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RECOMMENDATIONS AND GUIDELINES

The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH

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Scope and methodology

This document is intended to give clinical guidance for the diagnosis of symptomatic recurrent pulmonary embolism (PE) and/or deep vein thrombosis (DVT). We define recurrent PE and DVT as those events occurring after an initial course of adequate antithrombotic treatment for a first venous thromboembolic event (VTE) [1,2]. The issue of a correct diagnosis of recurrence is clinically relevant because many patients with a previous VTE will complain of signs or symptoms suggesting the possibility of a recurrent event. Indeed, in patients with a previous DVT, symptoms and signs of post-thrombotic syndrome are often confusing for the clinician (and patient) and are interpreted as possible recurrent DVT. Moreover, only 20–30% of all suspected recurrences of both DVT and PE have been confirmed by central adjudication committees in randomized controlled trials [3]. However, even if only a minority of patients will be objectively diagnosed with a recurrent VTE [1], this remains a major clinical problem occurring in approximately 11% of patients after 1 year from the first unprovoked event and in approximately 40% of patients after 10 years [4].

The guidance in this document must be distinguished from a guideline based on a systematic literature review, which it is not. Such guidelines have previously been published, though not covering all topics discussed in this report [2]. This guidance outlines factors that may influence decision-making in the diagnostic process with reference to published evidence-based guidelines. Furthermore, the guidance statements presented here do not apply to patients with venous thrombosis in unusual sites, such as the splanchnic or cerebral veins, for which no or little data exist on diagnosing recurrent events.

The guidance statements included in this document are predicated on the following premises:

1 For each of the clinical situations described herein, our guidance statements are applicable to an average patient with a suspicion of recurrent PE and/or DVT. There may be circumstances for which our guidance statements do not apply and the diagnostic process should be at the treating physician's discretion.
2 The language used to reflect the strength of our guidance statements adopts the convention used in the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system [5].
3 The wording 'we recommend' reflects a strong guidance statement, whereby the clinician should adopt the practice in most cases.
4 The wording 'we suggest' reflects a weak guidance statement, whereby the clinician may adopt the practice in some cases and an alternative practice also may be acceptable.

Definition of terms

The definitions of recurrence and progression are as follows:

1 VTE recurrence: PE and/or DVT occurring after a successful acute treatment; 'successful' means a clear clinical improvement of patient symptoms and signs; 'acute' means the first 2 weeks of treatment.
2 Early VTE recurrence: VTE occurring within the first 3 months.
3 Late recurrence: VTE occurring after the initial 3 months.
4 VTE progression: new PE and/or DVT occurring or worsening during the acute treatment.

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Table 1 The Geneva and Wells CPR for PE*

Variable	Points	Risk class	Points
(A) Geneva CPR			
Recent surgery	+3	Low	0–4
Previous DVT or PE	+2	Intermediate	5–8
		High	> 8
Heart rate > 100 bpm	+1		
Age 60–79 years old	+1		
> 79 years old	+2		
Chest radiograph: atelectasis	+1		
Elevated hemidiaphram	+1		
P_{aO_2}			
< 49 mm Hg (6.5 kPa)	+4		
49–59 mm Hg (6.5–7.99 kPa)	+3		
60–71 mm Hg (8–9.49 kPa)	+2		
72–82 mm Hg (9.5–10.99 kPa)	+1		
P_{aCO_2}			
< 36 mm Hg (4.8 kPa)	+2		
36–38.9 mm Hg (4.8–5.2 kPa)	+1		
(B) Revised Geneva CPR			
Age > 65 years old	+1	Low	0–3
Previous history of PE or DVT	+3	Intermediate	4–10
		High	> 10
Surgery or fracture within 1 month	+2		
Active malignancy	+2		
Heart rate			
> 75–94 bpm	+3		
> 94 bpm	+5		
Pain on leg venous palpation and unilateral edema	+4		
Unilateral leg pain	+3		
Hemoptysis	+2		
(C) Wells CPR			
Clinical signs of DVT	+3	Low	< 2
Recent surgery or immobilization	+1.5	Intermediate	2–6
		High	> 6
		Unlikely	0–4
		Likely	> 4
Heart rate > 100 bpm	+1.5		
Previous history of PE or DVT	+1.5		
Hemoptysis	+1		
Malignancy	+1		
Alternative diagnosis less likely than PE	+3		

CPR, clinical prediction rule; DVT, deep vein thrombosis; PE, pulmonary embolism.
*For additional clinical prediction rules, see: Hogg K, Wells PS, Gandara E. The diagnosis of venous thromboembolism. Semin Thromb Hemost 2012; 38: 691–701.

Table 2 The Wells clinical prediction rule for deep vein thrombosis*

Variables	Points	Risk class	Points
Active cancer (treatment within last 6 months or palliative)	+1	Low	0
		Intermediate	1–2
Calf swelling ≥ 3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity)	+1	High	> 2
		Unlikely	0–1
		Likely	> 1
Swollen unilateral superficial veins (nonvaricose, in symptomatic leg)	+1		
Unilateral pitting edema (in symptomatic leg)	+1		
Previous documented deep vein thrombosis	+1		
Swelling of the entire leg	+1		
Localized tenderness along the deep venous system	+1		
Paralysis, paresis, or recent cast immobilization of lower extremities	+1		
Recently bedridden ≥ 3 days or major surgery requiring regional or general anesthetic in the past 12 weeks	+1		
Alternative diagnosis at least as likely	−2		

*For additional clinical prediction rules, see: Hogg K, Wells PS, Gandara E. The diagnosis of venous thromboembolism. Semin Thromb Hemost 2012; 38: 691–701.

Clinical prediction rules

Nine clinical prediction rules (CPRs) are available for patients with suspected PE and seven for patients with suspected DVT [6–10]. None was specifically designed for patients with suspected recurrence. The most studied and used CPRs for PE are the Wells (original and simplified) and Geneva (original and revised), and for DVT, the Wells (original and simplified) (Tables 1 and 2). No CPRs have been subsequently validated in a large population of patients with suspected recurrence only. For this reason, the American College of Chest Physicians (ACCP) 2012 guidelines do not recommend an initial clinical assessment with a CPR in patients with a suspicion of DVT recurrence [2]. Indeed, patients with a previous VTE are more likely to be classified as having a high clinical probability by CPRs, as a history of previous VTE is one of the items used to determine clinical probability in both Wells (PE and DVT) and Geneva CPRs. This also means that patients with a history of previous VTE have been included in the derivation cohort of Wells and Geneva CPRs and, thus, such CPRs should, at least in theory, also apply to these patients. For this reason, even taking into account the lack of specifically designed studies, we propose the inclusion of CPRs in the diagnostic approach to suspected recurrence of VTE. When CPRs are used, the use of dichotomized results (e.g. unlikely and likely) is in our opinion to be preferred to the three categories.

Guidance statements

1 We *suggest* the use of a validated CPR to determine a pretest probability score to drive the diagnostic process in patients with suspected recurrent PE.
2 We *suggest* the use of a validated CPR to determine a pretest probability score to drive the diagnostic process in patients with suspected recurrent DVT.

D-dimer

Thanks to its high negative predictive value, the D-dimer test represents an excellent non-invasive triage test in patients with suspected VTE [11]. A large number of D-dimer assays have been evaluated: in general, enzyme-linked immunofluorescent immunoassays and microplate enzyme-linked immunosorbent assay methods have the highest sensitivity (> 90%) for both DVT and PE [11]. However, the specificity of these assays is only 40–50%. Latex quantitative assays have similar characteristics, while latex semiquantitative and whole-blood assays have lower sensitivity but higher specificity [11]. These differences, as well as differences in specific assays, have implications for the use of D-dimer assays as screening tests for recurrent VTE. To maximize the negative predictive value of assaying D-dimer, a high-sensitivity assay should be used. The results of D-dimer assays should take into account the higher normal values that occur in elderly subjects. Age-adjusted cut-off values for D-dimer assays have been proposed [12–14], but further prospective research is required before recommendations can be made. If proved to be accurate, age-based cut-offs will be clinically useful since they are likely to increase the ability of the test to exclude the suspected disease.

The main limitation of D-dimer testing in patients with suspected recurrent VTE is related to the high rate of elevated values normally detected after stopping oral anticoagulant therapy (OAT). In one study, 15.5% of patients were found to have an elevated D-dimer at the time of OAT withdrawal and 46% of patients had an elevated D-dimer 3 months later [15,16]. The ACCP guidelines recommend for the diagnosis of recurrent DVT initial evaluation with proximal compression ultrasonography (CUS) or a highly sensitive D-dimer over venography, computed tomographic venography, or magnetic resonance imaging (MRI) [2]. High-sensitivity D-dimer testing is recommended when a prior CUS is not available [2].

Five prospective cohort management studies have reported results for strategies involving D-dimer testing in patients with suspected recurrent DVT [2,17–21]. One study retrospectively evaluated the accuracy of D-dimer in excluding PE in a population of patients with previous VTE [22], and one evaluated D-dimer combined with a CPR and computed tomographic pulmonary angiography (CTPA) in a defined diagnostic algorithm [23]. D-dimer was assessed both as a single first screening test [19,20] and in combination with clinical probability [18,21,22]. In one study, a negative D-dimer was used to exclude recurrent DVT in patients with a negative CUS result [17].

The D-dimer assays used in DVT studies were latex quantitative [17–21] or whole-blood assays [21]. No D-dimer assays with very high sensitivity – such as enzyme-linked immunofluorescent immunoassays – were investigated. Conversely, high-sensitivity D-dimer assays were used in PE studies [22]. Even if a limited number of patients have been tested, it is reasonable to assume that D-dimer sensitivity in patients with a suspicion of VTE recurrence is comparable to D-dimer performance in patients with a suspicion of a first episode [2]. After a 3-month follow-up, in the Rathbun study, only 1 of 134 patients with a suspected recurrent DVT and a negative D-dimer had confirmed VTE (0.75%, 95% confidence interval [CI] 0.02–4.09%) [19]. In the Nijkeuter study, none of the patients with a suspicion of recurrent PE and an unlikely pretest probability and negative D-dimer had a thrombotic event during follow-up (0%, 95% CI 0–6.9%) [23]. However, in general, the strategy of combining D-dimer and pretest probability assessment to exclude DVT or PE may have limited usefulness, due to a high frequency of positive D-dimer results in patients with suspected recurrence: in the Aguilar and Nijkeuter studies, the combination of D-dimer and pretest probability assessment was able to exclude recurrence in only 15% and 18%, respectively, of patients, and in the Le Gal study, similarly, PE was ruled out by a negative D-dimer test result in only 15.9% (49 of 308) of the patients with previous VTE [18,22].

Guidance statements

1 We *suggest* that in patients with suspected recurrent VTE and a *likely* or *intermediate/high* pretest probability, D-dimer testing should not be performed and patients should be investigated initially with imaging tests.
2 We *suggest* that imaging tests may be withheld in patients with suspected recurrent VTE if they have a *low or unlikely* pretest probability and a high sensitive D-dimer assay is negative.
3 We *suggest* that in the presence of equivocal findings on CUS, further evaluation should include D-dimer testing and possibly alternative imaging.

Imaging tests

Pulmonary embolism

Pulmonary angiography, the reference standard imaging test for PE, is invasive, costly, and sometimes difficult to interpret [24]. CTPA has simplified the diagnostic approach to patients with a suspected first episode of PE. However, to improve the accuracty of PE diagnosis, a proper combination of clinical evaluation, plasma D-dimer measurement, and CTPA is essential to correctly initiate or withhold PE-specific treatment.

A systematic review of the literature has shown that the percentage of patients with residual pulmonary thrombi after a previous PE was 87% at 8 days after the diagnosis, 68% after 6 weeks, 65% after 3 months, 57% after 6 months, and 52% after 11 months [25]. Similar data have been reported for lung scan: normalization varied from 35% to 43% in studies that used perfusion scin-

tigraphy [26,27]. The agreement between CTPA and lung scan for detecting residual defects is low, with a *k* agreement between tests of < .2 [28].

The application of a diagnostic algorithm based on the sequential application of a CPR, a quantitative D-dimer test, and CTPA in patients with a previous episode of PE enrolled in the Christopher study was retrospectively analyzed [23]. Only one patient with negative CTPA results had a fatal recurrent PE during follow-up (0.8%, 95% CI 0.02–4.3%). CTPA was tested alone or as a part of an algorithm in other studies, but no separate data on patients with previous PE were provided [29,30].

The availability of baseline imaging at the completion of anticoagulant treatment to be compared with the results of imaging tests carried out at the time of suspected recurrent VTE was shown to safely and effectively rule out recurrence in a significant proportion of patients and to be more accurate than in patients with no baseline imaging [31,32]. However, costs and safety issues (i.e. radiation, contrast-induced nephropathy) should be taken into account.

Characteristics of the thrombus (e.g. density, acute or obtuse angles with the vascular wall) and of pulmonary arteries (e.g. intramural calcifications, bronchial arteries) on CTPA or MRI are currently used by radiologists to distinguish an acute PE from a residual thrombus, but no management study has formally validated these approaches.

In principle, it would be useful to order the same test used for the diagnosis of the first event in case of suspected recurrence.

Finally, there is no evidence to suggest that the diagnostic approach to patients with suspected recurrent PE after a first episode should differ from the approach to be used in patients with multiple previous events.

Guidance statements

1 We *recommend* CTPA as the preferable imaging test in patients with suspected recurrent PE.

2 We *suggest* that evaluation by ventilation/perfusion (V/Q) lung scan be carried out in patients with suspected recurrent PE who have an available baseline scan.

3 We *suggest* that commonly accepted criteria for PE diagnosis in patients with no history of VTE also be used for the diagnosis of PE in patients with suspected recurrence: a central filling defect or complete occlusion on CTPA of segmental or more proximal branches of pulmonary arteries; a filling defect or a cut-off of a vessel of > 2.5 mm on pulmonary angiography; a new perfusion defect of ≥ 75% of a segment with corresponding normal ventilation (high-probability lung scan) [33].

4 We *suggest* that routine CTPA or lung scan should not routinely be performed as baseline imaging tests in all patients with a previous episode of PE at the completion of anticoagulant treatment. However, it may be considered in those thought to be at high risk for recurrence.

Deep vein thrombosis

CUS is the most widely used imaging study for the diagnosis of DVT. The inability to fully collapse a venous segment under gentle ultrasonographic probe pressure is considered diagnostic of DVT [2]. Proximal CUS assesses compressibility of the femoral and popliteal veins to the point where the latter joins the calf veins (trifurcation). Whole-leg CUS assesses the deep veins of both the proximal leg and calf [2].

The presence of residual vein thrombosis is the main drawback of CUS when used for diagnosing a recurrent ipsilateral DVT. The rate of normalization of an abnormal CUS of the popliteal and the common femoral veins after a first episode of proximal DVT was reported to be 29%, 44%, 54%, and 60% at 3, 6, 9, and 12 months, respectively [34]. The availability of baseline imaging at the completion of OAT to be compared with imaging results at the time of suspected recurrent VTE has been shown to safely and effectively rule out recurrence in a significant proportion of patients [31,32]. As opposed to CTPA, CUS is a relatively inexpensive and safe test. Comparing the new CUS to the baseline imaging test allows clinicians to evaluate for an increase in the residual vein thrombosis diameter. However, the definition of recurrence based on the comparison of the residual clot diameter with baseline data vary: 1–2 mm in one study [35], ≥ 2 mm in two studies [36,37], and > 4 mm in two studies [35,38]. Furthermore, interobserver agreement on measurement of residual vein diameter is not optimal, with a mean difference between paired measurements of 2.2 mm (95th centile, 8.0 mm) [39]. Despite these limitations, comparison of the residual clot diameter is the best available tool. Other characteristics of the thrombus (length, Doppler flow, intraluminal appearance) are potentially useful but have been much less studied [2].

Several management studies have used serial proximal CUS in suspected recurrent DVT, with repeatedly normal results or unchanged residual vein thrombus ruling out recurrence. CUS was repeated once at day 7 [21], or twice, at day 2 (± 1) and at day 7 (± 1) [33,34] or at dayd 7–10 [20], with a frequency of false-negative results ranging from 1% to 5%.

In a prospective study using MRI, it was determined that the abnormal MRI signal indicating an acute thrombus had vanished 6 months after the acute event, suggesting this may represent an accurate test for recurrence [40]. However, neither MRI nor CT venography has been tested in patients with suspected recurrent DVT.

Finally, there is no evidence to suggest that the diagnostic approach to patients with suspected recurrent DVT after a first episode should differ from the approach to be used in patients with multiple previous events.

Guidance statements

1 We *recommend* proximal CUS as the preferable imaging test in patients with suspected recurrent DVT.

2 We *suggest* that proximal CUS be performed at the time of OAT withdrawal to obtain baseline measurement of residual vein thrombosis.

3 We *recommend* the compression of the vein in the transverse plane as the main CUS maneuver to diagnose recurrent DVT. The presence of a new, noncompressible venous segment is the main diagnostic criterion for recurrence.

4 We *suggest* the measurement of residual vein diameter as the main characteristic for diagnosing an ipsilateral recurrent DVT in a previously abnormal segment. We *suggest* evaluation of the increase in residual vein diameter in popliteal and femoral veins. If the vein diameter is > 4 mm, the patient should be treated for a recurrent ipsilateral proximal DVT; if 2–4 mm, we recommend that CUS be repeated after 7 days and that treatment be initiated if the diameter is > 4 mm at this time; if < 2 mm, we suggest further imaging test at 7 days only in patients with a high clinical probability of recurrence.

5 We *suggest* a whole-leg CUS in patients with suspected recurrent distal DVT. No criteria can be suggested in addition to simple compressibility of the distal vein segment. However, given it is unclear that all calf DVT require anticoagulant treatment, serial CUS without anticoagulants to monitor for progression is an acceptable alternative form of management. This approach should be preferably considered when a baseline whole-leg CUS is available.

6 We *recommend* that, in patients with suspected recurrent VTE venography, MRI and CT venography should be used as imaging tests only if CUS is unavailable or if the results of CUS are inadequate for interpretation.

Addendum

W. Ageno, A. Squizzato, P. S. Wells, H. R. Buller, and G. Johnson contributed to the concept of this manuscript and to the intepretation of the data, to critical writing, and to the final approval of the version to be published.

Disclosure of Conflict of Interest

The authors have no conflict of interest to declare.

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