How can we improve the diagnosis of deep vein thrombosis and pulmonary embolism at the primary level?

"...the use of validated clinical diagnostic rules in combination with point-of-care D-dimer tests allows the diagnostic scores to be completed entirely in the primary care setting and safely rules out deep vein thrombosis in approximately 50% of patients."

Keywords: deep vein thrombosis • diagnosis • primary care • pulmonary embolism

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is not uncommon in primary care, with a reported incidence of almost one case per 1000 person-years [1]. VTE is highly feared for its associated mortality, since the risk of PE-related early mortality may be higher than 15%, as well as its associated morbidity, since patients with VTE may also develop long-term complications such as chronic thromboembolic pulmonary hypertension or postphlebitic syndrome [2]. On the other hand, anticoagulation is an effective treatment for VTE, but carries a non-negligible rate of major bleeding events, ranging from 2% in clinical trials to 7.4% in population cohort studies [3].

When VTE is suspected, it is therefore mandatory to quickly achieve the correct diagnosis. Nonetheless, this process is particularly difficult in primary care, because of the limited number of available diagnostic tools and the nonspecific clinical presentations of DVT and PE. Therefore, the ultimate aim is to determine in which patients DVT or PE can be safely ruled out and which patients should be referred for additional diagnostic workup in secondary care.

The current diagnostic approach to VTE is based on the combination of three tools: diagnostic clinical prediction rules (CPRs) for assessing the pretest probability; D-dimer measurement; and imaging tests (i.e., venous ultrasonography for DVT and computed tomography pulmonary angiography [CTPA] or ventilation-perfusion lung scan for PE).

In patients who present with suspected DVT, the CPR developed by Wells and colleagues is currently the most used worldwide [4]. The Wells CPR includes information from patients' medical history (active cancer, recent immobilization of the lower extremities, recent bedridden or major surgery), physical examination (tenderness along the deep venous system, entire leg swollen or calf difference greater than 3 cm, pitting edema and collateral superficial veins) and a subjective variable (i.e., an alternative diagnosis for patients' symptoms) [4].

As the Wells CPR has been developed for secondary care outpatients, its applicability to primary care is still uncertain. A prospective validation study showed that the Wells CPR, in combination with a negative quantitative D-dimer test, did not adequately rule out DVT in the primary care setting [5]. This result could be partly due to different population characteristics, since secondary care patients are often selected by primary care physicians, and partly to the subjectively estimated probability of an alternative diagnosis, which might be assessed differently by general practitioners and by specialists.

Oudega and colleagues have developed a specific primary care CPR for suspected DVT that included eight simple diagnostic indicators (male gender, oral contraceptive use, presence of malignancy, recent surgery, absence of leg trauma, vein

Nicoletta Riva
Research Center on Thromboembolic Disorders & Antithrombotic Therapies, Department of Clinical & Experimental Medicine, University of Insubria, Varese, Italy

Francesco Dentali
Research Center on Thromboembolic Disorders & Antithrombotic Therapies, Department of Clinical & Experimental Medicine, University of Insubria, Italy

Walter Ageno
Research Center on Thromboembolic Disorders & Antithrombotic Therapies, Department of Clinical & Experimental Medicine, University of Insubria, Varese, Italy

Alessandro Squizzato
Author for correspondence:
Research Center on Thromboembolic Disorders & Antithrombotic Therapies, Department of Clinical & Experimental Medicine, University of Insubria, Varese, Italy; and
U.O. Medicina 1, Ospedale di Circolo, viale Borri 57, 21100 Varese, Italy
Tel.: +39 0332 278831
Fax: +39 0332 278595
alessandro.squizzato@uninsubria.it

Future Medicine part of fsg

distension, calf difference greater than 3 cm, abnormal quantitative D-dimer test) [6,7]. A direct comparison between the Oudega CPR and the Wells CPR showed that suspected DVT can be safely ruled out using either of the two diagnostic CPRs in combination with a point-of-care (POC) qualitative D-dimer assay [8]. Almost 50% of patients had a low clinical probability and a negative D-dimer test, and they could avoid referral for further testing with a very low percentage of missed DVT (1.6% for the Wells CPR and 1.4% for the Oudega CPR) [8].

In patients who present with suspected PE, two clinical diagnostic CPRs are currently available: the Wells CPR and the revised Geneva CPR. Similarly to DVT, the Wells PE CPR includes variables from patients' medical history (previous VTE, active cancer, recent immobilization or surgery) and physical examination (tachycardia, hemoptysis, and signs or symptoms of DVT), together with the possibility of an alternative diagnosis [9]. On the other hand, the revised Geneva CPR comprises only eight objective clinical variables (previous VTE, recent surgery or fracture, active cancer, age, heart rate, hemoptysis, unilateral lower-limb pain and unilateral leg edema) [10]. Each of these two CPRs also exist in a simplified version, easier to remember, according to the points assigned to the variables and the cut-offs used for risk categorization.

The Prometheus study, a prospective validation study conducted on patients referred to seven Dutch hospitals for suspected acute PE, provided a direct comparison of these CPRs using a computerized scoring system [11]. The Wells CPR and the simplified Wells CPR showed similar performance compared with the revised Geneva CPR. All four CPRs excluded PE in approximately 20% of patients who had a low clinical probability and a normal high-sensitivity quantitative d-dimer assay, with a failure rate of only 0.5–0.6% [11].

> "...high-sensitivity D-dimers pay the expense of only moderate specificity (~50%), with false positives resulting from inflammatory or infectious diseases, malignancy, trauma or surgery, pregnancy, advanced age and so on."

D-dimers are degradation products of crosslinked fibrin, generated during fibrinolysis, and their circulating levels are typically raised in patients with VTE. Among the numerous laboratory D-dimer assays, ELISA, microplate ELISA and latex quantitative assay have the highest sensitivity (93–97%) [12]. Moreover, various POC tests, which could be performed in the general practitioner's office or at the patient's house, have been recently introduced. The quantitative POC D-dimer tests have a very high sensitivity, similar to the laboratory-based ELISA, which is currently advocated as the best assay for excluding VTE in suspected patients [13]. Nonetheless, high-sensitivity D-dimers pay the expense of only moderate specificity (~50% [12,13]), with false positives resulting from inflammatory or infectious diseases, malignancy, trauma or surgery, pregnancy, advanced age and so on.

The conventional cut-off for D-dimer (500 µg/l) has been compared with age-adjusted cut-off values (age × 10 µg/l for patients aged above 50 years) in a recently published meta-analysis [14]. In patients with suspected VTE and nonhigh clinical probability, the application of age-adjusted cut-off values substantially increased specificity, while sensitivity remained above 97% across all age categories [14].

Selective D-dimer cut-off values, according to the clinical pretest probability (C-PTP) of the Wells CPR, have been evaluated in a randomized controlled trial conducted in five Canadian tertiary care centers [15]. In patients with suspected DVT, a selective testing strategy has been proposed, which consisted in using D-dimer cut-off 1000 µg/l for outpatients with low C-PTP and 500 µg/l for outpatients with moderate C-PTP, and in omitting D-dimer test and straight performing venous ultrasonography for outpatients with high C-PTP or inpatients. The selective strategy was as safe as the uniform testing strategy (testing D-dimer in all patients using a single cut-off 500 µg/l), since the incidence of symptomatic VTE during the 3-month follow-up was 0.5% in both study groups. Moreover, the selective strategy was more efficient, reducing the number of required ultrasonography by 7.6% and the number of required D-dimer tests by 21.8% [15].

A similar strategy has been assessed in a *post-hoc* analysis of two cohort studies on patients with suspected PE [16]. D-dimer threshold has been evaluated at 1000 µg/l for patients at low risk and 500 µg/l for patients at moderate risk, according to the Wells PE CPR. Although this finding needs to be confirmed in a prospective management study, applying a selective D-dimer cut-off excluded PE in 36% of patients, reducing the need for CTPA by 11% compared with standard management, but increasing the failure rate (the 3-month incidence of VTE was 2.1%) [16].

Specific imaging techniques are required to confirm the diagnosis of VTE. Obviously, patients need to be referred to hospital for CPTA or ventilation-perfusion lung scan; nonetheless, in patients with suspected DVT, compression ultrasonography (CUS) might be easily performed at the general practitioner's office. The Erasmus study showed that two-point CUS, which examines only proximal veins (the common femoral vein at the groin and the popliteal vein at the popliteal fossa), was as accurate as the

whole-leg color Doppler ultrasonography [17]. Proximal CUS can be learned in few hours, is reproducible and is widely available; however, in patients with normal imaging and abnormal D-dimer levels, the CUS should be repeated within 1 week, in order to detect calf DVTs that extend to the proximal veins [17].

The guidelines of the American Academy of Family Physicians support the use of validated clinical diagnostic rules for establishing the pretest probability of VTE, especially the Wells CPRs for DVT and PE [18]. In selected patients with low pretest probability, a negative high-sensitivity D-dimer assay has a very high negative predictive value to reduce the need for further diagnostic investigations. *Vice versa*, in patients with intermediate or high pretest probability, D-dimer testing is not required, whereas imaging testing is warranted to confirm or reject the diagnosis [18]. While awaiting the results of imaging tests, the American College of Chest Physicians Guidelines suggest treatment with parenteral anticoagulant drugs for all patients with high clinical suspicion of acute VTE [19].

In conclusion, the use of validated clinical diagnostic rules in combination with POC D-dimer tests allows the diagnostic scores to be completed entirely in the primary care setting and safely rules out DVT in approximately 50% of patients. Moreover, providing adequate training, general practitioners might also perform two-point CUS in their offices, without the need for additional imaging in secondary care.

On the other hand, the exclusion of PE with the use of clinical rules and D-dimer is particularly appealing, since CTPA could be associated with long-term radiation complications, contrast-induced nephropathy, allergic reactions and high healthcare costs. However, these patients might still need referral to hospital for additional diagnostic workup for alternative diagnosis. Special situations, such as recurrent VTE or pregnancy, still require to be managed by thrombosis specialists in a secondary or tertiary care setting.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Huerta C, Johansson S, Wallander MA, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch. Intern. Med.* 167(9), 935–943 (2007).

2 Torbicki A, Perrier A, Konstantinides S *et al.*; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur. Heart J.* 29(18), 2276–2315 (2008).

3 Wiedermann CJ, Stockner I. Warfarin-induced bleeding complications – clinical presentation and therapeutic options. *Thromb. Res.* 122(Suppl. 2), S13–S18 (2008).

4 Wells PS, Anderson DR, Bormanis J *et al.* Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 350(9094), 1795–1798 (1997).

5 Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. *Ann. Intern. Med.* 143(2), 100–107 (2005).

6 Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb. Haemost.* 94(1), 200–205 (2005).

7 Büller HR, Ten Cate-Hoek AJ, Hoes AW *et al.*; AMUSE (Amsterdam Maastricht Utrecht Study on thromboEmbolism) Investigators. Safely ruling out deep venous thrombosis in primary care. *Ann. Intern. Med.* 150(4), 229–235 (2009).

8 van der Velde EF, Toll DB, Ten Cate-Hoek AJ *et al.* Comparing the diagnostic performance of 2 clinical decision rules to rule out deep vein thrombosis in primary care patients. *Ann. Fam. Med.* 9(1), 31–36 (2011).

9 Wells PS, Anderson DR, Rodger M *et al.* Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb. Haemost.* 83(3), 416–420 (2000).

10 Le Gal G, Righini M, Roy PM *et al.* Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann. Intern. Med.* 144(3), 165–171 (2006).

11 Douma RA, Mos IC, Erkens PM *et al.*; Prometheus Study Group. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Ann. Intern. Med.* 154(11), 709–718 (2011).

12 Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J. Thromb. Haemost.* 5(2), 296–304 (2007).

13 Geersing GJ, Janssen KJ, Oudega R *et al.* Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ* 339, b2990 (2009).

14 Schouten HJ, Geersing GJ, Koek HL *et al.* Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. *BMJ* 346, f2492 (2013).

15 Linkins LA, Bates SM, Lang E *et al.* Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. *Ann. Intern. Med.* 158(2), 93–100 (2013).

16 van der Hulle T, den Exter PL, Erkens PG *et al.* Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism. *J. Thromb. Haemost.* 11(11), 1986–1992 (2013).

17 Bernardi E, Camporese G, Büller HR *et al.* Erasmus Study Group. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. *JAMA* 300(14), 1653–1659 (2008).

18 Qaseem A, Snow V, Barry P *et al.*; Joint American Academy of Family Physicians/American College of Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann. Fam. Med.* 5(1), 57–62 (2007).

19 Kearon C, Akl EA, Comerota AJ *et al.*; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(Suppl. 2), e419S–e494S (2012).