Deep vein thrombosis and pulmonary embolism

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Lancet 2016; 388: 3060–73
Published Online June 30, 2016
http://dx.doi.org/10.1016/S0140-6736(16)30514-1

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Deep vein thrombosis and pulmonary embolism, collectively referred to as venous thromboembolism, constitute a major global burden of disease. The diagnostic work-up of suspected deep vein thrombosis or pulmonary embolism includes the sequential application of a clinical decision rule and D-dimer testing. Imaging and anticoagulation can be safely withheld in patients who are unlikely to have venous thromboembolism and have a normal D-dimer. All other patients should undergo ultrasonography in case of suspected deep vein thrombosis and CT in case of suspected pulmonary embolism. Direct oral anticoagulants are first-line treatment options for venous thromboembolism because they are associated with a lower risk of bleeding than vitamin K antagonists and are easier to use. Use of thrombolysis should be limited to pulmonary embolism associated with haemodynamic instability. Anticoagulant treatment should be continued for at least 3 months to prevent early recurrences. When venous thromboembolism is unprovoked or secondary to persistent risk factors, extended treatment beyond this period should be considered when the risk of recurrence outweighs the risk of major bleeding.

Introduction

Deep vein thrombosis and pulmonary embolism are manifestations of venous thromboembolism. Although deep vein thrombosis develops most often in the legs, the deep veins of the arms, the splanchnic veins, and the cerebral veins can be affected. In this Seminar we focus on the epidemiology, diagnosis, and treatment of deep vein thrombosis of the legs and pulmonary embolism. Prevention of venous thromboembolism is outside the scope of this Seminar.

Epidemiology

Venous thromboembolism is a major global burden with about 10 million cases occurring every year, thereby representing the third leading vascular disease after acute myocardial infarction and stroke.[1] Just under half a million deep vein thromboses and 300 000 pulmonary embolisms occur every year in six European countries with 300 million inhabitants.[2] The yearly economic burden of venous thromboembolism in the USA has been estimated to be US$7–10 billion.[3] Incidence is steadily increasing because of population ageing, a higher prevalence of comorbidities associated with venous thromboembolism, such as obesity, heart failure, and cancer, and the improved sensitivity and widespread use of imaging tests to detect venous thromboembolism.[1,4]

The annual average incidence increases exponentially with age to up to one case per hundred people older than 80 years.[1,5,6] From age 45 years onwards, the lifetime risk of developing venous thromboembolism is 8%.[1,7] Compared with white individuals, incidence is higher in black people[8] and lower in Asian people,[1] a disparity for which cause has not yet been elucidated. Risk does not differ by sex, although it seems to be two-times higher in men than in women when venous thromboembolisms related to pregnancy and oestrogen therapy are not considered.[9]

Venous thromboembolism is associated with substantial morbidity and mortality. Although the 30 day mortality rate after pulmonary embolism is decreasing,[10,11] about 20% of patients with pulmonary embolism still die before diagnosis or shortly thereafter, particularly if the embolism is associated with haemodynamic instability.[12] Long term, venous thromboembolism is a chronic disease and about 30% of all patients with venous thromboembolism have a recurrence within 10 years.[6,13] The sequelae of venous thromboembolism are also associated with substantial disability and include the post-thrombotic syndrome, which develops in 20–50% of patients with deep vein thrombosis,[14] and chronic thromboembolic pulmonary hypertension, which complicates 0·1–4·0% of pulmonary embolisms.[15]

Although our knowledge of risk factors has increased over the past decades, a third to a half of venous thromboembolism episodes do not have an identifiable provoking factor and are therefore classified as unprovoked.[16] The remaining episodes are caused (provoked) by transient or persistent factors that additively or multiplicatively increase the risk of venous thromboembolism by inducing hypercoagulability, stasis, or vascular wall damage or dysfunction (panel).[6,17] Strong risk factors for venous thromboembolism include surgery, immobilisation, and cancer. Risk is especially high for patients undergoing major orthopaedic surgery; with postoperative rates of around 1% despite pharmacological thromboprophylaxis.[18] About 20% of all

Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane Library for papers published in English from Dec 1, 2009, to March 31, 2016, using combinations of the following terms: "deep vein thrombosis", "pulmonary embolism", "venous thromboembolism", "epidemiology", "diagnosis", "prognosis", and "treatment". We gave preference to publications from the past 5 years, but did consider highly regarded older publications. We screened the reference lists of articles identified by the search strategy and included those judged relevant. Pertinent reviews are cited to provide readers with more details and references than we are able to address in this Seminar.

venous thromboembolisms are cancer-related,[19] whereas surgery and immobilisation both account for 15% of cases.[5] The most frequent heritable risk factors besides non-0 blood group are the factor V Leiden and prothrombin gene mutations, which have a prevalence in the European population of 3–7% and 1–2%, respectively.[20] Since heritable risk factors only slightly predict recurrent venous thromboembolism, thrombophilia testing seems to have limited or no relevance for the long-term management of venous thromboembolism. Although the list of genetic determinants of venous thromboembolism is constantly updated and evidence is emerging to support testing several single nucleotide polymorphisms in a single chip, they do not have relevance yet for clinical practice.[21]

Diagnosis

Clinical presentation

Clinical manifestations of deep vein thrombosis of the legs include swelling or pitting oedema, redness, tenderness, and presence of collateral superficial veins. Signs and symptoms of pulmonary embolism comprise sudden onset of dyspnoea or deterioration of existing dyspnoea, chest pain, syncope or dizziness due to hypotension or shock, haemoptysis, tachycardia, or tachypnoea. Abnormalities on chest radiography, electrocardiography, or blood gas analysis are not specific for pulmonary embolism, but might be useful in the differential diagnosis. About 70% of patients with symptomatic pulmonary embolism have concomitant deep vein thrombosis, which is symptomatic in up to a quarter of cases.[6,13] Conversely, silent pulmonary embolism is present in at least a third of patients with symptomatic deep vein thrombosis.[22]

The great challenge in the diagnostic investigation of suspected venous thromboembolism is to accurately and rapidly identify patients in whom prompt treatment is needed to prevent thrombus extension or embolisation, from patients without disease, in whom unnecessary diagnostic tests and anticoagulant therapy should be avoided. The diagnosis of venous thromboembolism on the basis of clinical manifestations alone is unreliable because of the poor specificity of signs and symptoms.[23] Imaging is therefore warranted to confirm or refute the diagnosis. However, among patients with clinically suspected deep vein thrombosis or pulmonary embolism, the prevalence of the disease is only about 20%; with a broad variation across countries and clinical settings (range 4–44%).[24–26] It is therefore undesirable to image every patient with suspected venous thromboembolism because of the potential harms of these procedures, including radiation exposure and the risk of contrast-induced nephropathy, as well as associated health-care costs and use. To guide decisions about who should be referred for imaging, diagnostic algorithms consisting of clinical probability assessment and D-dimer testing have been established.

***Panel:* Risk factors for venous thromboembolism**

Clinical and environmental risk factors

Hypercoagulability

- Older age
- Active cancer
- Antiphospholipid syndrome
- Oestrogen therapy
- Pregnancy or puerperium
- Personal or family history of venous thromboembolism
- Obesity
- Autoimmune and chronic inflammatory diseases (eg, inflammatory bowel disease)
- Heparin-induced thrombocytopenia

Vascular damage

- Surgery
- Trauma or fracture
- Central venous catheter or pacemaker

Venous stasis or immobilisation

- Hospitalisation for acute medical illness
- Nursing-home residence
- Long-haul travel for more than 4 h
- Paresis or paralysis

Heritable risk factors

- Factor V Leiden
- Prothrombin 20210G→A mutation
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Non-0 blood group

Clinical probability assessment and D-dimer testing

Clinical decision rules, which are based on clinical probability scores, are used to stratify patients and guide the selection and interpretation of further diagnostic tests. The Wells' deep vein thrombosis score consists of ten items and is the most frequently used score in clinical practice for patients with suspected deep vein thrombosis (table 1).[32] The best validated scores for suspected pulmonary embolism are the Wells' pulmonary embolism[28] and revised Geneva scores,[30] which incorporate risk factors for venous thromboembolism and signs and symptoms of pulmonary embolism (appendix). These scores have been modified over the years to simplify their calculation,[29,31] while still maintaining good performance.[33,34] Although clinical decision rules seem to have similar performance as empirical clinical evaluation,[25] they are preferred to standardise clinical assessment and increase reproducibility among less experienced physicians. The Wells' scores and revised Geneva rules were originally intended as three-level rules (low, intermediate, or high clinical probability), but are now mostly used dichotomously, classifying patients as venous thromboembolism likely or high probability versus

See Online for appendix

	Original points	Simplified points
Wells' score for deep vein thrombosis[27]*		
Active cancer	+1	NA
Paralysis, paresis, or recent plaster cast on lower extremities	+1	NA
Recent immobilisation >3 days or major surgery within the past 4 weeks	+1	NA
Localised tenderness of deep venous system	+1	NA
Swelling of entire leg	+1	NA
Calf swelling >3 cm compared to asymptomatic side	+1	NA
Unilateral pitting oedema	+1	NA
Collateral superficial veins	+1	NA
Previously documented deep vein thrombosis	+1	NA
Alternative diagnosis at least as likely as deep vein thrombosis	−2	NA
Wells' score for pulmonary embolism[28,29]†‡		
Alternative diagnosis less likely than pulmonary embolism	+3	+1
Clinical signs and symptoms of deep vein thrombosis	+3	+1
Heart rate >100 beats per min	+1·5	+1
Previous deep vein thrombosis or pulmonary embolism	+1·5	+1
Immobilisation or surgery within the past 4 weeks	+1·5	+1
Active cancer	+1	+1
Haemoptysis	+1	+1
Revised Geneva score for pulmonary embolism[30,31]§¶		
Heart rate ≥95 beats per min	+5	+2
Heart rate 75–94 beats per min	+3	+1
Pain on lower-limb deep venous palpation and unilateral oedema	+4	+1
Unilateral lower-limb pain	+3	+1
Previous deep vein thrombosis or pulmonary embolism	+3	+1
Active cancer	+2	+1
Haemoptysis	+2	+1
Surgery or fracture within the past 4 weeks	+2	+1
Age >65 years	+1	+1

*Classification for original Wells' score for deep vein thrombosis: deep vein thrombosis unlikely if score ≤2; deep vein thrombosis likely if score >2. †Classification for original Wells' score for pulmonary embolism: pulmonary embolism unlikely if score ≤4; pulmonary embolism likely if score >4. ‡Classification for simplified Wells' score for pulmonary embolism: pulmonary embolism unlikely if score ≤1; pulmonary embolism likely if score >1. §Classification for original revised Geneva score for pulmonary embolism: non-high probability of pulmonary embolism if score ≤10; high probability of pulmonary embolism if score >10. ¶Classification for simplified revised Geneva score for pulmonary embolism: non-high probability of pulmonary embolism if score ≤4; high probability of pulmonary embolism if score >4.

Table 1: **Clinical decision rules for deep vein thrombosis and pulmonary embolism**

venous thromboembolism unlikely or non-high probability (table 1).[35]

Since clinical decision rules cannot safely exclude the diagnosis of deep vein thrombosis or pulmonary embolism alone,[25] they have to be used in conjunction with D-dimer testing. In patients who are thought unlikely to have venous thromboembolism based on the clinical decision rule, the diagnosis can be safely excluded based on a normal D-dimer level (below the defined threshold value for the test).[25,26] With this approach, imaging and treatment can be withheld in approximately a third of patients with suspected deep vein thrombosis or pulmonary embolism, of whom less than 1% will subsequently be diagnosed with venous thromboembolism in the following 3 months, which is considered an acceptable rate.[25,26]

Quantitative D-dimer assays have a higher sensitivity, but lower specificity, than qualitative tests,[36] which results in fewer false negative results at the cost of more patients being referred for imaging.[25] Point-of-care D-dimer tests can be done immediately at the emergency department or in the physician's office and provide results within 10–15 min. These tests also seem to safely exclude venous thromboembolism in combination with clinical decision rules,[37] which potentially simplifies the diagnostic work-up in the primary care setting and reduces the need for referral to secondary care.[38] To optimise the trade-off between sensitivity and specificity, the local prevalence of venous thromboembolism should be taken into account when a particular clinical decision rule and type of D-dimer assay is chosen, since test characteristics can vary across different clinical settings.[24,25] In patients classified as venous thromboembolism likely by the clinical decision rule, the negative predictive value of D-dimer testing is reduced,[28,39] and these patients should therefore be referred for imaging directly (figure 1).

The performance of clinical decision rules and D-dimer testing varies across high-risk subgroups. For example, a lower specificity for both clinical decision rules and D-dimer assays has consistently been shown in patients with cancer and in hospitalised patients.[26,40–43] As a consequence, the diagnostic algorithm yields more false positive results and a lower proportion of patients in whom imaging can be withheld. Moreover, in patients with cancer, ruling out deep vein thrombosis based on a venous thromboembolism unlikely classification and normal D-dimer test has been found to be neither safe nor efficient.[26] Therefore, in these subgroups, physicians might consider proceeding to imaging directly. Among patients with previous venous thromboembolism, a venous thromboembolism unlikely classification in combination with a normal D-dimer safely rules out venous thromboembolism, but more patients need imaging.[26,44] Although a specific clinical decision rule has been proposed for pregnant women with suspected deep vein thrombosis, external validation is needed before broader application.[45]

D-dimer levels naturally increase with age and the specificity of D-dimer testing for venous thromboembolism is therefore lower in older people. To increase the usefulness of D-dimer in these patients, an age-adjusted D-dimer threshold, defined as a patient's age times 10 μg/L, was derived for patients older than 50 years.[46] Compared with the conventional, fixed threshold of 500 μg/L, the age-adjusted threshold has a higher specificity and similar sensitivity across all age categories above 50 years,[46,47] thereby increasing the absolute proportion of patients in whom imaging can be safely withheld by 5–6%.[46,48] The safety of this age-adjusted D-dimer threshold was recently validated in a large prospective study of 3346 outpatients with clinically suspected pulmonary embolism.[33]

The performance of the age-adjusted D-dimer threshold in patients with clinically suspected deep vein thrombosis is under investigation.

Another proposed approach for patients with suspected pulmonary embolism is the application of the Pulmonary Embolism Rule-out Criteria (PERC) in patients with a low clinical probability according to a three-level clinical decision rule.[42] If such a low-risk patient meets all PERC criteria, physicians can refrain from D-dimer testing and consider the disease excluded.[49,50] However, the safety of this strategy has not yet been validated in a prospective management study. Others have proposed a D-dimer threshold that varies according to the pretest probability or even a single D-dimer test to exclude venous thromboembolism, but these strategies also await confirmation.

Generally, the use of clinical decision rules and D-dimer testing standardises the diagnostic work-up for venous thromboembolism, reduces the use of invasive tests, and is cost-effective.[51] Familiarity with and implementation of clinical decision rules are important, because inadequate use can result in inappropriate management and a higher risk of fatal or non-fatal venous thromboembolism.[52,53]

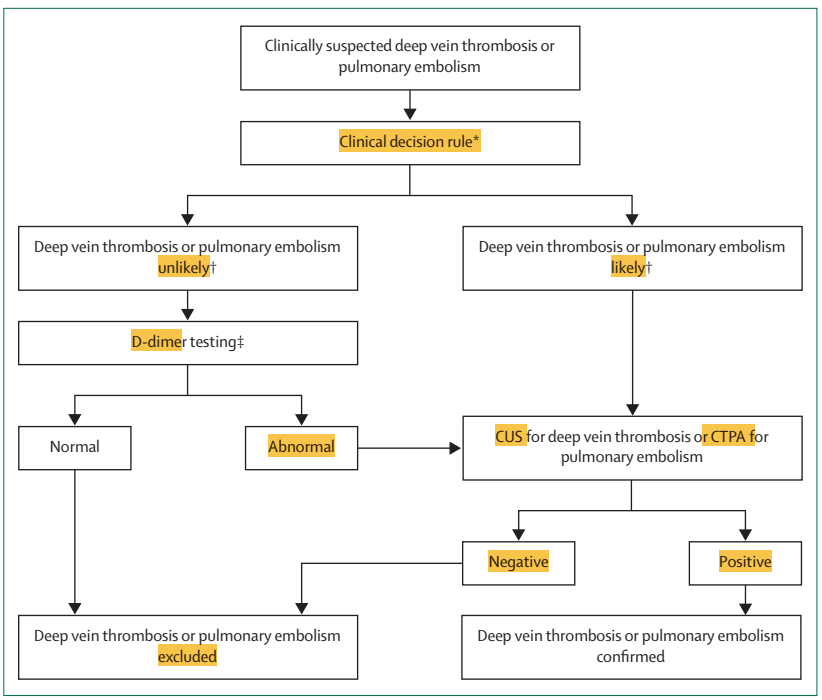

Figure 1: **Diagnostic algorithm for suspected deep vein thrombosis and pulmonary embolism**
CTPA=computed tomography pulmonary angiography. CUS=compression ultrasonography. *Wells' deep vein thrombosis score for suspected deep vein thrombosis and Wells' pulmonary embolism score or revised Geneva score for suspected pulmonary embolism. †Patients are classified as non-high probability or high probability of deep vein thrombosis by the revised Geneva score, whereas the Wells' deep vein thrombosis and pulmonary embolism scores classify patients as unlikely or likely to have deep vein thrombosis or pulmonary embolism, respectively. ‡Fixed (≤500 μg/L) D-dimer testing in patients with suspected deep vein thrombosis and fixed or age-adjusted (age × 10 μg/L in patients older than 50 years) D-dimer testing in patients with suspected pulmonary embolism.

Imaging for deep vein thrombosis

Patients who are likely to have deep vein thrombosis according to the Wells' deep vein thrombosis score, and those classified as deep vein thrombosis unlikely on the score but with a D-dimer higher than the conventional fixed threshold should be referred for diagnostic imaging (figure 1). Compression ultrasonography has replaced contrast venography as the preferred method for the diagnosis of deep vein thrombosis. Compression ultrasonography is done following two main approaches: whole-leg compression ultrasonography evaluates the entire deep vein system from the groin to the calf, whereas only the popliteal and femoral vein segments are imaged with limited (two-point) compression ultrasonography. In patients with an initial normal limited-compression ultrasonography, the examination should be repeated after 1 week to ascertain that distal (ie, below-knee) deep vein thrombosis has not propagated proximally.[54] Whole-leg and limited compression ultrasonography are considered equivalent in terms of safety since large management studies show both approaches to yield false negative results below 1%.[55–61]

The decision to use one approach over the other varies by centre and needs to take into consideration the advantages and disadvantages of both approaches as well as the available expertise and facilities. Whole-leg compression ultrasonography is completed in about 10–15 min when done by experienced personnel, with good inter-observer agreement[62] and only a few inconclusive results.[59,61] It allows exclusion of both proximal and distal deep vein thromboses in a single evaluation and helps with the differential diagnosis if none are detected.[59,62] The use of whole-leg compression ultrasonography in all symptomatic patients is associated with a 4–15% absolute increase in the diagnosis of deep vein thrombosis due to the detection of isolated clots in the deep calf veins.[63] The prognostic relevance of these clots remains uncertain and there is controversy about their optimum management.[64]

Limited-compression ultrasonography requires less expertise and can be done in 3–5 min in a routine setting. However, a serial examination is required in at least 70% of patients, which can be burdensome and is not always feasible.[56,58,60] Moreover, only 1–6% of patients who undergo the second examination are subsequently diagnosed with deep vein thrombosis.[27,60,65] If repeated testing is confined to the group of patients with both a deep vein thrombosis likely Wells' score and an abnormal D-dimer, the number of patients who require serial ultrasonography can be reduced by at least a third.[27,66–68] The diagnosis of pelvic or inferior caval deep vein thrombosis can be challenging with compression ultrasonography and so CT or magnetic resonance venography should be considered to exclude the diagnosis in patients with a high clinical suspicion or pregnant women.[69]

About 10% of patients with suspected deep vein thrombosis have a history of deep vein thrombosis.[26] The diagnosis of recurrent deep vein thrombosis by

compression ultrasonography is hampered by persisting abnormalities of the deep veins in approximately 50% of patients 1 year after the initial event, which is reflected by the poor inter-observer agreement of this test.[13,70] If comparison of the residual clot with a previous compression ultrasonography is not possible or is inadequate, additional tests such as CT venography should be considered. Preliminary observations suggest a high accuracy for magnetic resonance direct thrombus imaging with good inter-observer agreement and adequate images in most cases.[71]

Imaging for pulmonary embolism

Patients who are classified as pulmonary embolism likely by the Wells' pulmonary embolism score or with a high clinical probability by the revised Geneva score, as well as those with a D-dimer above the age-adjusted threshold, should be referred for imaging. CT pulmonary angiography (CTPA) has replaced ventilation-perfusion lung scintigraphy and pulmonary angiography as the first-line imaging test for pulmonary embolism in most centres. CTPA is widely available and modern scanners have a high sensitivity for pulmonary embolism, which allows for its use as a stand-alone test.[72–74] For example, in two large studies of pulmonary embolism management, the risk of venous thromboembolism at 3 months in patients in whom anticoagulant therapy was withheld based on a normal CTPA was 0·5% and 1·3%.[33,35] Additionally, inadequate scans with CTPA are few (0·6–3·0%) and CTPA can provide an alternative diagnosis when pulmonary embolism is excluded.[75] The use of CTPA as first-line imaging for suspected pulmonary embolism can increase the detection of small, subsegmental pulmonary embolism, which might have a questionable clinical relevance,[76] although such isolated peripheral emboli are uncommon.[35,77] Ventilation-perfusion lung scanning is as safe as CTPA for diagnosing pulmonary embolism and is associated with lower radiation exposure,[78] but it is often not readily available and the test results are non-diagnostic in 30–40% of patients.[74] Ventilation-perfusion lung scanning has a role when CTPA is contraindicated because of severe renal insufficiency or allergy to contrast medium, and can be considered in pregnant women and young women to reduce radiation exposure to the breast.[79] In haemodynamically unstable patients with suspected pulmonary embolism who require a rapid diagnosis and cannot undergo CTPA, bedside transthoracic echocardiography can be used to disclose signs of right ventricle dysfunction, which could justify emergency reperfusion.[79]

In patients with suspected recurrent pulmonary embolism, CTPA is the preferred imaging test.[80] Residual pulmonary thrombotic obstruction might complicate interpretation of imaging tests.[81] Nevertheless, in a management study of patients with suspected recurrent pulmonary embolism, the combination of an unlikely clinical decision rule and normal D-dimer safely excluded recurrent pulmonary embolism in 17% of patients who had no venous thromboembolism during 3 months of follow-up, whereas the 3 month incidence after a normal CTPA was 3%.[43]

Several other imaging techniques have been evaluated for the diagnosis of pulmonary embolism, such as MRI[82] and single-photon emission CT (SPECT),[83] but accuracy data are sparse with limited direct comparisons against CTPA, and these modalities should therefore at present be considered experimental.[84]

Treatment

Anticoagulant therapy

Anticoagulant therapy is the mainstay for the treatment of venous thromboembolism and is classically divided into three phases: the acute phase of the first 5–10 days after venous thromboembolism diagnosis, a maintenance phase of 3–6 months, and an extended phase beyond this period.[85] During the acute phase, treatment options include subcutaneous low-molecular-weight heparin or fondaparinux, intravenous unfractionated heparin, or the direct oral factor Xa inhibitors rivaroxaban and apixaban (table 2). Unfractionated heparin needs dose adjustments based on activated partial thromboplastin time results, whereas weight-adjusted low-molecular-weight heparins can be given in fixed doses without monitoring. Low-molecular-weight heparins are preferred over unfractionated heparin because of both superior efficacy and safety.[86,87] However, unfractionated heparin should be used in patients undergoing thrombolysis because of its shorter half-life, ease of monitoring, and the possibility to immediately reverse the anticoagulant effect with protamine. Unfractionated heparin is also preferred in people with severe renal impairment (creatinine clearance less than 30 mL per min) in whom accumulation of low-molecular-weight heparin and fondaparinux is expected given their dependence on renal clearance. In patients with suspected or confirmed heparin-induced thrombocytopenia, heparin should be stopped immediately and anticoagulation continued with parenteral anticoagulants such as fondaparinux, argatroban, or lepirudin.[88]

After at least 5 days overlap with vitamin K antagonists, heparins or fondaparinux can be discontinued once the international normalised ratio (INR) has repeatedly been above 2·0. Vitamin K antagonists have a narrow therapeutic index due to multiple drug–drug and drug–food interactions, which result in substantial interpatient and intrapatient variability. Routine monitoring is therefore required to maintain the INR between 2·0 and 3·0.

Over the past decade, direct oral anticoagulants, comprising the thrombin inhibitor dabigatran etexilate and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, have been introduced for the treatment of venous thromboembolism. These agents overcome many disadvantages of vitamin K antagonists. Direct oral anticoagulants have little interaction with other

	Route of administration	Renal clearance	Half-life	Initial treatment dosing	Maintenance treatment dosing	Extended treatment dosing
Unfractionated heparin	Intravenous	~30%	~1·5 h	Maintain aPTT 1·5-times upper limit of normal	..	..
Low-molecular-weight heparin	Subcutaneous	~80%	3–4 h	Weight-based dosing	Weight-based dosing*	..
Fondaparinux	Subcutaneous	100%	17–21 h	Weight-based dosing	Weight-based dosing	..
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8–11 h; warfarin 36 h; phenprocoumon 160 h	Target at INR at 2·0–3·0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2·0–3·0	Maintain INR at 2·0–3·0
Dabigatran	Oral	~80%†	14–17 h	Requires at least 5 days heparin lead-in	150 mg twice a day	150 mg twice a day
Rivaroxaban	Oral	~33%‡	7–11 h	15 mg twice a day for 3 weeks	20 mg once a day	20 mg once a day
Apixaban	Oral	~25%‡	8–12 h	10 mg twice a day for 1 week	5 mg twice a day	2·5 mg twice a day
Edoxaban	Oral	~35%‡	6–11 h	Requires at least 5 days heparin lead-in	60 mg once a day§	60 mg once a day§
Aspirin	Oral	~10%	15 min	..	..	80–100 mg once a day

aPTT=activated partial thromboplastin time. INR=international normalised ratio. *Treatment with low-molecular-weight heparin is recommended for patients with active cancer and pregnant women. †Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL per min. ‡Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL per min. §The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30–50 mL per min, a bodyweight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.

***Table 2*: Anticoagulant therapies for deep vein thrombosis and pulmonary embolism**

medications and food and can be given in fixed doses without routine monitoring, hence greatly simplifying treatment (table 2). The concurrent use of strong P-glycoprotein inhibitors or potent cytochrome P450 3A4 inhibitors or inducers (eg, certain protease inhibitors, antimycotics, and antiepileptic drugs) should be avoided since they can influence the exposure to direct oral anticoagulants.[89] Direct oral anticoagulants have a rapid onset of action with peak levels reached within 2–4 h and a half-life of about 12 h, which is much shorter than that of vitamin K antagonists. Whereas vitamin K antagonists are only minimally cleared by the kidneys, renal clearance for direct oral anticoagulants ranges from 27% to 80% (table 2). Dabigatran and edoxaban require a 5 day lead-in with low-molecular-weight heparin, whereas rivaroxaban and apixaban have been evaluated in a single-drug approach without previous heparin, although a higher dose during the first 3 weeks and 7 days, respectively, is necessary.

The efficacy and safety of the four direct oral anticoagulants for the treatment of deep vein thrombosis and pulmonary embolism were compared with vitamin K antagonists in six large phase 3 trials,[90–95] which consistently showed the non-inferiority of direct oral anticoagulants with respect to recurrent venous thromboembolism and a lower risk of clinically relevant bleeding. A subsequent meta-analysis confirmed these findings and reported that direct oral anticoagulants are associated with a significant overall 39% relative reduction in the risk of major bleeding.[96] These results were consistent across subgroups of high-risk patients, including those with pulmonary embolism, aged 75 years or older, bodyweight of 100 kg or more, and those with moderate renal insufficiency (creatinine clearance 30–50 mL per min). Given the similar efficacy, superior safety profile, and ease of use compared with vitamin K antagonists, direct oral anticoagulants should be considered as the first-line anticoagulant treatment option for venous thromboembolism.[97] In the general population, data from post-marketing studies for rivaroxaban have shown similar safety and efficacy profiles as seen in the trials,[98,99] but such data are scarce for other direct oral anticoagulants in the treatment of venous thromboembolism.

Direct oral anticoagulants have not been compared with each other and there is no strong evidence to recommend one drug over another. When choosing between the direct oral anticoagulants, physicians should consider the pharmacokinetics, individual patient characteristics, disease severity, the treatment regimen, and patient's preference. For example, in the acute phase, on one hand a single-drug approach with rivaroxaban and apixaban might be more practical than the lead-in with parenteral heparins that is required before initiating dabigatran or edoxaban. On the other hand, this short course of heparin might be comforting to the physician treating more extensive venous thromboembolism. In the maintenance and extended phases, the once-daily dosing regimen of rivaroxaban and edoxaban might increase compliance. In patients with moderate renal impairment, factor Xa inhibitors might be preferred over dabigatran because their clearance is less dependent on renal function. Vitamin K antagonists remain the first choice in patients who have severe renal impairment, patients who need to continue on drugs that strongly interact with direct oral anticoagulants (eg, certain protease inhibitors or antimycotic drugs[89]), and in patients who might benefit from treatment monitoring, such as those with expected low compliance.

One concern about the use of direct oral anticoagulants has been the absence of specific drugs to reverse their anticoagulant effect in patients with life-threatening bleeding or in those requiring emergency procedures. Recently, a specific reversal agent for dabigatran, idarucizumab, was licensed,[100] and reversal agents for factor Xa inhibitors are under investigation.[101,102] Notably, the anticoagulant effect of direct oral anticoagulants wanes rapidly because of the short half-life. Preliminary observations suggest that major bleeding events that occur during treatment with direct oral anticoagulants are associated with a less severe clinical presentation,[103] infrequently require invasive interventions,[99,104] and, at least for patients with atrial fibrillation, have a lower case-fatality rate than bleeding related to vitamin K antagonists.[105]

In patients with active cancer and venous thromboembolism, low-molecular-weight heparin monotherapy is recommended over vitamin K antagonists due to a 50% lower risk of recurrent venous thromboembolism and similar rates of major bleeding.[106–108] In patients with severe renal insufficiency, dose reductions or a switch to vitamin K antagonists might be necessary. Data are few for the use of direct oral anticoagulant for the treatment of venous thromboembolism in these patients and their efficacy and safety relative to low-molecular-weight heparin have not been investigated. Therefore, although not contraindicated, direct oral anticoagulants should not represent the first choice for venous thromboembolism in active cancer.[97] However, we await the results of ongoing trials. Pregnant women with venous thromboembolism also require treatment with low-molecular-weight heparin because vitamin K antagonists and direct oral anticoagulant cross the placental barrier and can cause fetal harm.[98] Vitamin K antagonists can be safely used in breastfeeding women, whereas direct oral anticoagulants are contraindicated in these women.

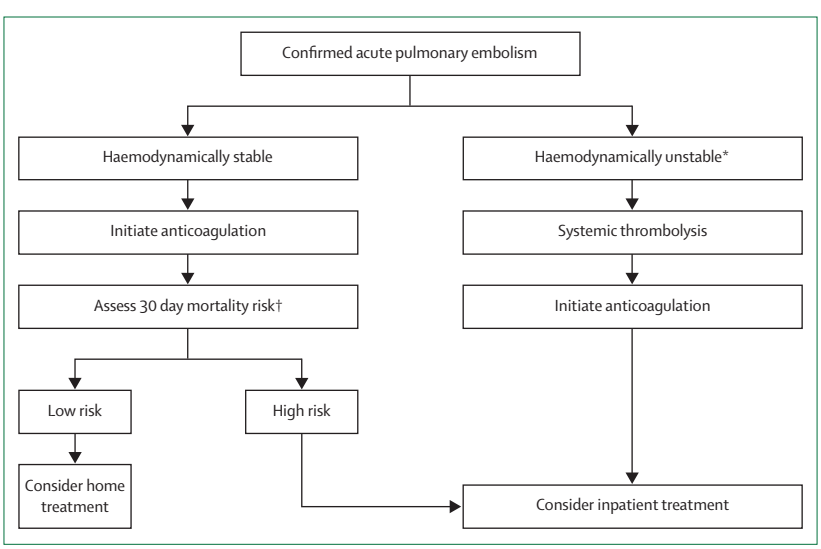

Figure 2: **Acute management of pulmonary embolism**
*Shock or refractory arterial hypotension. †The Pulmonary Embolism Severity Index or its simplified version may be used to assess the 30-day mortality risk (appendix).

Home treatment

Haemodynamically stable patients with pulmonary embolism who are at low risk of death can be considered for direct or early discharge within 24–48 h.[79] Various approaches have been proposed to select patients for home treatment including application of the Hestia criteria,[109] the Pulmonary Embolism Severity Index (PESI),[110] and the simplified PESI (appendix).[111] The PESI score is the most extensively validated score and uses readily available clinical parameters to stratify patients at low (1%) or high (11%) 30-day mortality risk.[79] Approximately half of patients with pulmonary embolism are classified by the PESI as low risk[112] and evidence from one randomised trial showed that early discharge in these patients is as safe and effective as inpatient treatment.[113] Most patients with deep vein thrombosis can be managed on an outpatient basis.

Thrombolysis

Patients with pulmonary embolism associated with haemodynamic instability have a high risk of early mortality. Immediate treatment with intravenous thrombolytic agents is needed to rapidly restore pulmonary perfusion (figure 2).[79,97] The benefit–risk ratio of thrombolysis in haemodynamically stable pulmonary embolism associated with right ventricular dysfunction has been recently questioned by the findings of the PEITHO trial which showed that, compared with placebo, thrombolysis did not lower mortality (odds ratio 0·65, 95% CI 0·2–1·9) and was associated with a significant 9% absolute increase in major bleeding including a 2% higher absolute risk of haemorrhagic stroke.[114] Based on these findings, thrombolysis should be withheld in normotensive pulmonary embolism patients with right ventricular dysfunction. These patients should, however, be monitored closely for signs of haemodynamic decompensation that would make them eligible for thrombolysis.

In selected patients with ileofemoral deep vein thrombosis with severe symptoms and low risk of bleeding, in-hospital treatment with endovascular techniques, such as catheter-directed thrombolysis, can be considered,[14,69] although the risk–benefit ratio of this approach is not yet clear. Compared with standard anticoagulant treatment, catheter-direct thrombolysis seems to reduce the overall incidence of post-thrombotic syndrome after 24 months, with unclear benefits for severe post-thrombotic syndrome[115,116] and at the cost of an increased risk of adverse events, including procedural complications and bleeding.[117]

Caval filters

Inferior vena cava filters are indicated in patients who have absolute contraindications to anticoagulation, such as those with active bleeding or with objectively confirmed recurrent pulmonary embolism despite adequate anticoagulant treatment.[79,97] Filters should not routinely be added to anticoagulation in patients with poor cardiopulmonary reserve or high risk of pulmonary embolism since they do not reduce the risk of recurrent pulmonary embolism.[118] Retrievable filters should be preferred over permanent filters because they can be removed after a short time once anticoagulation is safely restarted to decrease the long-term risk of deep vein thrombosis and late filter complications. However, removal is often not pursued in clinical practice.[119] Surprisingly, caval filters are increasingly used in some part of the world, despite evidence against their routine application.[120,121]

Elastic compression stockings

Graduated elastic compression stockings have been an integral part of deep vein thrombosis treatment because of a proven lower risk of post-thrombotic syndrome with their use.[122,123] However, this notion was recently challenged by a randomised trial that showed no benefit of graduated, knee-length, elastic compression stockings compared with placebo stockings.[124] Although the effectiveness of stockings is now in doubt, they have limited local side-effects and should be considered for relieving symptomatic swelling in patients with proximal deep vein thrombosis.[14]

Treatment duration

Anticoagulant therapy should be continued for at least 3 months to prevent early recurrences.[97] Thereafter, estimations of the anticipated risks of recurrent venous thromboembolism and bleeding are crucial to determine the optimum duration (figure 3). Anticoagulants reduce the risk of recurrent venous thromboembolism by 80% to 90%,[125,126] at the cost of a 1% to 3% annual risk of major bleeding.[96,127] Since recurrent events and anticoagulant-related major bleeding are both associated with substantial morbidity and mortality,[128] extended treatment beyond 3 months should be considered when the risk of recurrence exceeds the risk of major bleeding.[129] It has been proposed that continuation is justified when the annual risk of recurrence is higher than 3%[130] or 5%.[131] If subsequent studies confirm the lower long-term major bleeding risk of direct oral anticoagulant, an even lower threshold might be deemed acceptable to continue anticoagulation. For the decision to extend anticoagulation, one should also take into account that the risk of recurrent pulmonary embolism is three-times higher in patients with an initial pulmonary embolism diagnosis than in those with proximal deep vein thrombosis.[132] Given the considerable case-fatality rate of recurrent pulmonary embolism,[128,133] the threshold to continue anticoagulation could be lower in patients

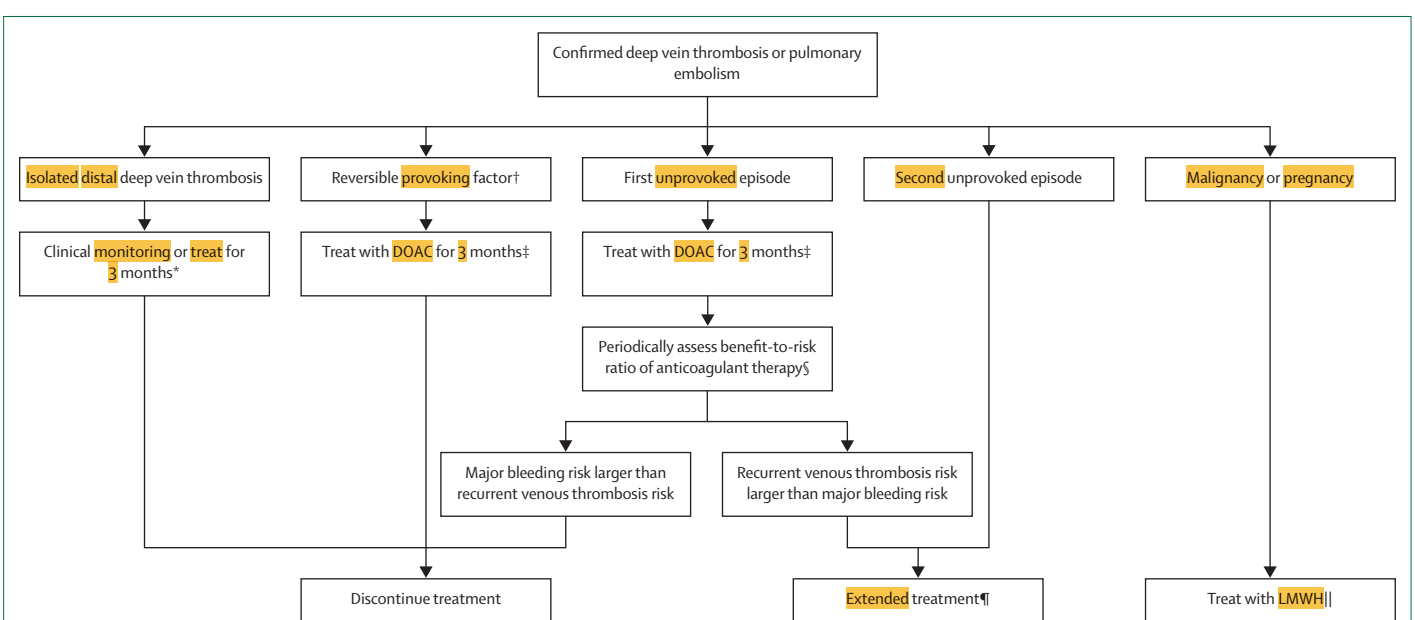

Figure 3: **Treatment of deep vein thrombosis or pulmonary embolism**

DOAC=direct oral anticoagulant. LMWH=low-molecular-weight heparin. *Treatment may be preferred in patients with severe symptoms or at high risk of extension or recurrence. †Reversible provoking factors include surgery, immobilisation, and oestrogen use. ‡Vitamin K antagonists are preferred in patients with a creatinine clearance of 30 mL per min or less, in patients who need to continue on drugs that strongly interact with direct oral anticoagulant such as strong P-glycoprotein inhibitors, and when regular monitoring is warranted. §Clinical prediction rules for recurrent venous thromboembolism and bleeding have not yet been prospectively validated; gender and D-dimer levels after stopping of anticoagulants may be useful to assess the risk of recurrence. ¶ Treatment can be continued with the same anticoagulant given during the first 3 months; assess patients periodically for bleeding risk and reconsider extended treatment. ||Patients with cancer should be treated for at least 6 months and as long as the cancer is active; switching to vitamin K antagonists is allowed during the post-partum period.

with pulmonary embolism. Treatment can be limited to 3 months in patients with venous thromboembolism secondary to a major transient risk factor, such as major surgery, since the annual risk of recurrence after stopping treatment is only 1%.[134,135] By contrast, the 6 month risk of recurrence in patients with cancer is around 8% despite treatment,[106,107] which strongly supports continuing anticoagulation as long as the cancer is active.[97]

In patients with a first unprovoked venous thromboembolism, the risk of recurrence after stopping treatment is approximately 10% at 1 year and 30% at 5 years, which outweighs the annual risk of anticoagulant-related major bleeding.[97] Importantly, this risk appears not to be dependent on the initial treatment duration,[133,135] which supports the notion that physicians should either stop or continue anticoagulation indefinitely after 3–6 months. A longer, time-limited, treatment duration will merely delay recurrent episodes. However, considering extended treatment for all patients with unprovoked venous thromboembolism will inevitably expose a substantial proportion of patients to an unnecessary risk of bleeding. In an attempt to identify those at lower risk of recurrence in whom anticoagulation can be discontinued, various clinical prediction scores,[136–138] D-dimer testing,[139–142] and imaging for residual vein obstruction in patients with proximal deep vein thrombosis have been proposed.[143] Although these tools have the potential to guide the decision to stop or continue anticoagulation, their use is currently not widely adopted due to conflicting results, practical limitations, or lack of validation data. For example, residual vein thrombosis moderately and inconsistently predicts recurrent venous thromboembolism,[143] cannot be used in patients with pulmonary embolism, and is limited by the poor interobserver agreement and lack of standardisation. A repeated normal D-dimer test during anticoagulation and 1 month after discontinuation is still associated with an annual risk of recurrence of 3–7%.[139,140,144] Moreover, a D-dimer-based approach might prove impractical since it requires additional clinic visits to test off-treatment D-dimer levels and could expose patients to an increased risk of recurrent events during the untreated period. In addition, the performance of an age-adjusted or sex-adjusted D-dimer cutoff, as well as the generalisability of the results to any D-dimer assay, needs further evaluation. Clinical prediction rules such as the Men continue and HERDOO2,[136] DASH scores,[137] and Vienna,[138] which use clinical parameters and D-dimer testing to estimate a patient's individual risk of recurrence (appendix), are promising, but need validation in large prospective management studies before their use in clinical practice can be recommended. Risk scores to predict anticoagulation-related bleeding that were derived in the vitamin K antagonist era seem to have a poor performance in the setting of venous thromboembolism and should therefore not be adopted to guide treatment duration.[145] Recently, a prognostic model was proposed to estimate the risk of major bleeding during the initial and later phases of rivaroxaban treatment for venous thromboembolism,[146] but it has not yet been externally validated. The use of concurrent drugs with potential pharmacodynamic interactions with anticoagulant treatment, such as non-steroidal anti-inflammatory drugs and antiplatelet drugs, might increase the risk of bleeding and should be discouraged.

The clinical relevance and risk–benefit of anticoagulant treatment for isolated distal deep vein thrombosis or isolated subsegmental pulmonary embolism is being debated.[64,76] Clinical surveillance or shorter courses of anticoagulation might be a reasonable alternative to standard anticoagulant regimens in patients without severe symptoms or risk factors for thrombosis extension, but new studies are needed to establish the efficacy and safety of this approach.

Recurrent venous thromboembolism during treatment is uncommon due to the high effectiveness of anticoagulants. Recurrent venous thromboembolism is more likely to develop in patients with a persistent, intrinsic thrombotic tendency, such as those with active cancer or antiphospholipid antibodies, or in patients who are non-adherent, sub-therapeutically managed, or receiving concomitant drugs that interfere with anticoagulant therapy. When recurrent venous thromboembolism develops in patients taking a vitamin K antagonist or direct oral anticoagulant, they can be switched to low-molecular-weight heparin, at least temporarily. If recurrence happens during treatment with low-molecular-weight heparin, a dose increase of 25% is often recommended.[147]

Anticoagulants for extended treatment

Physicians who decide to extend anticoagulation beyond 3–6 months can choose from several oral treatment options (table 2). Vitamin K antagonists, apixaban, rivaroxaban, and dabigatran significantly reduce the risk of recurrent venous thromboembolism by 80–90% compared to placebo or observation.[148] This benefit comes at the cost of a two-to-five-times relative increased risk of clinically relevant bleeding, although absolute bleeding rates were low.[149] Compared with vitamin K antagonists, extended treatment with dabigatran was similarly effective, but associated with a lower risk of bleeding.[149] Similar data have been obtained for edoxaban.[150] Two doses of apixaban have been evaluated for extended treatment.[151] Both the therapeutic (5·0 mg twice a day) and prophylactic (2·5 mg twice a day) doses reduced the risk of recurrent venous thromboembolism by 80% compared to placebo with no increase in major bleeding, although the study was not powered to detect differences in bleeding.[151] Compared with the therapeutic dose, the prophylactic dose was associated with a numerically lower risk of clinically relevant non-major bleeding and might therefore be preferred. Two randomised studies have evaluated aspirin for secondary prevention of

venous thromboembolism.[152,153] In a pooled analysis, aspirin reduced the risk of recurrent venous thromboembolism by approximately 30% compared to placebo without an increase in major bleeding.[154] Indirect comparisons suggest that aspirin is much less effective than oral anticoagulants and carries a comparable risk of major bleeding.[148] Possible future alternatives for extended treatment with no apparent bleeding risk include sulodexide[155] and statins,[156] which, however, need further clinical evaluation.

Given the lack of direct comparisons, there is no evidence to recommend one direct oral anticoagulant over another for extended treatment of venous thromboembolism. Aspirin should not be considered an appropriate alternative to anticoagulants given its lower efficacy. Treatment for the extended phase should be tailored to the individual patient. It may be pragmatic to just continue the same treatment that was provided during the first 3–6 months. In all patients, it remains crucial to periodically reassess the balance of bleeding and recurrent venous thromboembolism risks to ascertain that extended treatment remains appropriate.

Future research

Venous thromboembolism is a common disease accounting for major global morbidity and mortality. A wide range of physicians are involved in its diagnostic and therapeutic management. The introduction of direct oral anticoagulants has marked the beginning of a new era in the treatment of venous thromboembolism; however, many diagnostic and therapeutic research questions are still unanswered. Does the widespread use of imaging in combination with advances in imaging techniques truly result in overdiagnosis, and what is the optimum diagnostic approach to avoid this? Is age-adjusted D-dimer testing also safe and efficient in patients with suspected deep vein thrombosis? Should there be a preference for one direct oral anticoagulant over another based on efficacy and safety profiles? Are direct oral anticoagulants a suitable alternative for patients with venous thromboembolism and active cancer, heparin-induced thrombocytopenia, or the antiphospholipid syndrome? Can anticoagulation be safely withheld in patients who are perceived to have a lower clot burden, such as those with subsegmental pulmonary embolism or isolated distal deep vein thrombosis? Can the use of elastic compression stockings for proximal deep vein thrombosis be completely abandoned or are they still useful? What is the best approach to select patients with unprovoked venous thromboembolism in whom anticoagulation can be safely stopped? Are alternatives for extended treatment, such as sulodexide and statins, clinically beneficial? What is the clinical efficacy and safety profile of the new reversal agents for direct oral anticoagulants? And is there a role for catheter-directed thrombolysis in the management of high-risk patients with pulmonary embolism or patients with severe ileofemoral deep vein thrombosis?

Contributors

All authors contributed to the design of the manuscript. MDN and NvE did the literature search and drafted the manuscript, with both authors contributing equally. HRB provided supervision and critical revision of the manuscript for important intellectual content. All authors approved the final Seminar.

Declaration of interests

MDN has received fees for consultancy from Bayer Health Care, Grifols, and Daiichi Sankyo outside the present work. HRB reports grants and personal fees from Sanofi-Aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Pfizer, Roche, ISIS Medical, Thrombogenics, and Boehringer Ingelheim, outside the submitted work. NvE declares no competing interests.

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