Diagnosis, treatment and long-term effects of venous thromboembolism
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Chapter 1

General introduction
Venous thromboembolism (VTE) is a common disease with an incidence of 1-2 per 1000 individuals. VTE refers to two entities: the presence of a thrombus in the deep veins, most often of the leg (deep venous thrombosis, DVT) and pulmonary embolism (PE), a potential fatal condition in which an embolism blocks one or more pulmonary arteries.

DVT was described for the first time during the Middle Ages; at that time a clinical diagnosis based on signs and symptoms. In 1271, Raoul, a 20 year-old man, suffered from unilateral pain and swelling of his right calf. Raoul’s physician advised him to wait and see. Unfortunately, his symptoms worsened and he developed a leg ulcer. This was the first description of DVT which probably was complicated by a severe manifestation of post-thrombotic syndrome.

**Diagnosis of venous thromboembolism**

In the 19th century, Rudolf Virchow, a German pathologist, already stated that PE and DVT are two manifestations of one common disease. More than one century later, scientists from Hamilton and Amsterdam yielded new evidence for this single disease concept, a view which was not taken seriously in Virchow’s own time. Clinical studies in patients with symptomatic PE showed that DVT is present in 80% of patients, as shown by venography, whereas, vice versa in 50-80% of patients with DVT, PE can be demonstrated by scintigraphic techniques. While decades ago the diagnostic workup of DVT and PE was different, nowadays the diagnostic management of the two entities partially overlaps. The first steps in the diagnostic management of VTE is to determine the clinical probability of VTE. Information regarding clinical signs and symptoms are used to classify patients in “high probability” and “low probability”. The most commonly used clinical decision rule is the Wells score. This score consists of items from the clinical history, physical examination and the physician’s judgment whether “VTE is more likely than another diagnosis”. When the low clinical probability is combined with a normal D-dimer test result, VTE is safely excluded in around one third of patients in whom this diagnosis is suspected, without the need for imaging tests. Despite this improvement in diagnostic yield, still in only 20-30% of patients who do have an indication for computed tomography pulmonary angiography (CTPA), the diagnosis of PE is confirmed. Moreover, CTPA may also cause adverse effects such as the risk of contrast nephropathy and increased risk of cancer from radiation exposure. Furthermore, adherence to the recommended, sequential algorithms and pre-test probability scores in clinical practice is poor, which may be partly due to lack of time at busy emergency departments. These concerns call for a more simple diagnostic strategy which also lead to a reduction in unnecessary CTPA at the lowest possible false negative rate of the overall diagnostic strategy.
Treatment of venous thromboembolism

During the Middle Ages, VTE was treated with leeches. At that time, this was not based on evidence, and leeches were used for treatment purposes in numerous illnesses.\(^3\) However, centuries later it was shown that leeches actually were not a bad choice as they have hirudin, a thrombin inhibitor, in their saliva.\(^{16}\)

From the first description of DVT in the Middle ages, it took six ages before heparin, the first anticoagulant for the treatment of VTE was discovered.\(^{3,17-20}\) Exactly one century ago in 1916, McLean was studying the procoagulant properties of ether and alcohol extracts of canine brain, liver and heart under the supervision of Howell, when he noticed that these extracts became anticoagulant after long-term exposure to air.\(^3,21\) A few years later, Howell discovered true heparin, a water-soluble mucopolysaccharide from dog liver.\(^{3,21,22}\) In 1933, Charles and Scott succeeded in producing pure crystalline heparin, allowing its use in humans.\(^{3,17,21}\)

The subsequent important achievement in the treatment of VTE was the discovery of vitamin K antagonists (VKA).\(^3,20\) The story of VKA started in North Dakota and Alberta in the early 1920s. After a mysterious haemorrhagic disease decimated cattle, a Canadian veterinary called Schoefield realised that the disease was caused by spoiled sweet clover that the cattle had been consuming.\(^{21}\) Although the cause of the haemorrhagic malady had been found, it took 10 years before Link and colleagues isolated the active compound, coumarin.\(^{23}\) The fast-acting variant of VKA warfarin was made commercial and was applied as rat poison. The unsuccessful suicide of a navy inductee with an overdose of warfarin demonstrated that this agent was not as toxic as initially assumed and opened the way to commercialisation as a therapeutic anticoagulant agent for human use.\(^{3,21,23}\) Interestingly, heparin and VKA never competed with each other as physicians realised that the two drugs were complementary: heparin being given parenterally with immediate effect, and VKA being taken orally, allowing longer courses of treatment.

In 1957, Barritt and Jordan conducted the still widely cited landmark trial in which patients with PE were included and randomised to anticoagulants (heparin and nicoumalone [VKA]) or no anticoagulants. Of the patients who did not receive anticoagulants, 25% died of PE and 25% had non-fatal recurrences. Of the patients treated with anticoagulants none died of PE and none had recurrences.\(^{24}\) Since then, for at least half a century, patients with VTE have been treated according to the regimen of initial heparin followed by VKA.

In 2009, another milestone was achieved in the field of VTE treatment. The results of the first phase 3 randomised controlled trial with a direct oral anticoagulant (DOAC) was published. Dabigatran, a thrombin inhibitor, showed to be as effective as VKA in the treatment of VTE, without the need of laboratory monitoring.\(^{25}\) Between 2009 and 2013, six trials comparing the efficacy and safety of DOACs with VKA in the treatment of VTE have been published. It has now been unequivocally shown that DOACs are at least as effective as
VKA in the treatment of VTE, with less major bleeding complications, especially intracranial and fatal haemorrhage.\textsuperscript{25-30} Nowadays, current international guidelines recommend DOACs over VKA for the indication of VTE, leading to simpler long-term treatment of VTE with a beneficial bleeding profile.\textsuperscript{31}

**Long-term effects of venous thromboembolism: post-thrombotic syndrome**

Post-thrombotic syndrome is a common complication of DVT and occurs in 20-50\% of the patients with an acute DVT.\textsuperscript{32-37} Clinical presentation may vary from minor signs including skin discoloration, venous ectasia and swelling, to severe manifestations such as chronic pain and leg ulcers impairing daily activities. Due to its high prevalence, severity and chronicity, PTS has a significant impact on quality of life and is associated with considerable socioeconomic consequences for both the patient and the health care system.\textsuperscript{35,38}

However, the pathophysiology of PTS is still poorly understood. It has been proposed that the signs and symptoms of PTS are caused by end-organ manifestation of venous hypertension, as a result of several processes such as tissue remodeling, impaired thrombus resolution and continued inflammation.\textsuperscript{39-43}

There is no gold standard test to diagnose PTS. In the past years various clinical scales have been used. The Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis recommends the use of the Villalta scale for diagnosis of PTS with the aim to enhance generalisability of research in this field. The Villalta scale consists of five patient-rated symptoms (heaviness, pain, cramps, pruritis, and paraesthesia) and five clinician-rated signs (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain on calf compression). For each item, a score of 0-3 is assigned using the contralateral unaffected leg as comparator. PTS is defined as a Villalta score of \(\geq 5\). The presence of a venous ulcer of the lower limb indicates severe PTS, regardless of the Villalta score.\textsuperscript{44}

As effective treatment for PTS is lacking, prevention in patients with acute DVT is the cornerstone. For years, it was accepted that elastic compression stockings (ECS) decrease the risk of developing PTS up to 50\%, as was shown in two independent randomised trials from the Netherlands and Italy.\textsuperscript{32,33} However, a recent, double-blind randomised controlled trial observed no difference in PTS incidence between ECS and placebo stockings\textsuperscript{34}, leading to discussions regarding the synthesis of the available evidence. Catheter-directed thrombolysis (CDT) of acute DVT might be another option to prevent PTS. It had been hypothesised that CDT might improve the patency of the vein resulting in less obstruction, less venous valve damage and ultimately less PTS complaints. The first randomised clinical trial treated patients with CDT plus standard anticoagulant therapy or standard therapy alone, sho-
wing 14% absolute risk reduction at the cost of 20 bleeding complications in patients treated with CDT.\textsuperscript{45} Ongoing randomised controlled trials will have to establish the role of CDT in the prevention of PTS. DOACs might also play a role in the prevention of PTS. Although adequate anticoagulation cannot dissolve clots by itself, it can facilitate endogenous thrombolysis by preventing further thrombus growth, which might lead to improved recanalisation and better preservation of venous valves. It is known that subtherapeutic INR levels while being treated with VKA is a risk factor for PTS.\textsuperscript{46-49} This implies that inadequate anticoagulant treatment might promote PTS development. As DOACs have a more predictable pharmacotherapeutic profile, leading to more stable anticoagulation than VKA, it is possible that treatment with DOACs leads to less PTS.

After the development of the first anticoagulant, many improvements have been achieved regarding the treatment and long-term effects of VTE. With the introduction of anticoagulants the mortality of VTE decreased dramatically from 25\% to 8\%.\textsuperscript{1,24,50} While decades ago patients with DVT were treated in hospital, the advent of low-molecular-weight heparins (LMWH) made hospital admission in case of DVT unnecessary.\textsuperscript{51,52} And, the recent approval of DOACs simplified the long-term treatment of VTE and made treatment with anticoagulants more convenient for patients.

Despite these numerous achievements, there are still many knowledge gaps and unsolved clinically needs in the field of VTE treatment and even more in the field of the long-term effects of DVT. This thesis will address some of these unsolved clinical issues.

**Outline of the thesis**

The first part of this thesis addresses novel diagnostic managements of pulmonary embolism. Chapter 2, evaluates whether age-adjusted D-dimer cut-off levels (patient’s age x 10µg/L) in patients of 50 years or older is associated with an increased diagnostic yield. Chapter 3 validates a simplified diagnostic algorithm for patients with clinically suspected acute PE, in which clinical probability and D-dimer tests are assessed simultaneously.

Part II focuses on the treatment of VTE in special patient groups, i.e. the elderly, patients who have recurrent VTE despite treatment with anticoagulants, and patients with short bowel syndrome. Elderly patients have the highest incidence of thrombotic complications but also have the highest risk of anticoagulant-associated bleeding. Chapter 4 addresses the balance between risks and benefits of DOACs compared with VKA in elderly patients. Despite the fact that anticoagulants have proven to be effective for the treatment of VTE, a minority of the patients develop recurrent VTE despite treatment with anticoagulants. Chapter 5 and 6 describe the management of recurrent VTE in anticoagulated cancer and non-cancer patients. Finally, short bowel patients receiving parenteral nutrition often require anticoagulants for
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prevention or treatment of VTE. DOACs may represent attractive alternatives to the current registered VKA and LMWH. In chapter 7 the pharmacokinetics and –dynamics of dabigatran etexilate and rivaroxaban are evaluated in patients with short bowel syndrome.

Part III of this thesis addresses the treatment of DOAC-associated bleeding complications. Chapter 8 describes the potential of non-specific reversal agents for DOAC-associated bleeding. Whereas lately a specific antidote for dabigatran etexilate has been approved, a specific reversal agent for factor Xa inhibitors is still lacking. Chapter 9 and 10 focus on the effect of four-factor prothrombin complex concentrate in a dose of 25 and 37.5 IU/kg body weight as potential reversal agent for factor Xa inhibitors, rivaroxaban and apixaban.

In part IV of this thesis the post-thrombotic syndrome is studied. Large clinical trials evaluated the efficacy and safety of the DOACs in the treatment of VTE. However, their effects on long-term outcome of DVT are poorly studied. In chapter 11 the incidence of PTS in patients treated with rivaroxaban for acute DVT is compared to the incidence of this syndrome in patients treated with VKA. Chapter 12 and 13 investigate the role of various pathogenic mechanisms for PTS through measurement of a panel of biomarkers in patients with and without PTS.

Finally, chapter 14 provides a summary of the main results of this thesis with a general discussion and future perspectives.


