comparable outcomes.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DATA ANALYSES

We included only patients with complete follow-up information (ie, a final diagnosis) in our analysis. Missing values on the items of the CPR were handled by defining these variables as absent, which results in zero points on that variable of the CPR. Baseline characteristics and the presence of all items of the CPRs for suspected DVT and PE patients are described separately. The failure rate and efficiency were quantified with corresponding 95% CIs, both for DVT and PE patients and correct and incorrect CPR use. For the assessment of reasons why the CPR was incorrectly applied, we counted the reasons and described them for DVT and PE separately. To further explore the incorrect application of the CPRs, we analysed the association between the aforementioned determinants and incorrect application of the CPR by performing multivariable logistic regression. Hereto, we defined correct or incorrect use as the binary outcome and the above described potential determinants as independent covariables. This regression analysis yields adjusted ORs. All statistical analyses were performed in SPSS (IBM SPSS Statistics software V.25).

RESULTS

In total, 1509 patients with suspected DVT and PE were included. In 32 (2.1%) patients, we had missing follow-up information, and thus the study population consisted of 1477 patients (993 with suspected DVT and 484 with suspected PE). The items of the CPRs had one to six missing values per variable (see online supplemental appendix table 1). The clinical characteristics of the included patients are shown in table 1. Patients suspected of having DVT were older (64 years vs 49 years) and more frequently male (42.2% vs 31.8%) as compared with patients suspected of having PE. The baseline characteristics of the patients with missing follow-up information were comparable with the study population. The overall prevalence of VTE was 18.1% (23.2% DVT and 7.9% PE).

Failure rate and efficiency of CPRs

The overall failure rate of both CPRs combined in the total study population was 1.8% (95% CI 1.02 to 3.06) and the overall efficiency was 53% (95% CI 50.4 to 55.5). The failure rate and efficiency split up for correct and incorrect use of the CPRs in the total study population, suspected DVT and PE group are shown in figure 1. In the total study population the failure rate increased from 1.51% (95% CI 0.77 to 2.86) when the CPR was correctly used to 3.31% (95% CI 1.07 to 8.76) when the CPR was incorrectly used and the efficiency decreased from 58.1% (95% CI 55.2 to 61.0) to 35.7% (95% CI 30.6 to 41.1) (figure 1). In 787 (79.3%) of the patients suspected of having DVT, the CPR was correctly applied by the GP (figure 2). Among these patients, 408 were not referred (efficiency of 51.8%) and 8 of them had a VTE; the failure rate was 1.96% (95% CI 0.91% to 3.98%; figure 1). In the 206 (20.7%) patients in whom the CPR was incorrectly applied, the failure rate was 7.02% (95% CI 2.27% to 17.83%); figure 1), and the efficiency in these patients decreased to 27.7%.

Of the 351 (72.5%) patients suspected of having PE and in whom the GP applied the CPR correctly, 253 (72.1%) patients were not referred (figure 3). Among these non-referred patients, two were diagnosed with VTE; failure rate was 0.79% (95% CI 0.14% to 3.13%; figure 1). In 133 (27.5%) patients with suspected PE, the CPR was

Table 1 Clinical characteristics with items of the clinical prediction rules of 993 patients suspected of deep venous thrombosis (DVT) and 484 patients suspected of pulmonary embolism (PE)

Characteristic	Patients suspected of DVT (n=993)	Patients suspected of PE (n=484)
Median age, years (range)	64 (15–96)	49 (13–94)
Male, n (%)	423 (42.6)	155 (32.0)
Active malignancy <6 months, n (%)	64 (6.5)	25 (5.2)
Surgery or immobilisation, n (%)	57 (5.7)	44 (9.1)
Oral contraceptive use, n (%)	59 (5.9)	n.a.
Absence of leg trauma, n (%)	782 (78.8)	n.a.
Distension of collateral veins, n (%)	231 (23.4)	n.a.
Calf swelling >3 cm, n (%)	338 (34.0)	n.a.
Clinical signs of DVT, n (%)	n.a.	20 (4.1)
Haemoptysis, n (%)	n.a.	10 (2.1)
PE most likely diagnosis, n (%)	n.a.	152 (31.7)
History of VTE, n (%)	n.a.	99 (20.5)
Heart rate >100 beats/min, n (%)	n.a.	115 (23.8)
Median score on CPR, points (range)	2 (0–7)	1.5 (0–7)
CPR score 'likely' risk category, n (%)	171 (17.2)	49 (10.1)
Median D-dimer, ng/mL (range)*	660 (100–16900)	370 (15–9000)
D-dimer 'positive' or >500 ng/mL, n (%)†	354 (42.5)	105 (23.3)
Diagnosis of VTE‡, n (%)	230 (23.2)	38 (7.9)

*Only counted when a quantitative D-dimer was measured.
†% of the patients in whom a D-dimer test was performed.
‡After 3 months of follow-up.
CPR, clinical prediction rule; VTE, venous thromboembolism.

incorrectly used by the GP. Sixty-four (48.1%) of these patients were not referred. None of them had a missed VTE.

The 14 (12 DVT, 2 PE) patients in whom a VTE diagnosis was missed are described in detail in online supplemental appendix table 2. Most had a low CPR score in combination with a negative D-dimer on the point-of-care assay (eight patients) or a D-dimer <500 ng/mL (three patients). Three of the undiagnosed DVT patients decided to decline for further diagnostic testing because of high age (89, 93 and 95 years), comorbidities and insufficient social network.

Reasons and determinants for incorrect CPR use
The most common reason in suspected DVT and PE patients was inappropriate D-dimer testing when the score on the CPR was high (figures 2 and 3). The second most common reason for incorrect CPR use was including patients: (1) already on anticoagulants, (2) that were pregnant or postpartum and (3) aged <18 years. Third, application of the Oudega rule rather than the Wells rule was the reason in more than a third of patients suspected of PE. The independent risk factors for incorrect use of the CPR and the ORs are shown in table 2. In patients aged between 50 and 75 years and in women, the CPRs were less frequently applied incorrectly (ORs respectively 0.71 (95% CI 0.54 to 0.94) and 0.69 (95%

CI 0.54 to 0.89)), while in patients with a history of heart failure and in suspected PE patients with a previous VTE, the CPRs were more frequently applied incorrectly (OR respectively 3.26 (95% CI 1.47 to 7.21) and 4.45 (95% CI 2.73 to 7.25)).

DISCUSSION
In this real-world evaluation of the impact of CPRs for VTE, we found that, if the Oudega and Wells rule were correctly used, the efficiency was high and the failure rate was acceptably low for patients suspected of DVT and PE. This is a reassuring finding; however, in almost a quarter of the 1477 patients, the CPR was incorrectly applied by GPs. This appears to lead to a considerably lower efficiency and a higher failure rate, especially in patients suspected of DVT. The most common mistakes in applying the CPRs were: D-dimer use when not needed, using the CPRs for inappropriate patients (eg, already using an anticoagulant) and applying the Oudega rule in patients with suspected PE. Incorrect application of the CPRs appeared to occur more frequently in patients with heart failure or in patients with a history of VTE (suspected PE only), whereas increasing age and female sex were associated with a lower risk of incorrect CPR application.
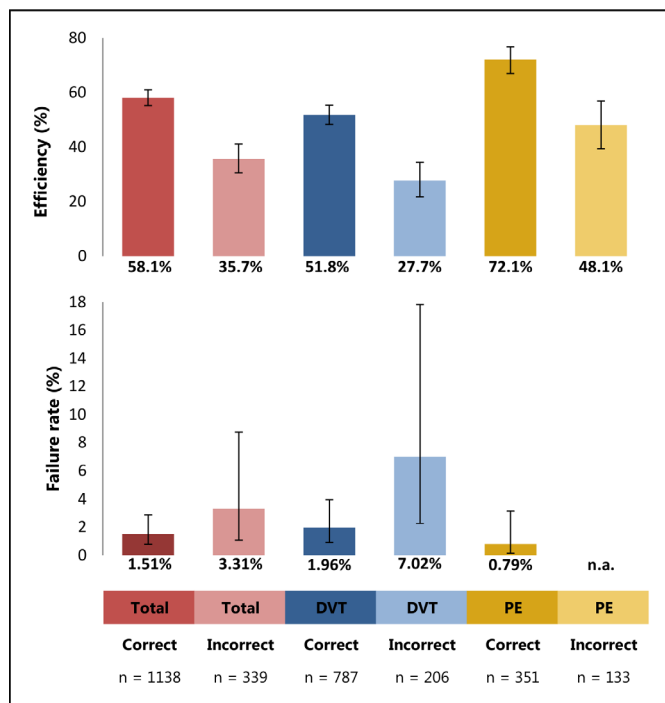
Figure 1 Bar plot of the efficiency and failure rate with corresponding 95% CIs of the evaluated clinical prediction rules, stratified for incorrect and correct use and in three groups: total included patients, patients suspected of DVT and patients suspected of PE. DVT, deep venous thrombosis; PE, pulmonary embolism.

The real-life impact of CPRs for both DVT and PE in primary care, including the effects of incorrect application of the CPRs, has—to the best of our knowledge—never been evaluated before. We included a large population of 1477 patients suspected of VTE, which results in an accurate estimate of the failure rate and efficiency of the CPRs. Similar as to previous studies, we confirmed that *correct* application of both CPRs in suspected VTE is associated with an acceptable low failure rate and a high efficiency. This study, however, also has some limitations. First, there is a difference of the reference standard between referred and non-referred patients. For patients referred to secondary care, the reference standard consisted of further diagnostic procedures, whereas in the non-referred patients, it consisted of a 3-month follow-up period. Differential verification might result in bias towards overestimating the safety.[17] This approach however is routinely applied in management studies in the field of diagnostic VTE research, thus allowing our outcomes to be compared with existing literature. Second, during the inclusion period, the point-of-care test for D-dimer (Clearview Simplify) was withdrawn from the market, because of too many false-negative results likely due to periprocedural quality-related faults when performing the test (ie, incorrect withdrawal of capillary blood or not keeping test cold enough until use). Although a direct consequence of implementing this point-of-care test in day-to-day practice, its effect surely needs to be incorporated into our main outcome and analyses.

These false-negative results likely resulted in more missed VTE diagnoses and therefore an underestimation of the safety of the CPRs. Indeed, 8 of all 14 patients in whom a VTE diagnosis was missed in our study had false-negative results on this qualitative Clearview Simplify D-dimer. This in part explains the observed failure rate for the stratified DVT and PE analyses that appears to be perhaps slightly higher than was observed in earlier studies and notably also explains the relatively wide 95% CIs that for some analyses cross the border of the commonly accepted safety threshold of 3.0%. In 357 patients (209 suspected DVT and 148 suspected PE), a quantitative D-dimer test was performed. Nevertheless, if we restrict our analysis to these patients, the main inferences of our analyses showing a higher failure rate in those in whom the CPRs are incorrectly remain the same (data not shown). Furthermore, three of the patients categorised as having a missed diagnosis of DVT were not referred to secondary care at their own request but did contribute to the calculated failure rate in the group in which the CPR was incorrectly applied. Thus, 'incorrect' use here was intentional. Third, we did not perform a sample size calculation a priori, given that for diagnostic validation studies (like ours), clear methodological recommendations on how to estimate a reliable sample size calculation are only recently proposed (ie, after the initiation of our study).[18] Nevertheless, our dataset did include a total number of 1447 patients suspected of VTE in primary care, with a total number of 268 outcome VTE events (230 DVT; 38 PE), allowing for robust statistical analyses notably for the full population; the stratified subanalyses for DVT and PE separately though should be interpreted with a little bit more caution, notably for those suspected of PE. Lastly, we could not report on the long-term clinical outcomes. It could be hypothesised that when the CPRs are incorrectly applied, the time to diagnose VTE potentially increases. It has been speculated that such delay in diagnosis could lead to a higher risk of long-term complications, such as the post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension, although these effects are still largely uncertain.[3 19]

Comparison with existing literature

The prevalence of DVT (23.2%) in this study corresponds with the previously described prevalence in primary care of 22%.[14] The prevalence of PE was low (7.9%) but roughly comparable with an earlier study in primary care that reported a prevalence of 12.2% and in fact almost similar to the overall prevalence of the recent Pulmonary Embolism Graduated D-dimer (PEGeD) study.[7 20] Apparently, the threshold of suspecting PE by physicians has lowered over time. This might be the result of the fact that physicians are more afraid to miss a PE than DVT given the associated morbidity and mortality, as well as the increasing availability of D-dimer testing and computed tomographic pulmonary angiography.[21] Hence, it can be argued that the inclusion of more low-risk patients in this real-life observational study has led to a higher efficiency
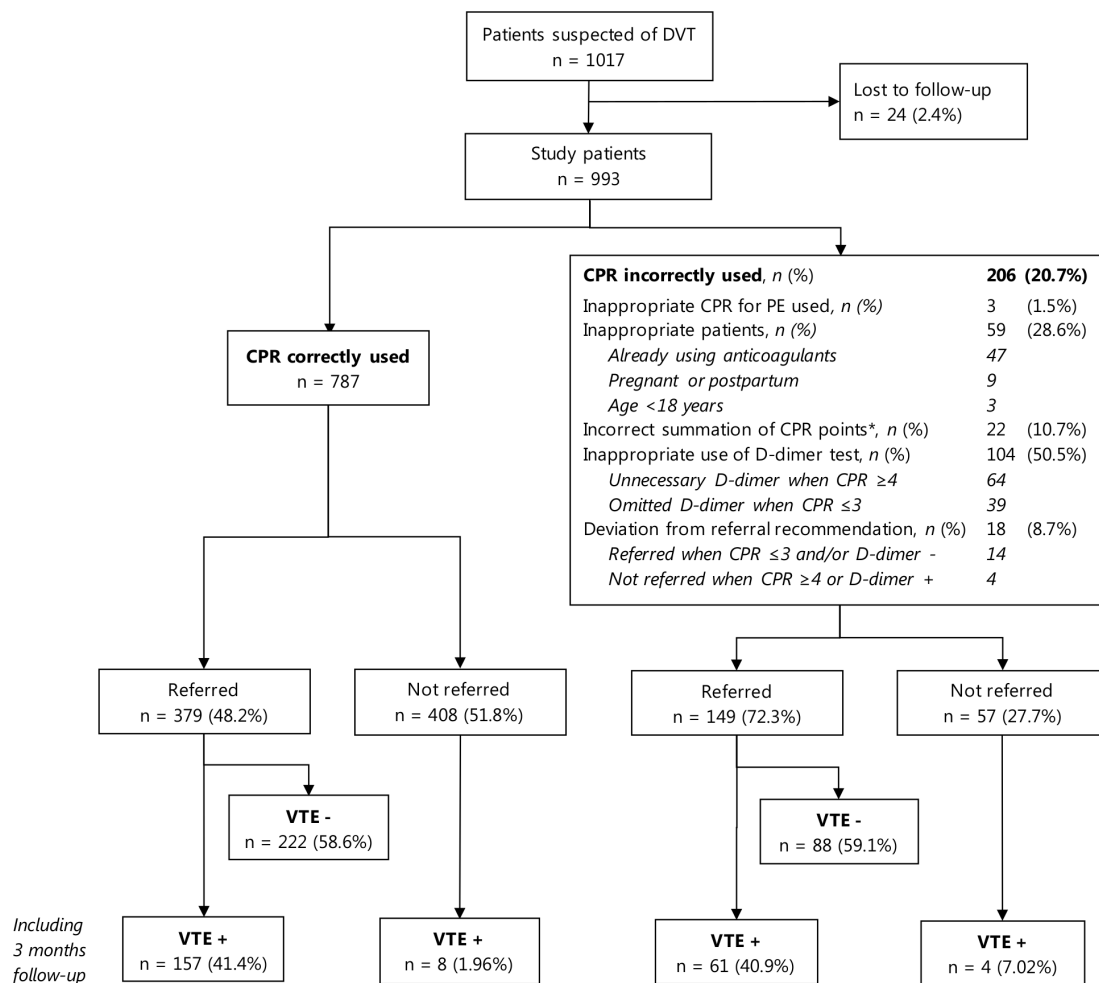
Figure 2 Flow chart of study patients suspected of DVT. *Only counted when incorrect dichotomization in CPR. CPR, clinical prediction rule; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

of using the CPR for PE (65.5%) as compared with the efficiency reported in the validation study of this CPR (45.5%).[7] When the CPR was correctly applied by the GP, we found a proportion of missed VTE diagnosis of 2.0% for patients suspected of DVT and 0.8% for patients suspected of PE. These failure rates are comparable with previous studies assessing the effects of using CPRs for VTE in primary care.[6 7 10] The incorrect use of the CPR in patients with suspected DVT resulted in a high failure rate of 7.0%. Although the CPRs were incorrectly used in a quarter of our included patients (20.7% for DVT and 27.5% for PE suspected patients), this proportion is still lower than reported by previous studies. Namely, the incorrect use of the Oudega rule for DVT in the previous implementation study was 32%.[10] Another study reported that the diagnostic management of patients suspected of PE at emergency departments was inappropriate in 43%.[11] In addition, they identified determinants for inappropriate management and concluded that clinicians are more frequently deviating from the guideline in patients in which contrast media may carry increased risk (eg, elderly) and in patients in which the symptoms could be ascribed to an alternative diagnosis. The latter might also be the case in our study population: we observed

that the CPRs were more frequently applied incorrectly in patients with heart failure. In these patients, the GP might first think of this disease as diagnosis—for instance peripheral oedema mimicking DVT or shortness of breath mimicking PE—and is therefore possibly more prone to (intentionally) deviate from the CPR. Unlike the findings from Roy and colleagues,[11] we could not confirm that increasing age is associated with an increased likelihood of incorrect CPR application. In fact, we observed the contrary; with increasing age, the odds of an incorrect application of the CPR seems to decrease. Furthermore, the association between female sex and incorrect application of CPRs is not reported before. Last, the CPR was more frequent incorrectly applied in suspected PE patients with a previous VTE, which is also in contrast with previous findings.[11] Importantly, we identified determinants for incorrect use of the CPR for the total group of patients suspected of both DVT and PE. It could be argued though that some determinants could be more specifically explaining incorrect CPR use in one of these VTE diseases.
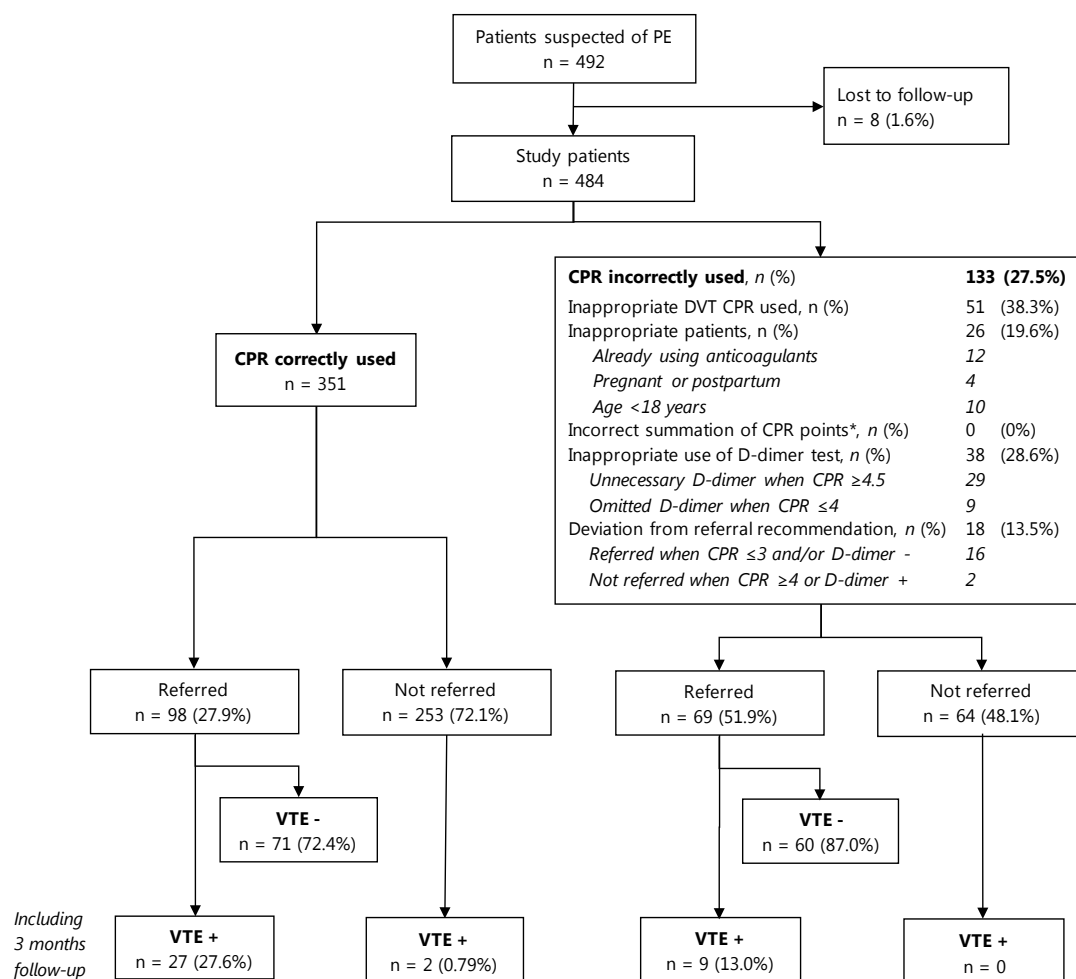
Patients suspected of PE
n = 492

Lost to follow-up
n = 8 (1.6%)

Study patients
n = 484

CPR incorrectly used, *n* (%) — **133 (27.5%)**
Inappropriate DVT CPR used, n (%) — 51 (38.3%)
Inappropriate patients, n (%) — 26 (19.6%)
Already using anticoagulants — 12
Pregnant or postpartum — 4
Age <18 years — 10
Incorrect summation of CPR points*, n (%) — 0 (0%)
Inappropriate use of D-dimer test, *n* (%) — 38 (28.6%)
Unnecessary D-dimer when CPR ≥4.5 — 29
Omitted D-dimer when CPR ≤4 — 9
Deviation from referral recommendation, *n* (%) — 18 (13.5%)
Referred when CPR ≤3 and/or D-dimer - — 16
Not referred when CPR ≥4 or D-dimer + — 2

CPR correctly used
n = 351

Referred
n = 98 (27.9%)

Not referred
n = 253 (72.1%)

Referred
n = 69 (51.9%)

Not referred
n = 64 (48.1%)

VTE -
n = 71 (72.4%)

VTE -
n = 60 (87.0%)

Including 3 months follow-up

VTE +
n = 27 (27.6%)

VTE +
n = 2 (0.79%)

VTE +
n = 9 (13.0%)

VTE +
n = 0

Figure 3 Flow chart of study patients suspected of PE. *Only counted when incorrect dichotomisation in CPR. CPR, clinical prediction rule; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Implications for practice

We believe our study has several implications for clinical practice. First, it is reassuring that correct application of CPRs for both suspected DVT and PE patients leads to a safe and efficient diagnostic management. Ruling out VTE in primary care in more than half of all suspected patients at an acceptable safety margin would be considered highly attractive by many GPs and as such our findings strengthen the evidence base of ruling out VTE in an outpatient, community healthcare setting. However, we showed that incorrect application is common in daily primary care practice and notably is associated with an increased risk of missing VTE in those not referred. Of note, VTE prevalence in those referred appears to be similar in those in whom the CPRs were correctly used versus those in whom it was incorrectly applied. Although strictly speaking not the objective of our study, we could hypothesise about opportunities to improve the correct implementation of CPRs for VTE in primary care. First, simplification of the CPRs might enhance correct application. The current CPRs for DVT and PE consist of seven different clinical items with scores ranging from 1 to 3 points per item. This could be one of the reasons for the frequent incorrect use of the CPRs, especially since VTE is relatively rare in primary care and GPs do not often use the CPRs.[22] Recently, a simplified CPR for PE has been developed and validated in secondary care: the YEARS algorithm.[23] This algorithm only consists of three clinical items with subsequent D-dimer testing in all patients, which potentially makes it easier to apply. Validation of this algorithm in the hospital setting showed that PE could be safely excluded with a 14% reduction of CT pulmonary angiographies as compared with the Wells rule for PE with a fixed D-dimer threshold.[24] Incorporating this new and simplified CPR might enhance guideline adherence of GPs but awaits validation in a primary care setting before using it in daily primary care practice.[25] Second, integration of a CPR in the electronic health system might also result in more correct use of the CPR and thereby adequate management but further research is needed. We showed that the two most common mistakes were including patients in whom the CPRs should not be used and inappropriate D-dimer testing. So, third, educational training in when and how to use the CPRs plus D-dimer

Table 2 Determinants for incorrect use of the clinical prediction rule in patients suspected of VTE

Variable	All patients*, n=1477, n (%)	Correct CPR, n=1138 n (%)	Incorrect CPR, n=339, n (%)	Univariable analysis, OR (95% CI)	Multivariable analysis†, OR (95% CI)
Age (years)					
≤50	543 (36.8)	403 (35.4)	140 (41.3)	1	1
>50 and ≤75	651 (44.1)	516 (45.3)	135 (39.8)	0.75 (0.58 to 0.99)	0.71 (0.54 to 0.94)
>75	283 (19.2)	219 (19.2)	64 (18.9)	0.84 (0.60 to 1.18)	0.75 (0.53 to 1.07)
Sex					
Men	578 (39.1)	712 (62.6)	187 (55.2)	1	1
Women	899 (60.9)	426 (37.4)	152 (44.8)	0.74 (0.58 to 0.94)	0.69 (0.54 to 0.89)
Heart failure					
No	1449 (98.1)	1123 (98.7)	326 (96.2)	1	1
Yes	28 (1.9)	15 (1.3)	13 (3.8)	2.99 (1.41 to 6.34)	3.26 (1.47 to 7.21)
COPD/asthma					
No	1307 (88.5)	1018 (89.5)	289 (85.3)	1	1
Yes	170 (11.5)	120 (10.5	50 (14.7)	1.47 (1.03 to 2.09)	1.38 (0.95 to 2.01)
Active malignancy					
No	1380 (93.9)	1066 (94.1)	314 (93.5)	1	1
Yes	89 (6.1)	67 (5.9)	22 (6.5)	1.11 (0.68 to 1.83)	1.11 (0.67 to 1.86)
Recent surgery/ immobilisation					
No	1369 (93.1)	1063 (93.7)	306 (91.1)	1	1
Yes	101 (6.9)	71 (6.3)	30 (8.9)	1.47 (0.94 to 2.29)	1.57 (1.00 to 2.47)
Previous VTE‡					
No	386 (80.1)	304 (86.9)	82 (62.1)	1	1
Yes	96 (19.9)	46 (13.1)	50 (37.9)	4.03 (2.52 to 6.44)	4.45 (2.73 to 7.25)

*Data were missing for the following variables: active malignancy (two patients), recent surgery or immobilisation (seven patients) and previous VTE (two patients).
†Due to missing data in 10 individual patients, 1467 patients were included in the multivariable analysis.
‡Results based only on 482 patients with suspected PE.
COPD, chronic obstructive pulmonary disease; CPR, clinical decision rule; PE, pulmonary embolism; VTE, venous thromboembolism.

testing might be an opportunity to improve correct application, for example, by educational outreach visits since GPs evaluated this as most encouraging.[10]

CONCLUSION

Correct application of CPRs for VTE in primary care is associated with a high efficiency and an acceptable low failure rate. Importantly, in nearly a quarter of patients, the CPRs were incorrectly applied that resulted in a lower efficiency and a higher failure rate. Such incorrect application of CPRs was more common in the presence of concurrent heart failure.

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SUPPLEMENTARY DATA

Table 1. Missing values of the characteristics of patients suspected of deep venous thrombosis and pulmonary embolism. DVT = deep venous thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism, CPR = clinical decision rule.

* During three months of follow-up.

** Only defined as missing when a D-dimer measurement should been done according to the CPR.

Characteristic	Missing values suspected DVT patients (n = 993)	Missing values suspected PE patients (n = 484)
Median age	0	0
Male	0	0
Active malignancy <6 months	6	2
Surgery or immobilisation	4	3
Oral contraceptive use	0	*n.a.*
Absence of leg trauma	1	*n.a.*
Distension of collateral veins	4	*n.a.*
Calf swelling >3 cm	2	*n.a.*
Clinical signs of DVT	*n.a.*	3
Haemoptysis	*n.a.*	2
PE most likely diagnosis	*n.a.*	4
History of VTE	*n.a.*	2
Heart rate >100 beats/minute	*n.a.*	5
Score on CPR	0	0
D-dimer **	41	11
Diagnosis of VTE*	0	0

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Table 2. Detailed description of non-referred patients with VTE after three months of follow-up.

DVT = deep venous thrombosis, PE = pulmonary embolism

Patient No.	Age (years)	Sex	DVT / PE	CPR score	D-dimer	Remarks
1	60	Female	DVT	1	Negative	
2	54	Male	DVT	2	Negative	
3	84	Male	DVT	2	Negative	
4	44	Female	DVT	2	Negative	
5	73	Female	DVT	2	Negative	
6	39	Male	DVT	3	Negative	
7	53	Male	DVT	3	Negative	
8	76	Female	DVT	0	280 ng/mL	
9	24	Male	DVT	5	240 ng/mL	
10	89	Female	DVT	2	Positive	Preference of patient to decline further diagnostic procedures
11	93	Female	DVT	3	Positive	Preference of patient to decline further diagnostic procedures
12	95	Female	DVT	2	2540 ng/mL	Preference of patient to decline further diagnostic procedures
13	73	Female	PE	1.5	Negative	
14	51	Male	PE	0	290 ng/mL	

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Oral contraceptive use	0	*n.a.*
Absence of leg trauma	1	*n.a.*
Distension of collateral veins	4	*n.a.*
Calf swelling >3 cm	2	*n.a.*
Clinical signs of DVT	*n.a.*	3
Haemoptysis	*n.a.*	2
PE most likely diagnosis	*n.a.*	4
History of VTE	*n.a.*	2
Heart rate >100 beats/minute	*n.a.*	5
Score on CPR	0	0
D-dimer **	41	11
Diagnosis of VTE*	0	0

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