Venous thromboembolism: Past, present and future

Sam Schulman1,2; Walter Ageno3; Stavros V. Konstantinides4,5
1Department of Medicine, McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada; 2Karolinska Institutet, Stockholm, Sweden; 3Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; 4Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; 5Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece

Summary
Venous thromboembolism (VTE), the third most frequent acute cardiovascular syndrome, is associated with a considerable disease burden which continues to grow along with the longer life expectancy of the population worldwide. In the past century, parenteral heparin prophylaxis was established for hospitalised patients at elevated risk of VTE. More recently, non-vitamin K antagonist oral anticoagulants (NOACs) with a direct inhibiting effect on factor Xa or thrombin, underwent extensive testing in clinical trials and have been approved for patients undergoing hip or knee replacement. Clinical investigation is ongoing in further areas of thromboprophylaxis, including medical prophylaxis in patients and high-risk situations in the outpatient setting. The diagnostic approach to suspected VTE is now based on advanced imaging techniques and robust diagnostic algorithms which ensure high sensitivity and specificity. Nevertheless, the role of clinical, or pre-test, probability assessment remains crucial to avoid overdiagnosis and treatment errors. Advances in reperfusion strategies, along progressive establishment of the NOACs as the new standard of anticoagulation treatment, have simplified the management of VTE, improving outcomes and particularly safety. While new molecular targets for anticoagulation are being investigated in the quest to further reduce bleeding risk, adjusting the initial regimen to the patient’s risk and finding the optimal duration of anticoagulation after an index VTE event will be some of the top priorities in the years to come. Importantly, and in parallel to new drugs and technical advances in imaging, incentives such as hospital accreditation and funding based on evidence-based practice need to be implemented to increase guideline adherence.

Keywords
Venous thromboembolism, deep-vein thrombosis, pulmonary embolism, prophylaxis, diagnosis, imaging, treatment, anticoagulants, reperfusion

Introduction
The disease burden of venous thromboembolism (VTE) worldwide has been highlighted by the introduction of World Thrombosis Day on October 13, 2014. With growing populations and longer life expectancy, we will see an increase in the prevalence of this disease. The use of adequate prophylaxis against VTE in risk situations and population is paramount for counteracting the thrombotic effects of the obesity epidemic, sedentary work and life style, older age, longer survival in cancer, and more frequent and complex medical and surgical interventions. The diagnostic tools available have been simplified with compression ultrasonography (CUS) for detection of deep-vein thrombosis (DVT), and improved with computed tomography (CT) for confirmation of pulmonary embolism (PE). There is, however, a challenge to speed and precision in diagnosis with prudent use of health care resources. Once DVT or PE has been detected, we have access to increasingly safer and more convenient anticoagulant therapies for the majority of patients. The non-vitamin K antagonist oral anticoagulants (NOACs) are now becoming the standard of care for a large proportion of patients with VTE. A small subset with limb-
spectively. The prototype vitamin K antagonist (VKA), dicouma-rol, was reported in 1945 as a useful prophylactic agent against thrombosis after surgery in 148 patients (9). In 1959, Sevitt and Gallagher from Birmingham, UK published probably the first controlled trial on prevention of VTE with acute fatal PE, verified by autopsy, as the primary outcome (10). They compared the vitamin K antagonist phenindione with control in 150 patients each with fracture of the femur. A by-product from the processing of sugar beets is dextran, and this was developed in Sweden as a plasma expander, enhancer of peripheral blood flow and thromboprophylactic agent (11, 12) and remained in use in Scandinavia for several decades.

It was suggested already in 1942 (13) and again in 1950 (14) that heparin in much smaller amounts than used for treatment of VTE should be effective for prevention thereof. The clinical trials with low-dose heparin were pioneered by V. V. Kakkar, starting with a study on 53 patients with hernia surgery in 1971 and the incidence of DVT, detected with \(^{125}\text{I}\) fibrinogen uptake test, was reduced from 26% to 4% (15). The addition to low-dose heparin of dihydroergotamine, which by its vasoactive effect improves venous emptying of pooled blood, improved the prophylactic effect. In a study in 1976 where 52 patients with total hip replacement were randomised to this combination versus low-dose heparin alone and a parallel group served as control, DVT identified with \(^{125}\text{I}\) fibrinogen uptake test or venography was found in 16%, 32% and 69%, respectively whereas proximal DVT was significantly reduced in both active prophylaxis groups (16). Low-molecular-weight heparin (LMWH) has longer half-life and better subcutaneous absorption as well as less binding to plasma proteins and platelets than unfractionated heparin and could therefore be injected once daily versus 2–3 times/day for unfractionated heparin. The first results from a randomised trial in prophylaxis were published in 1982 (17), and LMWH once versus twice daily after major abdominal surgery were compared. The once daily injection proved effective and safe. This modality remains the most common alternative, based on favourable study result for many surgical and medical types of patients.

Results from studies on hirudin derivatives to prevent coronary artery thrombosis in unstable angina (18) or DVT in total hip replacement (19) emerged in 1994, although these agents never gained popularity, probably for economic reasons. Similarly, the pentasaccharide fondaparinux, the smallest entity of heparin that still binds to antithrombin, was studied for multiple indications during the first decade of this millennium (20), but has limited use since the cost is typically three times that of LMWH. It has, however, demonstrated a favourable benefit/risk ratio compared to LMWH in acute coronary syndromes by reducing the risk of major bleeding (21) and in contrast to heparin or LMWH, fondaparinux can be used in patients with heparin-induced thrombocytopenia (22). For a historical perspective of the methods to prevent venous thromboembolism see Figure 1.

The current status

Orally available anticoagulants with a direct inhibiting effect on factor Xa or on thrombin have undergone extensive clinical trial programs in major orthopaedic surgery (23), for medically ill patients (24–26) and to a lesser extent in patients with cancer (27) and have during the past decade been approved for prevention of VTE after hip- or knee replacement. These NOACs are slowly gaining market shares from LMWH.

Despite the availability of several effective, safe and convenient prophylactic agents, their uptake in clinical practice is still suboptimal. The ENDORSE study investigated with a cross-sectional design the use of prophylaxis in 32 countries and demonstrated that only 58.5% of surgical patients at risk actually received prophylaxis according to guideline recommendations (28). For the medical patients at risk the adherence was even lower at 39.5%. The GLORY registry pointed out geographic differences in the choice of prophylactic methods between the United States and other Western countries for patients undergoing major orthopaedic surgery with the proportions receiving vitamin K antagonists or LMWH being 58%-41% and 2%-92%, respectively (29). Furthermore, additional use of intermittent pneumatic compression devices in these patients was more common in the United States than in the other countries (69% vs 33%). When vitamin K antagonists are used the intended therapeutic range is not always achieved or only achieved towards the end of the prophylaxis period. The @RISTOS registry
collected information on patients after cancer surgery and demonstrated a second peak of VTE after three weeks, with 40% of the events occurring beyond that time point, when prophylaxis already had been discontinued (30). Recent clinical practice guidelines have therefore recommended extended prophylaxis up to 4 weeks for most patients with major abdominal or pelvic (cancer) surgery (31, 32), but this has probably not become widespread clinical practice yet.

For the medically ill patients the situation is more complex due to multiple comorbidities and generally older age. Inadequate prophylaxis with underuse for patients at high risk for thrombosis as well as provision of anticoagulant prophylaxis to patients at very low risk seems to be a common occurrence (33). Moreover, medically ill patients usually continue to be moderately ill and have decreased mobility after discharge and are therefore at continued high risk for VTE (34). Recent trials on extended prophylaxis for these patients have failed to demonstrate a clearly favourable benefit/risk ratio (24–26, 35).

Future perspectives

Guideline adherence will become increasingly important with hospital accreditation and funding based on performance and evidence-based practice. It can thus be expected that an increasing proportion of patients will receive adequate prophylaxis against VTE. Clinical prediction rules and risk scores will be used routinely in electronic supportive tools to individualise prophylaxis. Ongoing trials will hopefully demonstrate which subsets of patients derive the best benefit from extended prophylaxis after hospitalisation for medical illness (36) or in outpatients with chemotherapy (37, 38). The NOACs will be studied in many types of surgery or trauma and will thereafter most likely replace injectable prophylactic agents. In view of the convenience of the NOACs, we can also expect longer duration of the prophylaxis for several indications.

Whether these optimistic perspectives will entail a reduction of venous thromboembolic events is difficult to predict. With older age, increasing complexity of diseases and their treatments the risk of thrombosis increases and sometimes results in breakthrough events despite prophylaxis. It is likely that we will see a reduction of thromboembolism among the less complicated patients, while we will see more events among the very ill patients that previously probably did not even survive.

Evolution of diagnostic modalities and algorithms

Up until the 1970s, the diagnosis of DVT was made on clinical grounds, because the inaccuracy of clinical diagnosis had not been appreciated and reliable diagnostic methods were not available in most hospitals. Unfortunately, signs and symptoms of VTE are nonspecific and, thus, large numbers of patients with clinically suspected venous thrombosis have been incorrectly labelled. Objective diagnostic methods were therefore required for a correct diagnosis, but their routine use subsequently appeared to be not sufficiently cost-effective, because only a minority of patients referred for imaging tests is actually confirmed to have VTE. To avoid unnecessary tests, and to improve their accuracy when performed according to the Bayes theorem, over the last 20 years the recommended diagnostic approach to patients with suspected VTE has been based on algorithms integrating clinical data, laboratory, and imaging tests (39).

Pre-test clinical probability assessment

A number of validated scores have become available to allow an accurate assessment of pre-test clinical probability also by less experienced doctors and should by now be commonly used in clinical practice. The Wells rule for DVT was first published in 1997 and combined five signs suggestive of DVT, three risk factors, and one negative variable to yield a score to be used to estimate the probability of DVT being present (40, 41). In this study, a reduction in the rates of false-negative and false-positive imaging tests was observed. The Wells rule was subsequently modified with the addition of one variable, which is the presence of previously documented DVT (42). A Wells rule was also developed for patients with suspected PE which, along with the Geneva score, represent the best known pre-test clinical probability scores in this setting (43, 44) (Tables 1–3). A number of studies have validated algorithms in which the results of these scores drive the decision to directly proceed with imaging tests or wait for the results of D-dimer measurement to possibly rule out VTE without any further assessment (42, 45, 46). It should be noted that all these scores and algorithms have been developed and validated in the outpatient setting and there is evidence to suggest that it is not sufficiently safe to rule out VTE based on these strategies in the hospitalised patients (47).

Biochemical assays

D-dimer, a product of cross-linked fibrin degradation, is available in nearly all laboratories. Several studies conducted in the last 25 years have consistently shown its high negative predictive value and accuracy in safely ruling out clinically suspected VTE when combined with low pre-test clinical probability (48). More recently, D-dimer has also been proposed as a stand-alone test to safely exclude PE when negative (49). The sensitivity of quantitative ELISA or ELISA derived D-dimer assays is higher than that of quantitative latex-derived assays and whole-blood agglutination assays (48). Recently, age-adjusted cut-offs for D-dimer have been validated and were shown to improve the accuracy of the test in ruling out PE (50, 51). Ongoing management studies aim to confirm these results in patients with suspected DVT. When pre-test clinical probability is not low and/or when the D-dimer levels are increased, patients should be referred for imaging tests.
Imaging tests

Contrast venography and pulmonary angiography have long represented the reference standards for the diagnosis of DVT and PE, respectively, but their use in clinical practice has been limited by their costs and their invasiveness.

Before ultrasonography became the diagnostic imaging test of choice for VTE, impedance plethysmography as well as other plethysmographic techniques such as strain–gauge, and air-cuff plethysmography, and \(^{125}\text{I}\)-fibrinogen leg scanning were used in clinical practice (52). Impedance plethysmography, introduced in 1974, was sensitive and specific to occlusive clots of the proximal veins of the lower limbs, but insensitive to distal DVT or to non-occlusive proximal DVT (52). \(^{125}\text{I}\)-fibrinogen leg scanning had major limitations as a diagnostic test for patients with clinically suspected DVT and was primarily proposed as a screening test in asymptomatic postoperative patients. However, the combination of this test with IPG was shown to result in high sensitivity and specificity and was in particular proposed for patients with suspected recurrence of DVT (53).

Compression ultrasonography is now the most commonly used imaging test because it is accurate, simple, reproducible, and relatively inexpensive (41). The addition of Doppler analysis does not improve the overall accuracy of the test (54). CUS can be limited to the proximal veins (i.e. the femoral and popliteal veins) or can be extended to the distal veins (below the popliteal vein). Limited CUS is simpler, faster, and more reproducible than extended CUS, but it is less sensitive, thus requiring repeat testing after 5-7 days to safely rule out DVT. Extended CUS requires more experienced operators and the availability of more advanced scanners, but it is conclusive after a single evaluation. The use of extended CUS may result in the diagnosis of isolated distal clots that do not require anticoagulant treatment. The two ultrasonographic strategies were shown to be similarly accurate when directly compared in two randomised controlled trials (55, 56). More recently, an algorithm that combines the two strategies has been proposed, in which patients with either positive D-dimer or high pre-test clinical probability undergo limited CUS and patients with both high D-dimer and pre-test clinical probability undergo extended CUS (57). This algorithm was shown to safely eliminate the need for repeat CUS and to reduce the number of required extended-CUS. Recent studies have suggested a potential role for CT and magnetic resonance imaging (MRI) in this setting. CT is an important diagnostic tool for the diagnosis of pelvic or inferior cava DVT, while MRI has shown high accuracy in preliminary

---

**Table 1: Wells rule for patients with suspected DVT (40).**

<table>
<thead>
<tr>
<th>Components</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (ongoing treatment or within previous 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilisation of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Previous history of DVT</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for more than 3 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Localised tenderness along distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling by more than 3 cm compared with asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis as likely or greater than that of DVT</td>
<td>-2</td>
</tr>
<tr>
<td>DVT unlikely</td>
<td>≤ 1</td>
</tr>
<tr>
<td>DVT likely</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>

**Table 2: Wells rule for patients with suspected PE (42).**

<table>
<thead>
<tr>
<th>Components</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs or symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt;100/bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilisation or surgery in previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous history of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>PE unlikely</td>
<td>≤ 4</td>
</tr>
<tr>
<td>PE likely</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>

**Table 3: Geneva score for patients with suspected PE (43).**

<table>
<thead>
<tr>
<th>Components</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>60–79</td>
<td>1</td>
</tr>
<tr>
<td>≥ 80</td>
<td>2</td>
</tr>
<tr>
<td>Previous history of DVT or PE</td>
<td>2</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100/bpm</td>
<td>1</td>
</tr>
<tr>
<td>PaCO(_2), kPa</td>
<td></td>
</tr>
<tr>
<td>&lt; 4.8</td>
<td>2</td>
</tr>
<tr>
<td>4.8–5.19</td>
<td>1</td>
</tr>
<tr>
<td>PaO(_2), kPa</td>
<td></td>
</tr>
<tr>
<td>&lt; 6.5</td>
<td>4</td>
</tr>
<tr>
<td>6.5–7.99</td>
<td>3</td>
</tr>
<tr>
<td>8–9.49</td>
<td>2</td>
</tr>
<tr>
<td>9.5–10.99</td>
<td>1</td>
</tr>
<tr>
<td>Chest X-ray findings</td>
<td></td>
</tr>
<tr>
<td>Band atelectasis</td>
<td>1</td>
</tr>
<tr>
<td>Elevation of hemidiaphragm</td>
<td>1</td>
</tr>
<tr>
<td>&lt;5 points: low probability of PE; 5–8 points: moderate probability of PE; &gt;8 points: high probability of PE.</td>
<td></td>
</tr>
</tbody>
</table>
studies and may be considered for selected patients (58). Future studies will need to confirm the role of these tests in this setting.

Ventilation/perfusion (or perfusion only) scan has long represented the standard diagnostic test for patients with suspected PE. This test was shown to be highly sensitive, but less specific due to the high prevalence of non-conclusive results (i.e. low and intermediate probability) (59). In addition, ventilation/perfusion scan is often not readily available. For these reasons, over the last 15 years CT pulmonary angiography (CTPA) scan has rapidly become the first-line imaging test for these patients. CTPA is widely available and increasingly accurate thanks to continuous advances in technology, in particular with the new generation multidetector-row scanners. CTPA can be used as a stand-alone test in the light of the improved negative predictive value of the test that is
# Table 4: Ongoing trials on specific patient populations and possible new or extended indications of NOACs for the treatment or secondary prevention of deep-vein thrombosis or pulmonary embolism.

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary clinical outcome(s)</th>
<th>Follow-up</th>
<th>Sample size</th>
<th>Study</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN CHOICE (NCT02064439)</td>
<td>Secondary VTE prevention</td>
<td>Rivaroxaban 10 mg or 20 mg once daily</td>
<td>Aspirin 100 mg once daily</td>
<td>Recurrent VTE, major bleeding</td>
<td>12 months</td>
<td>3,399</td>
<td>Phase 3b</td>
<td>October 2016</td>
</tr>
<tr>
<td>HOME-PE (NCT02811237)</td>
<td>Outpatient management of acute PE</td>
<td>Management based on the Hestia rule</td>
<td>Management based on the SPESI</td>
<td>Recurrent VTE, major bleeding, death</td>
<td>30 days</td>
<td>1,975</td>
<td>Phase 3b</td>
<td>June 2018</td>
</tr>
<tr>
<td>HoT-PE (2013–001657–28)</td>
<td>Outpatient management of acute PE</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>-</td>
<td>Recurrent VTE or PE-related death</td>
<td>3 months</td>
<td>1,100</td>
<td>Phase 4</td>
<td>January 2018</td>
</tr>
<tr>
<td>RIDTS (NCT02722447)</td>
<td>Isolated distal DVT</td>
<td>Rivaroxaban standard therapeutic dose for 6 weeks after an initial course of 6-week treatment</td>
<td>Placebo</td>
<td>Recurrent VTE</td>
<td>3 months</td>
<td>1,100</td>
<td>Phase 3b</td>
<td>June 2020</td>
</tr>
<tr>
<td>Hokusai-VTE Cancer (NCT02073682)</td>
<td>Cancer patients with acute VTE</td>
<td>Edoxaban standard therapeutic dose</td>
<td>Dalteparin standard therapeutic dose</td>
<td>Recurrent VTE, clinically relevant bleeding</td>
<td>6 months</td>
<td>1,000</td>
<td>Phase 3b</td>
<td>December 2017</td>
</tr>
<tr>
<td>VERDICT (NCT02664155)</td>
<td>Acute VTE in patients with moderate or severe renal dysfunction</td>
<td>Apixaban standard therapeutic dose for 7 days followed by 2.5 mg twice daily, or rivaroxaban standard therapeutic dose for 21 days followed by 15 mg once daily</td>
<td>Standard of care (heparin, INR-adjusted VKA)</td>
<td>Net clinical benefit (recurrent VTE, major bleeding)</td>
<td>3 months</td>
<td>800</td>
<td>Phase 3b</td>
<td>March 2019</td>
</tr>
<tr>
<td>PEITHO-2 (NCT02596555)</td>
<td>Intermediate risk PE</td>
<td>LMWH standard therapeutic dose for 72 hours followed by dabigatran standard therapeutic dose</td>
<td>-</td>
<td>Recurrent VTE or PE-related death</td>
<td>6 months</td>
<td>700</td>
<td>Phase 4</td>
<td>August 2019</td>
</tr>
<tr>
<td>TRAPS (NCT02157272)</td>
<td>Antiphospholipid syndrome</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>INR-adjusted warfarin</td>
<td>Recurrent thrombosis, major bleeding, death</td>
<td>4 years</td>
<td>536</td>
<td>Phase 3b</td>
<td>December 2018</td>
</tr>
<tr>
<td>SELECT-D (2012–005589–37)</td>
<td>Cancer patients with acute VTE</td>
<td>Rivaroxaban standard therapeutic dose for 6 months</td>
<td>Dalteparin 200 IU/kg daily for 1 month followed by 150 IU/kg during months 2–6</td>
<td>Recurrent VTE or PE-related death</td>
<td>6 + 6 months</td>
<td>530</td>
<td>Phase 3b</td>
<td>December 2018</td>
</tr>
<tr>
<td>Apixaban: VTE treatment in cancer (NCT02585713)</td>
<td>Cancer patients with acute VTE</td>
<td>Apixaban standard therapeutic dose</td>
<td>Dalteparin standard therapeutic dose</td>
<td>Major bleeding</td>
<td>6 months</td>
<td>315</td>
<td>Phase 3b</td>
<td>December 2020</td>
</tr>
<tr>
<td>RAMBLE (NCT02761044)</td>
<td>Treatment of VTE in young women</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>Apixaban standard therapeutic dose</td>
<td>Patient reported menstrual bleeding</td>
<td>3 months</td>
<td>308</td>
<td>Phase 3b</td>
<td>May 2019</td>
</tr>
</tbody>
</table>
close to 99% (60–62) (▶ Figure 2). However, the widespread availability of CTPA in the emergency departments has over the last years raised concerns since many patients at low pre-test probability of PE are inappropriately exposed to radiation. Furthermore, there is an increasing incidence of small subsegmental clots detected by CTPA, the clinical relevance of which deserves additional investigation. Recent studies suggest that PE diagnosed by CTPA is frequently overdia
diagnosed, with high rates of discordance (about 50%) between radiologists in particular when PE is solitary or located in subsegmental arteries (26). Breathing motion artefacts and beam-hardening artefacts are the most common causes of misdiagnosis (63). V/Q scan remains an important alternative in pregnant patients and, more in general, in women of child-bearing age to avoid exposure to radiation, as well as in patients with severe renal insufficiency or allergy to contrast medium. Alternative diagnostic strategies have been advocated to overcome these limitations, and recent studies have suggested a potential role for MRI (64). Research has also focused on single-photon emission CT in this setting (65), but additional investigation is necessary to confirm the role of these diagnostic tests.

### Continuing to optimise reperfusion and anticoagulation treatment

**Thrombolysis and other reperfusion options**

Thrombolytic agents have been used for the treatment of acute PE for almost half a century. In 1971, Miller et al. observed that streptokinase infusion over 72 hours resulted in a significant reduction of pulmonary artery pressure and the angiographic index of PE severity over the first three days (66). Subsequently, a number of randomised trials (reviewed in (67)) confirmed these findings. The first one, the Urokinase Pulmonary Embolism Trial (UPET), which enrolled 160 patients, remains one of the largest thrombolysis trials in acute PE to date (68). Twenty years later, another landmark trial was conducted by Goldhaber et al., comparing alteplase (100 mg infusion over 2 hours) to heparin alone in 101 patients; rapid improvement of right ventricular function, as assessed by 24-hour echocardiographic follow-up, and absence of PE recurrence were demonstrated in the alteplase group (69).

Today, intravenous thrombolysis continues to be the mainstay of therapy for high-risk (or massive) PE (39, 70, 71). Beyond this emergency situation, the benefits of thrombolysis are to be viewed against the risk of major bleeding, which occurs almost three times more frequently than under heparin anticoagulation alone, par-

---

**Table 4: Continued.**

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary clinical outcome(s)</th>
<th>Follow-up</th>
<th>Sample size</th>
<th>Study phase</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP (NCT02581176)</td>
<td>Cancer patients with acute VTE</td>
<td>Apixaban standard therapeutic dose for 6 months followed by 2.5 mg twice daily</td>
<td>-</td>
<td>Recurrent VTE, major or clinically relevant non-major bleeding</td>
<td>6 months</td>
<td>300</td>
<td>Phase 4</td>
<td>January 2021</td>
</tr>
<tr>
<td>CASTA-DIVA (NCT02746185)</td>
<td>Cancer patients with acute VTE</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>Dalteparin standard therapeutic dose</td>
<td>Recurrent VTE</td>
<td>6 months</td>
<td>200</td>
<td>Phase 3b</td>
<td>May 2017</td>
</tr>
<tr>
<td>ASTRO-APS (NCT02295475)</td>
<td>Antiphospholipid syndrome</td>
<td>Apixaban 5 mg twice daily</td>
<td>INR-adjusted warfarin</td>
<td>Recurrent thrombosis, major and non-major bleeding</td>
<td>13 months</td>
<td>200</td>
<td>Phase 3b</td>
<td>December 2017</td>
</tr>
<tr>
<td>MERCURY PE (NCT02584660)</td>
<td>Outpatient management of acute PE</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>Standard of care</td>
<td>Major bleeding, days of hospitalisation</td>
<td>3 months</td>
<td>120</td>
<td>Phase 3b</td>
<td>March 2017</td>
</tr>
<tr>
<td>RIVASVT-100 (NCT02627053)</td>
<td>Treatment of acute portal, mesenteric or splenic vein thrombosis</td>
<td>Rivaroxaban standard therapeutic dose</td>
<td>-</td>
<td>Major bleeding</td>
<td>3 months</td>
<td>100</td>
<td>Phase 4</td>
<td>December 2018</td>
</tr>
</tbody>
</table>

**Notes:**

- DVT = deep-vein thrombosis; NOAC = non-vitamin K–dependent oral anticoagulant(s); PE = pulmonary embolism; VTE = venous thromboembolism. Study acronyms (where available): ASTRO-APS = Apixaban for the Secondary prevention of Thromboembolism among patients with the Antiphospholipid Syndrome; CASTA-DIVA = Cancer Associated Thrombosis, A pilot treatment study using Rivaroxaban; HoT-PE = Home Treatment of patients with low-risk Pulmonary Embolism; MERCURY PE = MultiCenter trial of Rivaroxaban for early discharge of pulmonary Embolism; RIVASVT-100 = Rivaroxaban for the treatment of Splanchnic Vein Thrombosis; SELECT-D = Anticoagulation therapy in SELECTed Cancer patients at risk of recurrence of venous thromboembolism; TRAPS = Trial on Rivaroxaban in high risk patients with AntiPhospholipid Syndrome; VERDICT = VEnous thromboembolism in Renally impaired patients and DireCT oral anticoagulants.

---
ticularly when fatal or intracranial haemorrhage is considered (72). In light of this delicate balance, normotensive patients with acute intermediate- or low-risk PE are not likely to benefit from the routine use of systemic thrombolysis, and this treatment should only be considered as rescue treatment in case of haemodynamic decompensation despite effective anticoagulation (39, 71). This strategy is supported by the Pulmonary Embolism Thrombolysis (PEITHO) trial, which compared a single bolus of tenecteplase (plus heparin) with placebo (plus heparin) in 1,006 patients with acute PE and right ventricular dysfunction plus myocardial injury detected by imaging and a positive cardiac troponin test; in this ‘intermediate-high-risk’ group, the clinical benefits of thrombolysis were counterbalanced by intracranial and other major bleeding complications (73).

Emerging approaches to reperfusion treatment might help to achieve comparable efficacy while minimising the bleeding risk associated with systemic full-dose thrombolysis. Preliminary evidence from small studies suggests that reduced-dose systemic thrombolysis might represent an option for improving safety while maintaining efficacy of this treatment (74, 75). At the interventional front, catheter-directed, ultrasound-assisted low-dose thrombolysis has been proposed as an option for clearing pulmonar y (or proximal venous) thrombi (76). Data from two multicentre interventional trials in PE, a phase-2 randomised controlled study in 59 patients (77) and a prospective single-arm study in 150 patients (78), support the efficacy and particularly the safety (in terms of intracranial or other life-threatening bleeding) of this procedure. Further validation is needed, and it remains to be determined whether thrombus removal, and consequently the relief of the right ventricle from pressure overload, is adequately fast in patients with overt or imminent haemodynamic decompensation, and whether the use of ultrasound is really necessary for maximum penetration of the thrombolytic agent into the thrombus (79).

Experimental studies, including a mouse model of PE, have yielded intriguing data on shear-activated nanotherapeutics, i.e. the local delivery of tissue plasminogen activator at the site of partially obstructed (pulmonary) vessels by intravenously administered nanoparticles (80). Early translation will determine whether this approach may become an option for optimising the efficacy and safety profile of thrombolysis in the future.

**Anticoagulant agents and regimens**

The benefits of immediate anticoagulation (compared to no treatment) in patients with acute VTE were demonstrated by a controlled trial as early as 1960 (81). For many decades, initial treatment with a parenteral anticoagulant (in the beginning unfractionated heparin, meanwhile largely replaced by LMWH or the synthetic pentasaccharide fondaparinux since the beginning of the 21st century) followed by VKA represented the gold standard for the anticoagulant treatment of VTE. This strategy is still valid and included in current guideline recommendations; however, in the past decade, two classes of NOACs were approved for the treatment and secondary prophylaxis of acute PE: three direct factor-Xa inhibitors (rivaroxaban, apixaban, edoxaban), and one direct thrombin inhibitor (dabigatran etexilate). Large phase-3 trials showed that these drugs were non-inferior to the ‘standard’ treatment mentioned above with respect to efficacy outcomes, while their safety profile was overall superior to that of the comparator
arm, particularly in terms of bleeding severity (82, 83). As a consequence, the NOACs are progressively being established as the new standard of care in anticoagulation for VTE.

What is the optimal duration of anticoagulation after a first episode of VTE? The high long-term rate of VTE recurrence (84), particularly following the discontinuation of anticoagulation (85), is well recognised. More than 20 years ago, a landmark randomised controlled trial demonstrated the superiority of six-month treatment compared to only six weeks of anticoagulation (86). However, later studies failed to confirm an unchallenged ‘net’ clinical benefit of oral anticoagulation beyond the first three months, mainly due to the bleeding complications of chronic VKA treatment (87, 88). These doubts have resulted in a notoriously ‘time-resistant’ consensus that the duration of anticoagulation after a first episode of VTE should cover a minimum of three months, but its extension beyond that period should be decided on a case-by-case basis. To this date, uncertainty persists regarding the influence and relative weight of individual baseline or follow-up parameters as predictors of recurrence risk and there is a lack of robust, externally validated VTE recurrence and/or bleeding scores that might help us to assess the risk-to-benefit ratio of continuing treatment in the individual patient (89). This conundrum might be resolved by recent studies demonstrating a satisfactory efficacy and safety profile of extended (beyond the first 6 months) anticoagulation with NOACs (90), but also with contemporary VKA-based regimens (91). Not surprisingly therefore, we are already witnessing a trend towards increasingly longer or ‘indefinite’ anticoagulation periods for secondary VTE prophylaxis. The development of reversal agents against dabigatran (92) or the factor Xa inhibitors (93) may further support this paradigm shift by removing psychological barriers against long-term anticoagulation.

Major ongoing trials on the use of NOACs in specific patient populations are summarised in Table 4. These studies focus on optimising the management of patients with rare site vein thrombosis or distal DVT as well as those with intermediate- or low-risk PE. Furthermore, they are investigating the efficacy and safety of NOACs in specific patient populations, notably patients with cancer, renal dysfunction, or the antiphospholipid syndrome.

The search for the ideal anticoagulant, which will exert antithrombotic effects without impeding haemostasis and thus without major bleeding complications, continues. Coagulation factors XI and XII and (probably to a lesser extent) activatable fibrinolysis inhibitor (TAFI)a, have been identified as promising targets; they are currently being investigated in experimental studies or are already in various phases of clinical testing (94, 95) (Table 5). The results of these studies, which are being conducted in parallel with numerous focused NOAC trials (Table 4), will determine which of these agents can make it into the ‘post-NOAC era’ and whether they will mark yet another breakthrough in antithrombotic treatment in the years to come.

Conclusions

Over the last century, we witnessed major advances in the prevention, diagnosis, and treatment of VTE. The need to prevent VTE in high-risk hospitalised patients was placed on a firm scientific basis, and the use of effective and safe anticoagulant drugs resulted in a substantial reduction in the risk of PE-related mortality. While optimal prophylactic strategies are now well defined for some patient groups, further investigation is still needed in other areas including medical patients and the outpatient setting. The diagnostic approach to suspected VTE is now based on advanced imaging techniques with the ability to identify even very small clots in peripheral vessels. However, diagnostic pitfalls remain, and integration of clinical pre-assessment is crucial, as already suggested by theories developed more than 200 years ago. Finally, advances in our therapeutic armamentarium have greatly simplified the management of VTE, progressively improving outcomes and reducing the need for, or duration of, hospitalisation. New molecular targets are being investigated in search of the ideal next-generation anticoagulant with no (or a minimal) impact on haemostasis and bleeding risk. Optimising individually tailored, risk-adjusted VTE treatment strategies will continue to be one of the top priorities in the years to come.

Acknowledgements

The work of Stavros Konstantinides is supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and 01EO1503).

Conflicts of interest

Sam Schulman has received grant support/honoraria from Boehringer Ingelheim, Octapharma, Baxter, Bayer, and Bristol-Myers-Squibb. Walter Ageno has received research support from Bayer and Boehringer Ingelheim and has participated in advisory boards for Bayer, BMS-Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. Stavros Konstantinides has received consultancy and lecture honoraria from Boehringer Ingelheim, and the Wyss Institute; and institutional grants from Boehringer Ingelheim.

References

Thrombosis and Haemostasis 7/2017

Schulman et al. VTE: past, present and future


