Treatment of venous thromboembolism: focus on patient characteristics and bleeding complications
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General introduction
and outline of the thesis
General introduction

Venous thromboembolism (VTE) consists of the entities deep vein thrombosis (DVT), usually of the leg, and pulmonary embolism (PE), and is the result of blood clot formation in the veins. VTE is a common disease that affects approximately 1-2 per 1000 individuals per year (1). The German physician Rudolph Virchow (1821-1902) was the first to acknowledge that DVT and PE are both manifestations of the same disease. Virchow described three key elements in the formation of thrombosis: stasis, vessel damage and hypercoagulability, also known as Virchow’s triad (2,3). The triad has been revised over the years, but the key elements remain the cornerstone in the aetiology and the identification of risk factors of VTE.

Historical overview of treatment of VTE

Neither Greek nor Roman physicians reported cases suggestive of a DVT. The first description of a patient with DVT dates back to the middle ages (1271) (4,5). Physicians including Hunter hypothesized that blood clots formed the origin of the observed occlusion of the veins (6). Hunter therefore performed ligations of the vein directly above the thrombosis to prevent the blood clots from extending into the lungs (7). Since this technique was the only available effective treatment option for prevention of PE, it was widely used until the midst of the 20th century (8,9). In addition, immobilization, i.e. bed rest, was also a cornerstone in the treatment of VTE as it was thought to prevent migration of the clots (10).

The discovery of heparin in 1916 by McLean identified the first potent anticoagulant agent for the treatment of VTE (5,11). McLean was a medical student who studied the properties of natural procoagulants in several dog tissues at the laboratory of dr. Howell at Johns Hopkins, Baltimore (12). McLean found that phosphatides from heart, liver and brain tissue evolved into active anticoagulants over time when exposed to air (11,12). In 1922, Howell discovered the ‘true’ heparin; a water-soluble anticoagulant from canine liver (11,12). However, to be able to use heparin as a therapeutic agent in humans, the next step was to produce a purified heparin. Charles and Scott succeeded in the production of pure crystalline heparin in 1933, which was first administered to humans in 1935 (12,13).

The discovery of the oral anticoagulants starts at the beginning of the 20th century in North Dakota, USA and Alberta, Canada (5,12). A disease called ‘sweet clover disease’ affected and decimated cattle herds, due to development of spontaneous and often fatal haemorrhages at the end of the winter season. A veterinarian pathologist, Schofield, observed this phenomenon and discovered that the disease was caused by the consumption of spoiled sweet clover. He also found a prolonged clotting time in these animals (12,14). It
took until 1933 before Link and colleagues were able to identify the active component of sweet clover, coumarin, in their lab in the University of Wisconsin (15). The name warfarin was derived from the Wisconsin Alumni Research Foundation (WARFarin). Synthesized warfarin became first available as rat poison in 1948. At that time is was not used in humans due to assumed toxicity (12). But when a navy employee tried to commit suicide with warfarin and failed, warfarin was commercialized as an anticoagulant agent for treatment of thromboembolic diseases in humans (12,15). Because of the property differences between heparin and warfarin - heparin works immediately and is administered parenterally, while warfarin takes a few days to become effective and can be taken orally - the agents were used complementary (16). This led to the classical way of treating VTE: an initial course of heparin for 5-10 days overlapped with and followed by warfarin or another VKA. For more than 60 years this regimen was the preferred and widely used option for treatment of VTE, but also for the prevention of stroke in patients with atrial fibrillation (17).

The most recent development in the field of oral anticoagulants is that of the direct oral anticoagulants (DOACs). In contrast to VKA, which interfere with the synthesis of vitamin K-dependent clotting factors (II, V, VII, IX) in the liver, DOACs directly inhibit coagulation factor IIa (dabigatran etexilate [hereafter: dabigatran]) or factor Xa (rivaroxaban, apixaban, or edoxaban) (18). DOACs have the advantages of a stable pharmacokinetic and pharmacodynamic profile and a short half-life allowing for a fixed dose regimen and no need for regular laboratory monitoring or dose adjustments (19). Between 2009 and 2013, six phase 3 randomized controlled trials have been published comparing one of the DOACs with the standard-of-care at that time heparin/VKA in the treatment of acute symptomatic VTE (20-25). DOACs were found to be as effective as VKA in the treatment and secondary prevention of VTE and were associated with a reduction in risk of major bleeding, especially intracranial bleeding (ICH) (26). DOACs are currently recommended over VKA as first-line anticoagulant treatment option for patients with VTE (27).

Despite the progress made over the years and the growing amount of evidence on the treatment of VTE, there are still numerous gaps in the knowledge of how to apply DOACs in special patient populations. This thesis will focus on some of these unresolved needs in defined subgroups of patients with VTE. It aims to increase knowledge on the importance of right ventricular dysfunction and extent of PE in VTE treatment. In addition, patients preferences for treatment options in VTE are evaluated.

**Treatment of anticoagulant-related bleeding complications**

Although DOAC treatment reduces the risk of major bleeding in patients with VTE as compared to treatment with VKA, bleeding complications are still often observed with a
major bleeding risk of 1.4-2.1% per year in the phase 3 DOAC trials (28). Similar or sometimes slightly higher rates are found in studies with DOACs from clinical practice (29-31). ICH is the mostly feared bleeding complication of anticoagulant treatment due to high mortality and morbidity rates (32) and recent studies report the risk of ICH to be reduced by 56% in patients treated with DOACs compared to treatment with VKA (33). Gastrointestinal (GI) bleeds are the most common type of major bleeds in patients receiving DOACs (34) and occur slightly more often in patients treated with DOACs than with VKA (26). Thus haemorrhages remain a significant concern with the use of DOACs and optimal management is required to prevent long-term problems after bleeding complications.

In patients with a major or life-threatening bleeding event or the need for an emergency invasive procedure reversal of the anticoagulant effect might be indicated (35). If bleeding is caused by a VKA, the first step in reversal is the administration of vitamin K. Since this usually takes about 12-24 hours to reach a clear effect, current guidelines recommend the use of prothrombin complex concentrate (PCC) in acute major bleeding (35,36). PCC contains the vitamin K-dependent dependent coagulation factors II, IX, and X (and often factor VII) with variable amounts of the anticoagulant proteins C and S (18). PCC has been widely used in clinical practice, based on the effectiveness in restoring normal haemostasis (37,38). PCC is recommended over fresh frozen plasma, as the latter carries certain disadvantages, such as a large infusion volume and longer infusion duration (28).

For patients with a major bleeding caused by dabigatran, a specific antidote (idarucizumab) has recently become available. Idarucizumab is a monoclonal antibody fragment that has a very high affinity for binding with dabigatran (39). A recently published study showed that idarucizumab was effective in reversing the anticoagulant effect of dabigatran in patients with uncontrolled bleeding or the need to undergo an urgent procedure (40). The dose of 5 g, administered in two gifts of 2.5 g each, normalized coagulation assays in 100% of patients. Thromboembolic complications were observed in 6.3% of bleeding patients and in 7.4% of patients requiring an emergent intervention, and mortality rates in both groups were approximately 19% (40).

A specific antidote (andexanet alfa) to reverse the anticoagulant effects of factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, is currently under development. Andexanet alfa is a recombinant factor Xa protein with high affinity for fXa inhibitors (41). It is administered as a bolus dose followed by a 2-hour continuous infusion. A phase 3 study evaluating the effectiveness and safety profile of andexanet alfa is ongoing. A published interim analysis of 67 patient with acute major bleeding receiving andexanet alfa showed immediate normalization of the coagulation assays (42). Clinical haemostasis was achieved in 79% of patients at 12 hours after the infusion and 18% of patients suffered a thromboembolic complication in the follow-up period (42). This complication rate is rather high, but before any definite conclusions can be drawn, the full cohort analyses must be
awaited.

Since andexanet alpha is not yet available in clinical practice, currently the only alternative to reverse the effect of factor Xa inhibitors in case of life-threatening bleeding is PCC. High doses of PCC has been shown to normalize coagulation assays in healthy subjects receiving rivaroxaban (43) and apixaban (44). A retrospective review of 18 patients with ICH receiving rivaroxaban or apixaban, revealed a mortality rate of 33% during hospital stay. One (5.6%) thromboembolic event was observed 24 hours after PCC infusion and 6 patients had a favourable outcome at 3 months (45).

Even though several treatment options for anticoagulant-related bleeding are available, there are various aspects to be further investigated. This thesis aims to evaluate the clinical impact and outcome of major bleeding events with DOACs compared to VKA, also in the subgroup of women. In addition, the efficacy and safety of PCC in VKA related bleeding, including INR correction, mortality and thromboembolic complications is reviewed. Furthermore, insight is provided in clinical patient outcomes of bleeding caused by VKA and DOACs.

Outline of the thesis

Part I of this thesis describes patient characteristics in relation to treatment and outcome of VTE. Chapter 2 provides an overview of the epidemiology of VTE, including risk of recurrence, incidence rates of the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, and costs of VTE. In Chapter 3 and 4, we evaluate the importance of right ventricular dysfunction and anatomical extent of PE on the treatment and outcome of patients with pulmonary embolism. Chapter 5 focuses on differences between men and women in the presenting location of a VTE. Finally, in Chapter 6 the patient preference for a DOAC over a VKA is illustrated in patients with VTE.

Part II addresses the management and outcome of anticoagulant-related bleeding. Chapter 7 contains the findings of an individual patient data meta-analysis assessing differences in bleeding pattern and comparing the severity of the clinical presentation and clinical course of patients with major bleeding events treated with factor Xa inhibitors or VKA for VTE. Chapter 8 provides the in-depth results of the analysis on clinical impact of major bleeding in patients with VTE treated with edoxaban or VKA, including treatment and management of the bleeding episodes in both treatment arms. Chapter 9 presents an overview of the incidence, characteristics, diagnostics, treatment and outcome of abnormal vaginal bleeding events in women receiving apixaban or VKA. The occurrence, characteristics, management and subsequent clinical outcome of abnormal vaginal bleeds in women treated with edoxaban or VKA is described in Chapter 10.
With respect to the treatment of anticoagulant-related bleeding episodes, Chapter 11 summarizes the findings from a systematic review and meta-analysis on the efficacy and safety of 4-factor PCC in patients with acute bleeding events related to the use of VKA. In Chapter 12, the clinical outcome of bleeding events caused by VKA and treated with PCC are described, with a special interest for haemostatic efficacy at 24 hours. Chapter 13 addresses the management and subsequent clinical outcome of DOAC-related bleeding events and emergent invasive procedures while using a DOAC, and additionally, a comparison between clinical outcome of DOAC- and VKA-associated bleeding is made.

Finally, Chapter 14 provides a summary of the most prominent findings of this thesis.
References


