CLINICAL ASPECTS OF VENOUS THROMBOEMBOLISM IN SPECIAL PATIENT POPULATIONS

Suzanne M. Bleker

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COLOFON

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Author: Suzanne Mariëlla Bleker
Printing and layout: Ridderprint, www.ridderprint.nl

ISBN: 978-94-6299-663-2

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Further financial support for printing this thesis was kindly provided by: the AMC, LEO Pharma, Sanofi, Servier Nederland Farma B.V., Pfizer B.V., Aspen Netherlands, Bayer Healthcare, Astellas Pharma B.V., Boehringer Ingelheim B.V., Shire, ChipSoft, and Stichting tot Steun Promovendi Vasculaire Geneeskunde.

Clinical aspects of venous thromboembolism in special patient populations

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr.ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 16 november 2017, te 10.00 uur
door Suzanne Mariëlla Bleker
geboren te Rotterdam

Promotiecommissie

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General introduction and Outline of the thesis

S.M. Bleker
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General Introduction

Clinical research is a part of healthcare science that involves human participants. It studies the epidemiology and pathophysiology of disease, and it learns us how to most efficaciously and safely prevent, diagnose and treat illnesses (1–3). Two main types of clinical studies can be distinguished: interventional and observational studies (1). Interventional studies are experiments in which participants are assigned to specific interventions according to a pre-specified study protocol; interventions can be drugs, devices, or procedures. A new medical strategy may be compared to a standard-of-care strategy, but it may also be compared to placebo or to no intervention. Some clinical trials compare interventions that are already available in clinical practice. The safety and efficacy of the intervention is determined by measuring pre-specified outcomes. In clinical observational studies, outcomes are also assessed in (groups of) participants, but the participants are not assigned to specific interventions; instead, the participants undergo interventions or procedures as part of routine clinical care. Clinical studies are designed to answer specific questions and to translate basic research into new treatments, strategies and information to improve patient care.

The first known experiment resembling a clinical study is described in the "Book of Daniel" in the Bible, and was performed by Nebuchadnezzar II (634–562 B.C.), a military leader and king of Babylon for nearly 60 years (4,5). He put his people on a diet consisting of only meat and wine, which he believed would get them in better physical shape. Several men refused however, and preferred to eat only vegetables. The king approved their diet, but only for the duration of 10 days, after which he would assess everyone's health condition. During this assessment the vegetarians appeared healthier than the carnivores, which led him to permit the vegetable lovers to continue their diet. In retrospect, this likely is the first recorded experiment that guided a (public) health decision in humans.

In the field of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), incredible progression has been made throughout the centuries regarding our knowledge on the epidemiology, pathophysiology, prevention, diagnosis, treatment and prognosis of the disease in several settings. In 1271, the first case of DVT was reported in a 20-year old Norman cobbler (6). The man was advised by his physician to wait and see, but he subsequently developed an ulcer. According to the story, the ulcer was healed after applying dust from below a stone covering the tomb of king Saint Louis, and he still lived 11 years thereafter (6). In the era that followed, pregnancy was hypothesized to be the leading (and perhaps the only known) risk factor for DVT. It was thought that postpartum DVT was caused by accumulation of unconsumed breastmilk in the legs ("milk leg"), and in the late 1700s breast-feeding was encouraged to prevent DVT (7,8). Bloodletting was used to treat

DVT until the end of the 19th century (9). Because of fear for thrombus extension, strict bed rest was prescribed, and this constituted, at least from the end of the 19th century, the cornerstone of DVT treatment. In 1793, Hunter had started performing venous ligation above the level of the thrombus, to prevent migration of clots from the legs to the lungs (10). This technique became increasingly popular at the end of the 19th century, and was considered the only possible measure to prevent PE, even though it was associated with a high morbidity and mortality. This procedure was widely used until the mid-20th century. In the first half of the 20th century, anticoagulants were discovered, and in 1960 the first randomized controlled trial demonstrated that anticoagulant therapy strongly reduced the risk of recurrent VTE and mortality in patients with PE. Since then, numerous clinical studies have evaluated anticoagulants for the prevention and treatment of VTE, which have defined our current clinical practice (11,12).

Despite the progress that has been made in the past decades in the field of VTE, various clinical aspects of this disease have not been fully addressed. This thesis aims to evaluate several clinical elements of VTE in special patient populations, including pregnant patients and those with cancer. Furthermore, it aims to increase knowledge on the current treatment strategies and complications on the long-term for rare forms of VTE such as unsuspected pulmonary embolism (PE) and upper extremity deep vein thrombosis (UEDVT). Finally, insight is provided into the clinical impact of bleeding events with the use of oral factor Xa (fXa) inhibitors versus vitamin K antagonists (VKA) in patients with VTE.

Outline of the thesis

Part I describes several aspects of sex-specific VTE, in particular pregnancy, the use of hormonal contraceptives, and anticoagulant-associated vaginal bleeding.

Chapter 2 provides an overview of VTE risk factors for women, and how these interact with common types of hereditary thrombophilia. In **chapter 3** the rationale and design of the Highlow study are described. This randomized controlled trial evaluates two widely used doses of low-molecular-weight heparin (LMWH) for the prevention of pregnancy-associated recurrent VTE. Additionally, in **chapter 4** we present an interim report of the ongoing Highlow study. Finally, **chapter 5** focuses on vaginal bleeding in women with VTE, treated with apixaban or warfarin.

In **part II**, the relationship between cancer and VTE is addressed. **Chapter 6** summarizes the current understanding of the prevention and treatment of VTE in patients with cancer. In **chapter 7** we discuss the clinical and radiologic characteristics as well as the prognostic value of unsuspected PE in cancer patients. **Chapter 8** contains an interim

report of a prospective registry, which evaluates the current treatment strategies and long-term clinical outcomes in cancer patients with unsuspected PE, and **chapter 9** concerns the interobserver agreement on the diagnosis and extent of unsuspected PE in cancer patients.

Several aspects of UEDVT are discussed in **part III** of this thesis. First, in **chapter 10** an overview of the clinical characteristics, risk factors, diagnosis, management, prognosis and prevention of UEDVT is provided. **Chapter 11** includes the results of a systematic review on the clinical course of UEDVT in patients with and without cancer; **chapter 12** contains the findings of our recent cohort study on the current management strategies and long-term clinical outcomes of UEDVT and upper extremity superficial vein thrombosis (UESVT).

The final part of this thesis, **part IV,** concerns the clinical impact of bleeding with oral fXa inhibitors and VKA. **Chapter 13** provides the results of our study on the clinical presentation and course of bleeding events in patients with VTE, treated with apixaban or warfarin. The clinical impact of major bleeding events in patients with VTE treated with edoxaban or warfarin is reported in **chapter 14. Chapter 15** presents the results of an individual patient data meta-analysis, comparing the clinical impact and course of major bleeds between patients treated with fXa inhibitors or VKA.

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PART I

Sex-specific venous thromboembolism

Sex, thrombosis and inherited thrombophilia

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Blood Rev. 2014 May;28(3):123-33.

Abstract

The incidence of venous thromboembolism (VTE) is two-fold higher in women than in men during reproductive age, which is likely explained by the use of hormonal contraceptives and by pregnancy in this phase of life. After adjustment for these factors, men have a two-fold higher risk of developing a first VTE compared with women, which is in line with earlier observations that men have a two-fold higher risk of recurrent VTE. These findings indicate that the intrinsic risk of VTE is higher in men than in women. Hormonal contraceptives increase the risk of VTE and the risk varies per type, dose, and administration route. In women with a high baseline risk of VTE, avoidance of some hormonal contraceptives should be considered, as well as thrombosis prophylaxis during pregnancy. Presence of hereditary thrombophilia increases the risk of a first VTE episode. This review focuses on the differences in risk of VTE between men and women, hormonal risk factors for women, and how these interact with common types of hereditary thrombophilia.

Sex and the epidemiology of VTE

Venous thromboembolism (VTE) is a frequently occurring disease with an incidence of a first episode of 1–2 per 1,000 person-years (p.y.). The risk of developing VTE is relatively low for younger people (incidence 0.3 per 1,000 p.y. for individuals aged 20–44 years) but increases exponentially with age to 6.4 per 1,000 p.y. in individuals 80 years or older (1). In about half of all cases, VTE is associated with a clinical risk factor such as surgery, trauma, immobility, active cancer, use of hormonal contraceptives, pregnancy and the puerperium. In the remaining 50% of patients no such clinical risk factor is present and these episodes are referred to as unprovoked. In individuals between 20 and 44 years of age the incidence of VTE in women is about twice as high as the incidence rate in men, which is likely explained by the use of hormonal contraceptives and by pregnancy during this phase of life (1). Oral hormonal contraceptive use as a risk factor for VTE is present in about 1 in 2–4 women in cohorts that also included postmenopausal women (2,3). In a recent case-control study it was elegantly shown that after adjustment of reproductive risk factors, the risk of a first VTE is in fact twice as high in men as in women (odds ratio 2.1; 95%CI 1.9 – 2.4). This indicates that the intrinsic risk of VTE is higher in men than in women (4). It also reemphasizes the potential to reduce VTE on a population level, by prudent prescribing of hormonal contraception and targeted thrombosis prophylaxis in pregnant women at an increased risk of developing VTE.

After a first episode of VTE the risk of recurrence is highly dependent on the circumstances at the time of first VTE. The risk is lowest for postoperative VTE (0.7% per 100 p.y. during the first two years) and higher after VTE provoked by a non-surgical temporary risk factor including pregnancy and use of hormonal contraceptives (HC) (4.2% per 100 p.y. for the first two years) (5). After unprovoked VTE the risk of recurrence is estimated to be as high as 20% in the first two years, thereafter declining to an annual risk of recurrence of 5% (5–10). Interestingly, the risk of recurrent VTE is about twice as high for men compared with women. This was first described in 2004 and later confirmed by several studies (11–13). The exact mechanism explaining this phenomenon has not yet been elucidated. It may reflect a higher intrinsic risk of VTE in men compared with women as also seems the case for first episodes of VTE (4). Alternatively, it has often been suggested that the lower recurrence risk in women could be explained by further avoidance of hormonal risk factors. Many first VTE events in women are associated with oral HC, pregnancy or the puerperium and the risk of recurrence in women is likely lowered by discouraging further oral HC use and by the use of thrombosis prophylaxis during and after subsequent pregnancies. Inclusion of these women in comparisons between recurrence risk of women and men will therefore introduce bias. However, even population based studies that compared men with women who had their first

VTE unrelated to oral HC, pregnancy or the puerperium, showed a 2-fold higher risk of recurrence in men (2,8,12).

Besides exogenous risk factors there is a clear familial predisposition for VTE, which is in part explained by hereditary abnormalities in the coagulation cascade, commonly referred to as thrombophilia. The implications of having a type of hereditary thrombophilia, and indications for testing for the presence of these defects, remain subject of debate.

In this review we will focus on VTE risk factors for women, and how these interact with common types of hereditary thrombophilia.

Hormonal contraception and venous thromboembolism

In the 1960s combined oral HC, containing both an estrogen and a progestogen, was introduced as a promising new way to prevent unplanned pregnancy. Since then oral HC, also referred to as "the pill", has been a remarkable and lasting success. It is estimated that over 100 million women worldwide currently use oral HC (14). Apart from birth control, modern contraceptives afford various non-contraceptive benefits, ranging from regulation of menstrual disorders (such as menorrhagia and dysmenorrhea) to improvement of acne and hirsutism. In addition, in lower doses it can be used as hormone replacement therapy for women with perimenopausal complaints. Combined oral HC are the most frequently prescribed contraceptives, but several alternatives are available such as progestogen-only pills and non-oral HC including hormone releasing intrauterine devices (IUDs), injectables, subcutaneous implants, vaginal rings and skin patches.

The possibility that the use of oral HC may cause VTE was raised shortly after its introduction by a case report of a 40-year old woman who developed pulmonary embolism (PE) a few weeks after having started a combination of norethynodrel and mestranol for treatment of endometriosis (15). In the following years many hundreds of similar case reports were published. Nowadays, a body of evidence underlines the association between HC and VTE.

Most currently available oral HC are preparations containing both an estrogen (i.e. ethinylestradiol) as well as a progestogen. There are numerous types of oral HC available, containing different doses of estrogen and different types of progestogens. The earliest preparations contained 150 µg of estrogen. As the reported increased VTE-risk associated with combined oral HC was attributed to the amount of estrogen, the dose has been reduced gradually over the past 50 years. It was lowered to 50 µg in the 1960s and to 30 µg and 20 µg in the 1970s. The lowering from 50 µg and higher dosages to 30 µg indeed reduced the VTE- risk by 30 to 50% (16–18). A further reduction of

the estrogen dose to 20 µg was shown to be associated with an additional 18–20% reduction in VTE risk (17,19).

Although the estrogens in combined oral HC seem to be most responsible for the VTE risk, the progestogens in combined oral HC modulate the prothrombotic effect of estrogens. Based on the type of progestogen a combined oral HC contains, a classification can be made into first, second and third generation contraceptives. The classification does not cover preparations containing drospirenone or cyproterone acetate and therefore these are referred to as 'other combined oral HC'. Progestogen-only preparations are also available and, in higher doses, these carry an increased risk of VTE as well (20,21).

Pathophysiology of increased VTE risk with hormonal contraceptive use

The use of HC increases levels of coagulation factors II, VII, VIII and X (22). Furthermore, its use leads to decreased levels of the natural anticoagulants protein S and antithrombin (23), and increased resistance to activated protein C (APC) which is in part explained by the decrease of free protein S and free tissue factor pathway inhibitor (TFPI) (24,25). In addition, a decrease of fibrinolytic activity is present during HC use, mainly through an increase of thrombin-activatable fibrinolysis inhibitor (TAFI) (26). Therefore, use of HC leads to a procoagulant risk profile through various mechanisms. In line with the observed differences in the risk of VTE with different progestogens (which will be addressed in the 'Oral contraceptives' section) a more pronounced APC resistance was found in users of third generation contraceptives (27,28) as well as in users of drospirenone and cyproterone acetate (29) compared with users of second generation contraceptives. This implies that coagulation markers may be a valid surrogate endpoint if studies with clinical endpoints are not available.

Oral hormonal contraceptives

Several large studies have shown that currently used combined oral HC increase the risk of VTE 2- to 6-fold (17,19,30–32). The risk is highest in the first three months of use, with an estimated odds ratio (OR) of 12.6, and this risk remains 5-fold increased after one year (17). Despite the low baseline incidence of VTE in women of reproductive age, the effect of oral HC on VTE in the population is large, considering that many women worldwide use oral HC. In the following paragraphs we provide an overview of the risk increase associated with all types of oral HC. The overview is mainly based on results from large case-control studies (17,33), a large cohort study (34) and a recent systematic review and network meta-analysis (35). The latter provides somewhat lower risk estimates compared with the other studies, in particular for third generation oral HC and oral HC containing cyproterone acetate and drospirenone. Interestingly, in the sensitivity analysis sources of bias were explored, showing lower risk estimates in indus-

try-sponsored studies, case-control studies and studies without objectively confirmed VTE. Thus, the presented risk estimates in this meta-analysis may be an underestimation and should be interpreted with caution. The associated estimated relative and absolute risks are also shown in Table 2.1.

Table 2.1. Estimates of relative and absolute risk of VTE in women without previous VTE for different types of hormonal contraceptives and hormone replacement therapy.

	Estimated RR (95% CI)	Observed or estimated ¶ absolute incidence (#/10.000 person years)
HORMONAL CONTRACEPTIVES		
Strong risk increase (RR 4–8)		
Oral ethinylestradiol / desogestrel		
• With 30–40 µg ethinylestradiol	4.21 (3.63 – 4.87)	11.8
Oral ethinylestradiol / gestodene		
• With 30–40 µg ethinylestradiol	4.23 (3.87 – 4.63)	11.0
Oral ethinylestradiol / drospirenone		
• With 30–40µg ethinylestradiol	4.47 (3.91 – 5.11)	9.3
• With 20 µg ethinylestradiol	4.84 (3.19 – 7.33)	10.0
Oral ethinylestradiol / cyproterone		
• With 30–40 µg ethinylestradiol	4.10 (3.37 – 4.99)	9.0
Transdermal ethinylestradiol / norelgestromin	7.90 (3.54 – 17.65)	9.71
Oral progesterone only, high dose (5–40mg) ¶	5.3 (1.5 – 18.7)	**16 ¶**
Vaginal ring: ethinylestradiol / etonogestrel	6.48 (4.69 – 8.94)	7.75
Moderate risk increase (RR 1.5–4)		
Oral ethinylestradiol / desogestrel		
• With 20 µg ethinylestradiol	3.26 (2.88 – 3.69)	6.8
Oral ethinylestradiol / gestodene		
• With 20 µg ethinylestradiol	3.50 (3.09 – 3.97)	6.8
Oral ethinylestradiol / levonorgestrel		
• Phasic	2.28 (1.85 – 2.83)	8.4
• Combined	2.19 (1.74 – 2.75)	7.5
Oral ethinylestradiol / norgestimate *	2.56 (2.18 – 3.01)	6.2
Oral ethinylestradiol / norethisterone ¶	3.9 (1.4 – 10.6)	**12 ¶**
Injectable depot medroxyprogesterone ¶	3.6 (1.8 – 7.1)	**11 ¶**
No risk increase		
Subcutaneous implant etonogestrel	1.40 (0.58 – 3.38)	1.70
Levonorgestrel releasing IUD	0.57 (0.41 – 0.81)	1.38
• Progestogen only, low dose		
• Norethisterone	0.56 (0.29 – 1.07)	2.1
• Desogestrel	0.64 (0.29 – 1.42)	2.0

Table 2.1. Estimates of relative and absolute risk of VTE in women without previous VTE for different types of hormonal contraceptives and hormone replacement therapy. (continued)

	Estimated RR (95% CI)	Observed or estimated ¶ absolute incidence (#/10.000 person years)
HORMONE REPLACEMENT THERAPY		
Modest risk increase (RR 1.5 – 3.0)		
Oral combined estrogen/progestogen ¶	2.6 (2.0 – 3.2)	**1.5 ¶**
Oral estrogen only ¶	2.2 (1.6 – 3.0)	**1.3 ¶**
No risk increase		
Transdermal (combined estrogen/ progestogen and estrogen only) ¶	1.2 (0.9 – 1.7)	**0.7 ¶**
Tibolone ¶	0.9 (0.8 – 1.1)	**0.5 ¶**

95CI: 95% Confidence Interval. RR: Risk Ratio.

Data in this table are mainly derived from observational studies (34,43).

¶ Where no data from observational studies are available, data from case-control studies (17,20,67) were used and estimates of the absolute VTE risk were obtained by multiplying RR with baseline incidence of venous thromboembolism of 3.1 / 10,000 person years for women aged 15–54 for hormonal contraception, and of 5.8 / 10,000 person years for women aged 45–59 for hormone replacement therapy (34).

* Studies assessing the VTE risk associated with this type of hormonal contraceptive have shown conflicting results.

Combined oral hormonal contraceptives

The first available types of progestogens were lynestrenol and norethisterone. These so-called first generation progestogens are not used very often nowadays. Compared with non-users, the relative risk of VTE in users of oral HC with a first generation progestogen was found to be increased 2- to 5-fold (35). Second generation progestogens include levonorgestrel and norgestrel. Combined oral HC containing these types of progestogen are the ones most prescribed worldwide. They carry the lowest, 2- to 4-fold risk increase of VTE compared with non-users (17,34,35). Gestodene, desogestrel and norgestimate comprise the third-generation progestogens, although sometimes norgestimate is categorized as a second generation progestogen. Use of third generation combined oral HC carries a 3- to 8-fold increased risk of VTE as compared with non-use, which is consistently higher than during use of a second generation oral HC (17,34–36).

Cyproterone acetate is a progestogen that has been on the market since 1988. Besides its contraceptive effects it has an anti-androgenic effect, and therefore preparations containing this progestogen are often prescribed for treatment of acne vulgaris, seborrhea, or mild idiopathic hirsutism. Preparations containing drospirenone, an anti-mineralocorticoid, were heavily marketed, arguing that these pills would have

less side effects compared with the older contraceptives such as bloating and mood swings. They have been available since 2000. Cyproterone acetate and drospirenone containing oral HC are associated with a 6- to 7-fold increased risk of VTE compared with non-users (17,34,35).

In April 2013 the French health regulator Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) decided to withdraw the combined oral HC Diane-35, containing 2 mg cyproterone acetate and 35 µg ethinylestradiol after several reports of women who had experienced VTE or an ischemic stroke while using this oral HC (37). Although the increased VTE risk associated with the use of cyproterone acetate was already well established, civic law suits by women with thrombosis have led to increased media attention emphasizing the thrombosis risk of oral HC, in particular third generation combined oral HC, cyproterone acetate and drospirenone.

According to a recent report of the European Medicines Agency (EMA), the benefits of the Diane-35 may outweigh the risks of VTE in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism in women of reproductive age, if other therapies have failed (38). In all other cases, a second generation oral HC with the lowest possible dose of ethinylestradiol should be prescribed, and prescription of third generation oral HC, cyproterone acetate or drospirenone should be discouraged.

Progestogen-only oral hormonal contraceptives

Preparations containing only a high dose of progestogen are used for therapeutic indications such as menstrual disorders and are associated with a 5-fold increased risk of VTE (20,21). The so-called mini-pill, which contains a low dose progestogen only is primarily used for contraceptive reasons and does not seem to be associated with an increased risk of VTE (19,20). Disadvantages include the need of careful compliance and the disruption of normal menstrual patterns, including irregular bleeding, short or long cycles, bleeding and spotting, prolonged bleeding, or no bleeding at all. (39).

Non-oral contraceptives

Compared with oral HC, the risk of VTE with the use of non-oral HC is less well studied. In this section we provide an overview of the available information on the risk of VTE associated with hormone releasing IUDs, injectables, subcutaneous implants, vaginal rings and skin patches. The associated estimated relative and absolute risks are shown in Table 2.2.

IUDs are among the safest and most effective methods of contraception available. These devices are T-shaped, made of plastic and release either copper or a progestogen, thereby exerting a long-acting reversible contraceptive effect. IUDs were introduced in the USA in the mid-1960s. Initially the IUD was a big success, as by the early 1970s

Table 2.2. Prevalence of hereditary thrombophilia and relative risk estimates for various clinical manifestations.

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation
Prevalence in the general population	0.02%	0.2%	0.03 – 0.13%	3 – 7%	0.7 – 4%
Relative risk for a first venous thrombosis	5 – 10	4 – 6.5	1 – 10	3 – 5	2 – 3
Relative risk for recurrent venous thrombosis	1.9 – 2.6	1.4 – 1.8	1.0 – 1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3 – 3.6	1.3 – 3.6	1.3 – 3.6	1.0 – 2.6	0.9 – 1.3

Figures are derived from studies that are reviewed in detail elsewhere (97).

approximately 10% of all women in the USA were using this contraceptive method. In the mid-1970s however, the most popular model of plastic IUD in the USA was linked to pelvic inflammatory disease (PID) and subsequent infertility, leading to its withdrawal from the US market (40). After that time new and better designed models were introduced. The levonorgestrel-releasing IUD was introduced in 2001. Although the IUD has not yet fully recovered its status as a safe contraceptive in the USA, it has become a very popular contraceptive option in other parts of the world. The levonorgestrel-IUD is now used by over 50% of women using contraception in China (41) and by 6–27% of female contraceptive users in different parts of Europe (40). It releases 10 to 20 mcg levonorgestrel per day and dispends its hormones mostly direct to the uterus, leading to lower blood levels compared with the levels seen in patients using a 30 mcg levonorgestrel-pill (150–200 pg/mL versus 800 pg/mL) (42). The levonorgestrel-IUD was not associated with an increased risk of VTE in several studies (33,34,43).

Depot medroxyprogesterone acetate (DMPA) is an injectable progestogen-only contraceptive that is administered intramuscularly or subcutaneously once every 12 weeks. It was approved by the FDA in the USA in 1992 for contraceptive use. Early on it was suggested that DMPA increased the risk of VTE, although the observed risk increase did not reach statistical significance (14). In 2010 however, a clearly increased risk of VTE was found to be associated with these contraceptives with an almost 4-fold increased risk of VTE compared with non-users (33).

The etonogestrel-containing implant is inserted under the skin and delivers a dose varying from 60–70 mcg per day in the first weeks of use to 25–30 mcg per day after three years. Etonogestrel is an active metabolite of the third-generation progestogen

desogestrel. Very little is known about the VTE risk associated with etonogestrel. No prothrombotic changes occurred with the etonogestrel-releasing implant, thus providing some indirect evidence that there may not be an increased VTE-risk (44). A recent epidemiological study found no clearly increased risk of VTE with subcutaneous implants with a relative risk of 1.4 (95%CI 0.6–3.4) compared with non-users of hormonal contraception (43).

Patches delivering HC transdermally are uninfluenced by the first pass metabolism in the gut wall and the liver. They contain 15–20 mcg of the estrogen ethinylestradiol per day and furthermore contain norelgestromin, the primary active metabolite of the third-generation progestogen norgestimate. Several studies compared the transdermal patch to oral HC containing norgestimate showing a similar to 2-fold increased risk (43,45–48). A recent population-based cohort study showed a relative risk of VTE in users of transdermal combined contraceptive patches of 7.9 (95%CI 3.5 to 17.7) compared with non-users of HC (43). These observations are in line with higher APC resistance in patients using the transdermal patch (49–52).

The vaginal ring delivers 15 mcg of ethinylestradiol per day, and also contains etonogestrel, a metabolite of the third-generation progestogen desogestrel. A recent cohort study showed that using a vaginal ring for contraception increased the risk for VTE 6.5-fold (95%CI 4.7 to 8.9) compared with non-users of HC of the same age, and had a relative risk of 1.9 (95%CI 1.3 to 2.7) compared with users of combined oral HC containing levonorgestrel (43). Conversely, another study did not find any statistically significant associations of the vaginal ring with VTE risk compared with low-dose estrogen containing HC (48). Few studies have looked at coagulation marker levels in women with a vaginal ring, and these have shown conflicting results as well (42,49,53).

Risk of VTE recurrence with the use of oral hormonal contraceptives

In a small follow-up study, women who used oral HC after a first VTE had a non-significant 2- to 3-fold increased risk of recurrence compared with women who had not used oral HC after their first VTE, regardless of whether the first VTE was provoked by oral HC use (54). After a first VTE associated with combined oral HC use, further use of combined oral HC is discouraged and it is strongly advised to switch to an alternative type of contraception (55,56). However, whether occurrence of VTE in a woman using contraceptives should be classified as either "unprovoked" or "provoked" remains somewhat controversial. Compared with women with an unprovoked VTE, the estimated relative risk of recurrence in women with a first VTE associated with oral HC use ranges from 0.3 to 1.2 (6,11,54,57,58). It should be noted however that in many studies that investigated the clinical course of VTE, classification between unprovoked and provoked VTE varies, and use of oral HC was not always systematically registered.

Hormone replacement therapy and venous thromboembolism

Hormone replacement therapy (HRT) includes solely estrogen or estrogen combined with a progestogen, and is available in various forms. The oral estrogen is either a conjugated equine estrogen (extracted from horse urine) or an esterified, synthetic estrogen (derived from soybean or wild Mexican yam). The estrogen dose usually comprises 1–2 milligrams of estradiol. It can be administered orally, vaginally, intra-nasally or as an implant, injection, skin patch, cream or gel. The progestogens used for HRT include synthetic derivates of progesterone, synthetic derivations of testosterone, and natural progesterones derived from plants. In combined HRT, progestogen can be taken either every day (continuous combined HRT), cyclically with estrogens taken daily and progestogens taken for part of the month (sequentially combined HRT) or less frequently. Nowadays HRT is mainly restricted to women in the menopause with severe climacteric symptoms such as flushes and perspiration.

Hormone therapy to substitute estrogen deficiency has for many years been believed to prevent atherosclerosis and death from cardiovascular disease (CVD); this belief was based on several observational studies performed since the early 1980's (59), and was the main reason to prescribe hormones to postmenopausal women at that time. In the late 1990's it became clear through large randomized controlled trials that hormone therapy in fact did not prevent arterial cardiovascular disease and even was associated with an excess risk of CVD in the first year of use (60–62). Furthermore, HRT is also associated with increased risks of breast and endometrial cancer (63,64).

In most of the earlier studies a higher VTE risk had already been observed with the use of HRT (59). Both observational studies and randomized controlled trials have consistently shown a 2- to 3-fold increased risk of VTE in women using oral HRT compared with non-users (60,65–68), which is comparable to the risk increase in users of second generation combined oral HC. The use of transdermal HRT does not seem to increase VTE risk; a pooled risk estimate for first VTE of 1.2 (95%CI 0.9 – 1.7) was calculated from four observational studies in a meta-analysis (67). No randomized clinical trials have been performed regarding this route of HRT administration. Tibolone, a synthetic steroid with estrogenic, progestogenic and androgenic properties, has not been associated with an increased VTE risk in several studies (66,69–71).

In women aged 15–44 the baseline incidence of VTE is lower than in women aged 45–49; the risk increases from 3.1 per 10,000 p.y. to 5.8 per 1,000 p.y (34). As women using HRT generally are older than women using hormonal contraceptives, it is important to realize that the absolute risk increase in women using HRT may be higher than for oral HC.

Risk of recurrence of VTE with the use of HRT

Use of HRT increases the risk of recurrent VTE. A randomized controlled trial demonstrated an approximately 4-fold increased risk of recurrence in women with a history of VTE who were using HRT compared with women receiving a placebo, with an absolute cumulative incidence of recurrent VTE of 10.7% and 2.3%, respectively, and the trial was terminated prematurely because of these findings (72).

Pregnancy and venous thromboembolism

One to two in 1,000 pregnancies is complicated by VTE, which is an important cause of short- and long-term maternal morbidity (73,74). Pulmonary embolism is the leading cause of maternal death in western countries (75). Compared with non-pregnant women of the same age, pregnant women have a 4- to 5-fold increased risk of developing VTE. The absolute risk of developing VTE is similar for the antepartum and postpartum period, but as the antepartum period is much longer than the postpartum period, the daily absolute VTE risk is highest postpartum (76,77). The VTE risk remains high up to 6 weeks postpartum, after which event rates sharply decrease (78).

Several factors contribute to the risk of pregnancy-related VTE (79). A history of VTE, higher age, lower socioeconomic status and antenatal hemorrhage all increase the risk of both antepartum and postpartum VTE (80). Postpartum VTE occurs more often in women with preeclampsia, postpartum hemorrhage and after cesarean section, especially after emergency cesarean section (80,81). Furthermore, known risk factors for VTE in the general population such as immobilization and obesity may increase the risk of pregnancy-related VTE as well.

Pathophysiology of increased VTE risk during pregnancy

There are several hemostatic alterations during pregnancy and the postpartum period that lead to a hypercoagulable state. These changes probably reflect evolutionary changes that protect the woman for excessive bleeding during delivery. All elements of the Virchow's triad, i.e. hypercoagulability, venous stasis and vascular damage, are more or less present during pregnancy and the postpartum period. First, hypercoagulability is demonstrated by the fact that pregnant women have higher levels of fibrinogen, factor VIII, Von Willebrand factor, D-dimer, prothrombin fragment F1+2 and thrombin-antithrombin complexes. Furthermore, natural anticoagulant activity is decreased, as reflected by reduced levels of protein S and an inherent acquired protein C resistance. Fibrinolytic activity is decreased because of an increase in plasminogen activator inhibitor (PAI) 1 and 2 activity and a decrease in tissue plasminogen activator (tPA) (Figure 2.1) (82). Second, venous stasis is promoted by hormone-mediated venous distension and

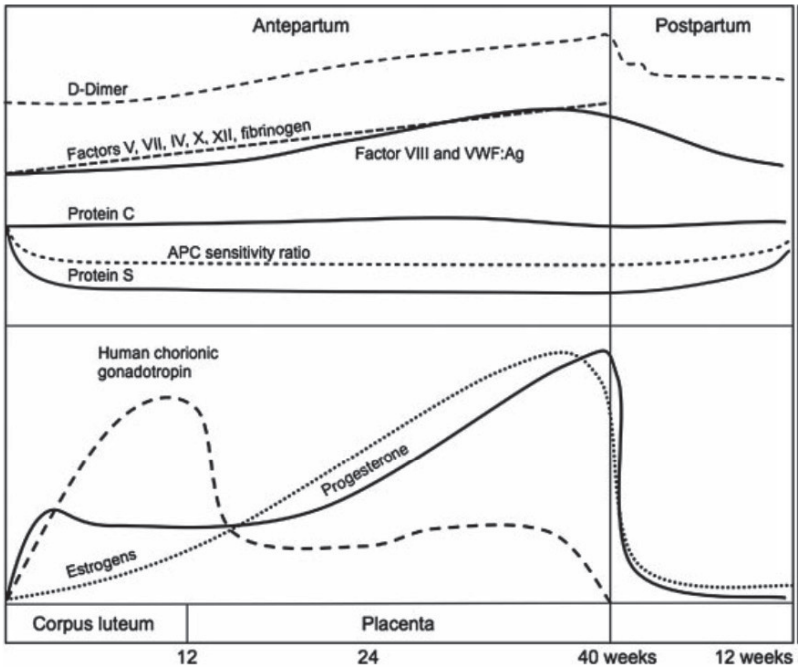

Figure 2.1. Qualitative levels and hemostatic direction of hormone changes during normal pregnancy.
APC: activated protein C; VWF:Ag: von Willebrand factor antigen.
Adapted with permission from Barco et al (82).

increased vascular volume, while venous return is reduced as a consequence of the pregnant uterus compressing the inferior vena cava and iliac veins. Third, vascular damage is induced by delivery, especially in the case of forceps or vacuum extraction and caesarean section.

Thrombophilia and venous thromboembolism

A familial tendency for developing VTE was first described in 1956 (83). Investigation of candidate coagulation proteins or genes in families with a high incidence of VTE led to the first description of a genetic abnormality in 1965, when Egeberg identified a deficiency of the physiological anticoagulant antithrombin in a family from Norway (84). In the past half century various other common genetic variants that increase the risk of VTE have been identified, including deficiencies of protein S and C, and the gain of function mutations factor V Leiden and prothrombin 20210A (85–96). These prothrombotic variations in the coagulation cascade are commonly referred to as thrombophilia.

Nowadays, some form of thrombophilia can be identified in about half of all patients with unprovoked VTE. The role of thrombophilia was subsequently studied in different clinical settings, including arterial thrombosis and adverse pregnancy outcomes such as (recurrent) pregnancy loss and preeclampsia (Table 2.2).

Thrombophilia is consistently associated with a relative risk of 2 to 10 of developing a first VTE (97). This relative risk combined with a high prevalence of thrombophilia in patients with VTE has inspired widespread testing for thrombophilia (98), yet the debate continues if and how presence or absence of thrombophilia should alter patient management. In contrast with the increased risk of developing a first VTE, presence of thrombophilia does not identify patients at a clearly increased risk of recurrent VTE (99). This phenomenon, for which several explanations are proposed, is referred to as the "thrombophilia paradox" (100). Hence, patients with a first VTE and thrombophilia should not be treated differently from patients with a first VTE without thrombophilia, and testing for thrombophilia in order to modify the risk of a recurrent VTE therefore is not justified for therapeutic purposes. However, testing in these patients can help to identify asymptomatic family members with thrombophilia who may benefit from preventive measures. In a survey among Dutch physicians that ordered thrombophilia tests, 42% of tests were ordered in patients with VTE (98). In the same survey, 16% of tested individuals were asymptomatic and had a positive family history of VTE. As will be discussed in the following paragraphs, in the presence of certain types of thrombophilia, avoidance of certain HC can be considered as well as thrombosis prophylaxis during pregnancy and/or postpartum. More vigorous thrombosis prophylaxis for carriers of thrombophilia in other settings such as surgery or plaster cast immobilization has not been studied. Although widespread testing helps to identify patients at risk, the costs of testing every patient with VTE for thrombophilia would be substantial.

Clinical implications for women with a high baseline risk of VTE, regarding hormonal contraceptives and hormone replacement therapy

For women with a positive family history of VTE, hereditary thrombophilia, or both, in some cases avoidance of HC or HRT should be considered. Although a positive family history of VTE in itself is a very poor predictor of the presence of thrombophilia (101), having a first degree relative with VTE increases the risk of developing VTE 2-fold, irrespective of the presence of thrombophilia. The risk rises up to 3-fold if familial VTE occurred before the age of 50 and up to 4-fold if multiple first degree family members have had VTE (102). This probably reflects a familial thrombotic tendency in which yet unknown types of thrombophilia have co-segregated.

The annual incidence of a first VTE, provoked and unprovoked combined, in men and women who have a first degree relative with VTE and a deficiency of antithrombin, protein C or protein S is around 1.5%, and this risk is approximately 0.5% in carriers of the factor V Leiden or prothrombin 20210A mutation (103–105). Also, the risk clearly increases with age (106). During oral HC use, VTE risk in asymptomatic women with antithrombin, protein C or protein S deficiency is 4.3% per year of its use, whereas in women who carry the factor V Leiden and the prothrombin 20210A mutation the risk during oral HC is 0.5% and 0.2% per year respectively (106–108).

For women with a positive family history of VTE and hereditary thrombophilia, one can estimate the effect of avoiding oral HC in order to prevent VTE (Table 2.3). To avoid one VTE event in patients with antithrombin, protein C or protein S deficiency and a positive family history for VTE, 28 women would need to refrain from oral HC. To identify these women, 56 female relatives would need to be tested. As for factor V Leiden or the prothrombin 20210A mutation, 333 women would need to avoid oral HC and 666

Table 2.3. Estimated number of asymptomatic thrombophilic women or women with a positive family history for VTE who should avoid using oral hormonal contraceptives to prevent one VTE, and estimated number needed to test.

Thrombophilia	VTE risk on oral HC (% per year)	Risk difference per 100 women	Number not taking oral HC to prevent one VTE	Number of female relatives to be tested
Antithrombin, protein C, or protein S deficiency				
Deficient relatives	4.3*	3.6	28	56
Non-deficient relatives	0.7*			
Factor V Leiden or prothrombin 20210A mutation				
Relatives with the mutation	0.5*	0.3	333	666
Relatives without the mutation	0.2*			
Family history of VTE				
General population, no family history	0.04#	0.03	3333	None
General population, positive family history	0.08#	0.06	1667	None

* Based on family studies as outlined in Table 2.1.

Based on a population baseline risk of VTE in young women 1.00 / 1,000 person years (1), a relative risk of VTE by use oral contraceptives of 4 (17), and a relative risk of 2 of VTE by having a positive family history (141).

female relatives would need to be tested. Finally, 3333 women with a positive family history of VTE would need to refrain from oral HC in order to prevent one VTE.

In conclusion, in asymptomatic women with a positive family history of VTE, it may be useful to test for thrombophilia if this woman intends to use HC or HRT, as testing positive for antithrombin, protein C or protein S deficiency may warrant the avoidance of these preparations in order to prevent VTE episodes. On the other hand, the risk of HC related VTE in women from families with known deficiencies of a natural anticoagulant is higher than in pill users from the general population, even if they do not carry the thrombophilic defect. Avoidance of HC could therefore be considered in all women from those families. Furthermore, the low prevalence of deficiencies of the natural anticoagulants in patients with VTE of 8.2% (109) implies that many patients with VTE would need to be tested to identify those few deficient female relatives.

Clinical implications for women with a high baseline risk of VTE, regarding pregnancy

Presence of certain risk factors during pregnancy and the postpartum period may justify preventive strategies, if the risk and burden of these strategies outweigh the risk of VTE. Preventive measures should be considered in patients with 1) a personal history of VTE, 2) a positive family history of VTE and/or presence of thrombophilia, and 3) cesarean section.

If thrombosis prophylaxis is warranted antepartum, low-molecular-weight heparin (LMWH) is the preferred anticoagulant in pregnant women, as it does not cross the placenta and thus is safe for the fetus (76,110). Vitamin K antagonists (VKA) cross the placenta and can cause potential fetal wastage, fetal bleeding and teratogenicity. Coumadin embryopathy (e.g. limb hypoplasia, stippled epiphyses or midfacial hypoplasia) mostly occurs after VKA exposure in utero during the first trimester of pregnancy (111–113). The use of VKA in the second or third trimester has been associated with an increased risk of minor neurological and cognitive abnormalities in school-age children (114). Hence, there is no place for VKA in the prevention or treatment of pregnancy-related VTE. Only for pregnant women with mechanical heart valves in whom concerns exist about the efficacy and safety of UFH or LMWH, treatment with VKA may be instituted from the 13th week of gestation with replacement by UFH or LMWH close to delivery. Women on VKA for the treatment of VTE who become pregnant are advised to switch to LMWH for the entire pregnancy. The need for daily injections is a disadvantage of LMWH, as long-term use in pregnant women leads to skin reactions in up to 40%, mostly type IV delayed hypersensitivity reactions at the injection site (115–118). When LMWH administration is problematic or contraindicated because of allergy or

renal insufficiency, unfractionated heparin (UFH) is the anticoagulant of choice, as this is also does not cross the placenta and thus is safe for the fetus. When HIT develops in a pregnant patient, a very uncommon complication (110), further use of UFH or LMWH is contraindicated. In these rare cases, alternative parenteral anticoagulant drugs are danaparoid and fondaparinux (76).

Both LMWH and VKA are safe in breast-feeding women. Small amounts of LMWH, danaparoid and fondaparinux might be excreted into breast milk, but since these anticoagulants are hardly absorbed into the gastrointestinal tract this does not pose a risk to the breastfed infant (76,119,120). UFH is not excreted in breast milk because of its high molecular weight. VKA, particularly acenocoumarol and warfarin, are non-lipophilic, polar and highly protein bound and are not detected in breast milk (121,122). There are some concerns that more lipophilic and less polar VKA such as phenindione, anisindione and phenprocoumon might be excreted into breast milk. Use of these oral anticoagulants during breast feeding should therefore be limited to women who are known to have instable International Normalized Ratios (INR) with shorter-acting VKA (76).

A personal history of VTE

Women with a personal history of VTE have a 2 to 10% absolute risk of developing recurrent VTE during a subsequent pregnancy in the absence of thrombosis prophylaxis, yielding an OR of 24.8 (95% CI 17.1 – 36.0) compared with pregnant women without previous VTE (74,123–125). Circumstances under which the first VTE occurred appear to influence the risk of recurrence. In two retrospective studies, women with a first VTE provoked by oral HC, pregnancy or the postpartum period had a non-significant higher risk of recurrent VTE during subsequent pregnancy than women with a first VTE that was unprovoked or provoked by a transient non-hormonal risk factor (124,125). Likewise, in a large retrospective cohort of women with VTE women with pregnancy-associated VTE had a significantly higher risk of recurrent VTE during subsequent pregnancy, compared with women with unprovoked VTE (126).

In the current guideline of the American College of Chest Physicians (ACCP), pregnant women are categorized into risk groups based on the circumstances under which prior VTE occurred. All women with a history of VTE should receive postpartum thrombosis prophylaxis for 6 weeks, as the absolute risk of pregnancy-related VTE in general is higher postpartum. The threshold to use antepartum prophylaxis is higher than the threshold for using postpartum prophylaxis given the burden of self-injecting with LMWH over several months as opposed to 6 weeks. Therefore, for women with a low risk of recurrence (a single episode of VTE associated with a major transient risk factor not related to pregnancy or use of estrogen), clinical vigilance antepartum rather than pharmacological thrombosis prophylaxis is justified. Women with a moderate (a single

Table 2.4. Summary of the 9th American College of Chest Physicians recommendations to prevent pregnancy-related VTE.

Antepartum∫ and postpartum prophylaxis	Postpartum prophylaxis during 6 weeks§	No pharmacological prophylaxis§
Women with a single unprovoked episode of VTE, or provoked by use of oral contraceptives, pregnancy or postpartum	Women with a history of a single episode of VTE related to a major nonhormonal transient risk factor	General population
Women with a history of multiple unprovoked episodes of VTE	Women with hereditary thrombophilia and a positive family history# of VTE	Women with a positive family history# of VTE
Women with a history of VTE and a persistent risk factor		
Women who are homozygous for factor V Leiden or prothrombin mutation who have a positive family history# of VTE	Women who are homozygous for factor V Leiden or prothrombin mutation who do *not* have a positive family history# of VTE	Women who are heterozygous for factor V Leiden of prothrombin mutation who do *not* have a positive family history# of VTE
	Women undergoing cesarean section with multiple risk factors that persist following delivery§	Women undergoing cesarean section without additional thrombosis risk factors§

All recommendations are weak, based on a low level of evidence leaving room to individualize prophylactic strategies based on patient's preferences (76).

∫ Antepartum prophylaxis should start as soon as possible after the conception.

§ Unless women can be categorized into one of the more aggressive prophylactic strategies in this Table.

A positive family history is defined as having a first degree relative with VTE.

episode of VTE that was hormone- or pregnancy-related or unprovoked) or high risk of recurrence (multiple prior unprovoked VTE or a persistent risk factor, such as paralysis) should receive thrombosis prophylaxis during the entire pregnancy (Table 2.4). Antepartum prophylaxis should then be instituted as soon as a pregnancy test is positive, as the risk of recurrence begins early in the first trimester (76).

Many centers use a prophylactic dose of LMWH in women with an indication for thrombosis prophylaxis during pregnancy and/or postpartum, but numerous treatment failures have been reported with an estimated risk of recurrent VTE of 5–6% (124,127,128). In the absence of randomized controlled trials, the ACCP guideline suggests prescribing either a prophylactic or intermediate dose of LMWH to these women. We are currently performing a randomized controlled comparing the two suggested doses in pregnant women with a history of VTE (www.ClinicalTrials.gov; NCT 01828697).

Presence of hereditary thrombophilia and pregnancy

In pregnant women with hereditary thrombophilia, a first degree family member with a history of VTE, or both, the decision to use thrombosis prophylaxis during or after preg-

nancy is based on the absolute risk estimate of developing a pregnancy-related VTE. Because of a paucity of high-quality evidence measuring the effectiveness and safety of thrombosis prophylaxis in preventing VTE in pregnant women, the authoritative ACCP guideline uses indirect evidence extrapolated from studies assessing the efficacy of prolonged thrombosis prophylaxis after orthopedic surgery, assuming a 65% relative risk reduction.

The absolute risk of developing pregnancy-related VTE in homozygous carriers of FVL without a positive family history is estimated to be 4.8%, and in the presence of a positive family history of VTE the absolute risk rises to 14.0% (129–132) (Table 2.5). In homozygous carriers of the prothrombin mutation, the absolute risk of pregnancy-related VTE is around 3.7% in patients without a positive family history (133). Hence, thrombosis prophylaxis both antepartum and postpartum is suggested in homozygous carriers of the FVL and prothrombin mutation. In the absence of a positive family history, it is suggested to use thrombosis prophylaxis solely postpartum with clinical vigilance antepartum (Table 2.4) (76).

Table 2.5. Risk of pregnancy-related VTE in thrombophilic women stratified by family history for VTE.

Thrombophilic defect	Prevalence in population, % (96,142–145)	Estimated RR OR (95%CI)	Absolute Risk of VTE*, % of pregnancies (95%CI)	
			Family studies	Non-family studies
Factor V Leiden, heterozygous	2.0–0.0	8.3 (5.4–42.7) (133)	3.1 (2.1–1.6) (106,107)	1.2 (0.8–8.8)
Factor V Leiden, homozygous	0.2–2.5	34.4 (9.9–920) (133)	14.0 (6.3–35.8) (129,130)	4.8 (1.4–46.8)
Prothrombin heterozygous	2.0	6.8 (2.5–58.8) (133)	2.6 (0.9–9.6) (105,108)	1.0 (0.3–3.6)
Prothrombin homozygous	Very rare	26.4 (1.2–259) (133)	-	3.7 (0.2–28.3)
Antithrombin deficiency	< 0.1–1.6	4.7 (1.3–37.0) (133)	3.0 (0.08–85.8) (135)	0.7 (0.2–2.4)
Protein C deficiency	0.2–2.3	4.8 (2.2–20.6) (133)	1.7 (0.4–4.9) (135)	0.7 (0.3–3.5)
Protein S deficiency	< 0.1–1.1	3.2 (1.5–5.9) (133)	6.6 (2.2–24.7) (135)	0.5 (0.2–2.0)

* Observed in family studies, estimated from multiplying the baseline risk of 1.40 per 1,000 by the RR in non-family studies (146).

Risk increase is stronger for lupus anticoagulant than for anticardiolipin or beta2 glycoprotein antibodies. Data are very limited; hence, the estimated absolute risk should be interpreted with caution.

Heterozygosity for the factor V Leiden mutation and prothrombin 20210A mutations carries an absolute risk of around 1.0% of developing pregnancy-related VTE compared with non-carriers. The absolute risk increases to 3.0% in the presence of a positive family history of VTE (104–108,133,134). For women with antithrombin, protein C, or protein S deficiency the absolute risk of pregnancy-related VTE is approximately 0.7% and in the presence of a positive family history of VTE the risk raises to 4.1% (133,135). Based on these risk estimates, clinical vigilance antepartum and postpartum thrombosis prophylaxis is suggested (Table 2.4). In the absence of a positive family history of VTE, antepartum and postpartum clinical vigilance is suggested rather than thrombosis prophylaxis (76). There is however considerable disagreement between guidelines about the indication for antepartum thrombosis prophylaxis in pregnant women with a deficiency of antithrombin, protein C or protein S. As these deficiencies are often regarded as high-risk thrombophilias, some suggest antepartum prophylaxis in these women too (136,137). The perception of high VTE risk antepartum however, is mainly based on older studies with methodological limitations (138). More recent studies did not confirm the high risk of VTE recurrence (133,135). Moreover, the majority of events occur in the postpartum period (139,140). The burden of self-injecting with LMWH

Table 2.6. Risk factors for VTE resulting in a baseline risk of postpartum VTE of > 3% (76).

Major risk factors (OR > 6)*	Minor risk factors (OR > 6 when combined**)
Immobility (strict bed rest for > 1 week in the antepartum period)	BMI > 30 kg/m 2
Postpartum hemorrhage > 1,000 ml with surgery	Postpartum hemorrhage > 1,000 ml
Previous VTE	Multiple pregnancy
Preeclampsia with fetal growth restriction	Preeclampsia
Thrombophilia	Thrombophilia
Antithrombin deficiency	Protein C deficiency
Factor V Leiden (homozygous or heterozygous)	Protein S deficiency
Prothrombin G20210A (homozygous or heterozygous)	
Medical conditions	Fetal growth restriction (gestational age + sex-adjusted birth weight < 25th percentile)
Systemic lupus erythematosus	
Heart disease	
Sickle cell disease	
Blood transfusion	Smoking > 10 cigarettes/day
Postpartum infection	

* Presence of at least one risk factor suggests a risk of postpartum VTE > 3%.

** Presence of at least two risk factors or one risk factor in the setting of emergency cesarean section suggests a risk of postpartum VTE of > 3%.

for several months and the risk of skin reactions therefore weighs strongly into the recommendation for postpartum thrombosis prophylaxis only in patients with these thrombophilias.

Other risk factors for pregnancy-associated VTE

Women having undergone a cesarean section are at increased risk of developing VTE, especially when this was performed in an emergency setting (80,81). Based on several clinical risk factors, the absolute risk of developing VTE in these women can be estimated (Table 2.6). Thrombosis prophylaxis is suggested for patients having undergone caesarean section with an absolute VTE risk of 3% or more, which is in line with prophylaxis treatment in medical patients (76). For women having undergone cesarean section without additional thrombosis risk factors, thrombosis prophylaxis is not recommended by the ACCP. In case of an indication for thrombosis prophylaxis, treatment is preferably continued until discharge from the hospital, with extended prophylaxis up to 6 weeks.

Summary

In individuals between 20 and 44 years of age, the incidence of a first VTE is higher in women than in men, which is likely explained by the use of hormonal preparations, pregnancy and the postpartum period. When adjusting for these factors, men seem to have a higher risk than women to develop a first VTE. This is in line with the observed higher risk of recurrence in men versus women but the exact mechanism explaining this phenomenon has not yet been elucidated.

HC and HRT are associated with an increased risk of VTE and the relative risk increase varies with different types of contraceptive method (i.e. the estrogen dose, type of progestogen and route of administration). Third and fourth generation combined oral HC yield a higher risk than second generation pills. Women planning to use contraception should be counseled regarding these risks and avoidance of hormonal contraception may be considered in women at the highest risk of VTE. After a first VTE associated with HC use or HRT, further use of these preparations is discouraged. In case of the need for contraception, it is advised to switch to a contraceptive method without increased VTE risk such as the levonorgestrel-IUD. Testing positive for certain types of inherited thrombophilia, a positive family history of VTE, or both may warrant the avoidance of specific HC in order to prevent VTE episodes.

During pregnancy and the puerperium, women have an increased risk of developing VTE. Postpartum thrombosis prophylaxis with or without antepartum prophylaxis should be considered for women with a history of VTE and women without a history of

VTE who have multiple risk factors such as a positive family history of VTE, thrombophilia or cesarean section. Although subject of ongoing debate, presence of most inherited thrombophilias should not lead to altered thrombosis prophylaxis.

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Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomized trial of two doses

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Thromb Res. 2016 Aug;144:62-8.

3

Abstract

Background: Women with a history of venous thromboembolism (VTE) have a 2% to 10% absolute risk of VTE recurrence during subsequent pregnancies. Therefore, current guidelines recommend that all pregnant women with a history of VTE receive pharmacologic thromboprophylaxis. The optimal dose of low-molecular-weight heparin (LMWH) for thromboprophylaxis is unknown. In the Highlow study (NCT 01828697; www.highlowstudy.org), we compare a fixed low dose of LMWH with an intermediate dose of LMWH for the prevention of pregnancy-associated recurrent VTE. We present the rationale and design features of this study.

Methods: The Highlow study is an investigator-initiated, multicenter, international, open-label, randomized trial. Pregnant women with a history of VTE and an indication for ante- and postpartum pharmacologic thromboprophylaxis are included before 14 weeks of gestation. The primary efficacy outcome is symptomatic recurrent VTE during pregnancy and 6 weeks postpartum. The primary safety outcomes are clinically relevant bleeding, blood transfusions before 6 weeks postpartum and mortality. Patients are closely monitored to detect cutaneous reactions to LMWH and are followed for 3 months after delivery. A central independent adjudication committee adjudicates all suspected outcome events.

Conclusion: The Highlow study is the first large randomized controlled trial in pregnancy that will provide high-quality evidence on the optimal dose of LWMH thromboprophylaxis for the prevention of recurrent VTE in pregnant women with a history of VTE.

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of short and long term morbidity during pregnancy and postpartum periods. Moreover, PE is one of the leading causes of maternal mortality in developed countries. In the United Kingdom for instance, between 2006 and 2008, 0.79 deaths per 100.000 maternities (95%CI 0.49–1.25) were attributed to VTE (1–3). VTE occurs in 1 to 2 per 1000 pregnancies, and the risk is 5-fold higher in pregnant women compared to non-pregnant women of the same age (2). The ante- and postpartum incidences of VTE are similar, but given the much longer duration of the antepartum period than the postpartum period, the daily absolute risk of VTE is highest postpartum (4,5). The majority of postpartum VTE occur in the first 6 weeks after delivery, with event rates decreasing sharply thereafter (6,7).

Women with a personal history of VTE have a 2% to 10% absolute risk of developing recurrent VTE during a subsequent pregnancy in the absence of pharmacologic thromboprophylaxis, with an odds ratio of 24.8 (95% CI 17.1 – 36.0) compared to pregnant women without previous VTE (2,8–10). Circumstances under which the first VTE occurred influence the risk of recurrence. In two retrospective studies, women whose first VTE was provoked by the use of oral hormonal contraceptives or was related to pregnancy had a higher risk of recurrent VTE during a subsequent pregnancy compared with women whose first VTE was unprovoked or provoked by a non-hormonal transient risk factor, although these differences did not reach statistical significance (9,10). Similarly, in a large retrospective cohort of women with prior VTE, those who had a history of pregnancy-associated VTE had a higher risk of recurrence during subsequent pregnancies compared to those with prior unprovoked VTE (4.5% versus 2.7% respectively; relative risk 1.7; 95% CI 1.0 – 2.8) (11).

The American College of Chest Physicians (ACCP) guideline recommends that all pregnant women with a history of VTE receive postpartum pharmacologic thromboprophylaxis (12). Low-molecular-weight heparin (LMWH) is the preferred anticoagulant for VTE prophylaxis in pregnant women, as it does not cross the placenta and is therefore safe for the fetus (13). The risk threshold for instituting antepartum thromboprophylaxis is higher than for postpartum thromboprophylaxis. The rational for this is the lower average daily risk of antepartum VTE and the need to self-inject LMWH for several months compared to 6 weeks postpartum. Therefore, in women with a low risk of recurrence (e.g. women with a single prior VTE associated with a major transient risk factor such as surgery, use of a plaster cast or trauma), close antepartum clinical surveillance rather than pharmacologic thromboprophylaxis is recommended. In contrast, women with a moderate or high risk of VTE recurrence (e.g. women with prior hormone/pregnancy-associated VTE or recurrent unprovoked VTE or VTE associ-

ated with a persistent risk factor such as paralysis) should receive thromboprophylaxis during the entire pregnancy (Table 3.1). Antepartum thromboprophylaxis should be commenced as early as possible, as the risk of VTE recurrence is increased from the beginning of pregnancy (14).

Table 3.1. Summary of the 9th American College of Chest Physicians (ACCP) recommendations to prevent pregnancy-related venous thromboembolism (VTE) in women with prior VTE (12).

Antepartum and postpartum prophylaxis	Postpartum prophylaxis during 6 weeks	No pharmacological prophylaxis
Women with a single unprovoked episode of VTE	Women with a history of a single episode of VTE related to a major nonhormonal transient risk factor[#]	General pregnant population
Women with a single episode of VTE provoked by use of hormonal contraceptives, pregnancy or the postpartum period		
Women with a single episode of VTE provoked by a minor nonhormonal transient risk factor[£]		
Women with a history of multiple unprovoked episodes of VTE		
Women with a history of VTE and a persistent risk factor		

VTE: venous thromboembolism; £ Long distance travel or minor trauma; # Surgery, major trauma or plaster cast immobilization in the 3 months prior to VTE.

The optimal LMWH dose for pharmacologic thromboprophylaxis of pregnancy-associated recurrent VTE is unknown, as no randomized controlled trials (RCTs) have been performed. Therefore the ACCP guideline suggests the use of either a prophylactic or intermediate (half therapeutic) dose of LMWH in this setting, without a preference for one dose over the other (12). Many centers prescribe a prophylactic dose. However, numerous treatment failures have been reported in retrospective studies and in the TIPPS trial, with an estimated recurrence risk of 5 to 8% using this strategy (9,10,15–18). Of note, compliance was not assessed in these studies and the results are inconsistent with those from another study (19). It has been postulated that an intermediate dose of LMWH could have superior efficacy compared to a prophylactic dose of LMWH, but potentially at the cost of a higher bleeding risk. Reassuringly, in a retrospective study in pregnant women receiving therapeutic doses of LMWH, there was no increased risk of clinically relevant or severe postpartum bleeding compared with women who had delivered in the same hospital without LMWH use (20). In another study, women receiving therapeutic LMWH during pregnancy were found to have an increased risk of

blood loss > 500mL and < 1000mL after vaginal delivery (21). The use of therapeutic-intensity LMWH for pharmacologic thromboprophylaxis during pregnancy is not widely accepted in view of the anticipated elevated bleeding risk in the peripartum period and because this strategy may preclude neuraxial anesthesia.

There is an urgent need for evidence regarding the optimal strategy in pregnant women who require pharmacologic thromboprophylaxis. To investigate the optimal LMWH dose for prevention of recurrent VTE in pregnant patients with a history of VTE, we are currently conducting the Highlow study (NCT 01828697). The results of this RCT are very likely to impact current clinical practice and modify consensus guidelines. We summarize herein the design of this study, and discuss the rationale for some of the unique study design features.

Study objective and hypothesis

We aim to compare a fixed low dose of LMWH with an intermediate dose of LMWH in the prevention of recurrent VTE in pregnant women with a history of VTE and an indication for ante- and postpartum thromboprophylaxis. We hypothesize that an intermediate dose is superior to a fixed low dose of LMWH in preventing recurrent VTE, with a comparable safety profile in terms of clinically relevant bleeding complications.

Study design

Overview of study organization

The Highlow study is an investigator-initiated, multicenter, international, randomized, open-label, superiority study for efficacy. Patients receive either a fixed low dose or an intermediate dose of LMWH during pregnancy and 6 weeks after delivery.

The protocol was reviewed and approved by the regulatory authority of the Netherlands and the ethics committee of the Academic Medical Center in Amsterdam. In each participating country, the protocol is or has been subsequently reviewed by the local regulatory authority and for each participating center by the local institutional review board or ethics committee. Informed consent is obtained from eligible patients prior to randomization. A central independent adjudication committee (CIAC) whose members are unaware of the treatment allocation will adjudicate all suspected episodes of recurrent VTE, major bleeding events, clinically relevant non-major bleeding events, cases of suspected type 1 allergy to LMWH injections, cases of suspected heparin-induced thrombocytopenia (HIT), and deaths. An independent data monitoring committee (DMC) monitors patient safety and outcomes at regular intervals during the study, and makes recommendations to the coordinating investigators. Monitoring is performed via an interdepartmental monitoring system.

Patient population and eligibility

Pregnant women of 18 years or older with a history of VTE and an indication for ante- and postpartum thromboprophylaxis (Table 3.1) are eligible for the study. The inclusion- and exclusion criteria are listed in Table 3.2. Patients enter the study as soon as a home test confirms pregnancy, up to 14 weeks after the last menstrual period.

Women previously enrolled in the Highlow study are allowed to participate during subsequent pregnancies, if the 6 weeks of postpartum thromboprophylaxis have been completed (after a full-term pregnancy, miscarriage, active termination or stillbirth).

Table 3.2. Inclusion- and exclusion criteria of the Highlow study.

Inclusion criteria

• Age ≥ 18 years
• Pregnancy confirmed by urinary pregnancy test, blood test or ultrasound examination
• Gestational age < 14 weeks since the first day of the last menstrual period
• Previous objectively confirmed VTE*, either:
  - Unprovoked, or
  - In the presence of oral contraceptive or estrogen/progestogen use, or
  - Related to pregnancy or the postpartum period, or
  - In the presence of a minor provoking risk factor£

Exclusion criteria
• Previous VTE related to a major provoking risk factor# as the **sole** risk factor • Indication for treatment with a therapeutic dose of anticoagulant therapy (e.g. acute VTE, atrial fibrillation, a mechanical heart valve, recurrent VTE for which an indefinite duration of anticoagulant therapy is used prior to pregnancy) • Inability to provide informed consent • Any contraindication listed in the local labeling of LMWH

VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; £ Long distance travel or minor trauma; # Surgery, major trauma or plaster cast immobilization in the 3 months prior to VTE
*Patient with a history of extensive superficial thrombophlebitis that was treated as deep vein thrombosis (i.e. if it was close to the deep venous system), are also eligible

Stratification and randomization

Once the patient has signed the informed consent form, the investigator provides information to a secure web-based randomization program (ALEA version 2.2), which randomly assigns the patient to either the fixed low dose or intermediate dose of LMWH. Randomly permuted blocks with maximum block size of 6 are applied, stratifying for center.

LMWH regimen

LMWH is injected subcutaneously once daily. Nadroparin is the preferred type of LMWH, but different types of LMWH are allowed in the study to reflect heterogeneity in

current clinical practice. Table 3.3A depicts the dosing schemes for all available types of LMWH. The fixed low dose regimen is based on weight at randomization and will not be changed throughout pregnancy or the 6 weeks postpartum. In the intermediate dose regimen, the patient's weight will be monitored at every follow-up visit and if necessary the dose will be changed accordingly.

Table 3.3.

A. Dosing schemes for all LMWH types in the Highlow study.

Fixed low dose						Intermediate dose					
Weight		nadro-	enoxa-	daltepa-	tinzapa-	Weight		nadro-	enoxa-	daltepa-	tinzapa-
In kg	In lbs	parin	parin	rin	rin	In kg	In lbs	parin	parin	rin	rin
< 100	< 220	2,850 IU	4,000 IU	5,000 IU	3,500 IU	< 50	< 110	3,800 IU	6,000 IU	7,500 IU	4,500 IU
						50 to < 70	110 to < 154	5,700 IU	8,000 IU	10,000 IU	7,000 IU
≥ 100	≥ 220	3,800 IU	6,000 IU	7,500 IU	4,500 IU	70 to < 100	154 to < 220	7,600 IU	10,000 IU	12,500 IU	10,000 IU
						≥ 100	≥ 220	9,500 IU	12,000 IU	15,000 IU	12,000 IU

All doses are administered once daily
LMWH: low-molecular-weight heparin; kg: kilograms; lbs: pounds; IU: International Units; mg: milligrams

B. Ratios of the intermediate dosages and the fixed low dosages

	nadroparin	enoxaparin	dalteparin	tinzaparin
Low dose group				
< 100 kg / < 220 lbs	ref	ref	ref	ref
Intermediate dose group				
< 50 kg / < 110 lbs	x 1.3	x 1.5	x 1.5	x 1.3
50 to < 70 kg / 110 to < 154 lbs	x 2	x 2	x 2	x 2
70 to < 100 kg / 154 to < 220 lbs	x 2.7	x 2.5	x 2.5	x 2.9
≥ 100 kg / ≥ 220 lbs	x 3.3	x 3	x 3	x 4.3

Ref = reference category

C. Ratios of the low dosages for obese patients

	nadroparin	enoxaparin	dalteparin	tinzaparin
Low dose group				
< 100 kg / 220 lbs	ref	ref	ref	ref
≥ 100 kg / ≥ 220 lbs	x 1.3	x 1.5	x 1.5	x 1.3

Ref = reference category

Prior to delivery, women are instructed to stop LMWH when contractions start or when membranes rupture. If delivery is planned, the last dose of LMWH is given at least 24 hours prior to delivery. In the fixed low dose group, neuraxial anesthesia is allowed if the interval after the last LMWH dose is more than 12 hours. In the intermediate dose group, an interval of 24 hours between the last injection and neuraxial anesthesia is required. LMWH is restarted 12 to 24 hours after delivery at the discretion of the obstetrician.

The use of LMWH is open-label, and the medication is prescribed by the treating physician and supplied by pharmacies in the standard setting of patient care or in accordance with national regulatory requirements.

Efficacy outcome variables

The primary efficacy outcome is symptomatic confirmed recurrent VTE, defined as the composite of recurrent DVT and PE during pregnancy and 6 weeks postpartum (Table 3.4). The secondary efficacy outcomes are 1) symptomatic confirmed recurrent VTE, defined as the composite of recurrent DVT and PE up to 3 months postpartum and 2) symptomatic confirmed superficial thrombophlebitis up to 3 months postpartum.

Table 3.4. Diagnostic criteria of confirmed symptomatic recurrent venous thromboembolism or superficial thrombophlebitis.

- Suspected (recurrent) DVT or superficial thrombophlebitis with one of the following findings:
  If there were no previous DVT investigations:
  - Abnormal CUS
  - An intraluminal filling defect on venography

  If there was a previous DVT investigation:
  - Abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression,
  - An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.
- Suspected PE with one of the following findings:
  - A (new) intraluminal filling defect in subsegmental or more proximal branches on spiral CT scan
  - A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram
  - A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on VPLS
  - Inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography
- Fatal PE is:
  - PE based on objective diagnostic testing, autopsy, or
  - Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death)

DVT: deep vein thrombosis; CUS: compression ultrasonography; PE: pulmonary embolism; CT: computed tomography; VPLS: ventilation/perfusion lung scan

Safety outcomes

The primary safety outcomes are major bleeding, the composite of major bleeding and clinically relevant non-major bleeding, early postpartum hemorrhage (within 24 hours postpartum), late postpartum hemorrhage (within 6 weeks postpartum), blood transfusion within 24 hours postpartum, blood transfusion within 6 weeks postpartum, and mortality. The definitions of major bleeding and clinically relevant non-major bleeding are based on the criteria of the International Society of Thrombosis and Hemostasis (22) and are provided in Table 3.5. The CIAC will adjudicate major bleeding, clinically relevant non-major bleeding, and postpartum hemorrhage (defined as more than 500mL).

The secondary safety outcomes are minor bleeding, bruises, mild skin complications (e.g. itching, swelling, pain), severe skin complications (e.g. local erythema, edema, vesicles or bullae), type 1 allergic reactions to LMWH, the medical necessity to switch to another LMWH type, confirmed HIT and congenital anomalies or birth defects. The CIAC will adjudicate type 1 allergic reactions to LMWH and HIT.

Table 3.5. Definitions of major bleeding, clinically relevant non-major bleeding and postpartum hemorrhage in the Highlow study (34).

Major bleeding
Is defined as overt bleeding and • Associated with a fall in hemoglobin of 2g/dL or more, or • Leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or • Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retro-peritoneal, or • Contributing to death
Clinically relevant non-major bleeding
Is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, discomfort such as pain or impairment of activities of daily life • Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract, or • Macroscopic gastro-intestinal hemorrhage: at least one episode of melena/hematemesis, if clinically apparent, or • Rectal blood loss, if more than a few spots, or • Vaginal blood loss, if more than a few spots, or • Hemoptysis, if more than a few speckles in the sputum, or • Intramuscular hematoma, or • Subcutaneous hematoma if the size is larger than 25 cm^2, or larger than 100cm^2 if provoked, or • Multiple source bleeding
Postpartum hemorrhage
Blood loss of more than 500 mL within 24 hours of delivery*

*According to the criteria of the World Health Organization

Duration of study treatment and follow-up

All patients have specified scheduled contacts; 2 weeks after starting treatment (in the outpatient clinic or by telephone), at 20 weeks of pregnancy (in the outpatient clinic or by telephone), at 30 weeks of pregnancy (in the outpatient clinic or by telephone), 24 hours to 1 week after delivery (in the outpatient clinic or by telephone), 6 weeks after delivery (by telephone) and 3 months after delivery (by telephone). During these contacts efficacy and safety of LMWH will be evaluated. In parallel, patients are followed at the outpatient clinic by a midwife or gynecologist. In case of a suspected efficacy or safety outcome, appropriate physical examination, laboratory or diagnostic testing is performed. Figure 3.1 depicts the flowchart from randomization until end of follow-up.

In the event that a pregnancy results in a miscarriage or stillbirth, the patient will continue the use of LMWH until 6 weeks after termination, and will be followed up as usual.

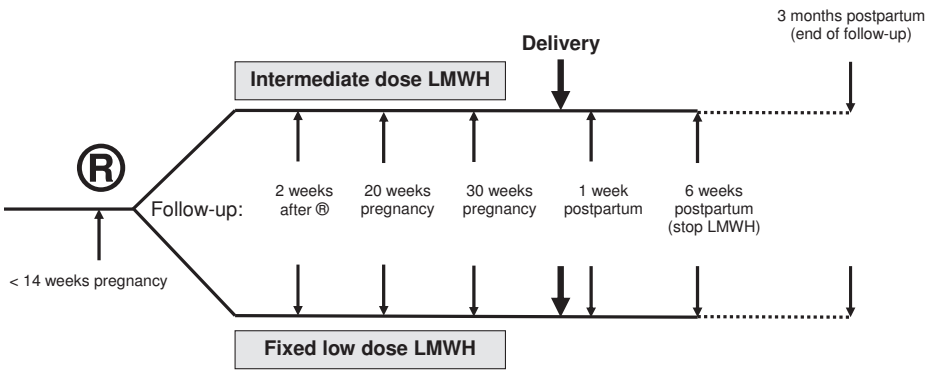

Figure 3.1. Flow chart Highlow study: from randomization to end of follow-up
® = randomization; LMWH: low molecular weight heparin

Laboratory tests

At baseline, creatinine level, platelet count and D-dimer are collected. Two weeks after randomization, the platelet count is determined in order to detect a possible HIT. Anti-Xa peak levels (optional) and platelet count are determined 2 weeks after randomization, at 20 weeks and at 30 weeks of pregnancy.

Baseline ultrasonography

If the patient has a history of DVT, it is recommended that an ultrasound examination of the affected leg be performed at baseline, if this has not yet been performed after initial treatment of the prior DVT. Knowing whether there is any residual thrombosis in the leg, will be helpful in interpreting a new ultrasound examination in case the patient

presents with a suspicion of a recurrent VTE during the study. However, a baseline ultrasound examination is not obligatory.

Sample size and statistical analysis

There is uncertainty about the actual incidence of recurrent VTE among pregnant women receiving pharmacologic thromboprophylaxis. Hence, an approach with a fixed sample size could lead to severe under-powering or undue lengthening of the study. The sample size calculation in this study is based on the required number of events. Assuming a 65% relative risk reduction with the intermediate dose, a total of 29 events would provide a power of 80% to demonstrate that an intermediate dose is superior to a low dose (two-sided $\alpha = 0.05$). Similar risk reductions have been achieved with current versus sub-standard anticoagulant treatment to prevent recurrent VTE in patients after elective hip arthroplasty (23). The efficacy analysis will be based on intention-to-treat (ITT) and the outcome is a symptomatic, objectively diagnosed recurrent VTE. The expected loss to follow-up is close to zero, hence no further sample size adjustment was made. Based on the available literature an incidence of recurrent VTE of 4 to 5% in the low dose group is expected, leading to a proposed sample size of 859 to 1074 women. However, this might be adjusted upward and downward based on the overall number of events observed during the primary analysis period in the study. The ITT population will consist of all patients who have been randomized. Patients will be analyzed in the treatment group to which they were assigned. The valid-for-safety-analysis population will consist of all patients who were randomized and received at least one dose of study treatment. The per-protocol (PP) population will consist of all randomized patients without any major deviation from the protocol. All efficacy analyses will be performed on the ITT population. Additionally, the primary efficacy outcome will be analyzed in the PP population.

Rationale for some aspects of the Highlow study

The Highlow study is the first large RCT in pregnancy that will provide high-quality evidence on the optimal prophylactic dose of LMWH in pregnancy in women with a history of VTE. At present, only two RCTs with major methodological weaknesses have evaluated the safety and efficacy of thromboprophylaxis (compared with placebo or no treatment) in pregnant women with a history of VTE, containing very small sample sizes of 40 and 16 patients respectively (24,25). Our study has several unique features that deserve explanation and that may help others design future studies on thromboprophylaxis in pregnant patients.

Rationale for open-label design

A double-blind design with labeling of the investigational medicinal product (IMP) would have been the ideal design for this study, but the associated costs make it impossible for investigator-initiated studies to implement such design. By law, IMPs should be available to subjects by the sponsor free of charge, but in several countries, including the Netherlands, an exception is made for registered medicines even if they are administered in a trial for another indication. Furthermore, in current practice LMWH is widely used in pregnant women in the dosages that are compared in the Highlow study, based on the ACCP guideline recommendations. Following these principles, the Highlow study uses a pragmatic open-label design, and we believe that our study will be representative of how LMWH is likely to be used in clinical practice. As the CIAC will adjudicate all primary outcome events blindly, we trust that the lack of blinded treatment will have little impact on the evaluation of efficacy and safety. Compliance will be assessed by history taking during follow-up visits and by collection of batch numbers and other details of used medication boxes.

Randomization < 14 weeks of gestation

Patients should be randomized before the 14th week of gestation in this study. We have carefully considered including patients at more advanced gestations, but as this would lead to the potential for selection of low risk patients with associated implications for generalizability, a decision was made to not include these patients. Furthermore, as the risk of VTE is already increased early in pregnancy, we believe that setting this cut-off enhances institution of prophylaxis as early as possible, following the recommendations of the current international guidelines.

Rationale for doses of LMWH in the 'intermediate dose group' and in obese patients in the 'low dose group'

The ACCP guideline recommends the following daily doses of LMWH for prophylaxis in pregnancy: nadroparin 2,850 International Units (IU), enoxaparin 4,000 IU, dalteparin 5,000 IU or tinzaparin 4,500 IU (12). We use the same doses in the 'fixed low dose' group, except for tinzaparin for which we chose 3,500 IU instead of 4,500 IU, mainly based on availability of syringes. The doses in the 'intermediate dose group' are approximately half of a therapeutic dose, and were chosen based on 1) the examples given in the ACCP guideline, 2) the availability of pre-filled syringes and 3) similarity in ratios between the intermediate and low dose for all LMWH types. We chose a ratio between the most common intermediate dose group (70 – 100kg) and the fixed low dose group of 2.5 to 3.0 (Table 3.3B). It should be emphasized that no direct evidence is available to guide choosing a low dose or intermediate dose of LMWH in pregnancy, and that guideline recommendations are extrapolated from thromboprophylaxis studies in patients undergoing

general surgery or hip arthroplasty. In the TIPPS trial, in which pregnant women with thrombophilia at increased risk of VTE or with previous placenta-mediated pregnancy complications were randomized to either antepartum thromboprophylaxis with dalteparin or to no dalteparin, the dose of dalteparin was increased from 5,000 IU to 10,000 IU at 20 weeks of gestation (18). This decision was based on results from pharmacokinetic studies, suggesting that at this point, the dose requirement increases (26).

No specific recommendations are given in the ACCP guideline regarding modification of prophylactic doses at extremes of body weight. Several studies on thromboprophylaxis in surgery or cancer patients have applied either dose elevations at cut-off values ranging from 70 to 100kg, or no dose elevation at all. In the FRUIT trial that evaluated the addition of LMWH to aspirin at less than 12 weeks gestation in women with inherited thrombophilia and prior delivery for hypertensive disorders and/or small-for-gestational age infants, the dalteparin dose was increased in women weighing above 80kg from 5,000 IU to 7,500 IU (27). The Royal College of Obstetricians and Gynecologists suggests a dose elevation above 90kg, and the product monograph of nadroparin recommends an increase of the prophylactic dose at a cut-off value of 100kg in patients undergoing hip arthroplasty (28). Thus, in the absence of consensus or evidence we pragmatically chose for a cut-off value of 100kg in the 'fixed low dose' group, above which the dose is elevated approximately 1.5-fold (Table 3.3C).

Prophylaxis following early termination of pregnancy

Limited data are available on the VTE recurrence risk after an induced abortion, miscarriage or stillbirth. In a study by Pabinger and colleagues, 2 of 83 patients (2.4%) with a terminated pregnancy had a recurrence, and this was the case in 1 of 53 patients (1.9%) after miscarriage and in 3 of 10 (30%) following stillbirth (9). Based on these observations, patients with early termination of pregnancy in the Highlow study should continue LMWH injections until 6 weeks after termination of pregnancy.

Debate on extended prophylaxis after 6 weeks postpartum

There has been some debate on the need of prolonging prophylaxis beyond the 6th week postpartum until the 12th week postpartum. The current ACCP guideline recommends prophylaxis until the 6th week postpartum, based on the fact that most pregnancy-related VTE episodes occur in the first 6 weeks postpartum (12,29,30). A recent study demonstrated that the risk of a primary VTE is 11-fold higher within 6 weeks after delivery than in the same period 1 year later. During the period of 7 to 12 weeks after delivery, the absolute VTE risk is low, with a 2-fold higher incidence as compared with the same period 1 year later (7). In the Highlow study patients are followed up until 12 weeks postpartum, which will allow us to assess the risk of recurrent VTE in the 6 weeks after cessation of LMWH.

Cutaneous reactions to LMWH

Hypersensitivity skin reactions following LMWH injections are frequently seen, but are probably underreported in most observational studies. It is estimated that at least half of all pregnant women experience these side effects and switch to at least one alternative LMWH type (31–33). One unique feature of our study is the close monitoring of skin reactions such as redness, swelling, pain and itchiness, and the necessity to switch to other LMWH types. In addition, the occurrence of easy bruising is carefully recorded.

Therapeutic doses of LMWH

One may wonder why we chose not to compare an intermediate dose to a therapeutic dose of LMWH. In preparation of the Highlow study design, we found that most experts did not support the use of therapeutic doses of LMWH in the prevention of recurrent VTE, mostly based on concern of bleeding. Although in one study therapeutic doses of LMWH in pregnancy were found not to be associated with an increase in postpartum hemorrhage (20), a study with a therapeutic dose arm seems premature. If we find an unacceptably high incidence of recurrent VTE in the intermediate dose group in the Highlow study, a next step could be a randomized trial comparing an intermediate to a therapeutic dose of LMWH.

Challenges in setting up the study internationally

Setting up the study in different countries is challenging. Legislation has hampered approval of the study protocol in several countries; the waiver regarding supply of study medication by the sponsor is a frequent problem as not all countries have such waiver by law. Furthermore, the academic sponsor (Academic Medical Center, Amsterdam, the Netherlands) is only able to provide patient research insurance for Dutch patients, which cannot be extended to foreign patients. Consequently, local patient research insurance often needs to be arranged which may be costly. The institutional ethics committee unfortunately did not waive the need for patient research insurance, even though we believe that the risk for patients participating in this study is negligible, as there is a large body of evidence on the safety LMWH in pregnancy. LMWH is widely used in pregnant patients outside of a trial setting for the very indication and in the doses that are investigated in the Highlow study (12,13). A modest inclusion fee of € 250 is available for every randomized patient with a completed case record form (CRF), to partly overcome the abovementioned expenses.

Conclusion

In conclusion, this study is likely to greatly impact patient care and modify guideline recommendations. Although we have met several challenges, especially in setting up the study internationally, we are convinced that our goal of including approximately a 1000 patients will be reached within the foreseeable future.

Trial status

The Highlow study is registered on ClinicalTrials.gov (NCT01828697). An updated list of the number of included patients, participating centers and countries can be found at www.highlowstudy.org

Acknowledgments

We would like to acknowledge all Highlow investigators (Supplementary Appendix).

This study is supported by the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0), by two French gynecological networks (GO-CIC and CROG) and by the French network on thrombosis (INNOVTE).

Sponsorship and financial support

An unrestricted grant is provided by Aspen Pharma to the Academic Medical Center in Amsterdam (the Netherlands), who is the sponsor of the Highlow study (Principal Investigator: Prof. Dr. S. Middeldorp).

In France, where CHU de Saint Etienne is the sponsor, a grant was acquired from the French Ministry of Health (PHRC national 2014).

The CIAC is based in Saint Etienne, France.

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Interim report of the Highlow study

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4

For the Highlow investigators
For this thesis

Abstract

Women with a history of venous thromboembolism (VTE) have a 2% to 10% absolute risk of developing pregnancy-associated recurrent VTE. Based on these figures, the evidence-based guidelines recommend ante- and postpartum pharmacological thromboprophylaxis for all pregnant women with a history of VTE and a moderate or high risk of recurrent VTE. The optimal dose of thromboprophylaxis in this setting is unknown. The Highlow study is a randomized controlled trial (RCT) comparing a fixed low dose of low-molecular-weight heparin (LMWH) with an intermediate dose of LMWH for the prevention of pregnancy-associated recurrent VTE in pregnant women with a history of VTE. Here we present an interim report of the study as of June 2016.

From 1 April 2013 to 28 June 2016, a total of 270 eligible patients were identified, of which 222 (82%) gave informed consent and were enrolled. Baseline characteristics of 181 patients with completed baseline data in the case report form are presented. In addition, we show the inclusion rates over time, demonstrating an exponential increase of participating centers and subsequently enrolled patients.

This report represents the largest number of pregnant women with a history of VTE participating in a RCT to date. The vast majority of eligible women is willing to participate in the study, and recruitment of these patients has been proven feasible.

Background

Women with a history of venous thromboembolism (VTE) have a 2% to 10% absolute risk of developing pregnancy-associated recurrent VTE without thromboprophylaxis (1–4). Based on these figures, evidence-based guidelines recommend postpartum pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) for all pregnant women with a history of VTE (5,6). Women with a moderate or high risk of recurrent VTE (i.e. women with a history of multiple VTE or a single VTE that is either unprovoked or associated with pregnancy, a hormonal risk factor, or a minor risk factor such as long distance travel), should also receive thromboprophylaxis antepartum. The optimal dose of LMWH for thromboprophylaxis in pregnant women at moderate or high risk of recurrent VTE is currently unknown. The American College of Chest Physicians (ACCP) antithrombotic guideline suggests the use of either a prophylactic or intermediate (half-therapeutic) dose of LMWH in this setting, without a preference of one dose over the other (5). The Highlow study is an investigator-initiated, multicenter, international, open-label, randomized controlled trial (RCT) comparing the efficacy and safety of a fixed low dose of LMWH versus an intermediate dose of LMWH for the prevention of pregnancy-associated recurrent VTE (NCT01828697). Women aged 18 years or older with a history of VTE, a confirmed pregnancy with a gestational age of less than 14 weeks, and an indication for thromboprophylaxis ante- and postpartum, are eligible for the study. The rationale and detailed design features of the Highlow study have been described elsewhere (7). While several challenges have been met, especially in setting up the study internationally, enrolment is progressing well. In April 2013 the first patient was enrolled in the Highlow study. Here we give an update of the study status as of June 2016.

Current status

Eligible patients

From 1 April 2013 to 28 June 2016, a total of 270 pregnant patients with a history of VTE, that fitted the in- and exclusion criteria of the Highlow study, were identified and recorded in 43 actively participating centers in 5 countries. Of these, 222 (82%) gave informed consent and were subsequently enrolled. Six of these patients participated twice; 1 had a full-term pregnancy and 5 had a miscarriage during first participation. Figure 4.1 depicts the selection of patients and reasons for exclusion.

Twelve centers reliably recorded eligible women that did not give informed consent. In these centers, 149 patients were identified in total, of which 101 gave their consent (68%; Table 4.1). The majority of patients that did not give consent either preferred a low dose of LMWH (42%) or did not give a specific reason (46%). Enrolment rates in these centers vary from 0% to 88%.

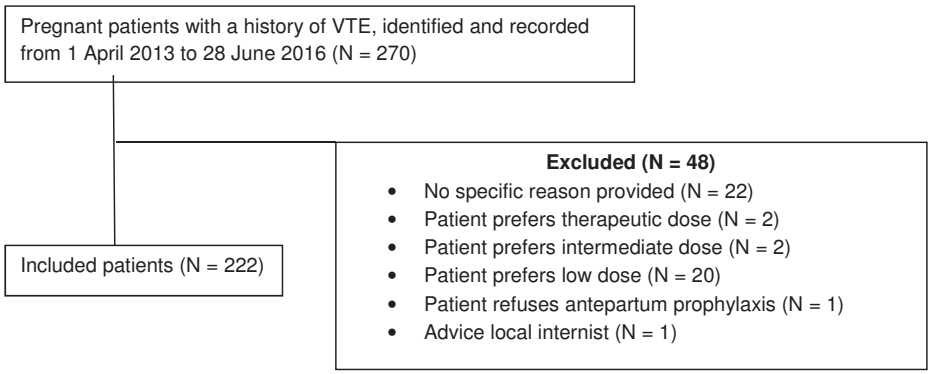

Figure 4.1. Flow diagram of the identification and inclusion of eligible patients

Table 4.1. Proportion of patients giving consent in 12 centers that recorded all eligible patients

Centre	Number of eligible patients identified	Number of patients giving consent	Proportion of patients giving consent
Academic Medical Center **(primary study center)**	64	52	83%
Rotunda Hospital, Dublin	17	14	82%
University Medical Center Groningen	12	3	25%
Jeroen Bosch Ziekenhuis, 's-Hertogenbosch	11	5	45%
Deventer Ziekenhuis	8	7	88%
Onze Lieve Vrouwe Gasthuis, Amsterdam	8	6	75%
Atrium Medisch Centrum, Heerlen	7	5	57%
Martini Ziekenhuis, Groningen	7	3	55%
University Medical Center Utrecht	5	3	60%
Máxima Medisch Centrum, Veldhoven	5	2	40%
Leiden University Medical Center	4	1	25%
Groene Hart Ziekenhuis, Gouda	1	0	0%
TOTAL	*149*	*101*	*68%*

Baseline characteristics of included patients

On 28 June 2016, baseline data in the case report form (CRF) had been completed for 181 patients. Table 4.2 lists the baseline characteristics of these patients. The mean age was 33 years ± 5.1, and the mean body mass index (BMI) at time of inclusion was 26.7 ± 5.9. The majority of patients had a history of lower limb deep vein thrombosis

(N = 102; 56%) or pulmonary embolism (N = 73; 40%). Of all previous VTE, the majority was hormone-related (N = 97; 54%) or related to pregnancy (N = 58; 32%). In total, 34 (19%) of prior VTE were unprovoked, and in 30 (17%) cases a minor risk factor, such as a minor trauma or airplane flight, had been present. Thrombophilia screening had been performed previously in 101 patients (56%) and more than half of these (59 patients, 58%) had positive tests, most often heterozygous factor V Leiden (N = 39; 64%) and heterozygous prothrombin 20210A mutation (N = 13; 22%).

Table 4.2. Baseline characteristics

Variables	N = 181
Age, *mean (SD)*	33 (5.1)
BMI, *mean (SD)*	26.7 (6.0)
Systolic blood pressure, *mean (SD)*	116 (12)
Nulliparous, *n (%)*	71 (39)
History of early termination of pregnancy/EUG, *n (%)*	77 (43)
History of preterm birth *, *n (%)*	16 (9)
History of fetal growth restriction, *n (%)*	10 (6)
History of cesarean section, *n (%)*	26 (14)
History of placenta-mediated complications, *n (%)*	17 (9)
Pregnancy-induced hypertension	8
Preeclampsia	7
HELLP syndrome	1
Not specified	1
History of postpartum hemorrhage[¥], *n (%)*	9 (5)
Number of previous VTE episodes, *n (%)*	
1	162 (88)
2	14 (9)
3	1 (1)
Not specified	4
Years between previous VTE[†] and randomization, *median (IQR)*	4.8 (2.1–1.4)
Site of previous VTE[‡], *n (%)*	
DVT of the lower extremity	102 (56)
DVT of the upper extremity	8 (4)
Pulmonary embolism	73 (40)
Splanchnic VTE	3 (2)
Cerebral VTE	8 (4)
Extensive superficial thrombophlebitis[§]	6 (3)
Other[¶]	11 (6)

Table 4.2. Baseline characteristics (continued)

Variables	N = 181
Provoking factor of previous VTE, *n (%)*	
Unknown	5
Unprovoked	34 (19)
Hormone-related	97 (54)
Combined oral contraceptive use	93
High dose progestogen	1
Assisted reproductive technique	1
Nuvaring	1
Not specified	1
Pregnancy-related	58 (32)
During pregnancy	31
Postpartum	25
Not specified	2
Minor risk factor	30 (17)
Air-travel related	3
Car-travel related	5
Minor trauma	5
Other**	4
Not specified	2
Major risk factor in 3 months prior to previous VTE, *n (%)*	9 (5)
Surgery	3
Immobilization	6
Thrombophilia screening performed, *n (%)*	101 (56)
Positive test	59 (58)
Factor V Leiden heterozygous	39 (64)
Factor V Leiden homozygous	2 (3)
Prothrombin 20210A mutation heterozygous	13 (22)
Prothrombin 20210A mutation homozygous	0
Antithrombin deficiency	0
Protein S deficiency	2 (3)
Protein C deficiency	2 (3)
Antiphospholipid syndrome	1 (2)
Known allergic skin reactions to nadroparin, *n (%)*	17 (9)
LMWH received prior to randomization, *n (%)*	55 (39)

Table 4.2. Baseline characteristics (continued)

Variables	N = 181
LMWH received after randomization, *n (%)*	
Nadroparin	89 (49)
Dalteparin	13 (7)
Tinzaparin	18 (10)
Enoxaparin	53 (29)
Not specified	8

SD: standard deviation; BMI: body mass index; EUG: extra-uterine gravidity; HELLP: hemolysis; elevated liver enzymes, low platelet count; IQR: interquartile range; VTE: venous thromboembolism; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin.
***** Preterm birth is defined as delivery before 37+0 weeks of gestation
¥ Defined as ≥ 500mL according to the criteria of the World Health Organization
† In case of multiple venous thromboembolism: the most recent event
‡ Some patients had venous thromboembolism at multiple sites at the same time
§ Superficial thrombophlebitis that was treated as deep vein thrombosis, i.e. treated with anticoagulant therapy for at least 3 months
¶ Including: retinal vein thrombosis, muscle vein thrombosis close to popliteal vein treated as deep vein thrombosis, isolated calf vein thrombosis, isolated pelvic vein thrombosis, retroperitoneal vein thrombosis, and ovaric vein thrombosis
** Including: two cases of active colitis, cystoscopy under general anesthesia, and legionella infection

Enrolment rates

Figure 4.2 shows the gradual increase in the number of actively recruiting hospitals, from June 2013 to June 2016. Consequently, the inclusion rate has been growing exponentially (Figure 4.3, Figure 4.4). To demonstrate a 65% relative risk reduction with the intermediate dose compared to the low dose of LMWH, a number of 29 recurrent VTE would provide a power of 80% to demonstrate superiority of an intermediate dose over a low dose. Based on an expected incidence of recurrent VTE of 4% to 5% in the fixed low dose group, the estimated sample size contains approximately 1000 women. This number may be adjusted upward and downward based on the overall number of events observed during the primary analysis period in the study. With current inclusion rates, we expect to reach a 1000 inclusions by the end of 2019 (Figure 4.5).

Discussion

This report of patients included in the Highlow study represents the largest number of pregnant women with a history of VTE participating in a RCT to date. Reassuringly,

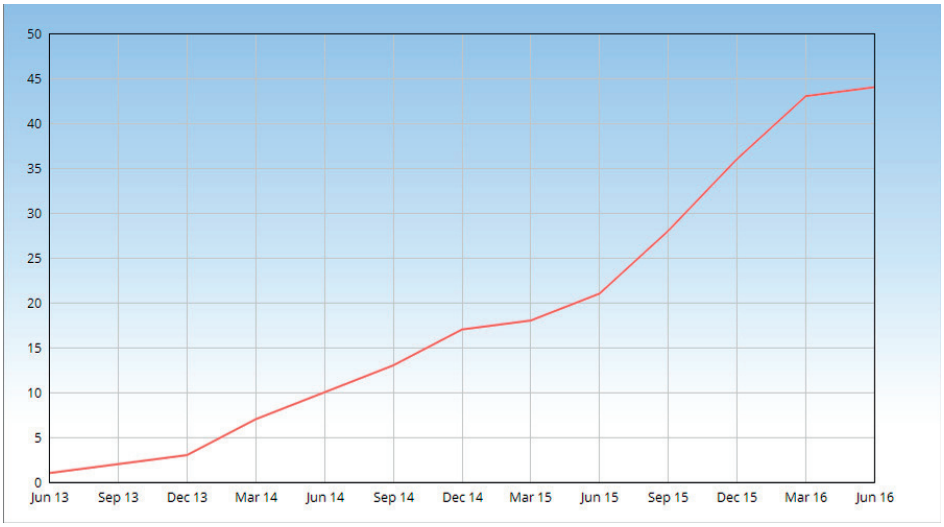

Figure 4.2. Number of actively recruiting hospitals

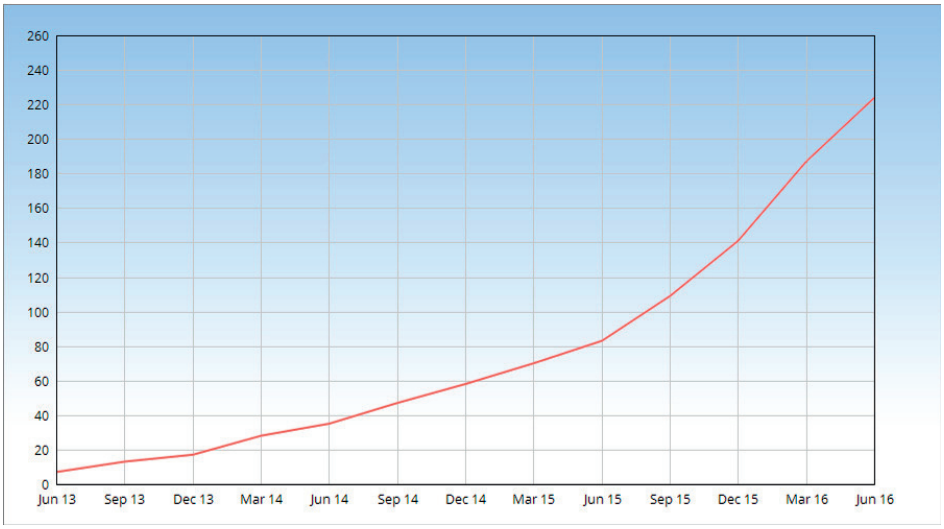

Figure 4.3. Total number of inclusions from April 2013 to June 2016

a large proportion of eligible women is willing to participate in the Highlow study. Hence, recruitment of these patients has been proven feasible.

Thus far, only two very small prospective trials, both with methodological limitations, have evaluated the efficacy of thromboprophylaxis in pregnant women with a history of VTE. One study included 16 patients and compared LMWH to placebo for antenatal prophylaxis. One patient in the placebo arm developed a recurrent VTE 29 days after

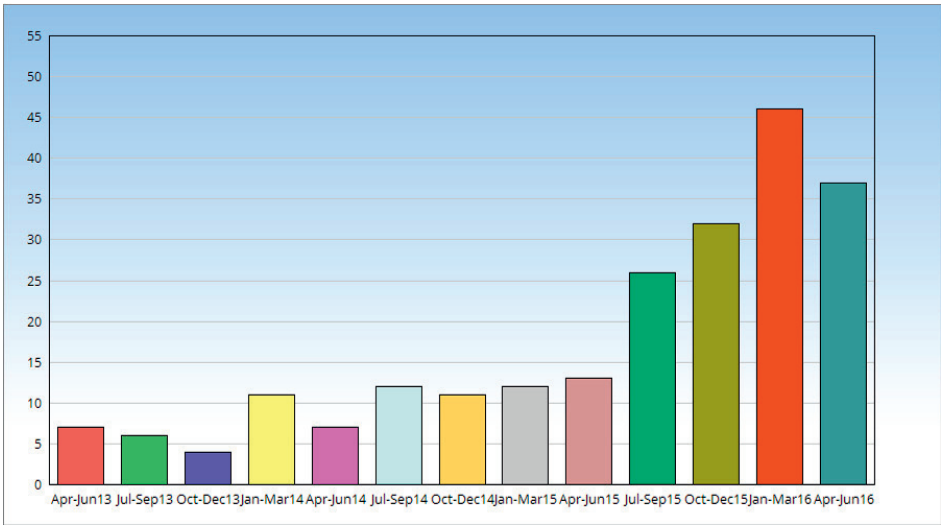

Figure 4.4. Number of inclusions per quartile from April 2013 to June 2016

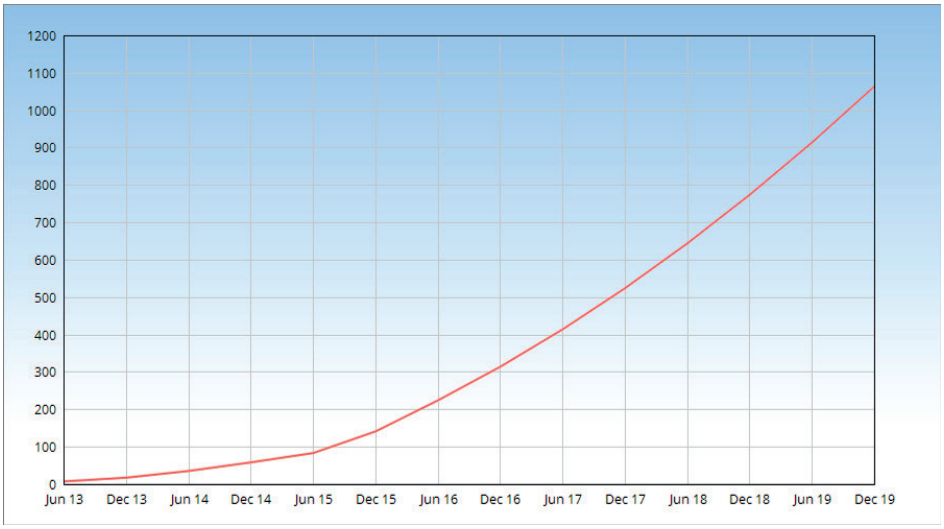

Figure 4.5. Expected enrolment

delivery (8). Another study compared heparin versus placebo antepartum in 40 patients; one recurrent VTE was observed in the placebo group two weeks after delivery (9). Several retrospective studies implicate that a low dose of LMWH is suboptimal for VTE prevention in pregnant women with previous VTE and a moderate to high risk of recurrent VTE, with reported recurrence rates of 5% to 6% (3,4,10–13). One study showed conflicting results (14). Due to the absence of direct evidence, the ACCP guide-

line suggests a prophylactic or intermediate dose of LMWH in this setting, without a preference of one dose over the other (5). The Highlow study will be the first providing direct evidence on the optimal dose of thromboprophylaxis and is therefore very likely to impact current clinical practice and modify consensus guidelines.

Our enrolment rates are very encouraging compared to previous studies evaluating thromboprophylaxis in pregnant women. Recently, a pilot study was undertaken to evaluate the feasibility of conducting a multicenter double-blind RCT comparing a prophylactic dose of LMWH to placebo in women with a high postpartum risk of VTE (15). Over 6 months, only 25 of 378 eligible women (7%) gave informed consent. Main reasons for declining informed consent were not being comfortable with injections (27%) and a lack of time for participation (15%). A second pilot study examined the feasibility to conduct an open-label RCT comparing 10 days of prophylactic dose LMWH to no LMWH for postpartum prophylaxis in women with a high VTE risk. Of 343 eligible patients, 37 (11%) provided consent, and reasons for declining consent were similar to the first pilot study (16). An explanation for the high consent rate in our study may be the fact that patients with a history of VTE have an indication for thromboprophylaxis anyway. Furthermore, patients with a history of VTE usually are very motivated to prevent this VTE from reoccurring.

The enrolment rates in our study vary substantially between centers, which is likely due to differences in counseling. Almost half of the patients that declined participation because they preferred a low dose, were identified in one center. Several factors and personal experiences play a role in decision making and it is important that the counselor is motivated and equipped to inform the patient well on all relevant aspects of participation. For example, a patient may prefer what is the routine dose in her hospital because it feels safe, despite the fact that this dose is not based on evidence. Some patients received a certain dose during a previous pregnancy and therefore prefer that dose again. Others prefer a low dose, driven by fear of bleeding with an intermediate dose. These gut feelings may lead to challenging informed consent conversations and one counselor may be better equipped than the other to convince the patient that participation is considered safe by the medical ethical committee, and that we at present really do not know which dose is most efficacious and safe.

The distribution of risk factors associated with prior VTE in our cohort is quite comparable to earlier studies on pregnant women with a history of VTE (2–4,11). For example, in our cohort 19% of previous VTE were unprovoked, where other studies reported figures ranging from 11% to 33% (2). An exception is that in two other studies, 15% and 16% of all VTE were related to combined oral contraceptives, which is much lower than the 54% that we report (2,4). However, in the study by Brill-Edwards and colleagues, women with known thrombophilia were excluded. Since there is a multiplicative risk increase with the use of oral contraceptives in women with hereditary thrombophilia

(17), this could explain the relatively low proportion of prior VTE related to oral contraceptive use in this cohort.

In more than half of our patients thrombophilia screening was performed, which probably reflects the fact that a substantial part of VTE occurred many years ago when thrombophilia testing was more commonly performed. Nowadays, thrombophilia screening is in general advocated against in patients with VTE except for specific cases, as it usually does not have therapeutic consequences (18,19). Of all tested patients in our cohort, a large proportion had confirmed thrombophilia. Similar percentages, ranging from 40% to 61%, have been reported in other studies on pregnant women with VTE (4,11,20). The distribution of thrombophilia types is comparable to the general population and existing cohorts, with heterozygous FVL and heterozygous prothrombin 20210A mutation being most prevalent (4,20).

Numerous challenges have been encountered at the start of the Highlow study, which is reflected by the slow inclusion rate in the beginning of the trial. Dedication, endurance and perseverance of our many enthusiastic, indispensable co-investigators and our own team have been key factors to get this study up and running. Although we are not there yet, we feel confident that with current inclusion rates, outcome results will be available in 2020.

Conclusions

The enrolment rates of the Highlow study show that recruitment of pregnant women with a history of VTE that need thromboprophylaxis ante- and postpartum, is feasible. Outcome results are expected in 2020.

Acknowledgments

We would like to acknowledge all Highlow investigators. This study is supported by an unrestricted grant from Aspen, and by the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0), by two French gynecological networks (GO-CIC and CROG) and by the French network on thrombosis (INNOVTE).

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Vaginal bleeding in women with venous thromboembolism treated with apixaban or enoxaparin and warfarin

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Thromb Haemost. 2017 Apr 3;117(4):809-815.

Abstract

Background: Abnormal vaginal bleeding can complicate direct oral anticoagulant (DOAC) treatment. We aimed to investigate the characteristics of abnormal vaginal bleeding in patients with venous thromboembolism (VTE) receiving apixaban or enoxaparin/warfarin.

Methods: Data were derived from the AMPLIFY trial. We compared the incidence of abnormal vaginal bleeding between patients in both treatment arms and collected information on clinical presentation, diagnostic procedures, management and outcomes.

Results: In the AMPLIFY trial, 1122 women were treated with apixaban and 1106 received enoxaparin/warfarin. A clinically relevant non-major (CRNM) vaginal bleeding occurred in 28 (2.5%) apixaban and 24 (2.1%) enoxaparin/warfarin recipients (odds ratio [OR] 1.2, 95% confidence interval [CI] 0.67–2.0). Of all CRNM bleeds, 28 of 62 (45%) and 24 of 120 (20%) were of vaginal origin in the apixaban and enoxaparin/warfarin group, respectively (OR 3.4; 95% CI 1.8–6.7). Premenopausal vaginal bleeds on apixaban were characterized by more prolonged bleeding (OR 2.3; 95%CI 0.5–11). In both pre- and postmenopausal vaginal bleeds, diagnostic tests were performed in 6 (21%) and in 7 (29%) apixaban and enoxaparin/warfarin treated patients, respectively. Medical treatment was deemed not necessary in 16 (57%) apixaban and 16 (67%) enoxaparin/warfarin recipients. The severity of clinical presentation and course of the bleeds was mild in 75% of the cases in both groups.

Conclusion: Although the absolute number of vaginal bleeding events is comparable between apixaban and enoxaparin/warfarin recipients, the relative occurrence of vaginal bleeds is higher in apixaban treated women. The characteristics and severity of bleeding episodes were comparable in both treatment arms.

Introduction

Women of reproductive age have a higher risk of venous thromboembolism (VTE) than men of the same age, which can likely be explained by the use of hormonal contraceptives and pregnancy in this phase of life (1–3). Direct oral anticoagulants (DOACs) have been introduced as an alternative for vitamin K antagonists (VKA) for the treatment of VTE, and were found to be safer and at least as efficacious (4).

Little is known on sex-specific complications of anticoagulant treatment with DOACs. In a meta-analysis of patients receiving rivaroxaban, apixaban and ximelagatran, women more often experience clinically relevant bleeding (the composite of major and clinically relevant non major [CRNM]) compared to men (5). In addition, recent studies have shown that abnormal vaginal bleeding is a frequent complication in women receiving DOACs, affecting 20% to 40% of all treated women (6–10). Furthermore, DOAC use has been associated with a higher frequency of heavy menstrual bleeding, and required more medical interventions and adaptations of anticoagulant treatment for abnormal uterine blood loss in comparison to treatment with VKA (7,8).

Most published data are limited to women using rivaroxaban. Therefore, for the present study, we compared the incidence of abnormal vaginal bleeding in a cohort of female VTE patients who received apixaban or enoxaparin followed by warfarin. In addition, we evaluated the characteristics, applied diagnostic procedures, treatment and subsequent clinical outcome of all vaginal bleeding events and explored the association of these characteristics with the received treatment.

Materials and Methods

Study Population and Design

The AMPLIFY study

Data for the present analysis were derived from the database of the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, of which the full study design has been previously published (11). Briefly, in the AMPLIFY study, patients with VTE were randomized in a double-blind fashion to either apixaban or enoxaparin followed by warfarin for a duration of 6 months. Patients were eligible for inclusion in the study if they were 18 years of age or older and had objectively confirmed, symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE; with or without DVT). Patients were excluded if they had 1) active bleeding, 2) a high risk of bleeding, 3) other contraindications for treatment with enoxaparin and warfarin, 4) cancer and an indication for long-term treatment with low-molecular-

weight heparin, 5) another indication for long-term anticoagulation therapy, or 6) dual antiplatelet therapy or treatment with aspirin at a dose of more than 165 mg daily.

The primary safety outcome was major bleeding, and the secondary safety outcome was the composite of major and CRNM bleeding. Major bleeding was, according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH), defined as clinically overt bleeding, either 1) associated with a fall in hemoglobin level ≥ 2 g/dL, 2) requiring transfusion ≥ 2 units of erythrocytes, 3) occurring in a critical site, or 4) contributing to death (12). CRNM bleeding was defined as clinically overt bleeding not meeting the criteria for major bleeding, but associated with 1) a medical intervention, 2) unscheduled contact with a physician, 3) interruption of study drug or 4) discomfort or impairment in carrying out activities of daily life. Bleeding events were prospectively reported and recorded during conduct of the AMPLIFY trial using standardized case report forms (CRFs). The protocol specified potential treatment strategies for bleeding events, but the decision to use these strategies was left at the discretion of the treating physician. Overall bleeding rates in the AMPLIFY study were censored at 2 days after the last intake of apixaban.

The protocol was reviewed and approved by each participating site's Institutional Review Board, and written informed consent was obtained from participants. The trial was registered with clinicaltrials.gov (NCT00643201). The AMPLIFY study was sponsored by Pfizer Inc. and Bristol Myers Squibb Company.

Current study

For the present study we included all women who participated in the AMPLIFY trial. In case a vaginal bleeding event occurred during the study period, the following data were collected by three independent investigators (MB, LS, SB) blinded for treatment allocation: characteristics of the vaginal bleed (duration, severity, frequency), pre- or postmenopausal status, performed diagnostic tests, applied medical interventions or treatments to stop the bleed, and the severity of clinical presentation and subsequent outcome of the bleed. All data were retrieved from CRFs, bleeding narratives and patient profiles. Only bleeding events that occurred during the on-treatment period (period in which patients received the study drug or within two days after the study drug was stopped or interrupted) were eligible.

Definition of abnormal uterine bleeding

Abnormal uterine bleeding (AUB) was, according to the International Federation of Gynecology and Obstetrics (FIGO), defined as prolonged menstrual bleeding, intermenstrual bleeding, heavy menstrual bleeding or menstrual blood loss causing anemia or requiring an unscheduled contact with a physician, a medical or surgical intervention, or adaptation of anticoagulant therapy. Since the definition of AUB is only applicable to premenopausal vaginal bleeding events, we described the characteristics of vaginal

bleeds separately for pre- and postmenopausal women. The results regarding diagnostics and applied treatment strategies in both pre- and postmenopausal women were combined due to small numbers in both groups.

Classification of clinical presentation and course

Previously, all CRNM bleeding events from the AMPLIFY study were blindly classified using predefined criteria for the severity of clinical presentation and course (13). This classification scheme included four different categories; category one representing the mildest and category four the most severe presentation or course (Table 5.1). For the current analysis, we extracted the adjudicated categories for all CRNM vaginal bleeds. As there was only one major vaginal bleeding event in the AMPLIFY study, we did not classify this event for clinical presentation and clinical course.

Table 5.1. Classification of clinically relevant non-major bleeding events

Category	Description
1	Bleeding events which were: - Self-controlled, and/or - Retrospective in nature, and/or - Required no emergency room/medical visit, stop of study medication, procedures or treatment
2	Bleeding events that could not be classified to any of the other three categories (i.e. only requiring temporary interruption of study medication, bleeding events only requiring contact)
3	Bleeding events requiring an emergency room/medical visit and procedures or treatment to control the bleeding, but no hospitalization
4	Bleeding events requiring hospitalization and procedures or treatment to control the bleeding

Statistical analysis

Differences in normally distributed continuous variables between groups were compared by means of the independent sample-t-test. The chi-square test was applied for group comparisons of categorical variables.

A logistic regression model was applied to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between bleeding characteristics and the different treatment groups (apixaban versus enoxaparin/warfarin). ORs were adjusted for NSAID use at randomization. For the analysis of the severity of clinical presentation and course of the bleeding, ORs for classifying as category 3 or 4 between apixaban and enoxaparin/warfarin associated bleeds were computed.

A *p*-value of less than 0.05 was considered to indicate a significant difference. Analyses were carried out using SPSS 20 for Windows (IBM Software, NY, USA).

Results

Study population

In the AMPLIFY trial, 1122 women were treated with apixaban and 1106 received enoxaparin followed by warfarin. There were no differences in baseline characteristics between apixaban and enoxaparin/warfarin treated women (11). Figure 5.1 provides insight in the incidence and type of bleeding events in the AMPLIFY trial for both treatment arms.

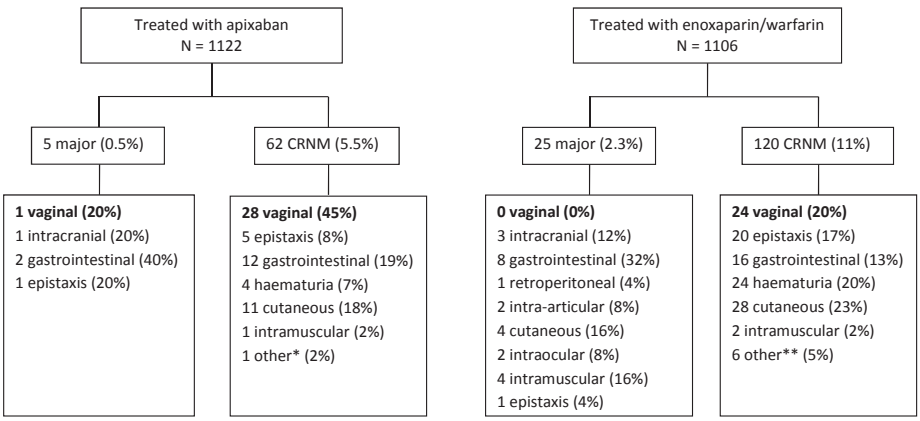

Figure 5.1. Bleeding events of women in the AMPLIFY trial
CRNM: clinically relevant non-major. *Blood in a hepatic cyst; **Including: 1 gingival bleeding, 1 haemorrhagic Baker's cyst, 1 mild haemoptysis, 2 subconjunctival bleeds, 1 patient with multiple hematomas after a motorised vehicle accident.

Major vaginal bleed

Major vaginal bleeding occurred in one of 1122 (< 0.1%) woman during the use of apixaban, and in none of those receiving enoxaparin/warfarin. The only observed major vaginal bleeding occurred in a 45 year old woman who had an index DVT and a history of endometriosis. She presented with heavy and intermenstrual bleeding on day 51 of the study, accompanied by a hemoglobin drop from 11.2 g/dL at baseline to 6.5 g/dL at the day of presentation. Diagnostics revealed uterine fibroids. Study medication was interrupted and 3 units of red blood cells were administered. Two weeks after the event a hysterectomy was performed for which a temporary inferior vena cava (IVC) filter was placed. A week after surgery the hemoglobin level reached 10.8 g/dL; three weeks later the IVC filter could be removed.

Clinically relevant non-major vaginal bleeds

CRNM vaginal bleeding was observed in 28 of 1122 (2.5%) women receiving apixaban and in 24 of 1106 (2.1%) women receiving enoxaparin/warfarin (OR 1.2, 95%CI 0.67–2.0). In total, 62 women receiving apixaban and in 120 women receiving enoxaparin/warfarin experienced any type of CRNM bleeding; hence vaginal bleeds represents 45% (24 of 62) of all CRNM bleeds in the apixaban and 20% (28 of 120) of all CRNM bleeds in the enoxaparin/warfarin group (OR 3.4, 95%CI 1.8–6.7; Figure 5.1). Figure 5.1 shows the bleeding locations in patients treated with apixaban and enoxaparin/warfarin; in both groups, vaginal and gastro-intestinal bleeds were relatively common, and in the enoxaparin/warfarin group cutaneous bleeds, hematuria, and epistaxis were also frequently observed.

Table 5.2. Baseline characteristics of women in the AMPLIFY trial with a CRNM vaginal bleeding

	Apixaban	Enoxaparin/ Warfarin	P-value
Number	28	24	N.A.
Age (years) - *mean (SD)*	46 (11)	44 (14)	0.77
BMI (kg/m^2) - *mean (SD)*	30 (6)	30 (8)	0.40
Randomization to bleeding (days) - *median (IQR)*	27 (8 – 85)	32 (9 – 80)	0.78
Index event - *n (%)*			0.23
DVT	20 (71)	14 (58)	
PE	5 (18)	9 (38)	
Both	3 (11)	1 (4)	
Risk factors for VTE - *n (%)*			0.43
Active cancer	1 (4)	1 (4)	
Known thrombophilia	0	2 (8)	
Previous VTE	7 (25)	3 (13)	
Immobilization	0	1 (4)	
Use of hormones	5 (18)	4 (17)	
None	18 (64)	15 (63)	
Unknown	1 (4)	0	
History of anemia - *n (%)*	12 (43)	9 (38)	0.46
Prior gynecological disorder*- *n (%)*	10 (36)	6 (25)	0.30
Antiplatelet use at randomization - *n (%)*	4 (14)	5 (21)	0.40
NSAID use at randomization - *n (%)*	8 (29)	2 (8)	0.07

*This includes the following gynecological disorders, that are associated with vaginal bleeding: uterine myoma, menorrhagia, ovarian cancer, endometrial hyperplasia, and active termination of pregnancy 5 days before the bleeding event.

NA: not applicable; CRNM: clinically relevant non-major; SD: standard deviation; IQR: interquartile range; VTE: venous thromboembolism; NSAID: non-steroidal anti-inflammatory drugs

Table 5.2 details the baseline characteristics of all women who had a CRNM vaginal bleed during the AMPLIFY trial. The time from randomization to first episode of vaginal bleeding was a median 27 days (IQR 8–85) in the apixaban and 32 days (IQR 9–80) in the enoxaparin/VKA group. No statistically significant differences were detected between women using apixaban and those using enoxaparin/warfarin. Although confidence intervals crossed unity, a trend was observed towards more frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) at randomization in apixaban recipients compared to women in the enoxaparin/VKA group (8 [29%] versus 2 [8%], p = 0.07). Therefore, subsequent ORs were adjusted for NSAID use at randomization.

Vaginal bleeding characteristics

Premenopausal women

The majority of women with CRNM vaginal bleeds were premenopausal (Table 5.3). Premenopausal vaginal bleeding events in women on apixaban were characterized by more prolonged bleeding (i.e. > 7 days; OR 2.3, 95%CI 0.5–11) compared to those using enoxaparin/warfarin, albeit this difference did not reach statistical significance. The occurrence of intermenstrual bleeding, heavy menstrual bleeding and anemia (i.e. hemoglobin < 11.9 g/dL) were comparable between both treatment groups (OR 1.3, 95%CI 0.2–7.3; OR 0.7, 95%CI 0.1–4.4; and OR 1.3 95%CI 0.3–5.5, respectively). In 13 of 22 (59%) of the apixaban associated and in 12 of 18 (67%) of the enoxaparin/warfarin associated premenopausal vaginal bleeds there was an unscheduled contact with a physician (OR 0.7, 95%CI 0.2–2.9).

Table 5.3. Characteristics of clinically relevant non-major vaginal bleeds

	Apixaban	Enoxaparin/warfarin
Number of women with vaginal CRNM bleeding events	28*	24
Premenopausal bleeding - *n (%)*	22 (79)	18 (75)
Prolonged menstrual bleeding	8 (35)	3 (17)
Intermenstrual bleeding	4 (18)	3 (17)
Heavy menstrual bleeding	18 (82)	15 (83)
Anemia**	13 (59)	7 (39)
Unscheduled contact	13 (59)	12 (67)
Classifying for AUB	All	All
Postmenopausal bleeding - *n (%)*	5 (21)	6 (25)
Anemia**	1 (20)	0
Unscheduled contact	4 (80)	4 (67)

**In one patient the pre- or postmenopausal status was unknown; **Anemia during study participation
CRNM: clinically relevant non-major; AUB: abnormal uterine blood loss

Table 5.4. Applied diagnostic tests and treatment of vaginal bleeding in both pre- and postmenopausal women

	Apixaban	Enoxaparin/warfarin
Number of women with vaginal CRNM bleeding events	28	24
Diagnostic tests applied - *n (%)*	6 (21)	7 (29)
Ultrasonography	2	4
Hysteroscopy	0	1
Biopsy	3	2
Diagnostic endometrial ablation	1	0
Diagnosis - *n (%)*	8 (29)	9 (38)
Uterine myoma	2	6
Uterine leiomyoma	1	0
Endometriosis	0	1
Endometrial hyperplasia	1	0
Ovarian cancer	0	1
Uterine cancer	1	0
Other	3*	1**
Hospital admission - *n (%)*	2 (7)	3 (13)
Treatment - *n (%)*		
Iron suppletion	8 (29)	1 (4)
Hormone therapy	1 (4)	3 (13)
Estrogen containing	0	1
Progestagen containing	1	2
IUD	1 (4)	0
Tranexamic acid	1 (4)	2 (8)
Combination	1 (4)	2 (8)
No treatment	16 (57)	16 (67)
Radiologic or surgical interventions - *n (%)*		
Hysterectomy	2 (7)	1 (4)
Endometrial ablation or curettage	2 (7)	2 (8)
Removal of Nuva-ring	1 (4)	0
No interventions	23 (82)	20 (84)
Unknown	0	1 (4)
Change in anticoagulant - *n (%)*		
Unchanged	18 (64)	13 (54)
Temporary interruption	8 (29)	8 (33)
Permanent stop	2 (7)	3 (13)

*These included bleeding after biopsy, bleeding due to a contraceptive vaginal ring, and a blood clot in the uterus with uncertain etiology; **Cervical polyp in combination with endometriosis
CRNM: clinically relevant non-major; IUD: intra-uterine device

Postmenopausal women

Eleven patients with a vaginal bleeding event were postmenopausal; five of those were using apixaban, and six were on enoxaparin/warfarin (Table 5.3). Six of eleven (55%) women had a known gynaecological disorder associated with bleeding prior to randomization; three had a uterine myoma, one had ovarian cancer, one had a history of endometrial hyperplasia, and one had uterine cancer.

Diagnostics and treatment

For both pre- and postmenopausal vaginal bleeding events, additional diagnostic tests were performed in 6 of 28 (21%) and 7 of 24 (29%) of apixaban and enoxaparin/warfarin recipients, respectively. In 8 of 28 (29%) of the apixaban treated women (5 premenopausal, 3 postmenopausal) a cause for the vaginal bleed could be detected compared to 9 of 24 (38%) of the women using enoxaparin/warfarin (7 premenopausal, 2 postmenopausal; Table 5.4). A uterine myoma was the underlying cause in 2 of 8 (25%) of the apixaban and 6 of 9 (67%) of the enoxaparin/warfarin recipients.

Medical treatment was deemed not necessary in 16 of 28 (57%) of the apixaban recipients and in 16 of 24 (67%) of those receiving enoxaparin/warfarin. Iron supplements only were given in 8 of 28 (29%) of apixaban and in 1 of 24 (4%) of enoxaparin/warfarin associated vaginal bleeds. Hormone therapy was started in 1 of 28 (4%) woman in the apixaban versus 3 of 28 (13%) women in the enoxaparin/warfarin group. In 5 of 28 (18%) and 3 of 24 (13%) women treated with apixaban and enoxaparin/warfarin, a radiological or surgical intervention was indicated to stop the bleeding. Anticoagulant treatment was temporarily stopped in 8 of 28 (29%) apixaban and 8 of 24 (33%) enoxaparin/warfarin recipients, whereas 2 of 28 (7%) and 3 of 24 (13%) patients respectively stopped anticoagulants permanently.

Clinical outcomes of vaginal bleeding events

Reassuringly, in approximately 75% of the women with a CRNM vaginal bleed, the clinical presentation and course were classified as "mild", (i.e. category 1 or 2). The OR for classifying as category 3 or 4 (i.e. a severe clinical course) in patients using apixaban versus those using enoxaparin/warfarin was 0.7 (95%CI 0.2–2.2).

Repetitive bleeding was common (14 of 28 [50%] of apixaban and 10 of 24 [42%] of enoxaparin/warfarin recipients), no difference was observed between the two treatment groups (OR 1.0, 95% CI 0.3–3.3); Table 5.5.

Table 5.5. Clinical outcomes of bleeding in women with vaginal CRNM bleeding

	Apixaban	Enoxaparin/ warfarin
Repetitive bleeding - *n (%)*	14 (50)	10 (42)
Recurrent VTE - *n (%)*	0	1(4)
Classification of CRNM vaginal bleed - *n (%)*		
Category 1	6 (22)	5 (21)
Category 2	14 (50)	10 (42)
Category 3	4 (14)	6 (25)
Category 4	4 (14)	3 (12)

CRNM: clinically relevant non-major; VTE: venous thromboembolism

Discussion

Overall, the occurrence of vaginal bleeding events was comparable between women treated with apixaban and enoxaparin/warfarin. However, if a CRNM bleeding occurred, the bleeding was observed to be more often of vaginal origin in women treated with apixaban compared to women treated with enoxaparin/warfarin. Hence, there is a difference in bleeding sites between patients treated with apixaban and enoxaparin/warfarin. In addition, premenopausal vaginal bleeds in women using apixaban appeared to be more frequently characterized by prolonged menstrual bleeding than in patients receiving enoxaparin/warfarin, although no statistically significant difference was observed between the groups. The severity of clinical presentation and course of the bleeds was mild in the majority of the cases, and was comparable for both treatment groups. Interventions to stop the bleeding were indicated infrequently and iron supplements were deemed sufficient by the treating physicians in a quarter of the apixaban associated bleeds. Overall, vaginal bleeds led to an unscheduled contact with a physician in more than 60% of the cases, to temporary cessation of the study drug in about 30%, and in 10% anticoagulants were permanently ceased, all reflecting the distress caused by these bleeds. No differences were observed between the treatment groups.

To our knowledge, this is the first study evaluating characteristics, diagnostics and treatment of vaginal bleeding events in women receiving apixaban. Previous studies mainly focused on rivaroxaban and the occurrence of vaginal bleeding (5–8,10). One study applied the same criteria for AUB as the present study, and observed that rivaroxaban was associated with prolonged menstrual bleeding in comparison to VKA ($P < 0.001$), and with more medical interventions and adaptation of anticoagulant treatment (7).

In a study including women with inherited bleeding disorders, a situation comparable to women receiving anticoagulants, vaginal bleeds were observed to be associated with a decreased quality of life (14). Hence, physicians should be vigilant of the occurrence of vaginal bleeds in women on anticoagulants, especially in the reproductive phase of life. It is important to inform women of this complication at start of treatment with anticoagulants, and they should be encouraged to seek medical attention when abnormal vaginal bleeding occurs. If this does occur, referral to a gynaecologist should be considered. The gynaecologist is able to determine whether there is an underlying condition and if so, treat this accordingly. However, in most of both pre- and postmenopausal vaginal bleeding events no underlying cause is identified, and therefore general measures should be considered. Potential therapies and preventative measures for vaginal bleeding are placement of a hormone releasing intra-uterine device, use of combined oral contraceptives, or use of tranexamic acid during menstrual periods, which all are not associated with an increased risk of VTE during the use of anticoagulants (1,8,15–17).

The underlying mechanism of differences in bleeding pattern and especially the higher relative number of vaginal bleeds in women using DOACs is unknown. DOACs directly target coagulation factors and a part of the DOAC dose remains in the gastrointestinal tract, due to incomplete absorption. Therefore, DOACs have a local effect on the gastrointestinal wall and mucosa potentially leading to a higher frequency of gastrointestinal bleeding compared to VKA treatment (18,19). One might speculate that DOACs, as opposed to VKA, also have a direct effect on the uterine wall, thereby increasing local bleeding tendency. Another possibility is that, as menstrual vaginal bleeding is a natural bleeding process, DOACs act synergistically with the natural anticoagulants necessary for menstrual bleeding and the menstrual cycle.

Our study has several strengths. First, the AMPLIFY study was a randomized, double-blind, double-dummy study in which data on bleeding events were prospectively collected on pre-designed forms. Another strength is that the adjudicators were blinded for treatment regimen at time of data collection. Therefore, bias due to misclassification of bleeding events will be minimal.

Some limitations deserve acknowledgement. A first limitation is the relatively small sample size. Although we included 2228 women from the AMPLIFY trial, a vaginal bleeding episode only occurred in 29 apixaban- and 24 enoxaparin/warfarin-treated patients. Therefore, possible existing differences in bleeding characteristics between the treatment groups may not have been detected. For example, the observed difference between apixaban and enoxaparin/warfarin may be driven by an imbalance of hormone treatment during anticoagulant treatment. In addition, the balancing property of randomization is lost which may have increased the potential for confounding. However, to address this, we adjusted the ORs for potential confounding factors

by means of multivariate regression models and therefore the impact on the present study results is likely to be limited. Third, although treatment cessation, unscheduled contact or hospital admission seem valid parameters of disease burden, we were not able to assess quality of life objectively. Future studies should provide more insight in the impact of vaginal bleeding on quality of life. Finally, due to the retrospective nature of this study, it was not possible to quantify the amount and composition of vaginal blood loss. In future prospective studies validated blood loss scores such as the pictorial blood assessment chart (PBAC) score could be applied to objectify vaginal bleeding events (20).

In conclusion, although the absolute number of vaginal bleeding events is comparable between apixaban and enoxaparin/warfarin, the relative occurrence of vaginal bleeds is higher in apixaban treated women. Hence, there is a difference in bleeding sites between apixaban and enoxaparin/warfarin. Bleeding characteristics did not differ between both treatment groups and the severity of the bleeds was mild in three-quarter of all women. We would advise clinicians to actively monitor and inform women on anticoagulants in order to early identify abnormal vaginal bleeding, so preventive and therapeutic measures can be installed timely.

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PART II

Cancer and venous thromboembolism

Prevention and treatment of venous thromboembolism in cancer patients: focus on drug therapy

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Drugs. 2016 Mar;76(3):331-41.

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Abstract

Venous thromboembolism (VTE) is a common complication in patients with cancer. The anticoagulant treatment of cancer-associated VTE is challenging due to the intrinsically high risk of recurrent VTE as well as major bleeding. Low-molecular-weight heparins (LMWH) are the recommended anticoagulants in this vulnerable population because of their stable pharmacokinetics and the absence of important drug interactions. However, LMWH therapy requires daily subcutaneous injections often for an indefinite treatment period. Direct oral anticoagulants are a more attractive option because of their fixed, oral dosing without routine monitoring, but they first have to be evaluated against LMWH in patients with cancer and VTE before being adopted in clinical practice. Routine primary prophylaxis with LMWH in ambulatory cancer patients is currently not recommended given the number needed to treat of 40 to 50 to prevent one venous thromboembolic event. Risk stratification based on tumor type, combination of clinical parameters, or coagulation biomarkers may identify cancer patients at very high risk of VTE. Ongoing trials are evaluating the effectiveness and safety of thromboprophylaxis in these high-risk patients. If a sufficiently large absolute benefit is demonstrated, this may eventually lead to common use of LMWH prophylaxis in ambulatory patients with cancer.

Introduction

Venous thromboembolism (VTE), which comprises lower-extremity deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer. It is estimated that 20% of all VTE cases occur in cancer patients (1), who present a 4- to 7-fold higher risk of developing VTE compared to patients without cancer (2–4). The absolute incidence of cancer-associated VTE varies greatly depending on the tumor type, cancer stage, and anticancer treatment. For example, the incidence of VTE is 10 per 100 person-years in patients with pancreatic or brain cancer, whereas in prostate or breast cancer it is 1 to 2 per 100 person-years, close to the risk in the general population (4–6). Metastatic disease (6,7) and chemotherapeutic treatment also carry a higher risk of developing VTE (1).

While the focus in literature has traditionally been on symptomatic VTE, it is increasingly recognized that about half of all cancer-associated VTE are incidentally diagnosed on imaging tests performed usually for staging purposes (8). In addition to lower extremity DVT and PE, cancer patients frequently experience VTE at unusual sites such as splanchnic vein thrombosis (SVT) and upper extremity DVT (UEDVT) (9,10).

The risk of VTE recurrence in cancer patients is approximately 3-fold higher than in patients without cancer (11,12) with an absolute incidence during the first 6 months of anticoagulant treatment of 8% (13–16) and a case-fatality rate up to 47% (13). In fact, VTE represents one of the leading causes of death in cancer patients (17,18). The all-cause mortality in the 6 months following VTE is around 30% (13,14,16), which is significantly higher than in matched cancer patients without VTE (19). This probably reflects the worse prognosis of biologically more aggressive cancers which are also more likely to cause VTE (20–24).

In this review we focus on the use of anticoagulant drugs for the prevention and treatment of symptomatic or incidental cancer-associated VTE. Finally, we will address recent data regarding the long-term outcome of cancer patients with VTE at unusual sites including SVT and UEDVT.

Challenges of anticoagulant treatment in cancer patients

The goal of anticoagulant treatment is to prevent recurrent VTE while minimizing the risk of bleeding. Optimizing this risk-benefit balance in cancer patients is challenging as they have a higher risk of recurrent VTE and a 2- to 6-fold greater risk of anticoagulant-related bleeding compared to the general population (11,12,25). The rate of major bleeding during the first 6 months of treatment is approximately 6 to 10% (12–15), with a case-fatality rate up to 30% (25–27). Bleeding complications may interfere with diagnostic or therapeutic interventions and delay cancer treatment. In addition, anticoagulant treatment is often temporarily stopped following a bleeding event which exposes these patients to an increased risk of recurrent VTE (28).

In addition to the bleeding risk factors common to the general population such as older age and impaired renal or liver function, other cancer-specific elements contribute to the bleeding tendency and include, among others, chemotherapy-induced mucosal lesions, unstable neovascularization in the tumor environment, and thrombocytopenia related to chemotherapy-induced bone marrow suppression or bone marrow invasion by hematological malignancies (29). Metastatic brain lesions are prone to bleeding and are associated with a 19% risk of significant intracranial hemorrhage during the first year of anticoagulant treatment (30).

The treatment of VTE in patients without cancer traditionally consists of an initial course of heparin followed by vitamin K antagonists (VKA) for at least 3 months (31). VKA treatment can be particularly demanding in cancer patients. Chemotherapy-induced oral mucosal lesions, nausea, and vomiting may decrease oral drug intake, and intestinal mucosal lesions or diarrhea may affect the gastrointestinal drug absorption (32). There may be high inter- and intra-individual variability of drug levels owing to interactions with drugs and food, and treatment may be interrupted because of invasive diagnostic or curative procedures resulting in a decreased quality of anticoagulation as reflected by a lower time in therapeutic range. In two large trials that evaluated VTE treatment in cancer patients, the time in therapeutic range was only 46% to 47% (13,16), compared to 60 to 70% in patients without cancer treated with VKA (33).

Low-molecular-weight heparins (LMWH) offer a more stable pharmacokinetic profile given the virtually absent interactions with food or drugs. However, the requirement of daily subcutaneous injections with frequent injection site reactions and subcutaneous hematomas may be burdensome for long-term treatment.

Recently, direct oral anticoagulants (DOACs) comprising the thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban, edoxaban, and rivaroxaban have become available for the treatment of VTE. Large phase 3 studies have shown that DOACs are as effective as VKAs in preventing recurrent VTE and cause significantly less bleeding (33). As discussed later, the evidence on the safety of DOACs in cancer patients is scarce. As with VKAs, nausea, vomiting, and intestinal lesions may affect the oral intake and gastrointestinal absorption. Antineoplastic agents such as tyrosine kinase inhibitors, hormonal therapy, and immunomodulatory agents that inhibit *P*-glycoprotein may lead to supratherapeutic drug levels, thereby increasing the risk of bleeding (34). In addition, factor Xa inhibitors are partly metabolized by the cytochrome P450 3A4 pathway and caution is warranted when co-administered with inducers or inhibitors of this enzyme.

Prevention of VTE

Surgical cancer patients

Patients with cancer undergoing major surgical procedures have a two-fold higher risk of VTE than patients without cancer (35,36). Perioperative thromboprophylaxis, usually with LMWH (37), is recommended in these patients (38). Thromboprophylaxis should be started preoperatively and continued for at least 7 to 10 days postoperatively (38,39). In patients undergoing abdominal or pelvic surgery for cancer the postoperative risks remain high for over a month following surgery (40–42). In the ENOXACAN II study which compared enoxaparin with placebo for extended VTE prophylaxis in 332 patients undergoing abdominal or pelvic cancer surgery, asymptomatic DVT was observed in 5.5% of enoxaparin treated patients compared to 13.8% in the placebo group (RR 0.40, 95% CI 0.2 to 0.9). No significant difference was observed in the rate of major bleeding. In a meta-analysis by Akl and colleagues, extended thromboprophylaxis up to 4 weeks after surgery was associated with a 80% lower risk of VTE (RR 0.21; 95% CI 0.1 to 0.9) with no significant increase in major bleeding (RR 2.9; 95% CI 0.1 to 72) (43). Based on these data, it is now recommended that cancer patients undergoing major abdominal or pelvic surgery receive extended thromboprophylaxis for 4 weeks postoperatively (38,39). An ongoing trial is evaluating the efficacy and safety of apixaban versus enoxaparin in 400 women undergoing surgery for suspected pelvic malignancy (https://clinicaltrials.gov/ct2/show/NCT02366871).

Hospitalized cancer patients

Cancer patients hospitalized for medical reasons are also at an increased risk of VTE and the presence of active cancer is one of the strongest predictors of in-hospital VTE in validated risk assessment scores (44–46). The rate of in-hospital VTE is 3-fold higher in cancer patients compared to patients without cancer with an absolute risk that ranges from 0.6% to 7.8% (47). Data on the efficacy and safety of thromboprophylaxis in hospitalized medical cancer patients is scant. A recent meta-analysis by Carrier and colleagues identified only three VTE prevention studies that compared either LMWH or fondaparinux with placebo and reported on the subgroup of cancer patients (48). This combined analysis showed that thromboprophylaxis was not associated with a reduction in the risk of VTE (RR 0.91, 95% CI 0.2 to 4). Major bleeding rates were not reported in any of the studies. Nevertheless, based on extrapolations from clinical trials in the general population, all international guidelines recommend thromboprophylaxis with heparin or fondaparinux in cancer patients hospitalized for medical reasons, in the absence of bleeding or other contraindications to anticoagulation. Trials on VTE prophylaxis with DOACs in hospitalized medical patients have led to disappointing

results and data are not available for the subgroups with cancer (49,50). The use of DOACs in these patients cannot be recommended at this moment.

Ambulatory cancer patients receiving chemotherapy

Most of the trials that evaluated LMWH for thromboprophylaxis in ambulatory cancer patients have restricted inclusion to one or more types of advanced stage cancers associated with a high VTE risk. In a recent Cochrane meta-analysis, LMWH was associated with a significant 47% relative reduction in symptomatic VTE compared to no anticoagulation (RR 0.53, 95% CI 0.4 to 0.8) (51). No significant difference in major bleeding (RR 1.3, 95% CI 0.8 to 2.2) or mortality (RR 0.95, 95% CI 0.8 to 1.1) was observed. Despite these results in favor of LMWH, current guidelines recommend against the routine use of pharmacologic thromboprophylaxis in ambulatory cancer patients. With a baseline risk of 5.2%, the relative risk reduction of almost 50% translates into an absolute risk reduction of 2.4% (51), hence a number of patients needed to treat of 42 to prevent one thromboembolic event. In general, this absolute risk reduction is deemed too low to justify daily subcutaneous injections for at least 3 months in patients with a limited life expectancy.

To increase the absolute benefit of LMWH thromboprophylaxis, some VTE prevention trials focused on a single high-risk tumor type. The FRAGEM trial randomly assigned 123 patients with advanced pancreatic cancer to therapeutic, weight-adjusted dalteparin versus standard of care (without anticoagulants) during 3 months of gemcitabine chemotherapy (52). Overall, 23% of patients in the standard of care arm developed arterial or venous thromboembolic complications that were symptomatic or incidental compared to 3% in the dalteparin arm (RR 0.15, 95% CI 0.04 to 0.6). Major bleeding rates were similar (3.4% vs. 3.2%). In the recently published CONKO-004 trial, 312 patients with advanced pancreatic cancer receiving gemcitabine were allocated to a half-therapeutic dose of enoxaparin (1 mg/kg/day) for 3 months followed by a once daily prophylactic dose enoxaparin versus standard of care (53). In the first 3 months of treatment, 1.3% of the enoxaparin treated patients developed symptomatic VTE compared to 9.9% of patients not receiving thromboprophylaxis (hazard ratio [HR] 0.12, 95% CI 0.03 to 0.5). Major bleeding occurred in 4.4% and 3.2% of patients (HR 1.4, 95% CI 0.4 to 3.7), respectively. Finally, in a third randomized trial dalteparin 5,000 IU daily was compared to no thromboprophylaxis in 75 patients with advanced pancreatic cancer (54). Consistent with earlier observations, 8% of patients in the dalteparin group developed symptomatic or asymptomatic VTE compared to 22% in the standard of care group ($P = 0.02$). Weighted combined analysis data from studies in pancreatic cancer patients suggest a 78% relative risk reduction in thromboembolic complications during the first months of chemotherapy (RR 0.22, 95% CI 0.1 to 0.4; Figure 6.1). With an overall baseline risk of 13%, this translates into an absolute risk reduction of 10% (95% CI 5 to 15%),

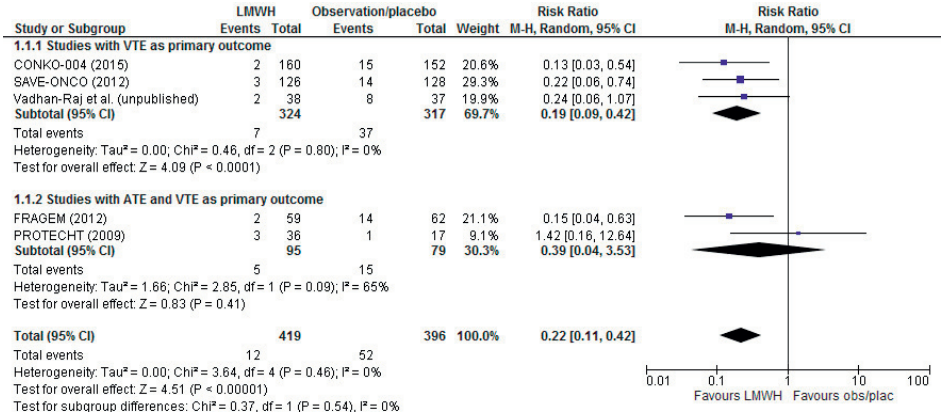

Figure 6.1. Low-molecular-weight heparin compared with no thromboprophylaxis in ambulatory patients with advanced pancreatic cancer: arterial or venous thromboembolism
VTE: venous thromboembolism; ATE: arterial thromboembolism; LMWH: low-molecular-weight heparin; M-H: Mantel Haenszel; CI: confidence interval

and a number needed to treat of 10 to prevent one thromboembolic complication. The pooled result of the FRAGEM and CONKO-004 trials suggest that this benefit is not offset by a significant increase in major bleeding (RR 1.25, 95% CI 0.5–3.3). When interpreting these results, however, it should be acknowledged that different LMWH regimens were used in the trials and efficacy outcome definitions were heterogeneous. Moreover, most studies had an open-label design without blinded outcome adjudication. Nevertheless, this emerging evidence indicates that patients with advanced, high-risk cancer such as pancreatic adenocarcinoma starting chemotherapy may safely benefit from thromboprophylaxis.

Other VTE prevention trials that restricted enrolment to a single tumor type were inconclusive (55,56). Patients with newly diagnosed multiple myeloma treated with chemotherapy regimens that include lenalidomide or thalidomide are at high risk of VTE (57–59). In these patients the American Society of Clinical Oncology recommends thromboprophylaxis with either LMWH or low-dose aspirin (39).

The use of DOACs as thromboprophylaxis in ambulatory cancer patients was evaluated in a dose-finding study which randomized 125 patients with advanced cancer to apixaban 5 mg, 10 mg, or 20 mg once daily, or placebo (60). Symptomatic VTE was diagnosed in 3 of 29 patients (10%) in the placebo group and in none of those on apixaban. Major bleeding occurred in 6% of patients on apixaban 20 mg, and none of those receiving lower doses of the drug. Although conclusions are hampered by the low sample size (the study was stopped prematurely due to the low accrual rate), these results appear promising and have prompted the ongoing AVERT trial (https://clinicaltrials.gov/ct2/show/NCT02048865) which randomly allocates cancer patients with a

high VTE risk to either apixaban 2.5 mg twice daily or placebo. The primary outcome is symptomatic or asymptomatic VTE during 7 months of follow-up. The targeted sample size is 574 patients and enrolment is expected to be complete in 2017.

What may be a way forward to prevent thromboembolic complications in ambulatory cancer patients? The net-clinical benefit of thromboprophylaxis could be increased by VTE risk stratification according to well-known risk factors. The Khorana score is a well-validated VTE risk assessment score that could be used to identify cancer patients at higher risk of VTE (61). The PHACS study randomized cancer patients at high risk of VTE according to the Khorana score to prophylactic dose dalteparin for 12 weeks versus no dalteparin (https://clinicaltrials.gov/ct2/show/NCT00876915). Recruitment is completed and results are expected soon. Some authors have proposed the use of biomarkers for VTE risk stratification in cancer patients although the evidence is not unequivocal (62). The Microtec study was a phase 2 study that randomized patients with advanced cancer and high levels of tissue factor exposing vesicles to either prophylactic dose enoxaparin or observation (63). During the 2-month follow-up, VTE was diagnosed in 4% of patients on enoxaparin compared to 27% in the observation group (HR 6.7, 95% CI 1.0–43), a difference largely driven by incidental DVT diagnosed on screening ultrasound. While these results require confirmation in larger studies, measurement of coagulant extracellular vesicles for VTE risk stratification in cancer patients may be difficult to implement in routine practice. Finally, the addition of circulating biomarkers to the Khorana score seemed to improve the identification of patients at risk (64), although the extended score needs validation.

Treatment of VTE in patients with cancer

Initial treatment

As for the general population with no cancer, the mainstay of the initial VTE treatment in cancer patients is parenteral anticoagulation. In a recent review of the literature on the initial treatment of VTE in cancer patients, LMWH and UFH were similarly effective in preventing recurrent VTE, while LMWH was associated with a significant 29% reduction in mortality at 3 months (65). Data on the use of fondaparinux as initial treatment of cancer-associated VTE are limited to a post-hoc analysis of the Matisse trials (66). No statistically significant differences in recurrent VTE, bleeding, and mortality were observed between fondaparinux and heparin. Based on the available data, LMWH is now recommended for the initial treatment of cancer-associated VTE (39,67). LMWH offers some advantages over UFH such as the subcutaneous administration at fixed weight-based doses, lower costs, and lower risk of heparin-induced thrombocytopenia

(68). UFH may, however, be considered in patients with a creatinine clearance less than 30 mL/min since it is largely dependent on hepatic clearance.

Long-term treatment

Type of anticoagulant

In the seminal CLOT study, nearly 700 patients with active cancer were randomized to receive 6 months of open-label dalteparin monotherapy (full dose in the first month, followed by a 75% dose for the remaining 5 months) or 5 to 10 days of dalteparin followed by VKAs targeted at an INR between 2 and 3 (13). During a 6-month follow-up, 9% of patients treated with dalteparin and 17% of those receiving VKA developed recurrent VTE (hazard ratio [HR] 0.48; 95% CI 0.3 to 0.8). No significant difference was observed in the rate of major bleeding (6% vs. 4%). Subsequently, three other trials reported similar results (Table 6.1) and a meta-analysis of all these studies demonstrated a significant 53% relative risk reduction in recurrent VTE with LMWH compared to VKAs with no difference in major bleeding (RR 1.07; 95%-CI 0.5 to 2.2) and survival (HR 0.96; 95%-CI 0.8 to 1.1) (69). Based on a superior efficacy and a similar safety profile relative to VKAs, LMWH is currently recommended for the treatment of cancer-associated VTE by all major international guidelines (39,67,70).

In the recent CATCH study, an open-label, randomized clinical trial with blinded outcome evaluation, full-dose tinzaparin was compared with VKA for VTE treatment in patients with active cancer (16). During the 6 month follow-up period, the incidence of recurrent VTE was comparable in patients treated with tinzaparin (7%) and warfarin (10%; HR 0.65, 95% CI 0.4 to 1.0) and no difference in major bleeding was observed (2.7% vs. 2.4%). Tinzaparin was, however, associated with a significant 42% relative reduction in clinically relevant non-major bleeding (11% versus 15%; HR 0.58, 95% CI 0.4 to 0.8). Taken together, the results of the CATCH study are in line with the earlier trials and support the use of LMWH for the treatment of cancer-associated VTE. The pooled analysis including the CATCH study results shows a 43% reduction in recurrent VTE with LMWH compared to VKAs (RR 0.57, 95% CI 0.4 to 0.8; Figure 6.2) and a comparable risk of major bleeding (RR 1.07, 95% CI 0.7–1.8; Figure 6.3).

The 6 trials evaluating DOACs for VTE treatment in the general population enrolled about 27,000 patients of whom 5% had either active cancer or a history of cancer at randomization. In the subgroup analysis of these patients, a significantly lower VTE recurrence rate was found in the DOAC recipients compared with patients receiving VKA (RR 0.57, 95% CI 0.4 to 0.9). No difference in major bleeding rate was observed (RR 0.77, 95% CI 0.44 to 1.33) (33). Although encouraging, these findings should be interpreted with caution. Cancer patients enrolled in the DOAC trials were probably healthier than those in studies specifically designed for patients with acute VTE and active cancer,

Table 6.1. Summary of randomized controlled trials evaluating the efficacy and safety of anticoagulant treatment of cancer-associated venous thromboembolism

Trial	Design	Number of cancer patients	Experimental arm	Control arm	Intended treatment duration	Recurrent VTE	Major bleeding	All-cause mortality
Lopaciuk et al., 1999 (95)	Open-label; unclear whether end-point assessment was blinded	12 (subgroup analysis)	nadroparin (6)	nadroparin à acenocoumarol (6)	3 months	NR NR	NR NR	67% 50%
López-Beret et al., 2001 (96)	Open-label; unclear whether end-point assessment was blinded	35 (subgroup analysis)	nadroparin (17)	nadroparin à acenocoumarol (18)	3 to 6 months	5.9% 22%	12% 11%	41% 33%
CANTHANOX, 2002 (27)	Open-label with blinded end-point	138	enoxaparin (71)	enoxaparin à warfarin (67)	At least 3 months	Combined: 10.5% Combined: 21.2%		NR NR
Cesarone et al., 2003 (97)	Open-label; unclear whether end-point assessment was blinded	192	enoxaparin (96)	enoxaparin à coumadin (96)	3 months	6.6% 10%	NR NR	2.1% 3.1%
CLOT et al., 2003 (13)	Open-label with blinded end-point	672	Dalteparin (336)	dalteparin à VKA (336)	6 months	9% 17%	6% 4%	39% 41%
ONCENOX, 2006 (15)	Open-label; no blinded end-point assessment	102	enoxaparin (68)	enoxaparin à warfarin (34)	6 months	6.6% 10%	9.0% 2.9%	33% 32%
Main-LITE, 2006 (26)	Open-label; no blinded end-point assessment	200	tinzaparin (100)	UFH à VKA (100)	3 months	7% 16%	NR NR	47% 47%
Romera et al., 2009 (98)	Open-label with blinded end-point	69 (subgroup analysis)	tinzaparin (36)	tinzaparin à acenocoumarol (33)	6 months	5.5% 21%	2.8% 9.1%	5.6% 6.1%
Van Gogh DVT, 2010 (99)	Open-label with blinded end-point	421 (subgroup analysis)	idraparinux (220)	heparin à VKA (201)	3 to 6 months	2.5% 6.4%	2.1% 1.5%	23% 24%
CATCH, 2015 (16)	Open-label with blinded end-point	900	tinzaparin (449)	tinzaparin à warfarin (451)	6 months	6.9% 10%	2.7% 2.4%	33% 31%

VTE: venous thromboembolism; UFH: unfractionated heparin; VKA: vitamin K antagonist

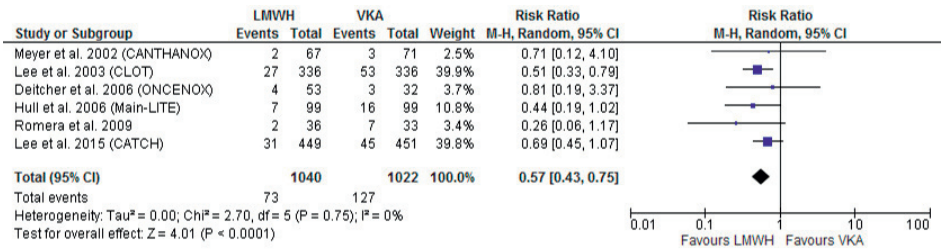

Figure 6.2. Low-molecular-weight heparin compared with vitamin K antagonists for treatment of venous thromboembolism in patients with active cancer: recurrent venous thromboembolism
LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; M-H: Mantel Haenszel; CI: confidence interval

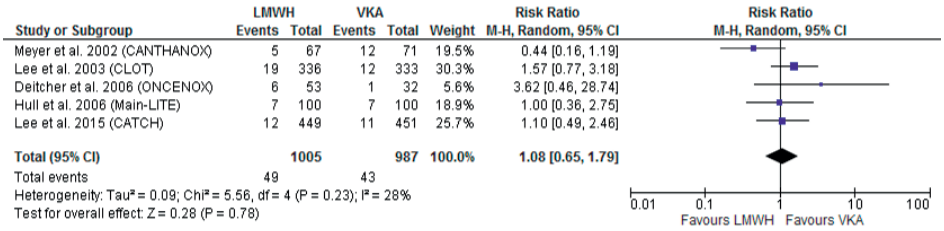

Figure 6.3. Low-molecular-weight heparin compared with vitamin K antagonists for treatment of venous thromboembolism in patients with active cancer: major bleeding
LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; M-H: Mantel Haenszel; CI: confidence interval

since patients for whom LMWH therapy was anticipated were excluded. Cancer was not consistently defined across the trials and cancer-specific information was either not available or not reported. Most importantly, DOACs were compared to VKA and not to LMWH which is currently the recommended treatment option. Several studies have recently been initiated to evaluate DOACs for the treatment of cancer-associated VTE.

The Hokusai VTE-cancer study is an ongoing international, randomized, open-label trial comparing the efficacy and safety of the factor Xa-inhibitor edoxaban with dalteparin monotherapy for the treatment of VTE in patients with cancer (https://clinicaltrials.gov/ct2/show/NCT02073682). This pragmatic study has incorporated various innovative features in its design to optimize the internal and external validity. The primary outcome is the combination of recurrent VTE and major bleeding, incidental VTE is an inclusion criterion as well as a component of the primary outcome, and the intended treatment duration is 12 months which is expected to provide valuable information on the anticoagulant treatment in cancer patients beyond 6 months. The study aims to enroll 1000 patients and has started recruitment in July 2015.

The Select-d study is a randomized, open-label trial comparing dalteparin with rivaroxaban for the treatment of symptomatic or incidental VTE in patients with active cancer (http://www.isrctn.com/ISRCTN86712308). After 6 months of treatment, patients with residual thrombosis will be randomized again to either placebo or extended rivaroxaban treatment for another 6 months. The study aims to enroll 530 patients and has started recruitment in 2013. Last, a single arm study in Korea is currently prospectively evaluating the efficacy and safety of rivaroxaban in a cohort of cancer patients with VTE (https://clinicaltrials.gov/ct2/show/NCT01989845).

Treatment duration

All studies evaluating treatment of cancer-associated VTE limited study treatment to a maximum of 6 months (Table 6.1), hence data regarding the optimal treatment duration are lacking. Based on the high risk of recurrent VTE, it is generally recommended to extend anticoagulant treatment beyond 6 months when the cancer is active or cancer treatment is ongoing (70). The decision to continue treatment should be weighed against the threat of major bleeding and the risk-benefit ratio should be reassessed periodically. Patient's preference and quality of life should also be taken into account. Isolated distal DVT, VTE associated with a superimposed reversible risk factor (e.g. surgery), or cancer that has responded to treatment or has not metastasized seem associated with a lower risk of recurrence and physicians could consider a shorter course of anticoagulant treatment in these cases (70).

Which anticoagulant should be used beyond 6 months remains a dilemma. In a survey conducted amongst thrombosis and non-thrombosis specialists, 44% preferred LMWH, 10% would choose VKA, and the remaining 45% would make a choice between LMWH or VKA on an individual patient basis (71). Unfortunately, the only randomized trial which evaluated the treatment of cancer-associated VTE beyond 6 months, the Longheva study, was prematurely terminated due to low accrual rates (https://clinicaltrials.gov/ct2/show/NCT01164046). The recently published DALTECAN study was a prospective, single-arm cohort study that evaluated the long-term safety of dalteparin in patients with active cancer and VTE (14). During the first month of treatment when patients were receiving full-dose dalteparin, the rates of major bleeding and recurrent VTE were 3.6% and 5.7%, respectively. Thereafter, the dalteparin dose was reduced to 75% and was associated with a higher monthly risk of major bleeding during month 2 to 6 (1.1%) than month 6 to 12 (0.7%). The risk of recurrent VTE per month was consistent during treatment from 2 to 12 months (0.7%). Two important messages emerge from these findings. First, the risk of anticoagulant-related major bleeding in cancer patients remains high, even with a reduced dose of LMWH. Second, the risk of recurrent VTE is still substantial after the initial 6 months of treatment which would support extending VTE treatment beyond 6 months.

Treatment of recurrent VTE during anticoagulant treatment

Recurrent VTE may develop in cancer patients despite appropriate anticoagulant therapy. Management of these cases is challenging, especially in light of the scant data supporting specific treatment strategies (72). Once heparin-induced thrombocytopenia is excluded in patients receiving LMWH, the dose could be increased by 25% with peak anti-factor Xa levels aimed at concentration of 1.6 to 2.0 U/mL in case of once daily dosing and 0.8 to 1.0 U/mL for a twice daily regimen (72). Patients treated with VKA should be switched to LMWH (69). In a recent registry of 212 cancer patients with recurrent VTE, 41% of patients continued with the same anticoagulant regimen, 31% had higher dosage of the same drug and in the remainder the drug was changed. During 3-month follow-up, 11% of patients had an additional recurrent VTE which, surprisingly, was not associated with the choice of increasing the dose of anticoagulant treatment. Patients continuing on or switching to VKAs after recurrent VTE were at significantly higher risk of an additional recurrent VTE than patients receiving LMWH (29% vs. 9%; HR 0.28, 95% CI 0.1 to 0.7). Major bleeding occurred in 8% of the patients, all of whom were on LMWH (OR vs. VKA 4.6, 95% CI 0.3 to 80).

Treatment of incidental VTE

Prospective studies evaluating the prognosis of incidental VTE in cancer patients are lacking. Several retrospective studies suggest that the risk of recurrent VTE is similar in patients with incidental VTE compared to those with symptomatic VTE (73–75). The evidence on the management of incidental VTE in cancer patients is limited to relatively small case series and retrospective studies which overall suggest that the risk of recurrent VTE is not negligible if left untreated (76–81). In an interim analysis of an ongoing international registry, Soler and colleagues observed no recurrences in 78 cancer patients with incidental PE while receiving anticoagulant treatment (82). An individual patient data meta-analysis of 926 cancer patients with incidental PE, reported a VTE recurrence rate of 6% in patients treated with LMWH compared with 12% of those left untreated and 6.4% of patients receiving VKAs (83). The risk of major bleeding was significantly higher in patients treated with VKA compared to those treated with LMWH (13% versus 4%, HR 3.2; 95%CI 1.4 to 7.4). In the absence of contraindications for anticoagulation, the international guidelines recommend the same initial and long-term treatment for incidental VTE as for symptomatic VTE (39,67,70). Whether selected subgroups such as those with isolated subsegmental PE (SSPE) may be treated more conservatively remains unknown. In a combined post-hoc analysis of two large prospective cohort studies, a similar rate of complications such as recurrent VTE, bleeding and mortality was found for symptomatic SSPE as for more proximal symptomatic PE (84). In a study by O'Connell and colleagues, however, cancer patients with incidental SSPE were found to have a better median survival than patients with more proximal incidental PE, and

a similar survival as patients without PE (76). Comparable results were reported by van der Hulle and colleagues, showing a mortality rate after 6 months of 42% in patients with a central or lobar incidental PE versus 30% in segmental or subsegmental PE (HR 1.8, 95% CI 1.4 to 2.3) (83).

An ongoing RCT is evaluating whether anticoagulant treatment can be safely withheld in patients with symptomatic SSPE and no evidence of concomitant DVT (https://clinicaltrials.gov/ct2/show/NCT01455818), but cancer patients are excluded from participation. Furthermore, an ongoing international, multicenter, observational study is recruiting consecutive cancer patients with incidental PE in over 30 centers worldwide, aiming to record current treatment approaches and to prospectively assess the risk of recurrent VTE, bleeding, and mortality during a 12 month follow-up (https://clinicaltrials.gov/ct2/show/NCT01727427). Results of this study are expected in 2017.

Treatment of splanchnic venous thrombosis (SVT)

There is scant information on the efficacy and safety of anticoagulant treatment in patients with SVT. The current guidelines recommend anticoagulant therapy for all patients with symptomatic SVT, for at least 3 months, based on observational studies (85–90) and on extrapolations from treatment of DVT of the leg and PE (70). Treatment of SVT may be complicated by an increased risk of bleeding associated with esophageal varices as a consequence of portal hypertension, and thrombocytopenia secondary to hypersplenism. In fact, some studies showed bleeding risks exceeding the risk of recurrent VTE (85–87,89). For incidentally detected SVT, the risks and benefits of anticoagulant treatment should be weighed on an individual basis (39,67,70). Factors that may support anticoagulant treatment are signs of acute thrombosis (i.e. acute abdominal symptoms or specific radiologic features), ongoing chemotherapy, or progression of thrombus during follow-up imaging (70). Therefore, if left untreated, repeated imaging to detect progression of the thrombus seems justifiable. Recently the results of an international registry of patients with SVT were published (91). In total, 604 patients, of which 22% had solid and 9% hematological cancer, were included and followed prospectively for a median duration of 2 years. Two-thirds of the patients with solid cancer received anticoagulant treatment, mostly heparin. In 136 cancer patients, the incidence of major bleeding was 4.4 per 100 patient-years (95% CI 2.1 to 9.3). There were 12 thrombotic events, corresponding to an incidence of 7.6 per 100 patient-years.

Treatment of catheter-related thrombosis

No randomized controlled trials specifically evaluated the treatment of central venous catheter (CVC) related thrombosis. International guidelines suggest the same initial and long-term treatment as for patients with DVT of the leg or PE (67,70). If thrombosis occurs in association with a CVC, the catheter should be removed when it is no longer

required or is not functioning (and cannot be made to function even after a period of systemic anticoagulation). Several studies have suggested that CVC-related thrombosis is associated with a low risk of recurrent VTE (92,93). In a prospective cohort of 74 cancer patients with CVC-related symptomatic UEDVT there were no recurrent VTE events and 4% experienced major bleeding events during 3 months of treatment with dalteparin followed by VKAs. In this study, CVC were not removed (93). In a recent retrospective cohort study of 99 consecutive outpatients with cancer with symptomatic CVC-related UEDVT, no recurrent VTE and two bleeding episodes occurred during a total median treatment duration of 110 days (94). In 80 patients who were followed after cessation of anticoagulant treatment, 5 recurrent VTE were observed during a median of 632 days. The catheter had been pulled out in 96% (94).

Based on expert consensus, guidelines suggest 3 months of anticoagulation for CVC-related UEDVT if the CVC is removed, otherwise anticoagulation may be prolonged beyond 3 months, at least as long as the catheter is in place (67,70).

Conclusion

VTE is a major cause of morbidity and mortality in patients with cancer, and cancer patients with VTE are at increased risk of recurrent VTE and major bleeding. Anticoagulant treatment is challenging in these patients who often receive multiple antineoplastic drugs, frequently undergo diagnostic or therapeutic interventions, and are susceptible to nausea and vomiting.

The combined evidence from clinical trials demonstrates the superiority of LMWH over VKA in preventing recurrent VTE, while the risk of major bleeding is comparable. Therefore, LMWH is currently the recommended treatment of cancer-associated VTE, including incidental VTE, UEDVT, and splanchnic DVT. Ongoing trials will evaluate the effectiveness and safety of DOACs in patients with cancer and VTE, but results are not expected before 2017. Given the rise in the incidence of cancer-associated VTE over the past two decades, the focus is shifting to VTE prevention and the importance of thromboprophylaxis is increasingly acknowledged. However, primary VTE prophylaxis in ambulatory cancer patients with LMWH is associated with a 2 to 3% absolute risk reduction, which in general is deemed too low to justify its routine use. Identifying cancer patients at high risk of VTE based on the tumor type, biomarkers, or risk assessment scores could increase the absolute benefit of thromboprophylaxis, but the effectiveness of such selection strategies has not yet been established.

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Cancer-associated unsuspected pulmonary embolism

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Thromb Res. 2014 May;133 Supl 2:S172-8.

Abstract

Clinically unsuspected pulmonary embolism (UPE) is frequently diagnosed in cancer patients undergoing routine computed tomography scans for staging purposes or treatment response evaluation. The reported incidence of UPE ranges from 1% to 5% which probably represents an underestimation. A significant proportion of cancer patients with UPE actually do have pulmonary embolism (PE) related symptoms. However, these can erroneously be attributed to the cancer itself or to cancer therapy leading to a delayed or missed diagnosis. The incidence of UPE is likely to increase further with the improvements of imaging techniques. Radiologic features of UPE appear similar to symptomatic PE with nearly half of the UPE located in central pulmonary arteries and one third involving both lungs. UPE in cancer patients is not a benign condition with rates of recurrent venous thromboembolic events, bleeding and a mortality rate comparable to cancer patients with symptomatic PE. Current guidelines suggest that UPE should receive similar initial and long-term anticoagulant treatment as for symptomatic PE. However, direct evidence regarding the treatment of UPE is scarce and treatment indications are largely derived from studies performed in cancer patients with symptomatic venous thromboembolism. Selected subgroups of cancer patients with UPE such as those with sub-segmental UPE may be treated conservatively by withholding anticoagulation and avoiding the associated bleeding risk, although this requires further evaluation.

Introduction

In the last two decades computed tomography pulmonary angiography (CTPA) has progressively replaced ventilation-perfusion scanning as the imaging modality of choice for the diagnosis of clinically suspected pulmonary embolism (PE) (1,2). Advancements in CT scanning technology have led to the introduction of newer generation multi-detector array CT scanners (up to 320 slices) with higher acquisition speed, better spatial resolution, and dramatic improvements of pulmonary artery visualization. Hence, the sensitivity for detecting pulmonary emboli has significantly increased, in particular for more peripherally located clots (3,4). Improved resolution has regarded not only CTPA, but also contrast enhanced CT (CECT) scans which are performed for other reasons than PE evaluation. As a consequence, incidentally diagnosed PE is increasingly detected on CECT scans, especially on those performed in cancer patients.

Compared to healthy individuals, patients with cancer have a four- to sevenfold increased risk of developing venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and PE (5). Several cancer-related factors contribute to the high VTE rate such as the disease-associated state of hypercoagulability and the prothrombotic effects of antineoplastic treatments (5). Moreover, cancer patients frequently undergo CECT scanning for diagnostic or staging purposes and treatment response evaluation, thereby increasing the chances of detecting unsuspected pulmonary emboli. In fact, about half of all PE in cancer patients are incidentally diagnosed (6–8). In this review we will discuss the clinical and radiologic characteristics as well as the prognostic value of unsuspected pulmonary embolism (UPE) in cancer patients.

Definitions

Various terms have been used to describe incidentally diagnosed PE, such as 'asymptomatic', 'incidental', 'silent', 'unexpected' and 'unsuspected'. In order to reduce this heterogeneity, a common definition of this condition has been proposed (9). Since clinically unsuspected PE does not mean that the patient has no symptoms, the term 'asymptomatic PE' should be avoided. The terms 'incidental' and 'unsuspected' are preferred and now recommended for PE with no clinical suspicion at the time of CT examination. We will use 'unsuspected pulmonary embolism (UPE)' throughout this review and refer to clinically suspected PE as 'symptomatic PE'.

Table 7.1. Incidence of unsuspected pulmonary embolism in cancer patients

Study	Study design	Cancer patients (N)	Cancer type	CT reassessment	CT scanner	Slice thickness	UPE	
Gosselin *et al.* (1998) (23)	Prospective cohort	588	Mixed	Yes	4-row MDCT	5–5 mm	10	(1.7%)
Boswell *et al.* (2004) (47)	Prospective cohort	2,085	Mixed	NR	NR	2 mm	44	(2.1%)
Storto *et al.* (2005) (16)	Retrospective cohort	410	Mixed	Yes	4-row MDCT	5 mm	14	(3.4%)
Sebastian *et al.* (2006) (48)	Prospective cohort	385	Mixed	No	4-row MDCT	5–5 mm	10	(2.6%)
Gladish *et al.* (2006) (17)	Retrospective cohort	403	Mixed	Yes	4-row MDCT	3.75 mm	16	(4.0%)
Cronin *et al.* (2007) (49)	Retrospective cohort	397	Mixed	Yes	NR	8 mm	13	(3.3%)
Larici *et al.* (2007) (50)	Retrospective cohort	787	Mixed	Yes	16-row MDCT	2.5 mm	15	(1.9%)
Ritchie *et al.* (2007) (15)	Prospective cohort	343	Mixed	Yes	4-row or 16-row MDCT	1–1 mm	18	(5.2%)
Hui *et al.* (2008) (51)	Retrospective cohort	765	Mixed	Yes	16-row MDCT	2.5 mm	17	(2.2%)
Sun *et al.* (2010) (7)	Retrospective cohort	8,014	Lung cancer patients	No	NR	NR	180	(2.2%)
Farrell *et al.* (2010) (14)	Retrospective cohort	342	Mixed	Yes	4-row or 16-row MDCT	1–1 mm	6	(1.8%)
Di Niso *et al.* (2010) (52)	Retrospective cohort	1,921	Solid tumors	Yes	NR	NR	24	(1.2%)
Browne *et al.* (2010) (11)	Prospective cohort	407	Mixed	Yes	64-row MDCT	1 mm and 5 mm	18	(4.4%)
Menapace *et al.* (2011) (53)	Retrospective cohort	135	Pancreatic cancer	No	NR	NR	4	(3.0%)
Shingare *et al.* (2011) (8)	Retrospective cohort	13,783	Mixed	No	4-row or 64-row MDCT	5–5 mm	395	(2.9%)
Bach *et al.* (2013) (31)	Retrospective cohort	3,270	Mixed	Yes	64-row MDCT	5 mm	129	(3.9%)

UPE: unsuspected pulmonary embolism; MDCT: multidetector computed tomography; NR: not reported.

Incidence and radiologic characteristics

Incidence

The absolute incidence of UPE in cancer patients ranges from 1% to 5% depending on tumor type and stage, hospitalization status and presence of additional risk factors (Table 7.1). In a meta-analysis by Dentali *et al.*, the weighted incidence of UPE in cancer patients was higher than in non-cancer patients (3.1% vs. 2.5% respectively) (10). The incidence of UPE is influenced by the type of CT scanner (thick-collimation single detector CT versus thin-collimation multidetector CT) and study design (e.g. report by a single radiologist versus double reading by one or two expert radiologists). In a study by Browne *et al.* the reduction of the slice thickness from 5 mm to 1 mm on CTPA scans increased significantly the sensitivity for clots in smaller arteries. In 7 of 18 (39%) UPE patients, clots were confidentially visualized only on the 1 mm reconstructed slices (11). It is to be expected that, in the near future, the peripheral pulmonary vasculature will be even better depicted with the introduction of 128-slice CT scanners in routine clinical practice.

The incidence and prevalence of UPE may be significantly underestimated. Douma *et al.* performed a retrospective analysis of the initial radiologic reports of staging CT scans in cancer patients and reported only three UPE in 838 patients corresponding to a prevalence of 0.4% (12). Similarly, Shinagare *et al.* and Di Nisio *et al.* reported a UPE prevalence in cancer patients of 1.5% (202 out of 13,783) and 1.2% (24 out of 1921), respectively. By contrast, studies in which CECT scans where systemically reassessed (retrospectively or prospectively) for the presence of UPE showed much higher incidences (Table 7.1). This inconsistency could be, at least in part, explained by the false negative initial readings. In a study by Engelke *et al.*, 2412 CECT images including 1869 images of cancer patients, were reassessed for UPE by a single radiologist (13). The authors found an overall false-negative diagnostic rate of 69.4% (39 out of 56), despite routine double reading during the first evaluation. Other studies reported rates of false-negative diagnosis of UPE up to 75% (14–17). Finally, in autopsy studies the prevalence of PE that was unsuspected ante-mortem was as high as 23% in cancer patients (18–20).

Several factors may explain the high rate of false negative scans. First, as PE evaluation is not the primary goal of CECT scans, clots in the pulmonary arteries may be overlooked. Second, radiologists may use incorrect window displays that are not optimized for pulmonary arteries, resulting in contrast enhanced blood being too dense (21). Third, attention of the radiologist may be drawn to other, more evident, intrapulmonary pathology such as a primary lung tumor or pulmonary metastases, the so-called 'satisfaction-of-search phenomenon' (16,22). Lastly, UPE may be underreported when radiologists assume this finding has little or no clinical significance in cancer patients.

Besides the potentially avoidable misdiagnosis of UPE, other technical issues may contribute to the underreporting of UPE on CECT scans. Confident diagnosis of a filling defect can be difficult when images are reconstructed at thick slice due to partial volume effects and movement artefacts (23). Moreover, visualization of the pulmonary artery tree at CECT scans is often suboptimal as the scan is not timed at the point of maximum opacification of the pulmonary trunk, reducing the sensitivity especially for more peripheral clots. Consequently, the diagnosis of UPE can be uncertain in selected cases, as reflected by the considerable inter-observer variability. Inter-observer variability among radiologists may be particularly high for the diagnosis of subsegmental PE (SSPE). Pena *et al.* reported that an independent expert radiologist agreed with the initial SSPE diagnosis in only 51% of the cases after reassessment of 70 CTPA scans (24). No studies have systematically addressed interobserver variability for PE assessment on CECT scans. In a retrospective study by Gladish *et al.* (17), PE was identified in 14 out of 403 routine CECT scans by two independent radiologists. Yet another 12 patients had possible emboli that were detected by only one reader, and in just two of them pulmonary emboli were confirmed by consensus.

Radiologic characteristics

As for symptomatic PE, about one-half of UPE is located in lobar or more central arteries (Table 7.2) (6–8,11,12,17,23,25–28) and bilateral lung involvement occurs in 23–46% of the cases (Table 7.2). When compared to symptomatic PE, UPE seems to be similar in terms of PE-associated CT-findings such as lung infarction and increased pulmonary artery caliber (29). The embolic burden of UPE in cancer patients was described by Den Exter *et al.* in a recent retrospective cohort study (30). A series of consecutive CECT scans in 48 cancer patients with UPE were reassessed by a single reviewer and compared to 113 CTPA scans of consecutive patients (cancer and non-cancer) with acute symptomatic PE. The median obstruction index, according to the Qanadli scoring system, was significantly higher in patients with symptomatic PE compared to UPE (30% vs. 18%, $p = 0.008$). However, as acknowledged by the authors, the embolic burden of UPE was probably underestimated. In the group of patients with UPE none was diagnosed with SSPE which may reflect the challenge of correctly detecting peripheral emboli with CECT scans. Similarly, in a study by Bach *et al.* the embolic burden of 129 cancer patients with UPE was significantly lower compared to 111 cancer patients with symptomatic PE (31). Regarding the relevance of embolic burden, den Exter *et al.* found no association between the obstruction index in UPE cancer patients and 6-month survival (30). No studies have addressed the presence of right ventricular diameter or dysfunction which was found to be associated with a poor clinical outcome in patients with symptomatic PE (32). Large prospective studies are needed to clarify the prognostic relevance of embolic burden or right ventricular dysfunction in UPE.

Table 7.2. Radiologic characteristics of unsuspected pulmonary embolism in cancer patients

		Most proximal thrombus location (%)						
	UPE (N)	Main artery	Lobar artery	Segmental artery	Subsegmental artery	Central arteries	Peripheral arteries	Bilateral (%)
Shinagare *et al.* (2011) (8)	202	62 (30.7%)	62 (30.7%)	65 (32.2%)	13 (6.4%)	124 (61.4%)	78 (38.6%)	NR
Sun *et al.* (2010) (7)	113	NR	NR	56 (49.6%)	0 (0.0%)	57 (50.4%)	56 (49.6%)	32 (28.3%)
O'Connell *et al.* (2011) (25)	70	7 (10.0%)	26 (37.1%)	20 (28.6%)	17 (24.3%)	33 (47.1%)	37 (52.9%)	NR
Sahut d'Izarn *et al.* (2012) (26)	66	4 (6.1%)	14 (21.2%)	38 (57.6%)	10 (15.2%)	18 (27.3%)	48 (72.7%)	NR
Font *et al.* (2011) (6)	56	NR	NR	NR	NR	36 (64.3%)	20 (35.7%)	23 (41.1%)
Den Exter *et al.* (2011) (27)	45	NR	NR	30 (66.7%)	4 (8.9%)	11 (24.4%)	34 (75.6%)	NR
Browne *et al.* (2010) (11)	18	4 (22.2%)	5 (27.8%)	6 (33.3%)	3 (16.7%)	9 (50.0%)	9 (50.0%)	NR
Gladish *et al.* (2006) (17)	16	0 (0.0%)	8 (50.0%)	7 (43.8%)	1 (6.3%)	8 (50.0%)	8 (50.0%)	6 (37.5%)
Gosselin *et al.* (1998) (23)	13	4 (30.8%)	4 (30.8%)	5 (38.5%)	0 (0.0%)	8 (61.5%)	5 (38.5%)	6 (46.2%)
Douma *et al.* (2010) (12)	3	NR	NR	2 (66.7%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	NR
Tiseo *et al.* (2012) (28)	21	2 (9.5%)	6 (28.6%)	13 (61.9%)	0 (0.0%)	8 (38.1%)	13 (61.9%)	5 (23.8%)
Total	609	83 (20.4%)	117 (28.8%)	229 (40.4%)	48 (8.5%)	302 (49.6%)	307 (50.4%)	67 (30.6%)

UPE: unsuspected pulmonary embolism; NR: not reported.

To summarize, the true prevalence and incidence of UPE remain uncertain. Radiologists should carefully evaluate the presence of UPE, especially in high risk groups such as cancer patients. The detection rate of UPE could be further improved by performing CECT scans during the arterial phase (11), provided that the quality of the cancer evaluation does not deteriorate.

Clinical and demographic characteristics

Cancer patients with UPE have a mean age of 60 to 70 years (8,27,33) and UPE rates appear similar between males and females. Data on the absolute UPE incidence stratified by tumor type is scarce. In a large retrospective cohort including 13,783 cancer patients, Shinagare *et al.* found the highest UPE incidence in patients with pancreatic cancer (4.9%), hepatobiliary cancer (4.8%), upper gastrointestinal tract cancer (3.7%), and colorectal cancer (2.6%) (8). Not surprisingly, the risk of UPE is higher in cancer patients who are hospitalized and in those with more advanced stage cancer and worse performance status (10,26). Other factors contributing to the risk of UPE are recent surgery, prior VTE, active chemotherapy, and the presence of a central venous catheter, although the evidence has not been always consistent (25,26). Cancer patients with UPE share a similar risk profile to those with clinically suspected PE, with UPE being more frequently associated with central venous catheters or chemotherapy treatment (26,27,34).

Symptoms

The finding of UPE implies that PE was clinically not suspected at the time of CT scanning. This, however, does not mean in itself that there were no symptoms or signs that could, or perhaps should, have raised the suspicion of the physician. Analyses of retrospective data from medical charts of cancer patients with UPE revealed that up to 75% had signs and symptoms possibly linked to the presence of PE at the time of the diagnosis. Compared to cancer patients without PE, shortness of breath, cough, and fatigue were significantly more prevalent among cancer patients with UPE (25). Rates of lung cancer and presence of pulmonary metastases in both groups were comparable. Similarly, in a case-control study by Sahut d'Izarn *et al.*, 27 of the 66 cancer patients (41%) with UPE had one or more symptoms possibly worsened by PE, such as dyspnea (23%), chest pain (9%), hemoptysis (1%) or leg pain (8%) as a sign of potential DVT (26). It is not unlikely that these numbers represent conservative estimates of the frequency of signs and symptoms as they were not systematically recorded in these retrospective studies. Hence, these findings suggest that a proportion of cancer patients with UPE are actually symptomatic at the time of diagnosis, but symptoms apparently do not

trigger the physician to order a dedicated CTPA for ruling out or ruling in PE. This could be explained by the poor specificity of many signs and symptoms of UPE (e.g. fatigue and dyspnea on exertion), that may erroneously be attributed to the cancer itself or its therapy (i.e. chemotherapy or radiotherapy), leading to a delayed or missed diagnosis of UPE.

Prognosis of UPE

VTE has been identified as a marker of worse survival in cancer patients irrespective of age, cancer stage or cancer histology (35). This poor prognosis is probably not a direct result of VTE, but more likely reflects an aggressive cancer biology. Few studies, none prospective, evaluated the clinical outcome of UPE in cancer patients (Table 7.3). To our knowledge, there are no reported cases of early UPE-related death in cancer patients, which is somewhat surprising given that a substantial proportion of UPE is located in central arteries (i.e. main or lobar arteries) (Table 7.2). However, it should be noted that all the available studies did not include patients with more severe cases of UPE associated with hemodynamic instability.

Unsuspected vs. symptomatic pulmonary embolism

Long-term mortality of 51 cancer patients with UPE versus 144 cancer patients with symptomatic PE was described by Den Exter *et al.* in a retrospective study (27). The clinical risk profile of both groups was similar and the vast majority of patients in both groups received long-term anticoagulant treatment (98% vs. 92%). No differences were observed between UPE and symptomatic PE patients in terms of the cumulative VTE recurrence risk (9.8% vs. 10.4%) or mortality rate (52.9% vs. 52.8%) after 12 months of follow-up. These results were later confirmed in a case-control study by Sahut d'Izarn *et al.* and in a retrospective cohort of lung cancer patients by Shinagare *et al.* (26,34). Both studies suggested similar mortality rates for cancer patients with symptomatic PE and UPE. In all of these studies, competing events such as death were not taken into account in the statistical analysis, possibly causing an overestimation of the absolute risk of VTE recurrence (36,37).

Sun *et al.* conducted a large retrospective cohort study including more than 8000 lung cancer patients. In total 180 patients developed PE (2.2%) of which 67 (37%) were symptomatic and 113 (63%) clinically unsuspected. Nearly half of the UPE patients were treated at the physician's discretion and most received warfarin. Treated patients had a median survival of 30.9 months compared to 6.1 months of patients not receiving anticoagulation corresponding to a fourfold increase in survival (hazard ratio 4.1; 95% CI, 2.3–7.6). This survival difference was not explained by differences in

Table 7.3. Prognosis of cancer patients with unsuspected pulmonary embolism

	Study design	UPE (N)	Cancer type	Follow-up time	Patients treated (%)	Mortality (%)	Recurrent VTE (%)	Major bleeding (%)
Sun *et al.* (2010) (7)	Retrospective cohort	113	Lung	NR	51 (45.1%)	NR	NR	NR
O'Connell *et al.* (2011) (25)	Case-control	70	Mixed	12 months	59 (84.3%)	NR	NR	NR
Sahut d'Izarn *et al.* (2012) (26)	Case-control	66	Mixed	6 months	66 (100%)	11 (16.7%)	4 (6.1%)	3 (4.5%)
Den Exter *et al.* (2011) (27)	Retrospective cohort	51	Mixed	12 months	51 (100%)	27 (52.9%)	5 (9.8%)	5 (9.8%)
Abdel-Razeq *et al.* (2011) (54)	Retrospective cohort	34	Mixed	NR	29 (85.3%)	9 (26.5%)	2 (5.9%)	NR
Shinagare *et al.* (2011) (8)	Retrospective cohort	32	Lung	Median: 6.0 months	30 (93.8%)	28 (87.5%)	6 (18.8%)	1 (3.1%)
Browne *et al.* (2010) (11)	Prospective cohort	18	Mixed	6 months	17 (94.4%)	NR	1 (5.6%)	0
Douma *et al.* (2010) (12)	Retrospective cohort	3	Mixed	3 months	2 (66.7%)	1 (33.3%)	0	NR

UPE: unsuspected pulmonary embolism; NR: not reported.

performance status, cancer stage or tumor response status between the two groups. However, patients were not randomized to anticoagulant treatment and the influence of unmeasured confounders on the survival benefits cannot be ruled out. As current international guidelines recommend anticoagulant treatment for all cancer patients with UPE, it will be hard to gather prospectively data on the natural course of UPE in absence of anticoagulation.

Unsuspected pulmonary embolism vs. no pulmonary embolism

In a 2:1 case control study, Sahut d'Izarn *et al.* compared the clinical outcome of 66 cancer patients with UPE and 132 non-matched cancer patients without PE. All UPE patients were given anticoagulant treatment, mainly low-molecular-weight heparin (LMWH). After adjustment for performance status and tumor stage, no difference in the risk of death at 6 months was observed between UPE patients and patients without PE (26). In another case-control study, O'Connell *et al.* compared the mortality rates of 70 cancer patients with UPE with 137 control patients without PE matched for age, sex, cancer type and stage (25). Fifty-nine patients with UPE (84%) received some form of anticoagulant treatment. Patients with UPE had a significantly lower median survival (8 vs. 12 months; hazard ratio 1.51; 95% CI 1.01–2.27). No data were reported regarding the occurrence of recurrent PE or (major) bleeding.

Isolated sub-segmental pulmonary embolism

The clinical relevance of PE confined to one or more sub-segmental branches, i.e. isolated SSPE has been increasingly the subject of debate. Although improved CT scanning techniques over the past two decades have led to an increased detection rate of small clots in peripheral (sub-segmental) arteries, a recent systematic review showed no concurrent changes in mortality rates, suggesting that symptomatic SSPE might be of less clinical significance or even clinically unimportant (38). Support for this hypothesis was provided by several retrospective studies that showed no recurrent VTE or PE-related deaths during 3 months follow-up among patients with SSPE that were left untreated (39). By contrast, in a combined post-hoc analysis of two large prospective cohort studies, Den Exter *et al.* recently suggested that the prognosis for patients with SSPE may be comparable to patients with more proximally located PE studies (40). The rates of recurrent VTE, bleeding, and mortality were not significantly different between the two groups. The proportion of patients with active malignancy among the 116 patients with SSPE and 632 patients with proximal PE was 18.1% vs. 17.9% respectively.

Only limited data is available on the prognostic relevance of clinically unsuspected SSPE. O'Connell *et al.* included 17 cancer patients with unsuspected SSPE of whom 13 were treated with some form of anticoagulation (25). The median survival of these patients was significantly better compared to patients with more proximal PE (7 vs.

12 months; hazard ratio 1.70; 95% CI 1.06–2.74) and did not differ from the survival of matched control patients without PE, suggesting that unsuspected SSPE in cancer patients is not associated with poor survival. These data suggest that withholding anticoagulant treatment may be a safe option in these patients.

Management

When PE or concurrent DVT is confirmed, international clinical guidelines suggest [41], or recommend [42], the same initial and long-term treatment for UPE as for patients with symptomatic PE (41,42). Based on these guidelines, cancer patients with UPE would receive LMWH for at least 3 months or until the disease is resolved, which in most cases would mean indefinite treatment. However, well-designed prospective studies on the treatment of UPE are lacking. This leaves doubts over the need for (indefinite) anticoagulation which appears associated with significant rates of major bleeding (Table 7.3). Insights into the natural course of UPE in the absence of anticoagulant treatment are mainly derived from retrospective series where data were retrieved from the subset of patients in whom UPE was left untreated. The small size and methodological quality of these studies hamper any generalization of these findings to the whole group of cancer patients with UPE. In the study of O'Connell *et al.* all four patients in whom SSPE was left untreated had complete resolution of the PE on the first follow-up CT scan, but one of them developed recurrent UPE on a subsequent scan (25). In another small case series, one patient with segmental UPE left untreated because of an increased risk of bleeding was diagnosed five weeks later with symptomatic bilateral PE (11). In a report by Storto *et al.* one out of four patients with UPE had progression of the PE on follow-up scans (16). Last, Gladish *et al.* reported no recurrent VTE in a series of eight cancer patients with UPE and no concurrent DVT (17). These small observational studies suggest that the risk of VTE recurrence in patients with UPE not receiving anticoagulant treatment is not negligible. Several treatment options including unfractionated heparin, (prophylactic to therapeutic dose) LMWH, vitamin K antagonists or vena cava filters have been reported for UPE, although none of these interventions was evaluated in properly conducted randomized clinical trials. While awaiting additional data on the management of UPE in cancer patients, it seems reasonable to provide the same anticoagulant treatment as for symptomatic PE in light of the apparent similar risk of recurrent VTE.

Patients with UPE may have a high risk of recurrent VTE despite anticoagulation, although the preliminary data are inconsistent. In the study of den Exter *et al.* the yearly VTE recurrence rates for both UPE and symptomatic PE were roughly 10% even though the majority of the patients were treated with LMWH (27). In an interim analysis of

cancer patients with UPE from the ongoing international RIETE registry study, Soler *et al.* observed no recurrences in 79 patients while receiving anticoagulation (33).

Selected subgroups of cancer patients with UPE such as those with unsuspected SSPE might benefit from a conservative 'watchful waiting' strategy instead of anticoagulation therapy (43,44). In a recent survey, a small proportion of physicians was reluctant to start anticoagulant treatment for unsuspected SSPE in a cancer patient (45). An ongoing randomized controlled trial is evaluating the safety of withholding anticoagulant treatment in symptomatic SSPE with no evidence of concomitant DVT (NCT01455818). However, patients with active malignancy are excluded from this study.

Future directions

Despite the growing attention in the literature for UPE in patients with cancer (Figure 7.1), a number of related issues remain unresolved. Future studies need to evaluate the actual incidence of UPE and assess risk factors for first and recurrent UPE. In cancer patients with symptomatic VTE, risk factors for recurrent VTE are female sex, lung cancer,

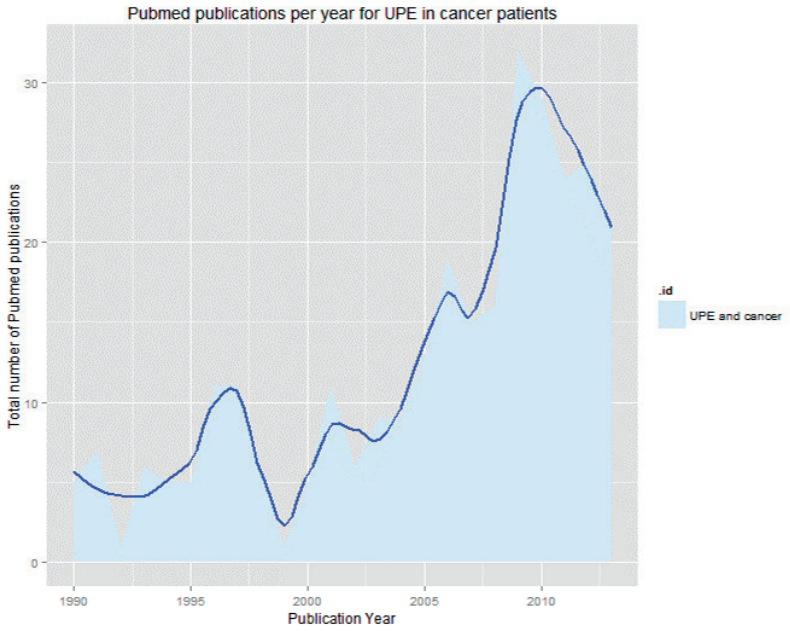

Figure 7.1: Pubmed trend for publications related to unsuspected pulmonary embolism in cancer patients from 1990–0013

advanced disease stage, and a prior history of VTE (46). Whether these factors maintain their predictive value in cancer patients with UPE is unknown.

The type, dose and duration of anticoagulant therapy need to be established. One aspect specific to UPE is the uncertainty regarding the time of clot formation. UPE might have developed just before its detection on CT examination or rather be present for long time which raises the question whether all patients with UPE should be treated with therapeutic doses LMWH in the initial phase of anticoagulation. Future dedicated studies should assess the efficacy and safety of the novel oral anticoagulants in cancer patients with VTE compared to current standard treatment. These new agents may offer a significant improvement in quality of life for these patients that are exposed to a long-term treatment.

An ongoing international prospective study is recruiting cancer patients with UPE in over 30 centers worldwide. The aim of this study is to evaluate current treatment approaches and to prospectively assess the occurrence of major clinical outcomes such as mortality, recurrent VTE and bleeding (NCT01727427). The results are expected in 2015 and hopefully will provide more insight into the clinical course of this condition.

Acknowledgments

We would like to thank Harry Büller for his comments on the manuscript.

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Treatment and long-term clinical outcome of unsuspected pulmonary embolism in cancer patients: interim report of an ongoing, international, observational, prospective cohort study

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8

For the UPE investigators
For this thesis

Abstract

Background: Unsuspected pulmonary embolism (UPE) is diagnosed in 1% to 5% of cancer patients undergoing routine contrast-enhanced computed tomography scans. There is uncertainty about the optimal treatment of UPE and whether selected subgroups, such as those with distal UPE, may be treated more conservatively. We sought to evaluate the current treatment approaches for UPE and to assess their efficacy and safety.

Methods: This is an interim report of an ongoing, prospective, international, multicenter study of consecutive cancer patients with UPE followed up to 12 months for recurrent venous thromboembolism (VTE), bleeding, and mortality. Treatment decisions were left to the discretion of the treating physician. We compared the cumulative incidence of recurrent VTE between patients with subsegmental and more proximal UPE. Furthermore, we compared the cumulative incidence of recurrent VTE and bleeding between patients receiving anticoagulation in therapeutic dosages and those receiving a prophylactic or intermediate dose.

Results: From 22 October 2012 to 24 June 2016, 490 patients were enrolled. The most proximal extent of UPE was a central or lobar pulmonary artery in 56% and a segmental or subsegmental artery in 44% of the cases. Anticoagulant therapy was started in 472 patients (96%), and the majority received a therapeutic dose of low-molecular-weight heparin for a median treatment duration of 169 days (interquartile range 90–215). After 12 months of follow-up, the cumulative incidence of recurrent VTE was 6.2%, the cumulative incidence of bleeding (comprising major, clinically relevant non major and minor bleeding) 17.1%, and the cumulative survival rate 58.6%. The cumulative incidence of recurrent VTE was 2.6% in patients with subsegmental UPE versus 6.7% in those with more proximal UPE ($p = 0.33$). Of the patients receiving a prophylactic or intermediate dose of anticoagulation, 6.9% had a recurrent VTE compared to 5.7% of the patients receiving a therapeutic dose ($p = 0.6$), and the incidences of bleeding in these groups were 11.3% and 19.3%, respectively ($p = 0.14$).

Conclusions: Cancer patients with UPE have a substantial risk of both recurrent VTE and bleeding during anticoagulant therapy. The risk of recurrent VTE appears to be lower for cancer patients with subsegmental UPE than for those with more proximally located clots.

Introduction

In cancer patients, clinically unsuspected pulmonary embolism (UPE) is a relatively frequent finding on contrast-enhanced computed tomography (CECT) scans performed as part of standard oncological staging or follow-up, with reported incidences ranging from 1% to 5% (1,2). The clinical relevance of UPE has been evaluated in a number of retrospective cohort and case-control studies that have suggested a similar prognosis as for symptomatic PE (3–5). In one study, patients with subsegmental UPE appeared to have a better survival than those with a more proximal UPE, but this finding could not be confirmed in other studies (6–8). Overall, the retrospective design of the studies in combination with a low number of included patients hamper any meaningful conclusions about the optimal management of UPE. The major guidelines suggests the same initial and long-term treatment for UPE as for symptomatic PE (9,10). Based on this suggestion, cancer patients with UPE should receive anticoagulant therapy for at least 6 months, with continued treatment as long as the disease is active or the patient is receiving anticancer treatment; in most cases, this results in indefinite treatment. There is a lack of studies specifically focused on the treatment and long-term clinical outcome of UPE in cancer patients. We therefore sought to evaluate the current treatment approaches for UPE in cancer patients and to assess the efficacy and safety of anticoagulant therapy in a large prospective cohort study.

Methods

Study design

This is an interim report of a prospective, observational, international, multicenter study of consecutive cancer patients with UPE (ClinicalTrials.gov; NCT01727427). Thirty-two centers in 9 countries are actively participating (Appendix). Ambulatory or hospitalized cancer patients with a first, objectively diagnosed UPE in the previous 2 months are eligible. Active cancer is defined as i) evidence of measurable solid cancer, ii) hematological malignancy not in remission, iii) ongoing systemic or locoregional anticancer treatment, or iv) cancer cured in the year before the UPE diagnosis. UPE is defined as one or more clots in the pulmonary artery tree detected on imaging performed for reasons other than a clinical suspicion of PE. Exclusion criteria include i) age less than 18 years, ii) ongoing anticoagulant therapy, and iii) a life expectancy of less than 3 months.

Treatment decisions are left to the discretion of the treating physician, as well as the decision to perform computed tomography pulmonary angiography (CTPA) to confirm the PE diagnosis and/or ultrasound examination of the legs to diagnose concomitant deep vein thrombosis (DVT). The initial treatment is defined as anticoagulant therapy

within the first 1 to 4 weeks after the diagnosis. The extended treatment includes anticoagulant therapy provided thereafter.

Follow-up visits are scheduled at 3, 6, and 12 months after inclusion, and can be performed at the outpatient clinic or by telephone. The main outcome events are recurrent venous thromboembolism (VTE), bleeding, and all-cause mortality. All outcome events are adjudicated centrally. Bleeding events are classified as major, clinically relevant non major (CRNM), or minor bleeding. Major bleeding is defined as overt bleeding, either i) associated with a drop in hemoglobin level of 2 g/dL or more, or ii) requiring transfusion of 2 or more units of blood, or iii) occurring in a critical site, or iv) contributing to death (11). CRNM bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with a medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life (12). All other bleeding events are classified as minor.

The protocol was approved by the ethical committee of each participating center. In some centers and in accordance with national laws, informed consent is not required because of the observational nature of this study. In other centers, written informed consent is obtained from all participants. Data are collected in an electronic case report form through a secure website. The study coordinators from the Academic Medical Center in Amsterdam perform frequent data checks to ensure quality, consistency, and completeness.

Study variables

The following variables are collected at baseline: age, sex, weight, height, other demographic characteristics, medical history, presence of VTE risk factors, relevant concomitant medications, type of cancer, presence of distant metastasis, anticancer treatment received, available laboratory results (i.e. hemoglobin, leucocyte count, thrombocyte count, creatinine, creatinine clearance, and D-dimer), UPE treatment (i.e. type and dose of anticoagulant treatment, other treatments received, and intended treatment duration), characteristics of the UPE (i.e. the exact location and the number of arterial branches affected), and clinical signs and symptoms suggestive of PE in the two weeks before the UPE diagnosis. During follow-up, data on UPE treatment (i.e. dose changes and definite or temporary interruption), hospitalization, anticancer treatment received, and clinical outcomes are collected.

Statistics

Baseline characteristics were summarized using descriptive statistics. The cumulative incidence of recurrent VTE and bleeding during anticoagulant therapy were estimated using competing risk analysis in which death was considered as a competing event. Patients were censored at the time of the last visit, end of follow-up, or loss to

follow-up. All-cause mortality was assessed by the Kaplan-Meier method. Bleeding was considered to have occurred during anticoagulant therapy if it occurred within 7 days after cessation of treatment. The overall cumulative recurrent VTE rate was compared between patients with central, lobar, segmental, and subsegmental UPE. In addition, the cumulative incidence of recurrent VTE was compared between patients with subsegmental and those with more proximal UPE. Finally, we compared the cumulative incidence of recurrent VTE and bleeding between patients receiving a therapeutic dose of anticoagulation and those receiving a prophylactic or intermediate dose for the extended treatment. Differences in cumulative incidences were assessed using Gray's test for competing risk analysis. All statistical analyses were performed in R (v3.2.1, R Foundation for Statistical Computing, www.R-project.org).

Results

Baseline characteristics

From 22 October 2012 to 24 June 2016, 490 patients were consecutively enrolled. Baseline characteristics are summarized in Table 8.1. The mean age was 67 years (range 24–94) and 59% were men. The most prevalent types of cancer were colorectal (20%), lung (16%), and gynecological cancer (9%). Distant metastasis was present in 62% of the patients.

Characteristics of the UPE

The most proximal extent of the UPE was reported in 479 patients (98%) and was central in 69 (14%), lobar in 201 (42%), segmental in 166 (35%), and subsegmental in 43 (9%) of the patients (Table 8.2). Common signs and symptoms associated with PE that were present in the 2 weeks before UPE diagnosis were fatigue in 130 (27%), dyspnea on exertion in 87 (18%), chronic dyspnea in 51 (10%), and cough in 54 patients (11%). Concomitant DVT was diagnosed in 107 patients (22%) and CTPA was performed to confirm the PE diagnosis in 68 patients (14%).

Treatment

Table 8.3 shows the treatment characteristics. Anticoagulant therapy was started in 472 patients (96%). Main reasons for withholding anticoagulant therapy were a high bleeding risk (21%), patient's preference (14%) and planned surgery (7%). UPE led to hospitalization or prolonged hospital stay in 190 patients (39%).

The intended treatment duration was lifelong in 30% and unknown or not yet decided at UPE diagnosis in 44%. For the initial treatment, a therapeutic dose of low-molecular-weight heparin (LMWH) was most frequently prescribed (85%). Similarly, the majority

Table 8.1. Baseline characteristics

Variables	N (%)
Total number of patients, *n*	490
Age, *mean (range)*	67 (24–44)
Male sex, *n (%)*	290 (59)
BMI, *mean ± SD*	25 ± 4.5
Inpatient at time of UPE diagnosis, *n (%)*	177 (36)
Ethnicity, *n (%)*	
Caucasian	449 (92)
Afro-American	14 (3)
Asiatic	2 (0.4)
Other	25 (5)
Medical history, *n (%)*	
Cardiovascular disease	73 (15)
Stroke	11 (2)
TIA	7 (1)
Myocardial infarction	22 (5)
Angina pectoris	6 (1)
Peripheral artery disease	25 (5)
Other	2 (0.4)
Heart failure	6 (1)
Atrial fibrillation	12 (2)
Chronic pulmonary disease	34 (7)
Venous thromboembolism	56 (11)
Pulmonary embolism	16 (3)
Deep vein thrombosis	42 (9)
Medication use at time of UPE diagnosis, *n (%)*	
Antiplatelet therapy	60 (12)
Prophylactic dose of anticoagulants	20 (4)
Risk factors for VTE, *n (%)*	
Recent surgery	39 (8)
Recent immobilization	63 (13)
Central venous catheter	113 (23)
Congestive heart failure	6 (1)
Malignancy, *n (%)*	
Colorectal	96 (20)
Lung	77 (16)
Gynecological	44 (9)
Pancreas	30 (6)

Table 8.1. Baseline characteristics (continued)

Variables	N (%)
Breast	30 (6)
Prostate	22 (5)
Kidney	19 (4)
Esophagus	18 (4)
Stomach	16 (3)
Melanoma	15 (3)
Bladder	14 (3)
Hematological	13 (3)
Other	93 (19)
Distant metastasis, *n (%)*	305 (62)
Liver	124 (41)
Lung	95 (31)
Brain	41 (13)
Other	129 (46)
Received treatment within 1 month prior to UPE diagnosis, *n (%)*	
Chemotherapy	258 (53)
Hormonal therapy	23 (5)
Radiotherapy	38 (8)
Biological therapy	27 (6)
Experimental therapy	13 (3)
Erythropoiesis stimulating agents	5 (1)
Leucocyte growing factors	20 (4)
Blood transfusions	23 (5)

SD: standard deviation; UPE: unsuspected pulmonary embolism; TIA: transient ischemic attack.

of patients received therapeutic-dose LMWH for the extended treatment phase (56%). Other patients received an intermediate dose of LMWH (14%), a prophylactic dose of LMWH (3%), an unspecified dose of LMWH (9%), fondaparinux (2%), unfractionated heparin (1%), a vitamin K antagonist (VKA; 3%), or a direct oral anticoagulant (DOAC; 3%) for the extended treatment. In 6 patients (1%) a (temporary) vena cava filter was placed. The median duration of anticoagulant therapy was 169 days (interquartile range [IQR] 90–215).

Outcome events

The median follow-up duration was 224 days (IQR 127–369). The overall cumulative recurrent VTE rate was 0.7% after 1 month, 4.8% after 6 months, and 6.2% after 12 months (Figure 8.1A). During anticoagulant therapy, these incidences were 1.0%, 4.3% and 4.3%,

Table 8.2. Characteristics of unsuspected pulmonary embolism

Variables	N (%)
Total number of patients, *n*	490
Most proximal extent of UPE, *n (%)*	
Not specified	11
Central	69 (14)
Lobar	201 (42)
Segmental	166 (35)
Subsegmental	43 (9)
Multiple	24 (5)
Single	12 (3)
Not specified	7 (1)
PE associated signs and symptoms within 14 days of UPE diagnosis, *n (%)*	
Fatigue	130 (27)
Dyspnea on exertion	87 (18)
Chronic dyspnea	51 (10)
Cough	54 (11)
Tachycardia (> 100 bpm)	30 (6)
New atrial fibrillation	1 (0.2)
Other complaints*	42 (9)

UPE: unsuspected pulmonary embolism; bpm: beats per minute

* Including: hemoptysis, thoracic pain, pain or difficulty when breathing, syncope, clinical signs of deep vein thrombosis of the leg, fever

respectively. The cumulative incidence of bleeding during anticoagulant therapy was 3.6%, 13.1% and 17.1% after 1, 6, and 12 months of follow-up, respectively (Figure 8.1B). Survival at the end of follow-up was 58.6% (Figure 8.1C). On 24 June 2016, 7 of 23 (30%) suspected recurrent VTE, 4 of 155 (3%) deaths, and 51 of 64 (84%) bleeding events had been centrally adjudicated. Of 7 suspected recurrent VTE, 6 (86%) events were confirmed. Of the 4 adjudicated deaths, 3 (75%) were judged to be the consequence of worsening cancer and 1 (25%) was due to a stroke. Of 51 bleeding events, 14 (28%) were classified as major, 23 (46%) as CRNM, and 13 (26%) as minor bleeding. One bleed was not considered a bleeding event by the adjudication committee.

The overall cumulative recurrent VTE rates after 12 months of follow-up for patients with central, lobar, segmental, and subsegmental UPE were 9.3%, 5.3%, 7.2%, and 2.6% respectively (Figure 8.2A). Although the cumulative incidence of recurrent VTE seemed lower in patients with subsegmental UPE compared to those with more proximal UPE, this difference did not reach statistical significance (2.6% versus 6.7%, $p = 0.33$; Figure 8.2B). We found no difference in the rate of recurrent VTE between patients

Table 8.3. Treatment

Variables	N (%)
Total number of patients, *n*	490
Anticoagulant therapy started, *n (%)*	471 (96)
Hospitalization or prolongation of hospital stay, *n (%)*	190 (39)
Intended treatment duration, *n (%)*	
3 months	16 (3)
6 months	104 (22)
Lifelong	140 (30)
Unknown	206 (44)
Initial treatment, *n (%)*	
LMWH, prophylactic dose	2 (0.4)
LMWH, intermediate dose	22 (5)
LMWH, therapeutic dose	398 (85)
LMWH, dose not specified	21 (5)
Fondaparinux	8 (2)
UFH	16 (3)
DOAC	4 (0.8)
Extended treatment, *n (%)*	
LMWH, prophylactic dose	12 (3)
LMWH, intermediate dose	68 (14)
LMWH, therapeutic dose	265 (56)
LMWH, dose not specified	46 (9)
Fondaparinux	8 (2)
UFH	6 (1)
VKA	13 (3)
DOAC	15 (3)
Not specified	38 (8)
Compressing stockings prescribed, *n (%)*	80 (16)
Vena cava filter, *n (%)*	6 (1)

LMWH: low-molecular-weight heparin, UFH: unfractionated heparin, DOAC: direct oral anticoagulant; VKA: vitamin K antagonist

receiving a prophylactic or intermediate dose of anticoagulation versus those receiving a therapeutic dose of anticoagulants for the extended treatment (6.9% versus 5.7%; p = 0.6; Figure 8.3A). Also, no significant difference in bleeding rate was observed, although there were numerically less bleeding events with the prophylactic or intermediate than with the therapeutic dose (11.3% versus 19.3%, p = 0.14; Figure 8.3B).

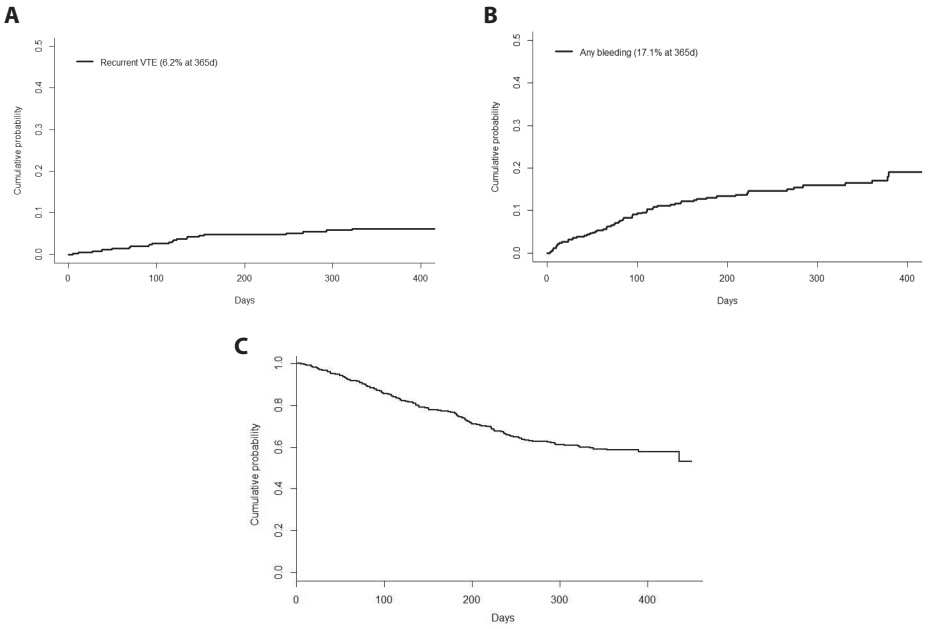

Figure 8.1. Cumulative probability of clinical outcomes

A. Cumulative incidence of recurrent venous thromboembolism
VTE: venous thromboembolism

B. Cumulative incidence of bleeding during anticoagulant therapy

C. Cumulative survival

Discussion

The results of this interim analysis of a multinational prospective cohort study provide information on the clinical characteristics, current treatment strategies, and the incidence of long-term complications in cancer patients with UPE in real-world clinical practice. Our data indicate that the risks of recurrent VTE and anticoagulant-related bleeding are substantial. The risk of recurrent VTE may be lower for cancer patients with subsegmental UPE compared to those with more proximally located clots, although this difference did not reach statistical significance. Furthermore, use of a therapeutic dose of anticoagulation for the extended treatment may be associated with a similar risk of recurrent VTE as compared to a prophylactic or intermediate dose, while it appears to carry a higher bleeding risk.

The overall incidence of recurrent VTE was 4.8% after 6 months in the current study, increasing up to 6.2% after 1 year. Even in the presence of anticoagulant therapy, the risk of recurrence after UPE appears to be substantial, and comparable to the risk of recurrence after symptomatic VTE (13). This finding supports the international

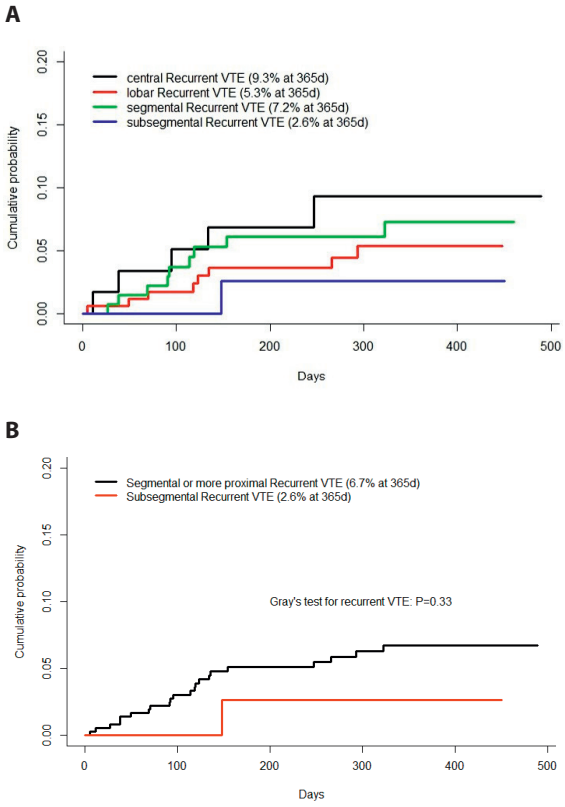

Figure 8.2. Cumulative probability of recurrent VTE based on location of UPE
A. Central versus lobar versus segmental versus subsegmental UPE
B. Subsegmental versus more proximal UPE

guideline recommendations to treat UPE similarly to symptomatic PE (10,14). A recent comparable study by Peris and colleagues reported a VTE recurrence rate of 4.5 events per 100 patient-years (p.y.) during anticoagulant therapy, increasing to 15.5 events per 100 p.y. after cessation of treatment (15). The higher incidence of recurrent VTE in the study by Peris and colleagues may in part be explained by the larger proportion of patients with central clots compared to your study. Furthermore, less than 10% of all outcome events were centrally adjudicated in the study by Peris and colleagues, which may have resulted in an overestimation of the number of recurrent VTE events. Other, mostly retrospective cohorts have also reported somewhat higher incidences of recurrent VTE of 6% after 6 months and 13% after 12 months of follow-up (3,16,17). Our data suggest that the risk of recurrent VTE may be lower in patients with subsegmental UPE. If this finding is confirmed in the full sample as well as in other studies, this would sug-

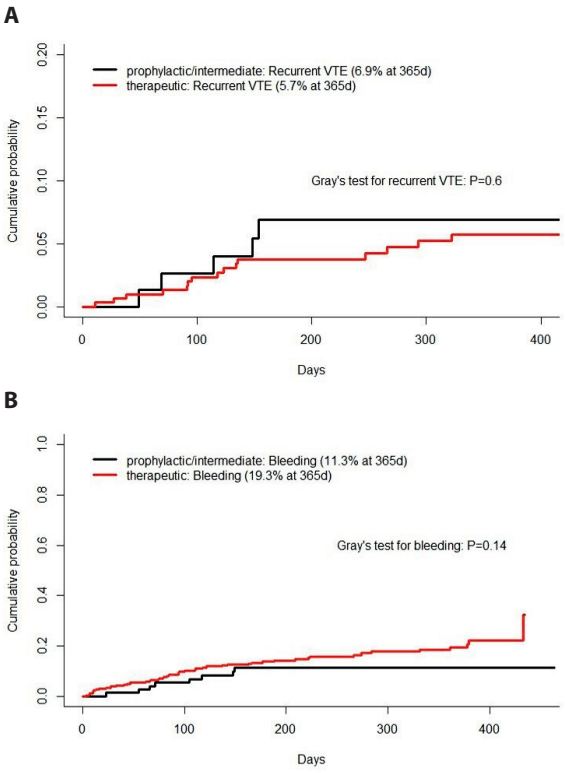

Figure 8.3. Cumulative probability of recurrent venous thromboembolism and bleeding according to dose of anticoagulation (prophylactic/intermediate [n = 83] versus therapeutic [n = 355])
A. Recurrent VTE
B. Bleeding

gest that in these patients the benefits of anticoagulant therapy may not necessarily outweigh the risk of bleeding. This would require confirmation in future adequately designed management studies.

Cancer patients are known to have a 2- to 6-fold higher risk of anticoagulant-related bleeding compared to patients without cancer (18,19). Not all outcome events of the current study have been centrally adjudicated yet, but based on the first adjudication results, the incidence of major bleeding during anticoagulant therapy is approximately 4% during 6 months of anticoagulant therapy, which is comparable to the recurrent VTE rate. In the study by Peris and colleagues however, the incidence of major bleeding during anticoagulant therapy was higher, with 10.1 major bleeding events during 100 p.y (15).

We observed that 56% of UPE were located in the central or lobar pulmonary arteries. In a recent individual patient data meta-analysis of 926 cancer patients with UPE enrolled in 9 retrospective and 2 prospective cohort studies, 37% of UPE were located in the central or lobar arteries (17). Another recent prospective study enrolled 715 consecutive cancer patients with UPE; 66% of the UPE were located in central or lobar arteries, whereas the other 34% were located in segmental or subsegmental arteries (15). In the recently published study by Font and colleagues, 63% of UPE were central or lobar (20). The proportion of patients with subsegmental UPE (2%) was lower than in the present study (9%), whereas the meta-analysis by van der Hulle and colleagues presented a much higher proportion (25%). Possible explanations for the different proportions include differences in case-mix and selection of patients. We recently observed that the agreement between radiologists regarding the most proximal location of UPE in cancer patients is fair, but decreases for more distally located clots (21), which could also partly explain differences in the distribution of UPE location across different studies.

Our study illustrates that patients with UPE are not necessarily asymptomatic. The most common complaints were fatigue (27%) or dyspnea on exertion (18%). In several retrospective studies, in which medical charts from cancer patients with UPE were checked, 40% to 75% had clinical signs and symptoms suggestive of PE at time of diagnosis (6,16,22). In one study, cancer patients with UPE significantly more often had complaints of dyspnea, cough, and fatigue compared to cancer patients without UPE (6). It appears that symptoms suggestive of PE in cancer patients are sometimes erroneously attributed to the underlying cancer or to side effects of cancer treatment, thereby potentially missing a PE diagnosis.

Some limitations of the current study need to be addressed. First, this is an interim report, and therefore not all data are completed yet and a large number of outcome events still needs to be centrally adjudicated. Second, centers participating in the current study are specialized in diagnosing and treating VTE, and the presented data may not fully represent daily practice in other settings of clinical care. Finally, confounding by indication cannot be ruled out when comparing outcome results between patients having received different doses of anticoagulation, and these comparisons need to be interpreted cautiously.

Strengths of the current interim report are the large number of patients included and the relatively long duration of prospective follow-up. Furthermore, all outcome events are centrally adjudicated which ensures accuracy of outcome results. Finally, this is the first study prospectively comparing clinical outcomes for different locations of UPE. We believe that in the near future this study will provide valuable additional data that may pave the way for future studies exploring the optimal treatment for cancer patients with UPE.

In conclusion, cancer patients with UPE are at substantial risk of developing both recurrent VTE and bleeding events during anticoagulant therapy. Cancer patients with subsegmental UPE may have a lower risk of recurrent VTE compared to patients with more proximally located UPE. Furthermore, use of a therapeutic dose of anticoagulation for the extended treatment may be associated with a similar risk of recurrent VTE as compared to a prophylactic or intermediate dose, while carrying a higher bleeding risk. These suggestions need to be confirmed in larger sample sizes, and preferably in randomized controlled trials.

Appendix. Investigator's list

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Unsuspected pulmonary embolism in cancer patients: interobserver agreement on the diagnosis and extent with a focus on distal clots

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Thromb Res. 2016 Nov;147:46-51.

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Abstract

Background: The incidence of unsuspected pulmonary embolism (UPE) in cancer patients is increasing. There is scant information on the interobserver agreement among radiologists about the diagnosis of distal unsuspected clots and the actual radiologic extension of UPE.

Methods: A total of 88 contrast-enhanced computed tomography (CT) scans of cancer patients with UPE were reassessed blindly by two expert thoracic radiologists. First, 62 scans were reassessed and the interobserver agreement on most proximal extent of UPE was calculated between the two expert radiologists as well as between the initial and expert reading, using the Kappa statistic. The sample was enriched with 26 additional scans for a total of 30 segmental and 29 subsegmental UPE to determine the interobserver agreement on distal clots.

Results: The level of agreement regarding the most proximal extent of UPE between the expert radiologists was very good (kappa 0.84; 95% CI, 0.73–0.95) and poor between the original radiologist and expert radiologists (kappa 0.39; 95% CI, 0.22–0.56). In the patients with segmental or subsegmental UPE on initial reading, the expert radiologists agreed with the segmental location in 12 out of 30 patients (40%) and with the subsegmental location in 17 out of 29 patients (59%). The interobserver agreement between the expert radiologists was good (kappa 0.68; 95% CI, 0.46–0.90) and moderate (kappa 0.48; 95% CI, 0.25–0.71), respectively.

Conclusions: While the interobserver agreement between radiologists on the most proximal location of UPE in cancer patients appears to be fairly good, it decreases significantly for more distally located unsuspected clots.

Introduction

Cancer patients frequently undergo contrast-enhanced computed tomography (CECT) scanning for disease staging and for monitoring of the effects of treatment. Advancements in CT techniques over the past decades have drastically improved pulmonary arterial visualization (1,2). As a consequence, unsuspected pulmonary embolism (UPE) is increasingly detected in cancer patients, with a prevalence ranging from 1% to 5% (3,4). The true prevalence of UPE may even be higher, since the contrast enhancement of the pulmonary arteries on oncological CECT scans is suboptimal for PE detection, especially for clots in the more distally located segmental and subsegmental arteries (5). In addition, inattentional blindness of the observer may occur, since PE evaluation is not the primary goal of the scan (6). Several studies which reassessed routine CT scans of cancer patients for UPE have reported false-negative rates ranging from 30% to 75% (5,7–9). At the same time, a risk of false positive readings has been reported for distally located, symptomatic PE, and this may be worse for distally located UPE (10).

The clinical significance of UPE in cancer patients is not clear. Several retrospective studies suggest that the risk of recurrent venous thromboembolism (VTE) is similar in patients with UPE as compared to those with symptomatic PE (11–13). Subsegmental UPE seems associated with a better prognosis than more proximal UPE (14), although data have been conflicting (15,16). Current guidelines suggest that UPE should receive similar treatment as for symptomatic PE (17,18). Therefore, it is relevant to correctly ascertain the diagnosis in order to avoid unnecessary exposure to anticoagulant therapy.

Although interobserver agreement among radiologists for symptomatic PE has increased over the years due to the introduction of multi-detector CT scans, concordance still remains suboptimal for subsegmental symptomatic PE (2,19–25). Studies reporting on interobserver agreement for UPE in cancer patients are scarce, and no data exist on the interobserver agreement regarding the most proximal extent of UPE (5,26).

The objectives of the present study were to (1) evaluate the interobserver agreement on the most proximal extent of UPE between two expert thoracic radiologists, and subsequently between original and expert reading, and to provide a detailed description of the anatomical characteristics of UPE in cancer patients, and (2) evaluate the interobserver agreement on the diagnosis of segmental and subsegmental clots between expert radiologists and between original and expert radiologists.

Methods

A total of 88 CT scans from cancer patients with UPE were reassessed.

Part 1

First, 62 consecutive CT scans from all patients included between April 2012 and November 2014 in three centers participating in an ongoing observational study on the management of UPE in cancer patients were reassessed (NCT01727427; Figure 9.1). In this international, prospective cohort, adult cancer patients with prospectively identified UPE are followed for 12 months for recurrent VTE, bleeding, and all-cause mortality. UPE is defined as one or more clots in the pulmonary artery tree detected on imaging performed for reasons other than a clinical suspicion of PE. For patients included in this registry, the local radiologist detailed the exact location of the UPE, and number of pulmonary arterial branches affected.

For the present study, baseline characteristics, including age, sex, and type of cancer, were collected. We recorded whether a computed tomography pulmonary angiogram (CTPA) was performed to confirm PE, and whether the presence of concomitant deep vein thrombosis (DVT) of the legs was verified by compression ultrasonography.

Two radiologists (LB and AR) with extensive experience in thoracic imaging, independently reassessed the thoracic images of all CT scans. Images were reviewed at least 6 months after

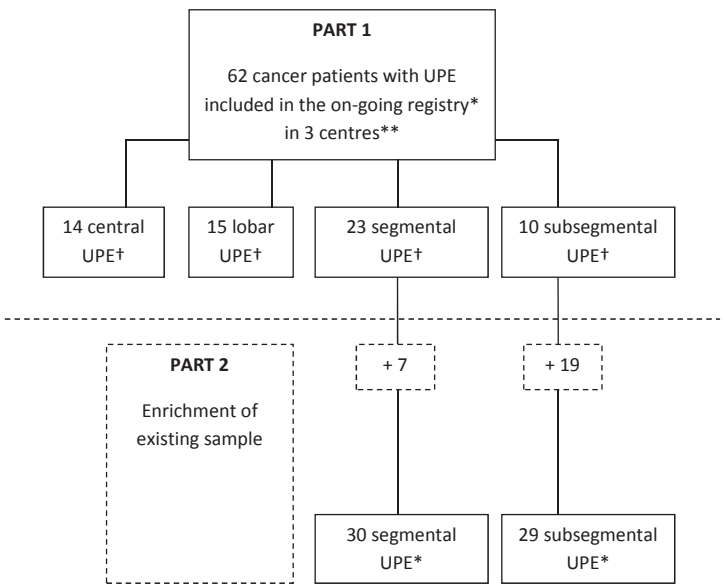

Figure 9.1. Flow diagram of part 1 and part 2 of the current study
* NCT01727427
** One academic and one non-academic center from the Netherlands, and one academic center from Italy
† According to the original reading
UPE: unsuspected pulmonary embolism

the test date to minimize recall bias. Reassessment was performed on a dedicated picture archiving and communication system (PACS) workstation (Impax 6.5, Agfa HealthCare NV, Mortsel, Belgium) using multiplanar reformats when needed. The window setting was left to the discretion of the reader. Readers were unaware of prior interpretation.

The radiologists assessed the following items: image quality (rated on a Likert scale from 1 to 5, corresponding to inadequate to excellent), contrast opacification of the subsegmental arteries (rated on a Likert scale from 1 to 5, corresponding to inadequate to excellent), confidence of the diagnosis of UPE (rated on a Likert scale from 1 to 5, corresponding to definitive no PE to definite PE), pulmonary arterial CT density in the pulmonary trunk in Hounsfield units (HU), the extent of PE (central, lobar, segmental, subsegmental, or no PE), and the number of thrombi (single or multiple). Central and lobar PE were collectively classified as "proximal PE" and segmental and subsegmental as "distal PE".

The agreement between the two expert thoracic radiologists regarding the most proximal extension of the UPE, as well as the interobserver agreement between the original radiologist and the expert radiologists, were evaluated. A consensus reading between the radiologists was performed in case of disagreement. After the first consensus reading there was no remaining discordance; hence, the involvement of a third radiologist was not needed. The result of the consensus meeting was used as the reference to calculate the interobserver agreement between the expert radiologists and original radiologist.

Part 2

Interobserver agreement is expected to be lower for the diagnosis of distal UPE, similar to the setting of symptomatic PE (10). In order to evaluate the interobserver agreement between the expert thoracic radiologists and between the original and expert radiologists, in the second part of the study we enriched the sample with 26 additional scans from consecutive patients with segmental and subsegmental UPE according to the original reading (Figure 9.1). Both patients included in the prospective cohort study (n = 33) as well as patients who were excluded due to a life expectancy of less than three months or anticoagulant use in therapeutic doses at the time of the UPE diagnosis (n = 26), identified in the same hospitals as in part 1, were eligible for this part of the study. The radiologists independently reassessed the thoracic images of the additional CT scans for the extent of the PE and the number of thrombi. For patients already included in part 1, the first reading result was used.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Cohen's kappa coefficient was used to measure the interobserver agreement, and results were based

on the cut-off values proposed by Landis and Koch: a kappa value of < 0.20 representing poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good agreement (27). In addition, we assessed differences in image quality, contrast opacification of the subsegmental arteries, confidence of the UPE diagnosis and arterial contrast score between scans for which the original and expert radiologists agreed on the most proximal extent, and those for which no agreement was reached. Means were compared using the t-test for independent variables, and medians were compared using the Median Test for k samples. Analyses were performed using SPSS Statistics v 20.0 (IBM Corp., Armonk, NY, USA).

Results

Part 1

The baseline characteristics of the cancer patients included in the first part of the study are summarized in Table 9.1. The mean age was 65 years and 58% were men. The most prevalent types of cancer were gastro-intestinal (37%), lung (10%), gynecological (8%), and breast (8%) cancer.

The expert radiologists agreed with each other on the most proximal location of the UPE in 55 of 62 patients (89%) resulting in a very good interobserver agreement (kappa 0.84; 95% CI, 0.73 to 0.95). The interobserver agreement between the expert radiologists and original radiologist was poor (kappa 0.39; 95% CI, 0.22 to 0.56; Table 9.2). Fifteen of 33 scans (46%) classified as distal UPE by the initial radiologist were considered to be proximal (i.e. central or lobar) by the experts. According to the expert radiologists, the most proximal extent of the UPE was central in 16 patients (26%), lobar in 24 (39%), segmental in 17 (27%), and subsegmental in 5 (8%) of which 2 multiple and 3 single subsegmental.

Subsequent CTPA was performed in 3 patients (2%), 1 with central, 1 with lobar and 1 with multiple subsegmental UPE based on initial reading, and confirmed the presence of PE in all. Ultrasonography of the legs was performed in 11 patients (6%) of which 3 with central, 4 with lobar, 1 with segmental, 1 with multiple subsegmental and 2 with subsegmental UPE, and confirmed DVT in 7 (64%). The overall mean image quality of the CT scans was good (4.1 out of 5; standard deviation [SD] 0.8), as was the mean contrast opacification of the subsegmental arteries (3.9; SD 1.0). The mean confidence of diagnosis of UPE was excellent (4.8; SD 0.4), and the arterial contrast opacification reached a median HU of 169 (interquartile range 145–244).

Table 9.1. Baseline characteristics of study population (Part 1)

	N = 62
Baseline characteristics	
Mean age, y (SD)	65 (10)
Male sex, n (%)	36 (58)
History of cardiovascular disease, n (%)	7 (4)
History of chronic pulmonary disease, n (%)	1 (1)
Cancer type, n (%)	
Lower GI tract	10 (16)
Upper GI tract	13 (21)
Lung	6 (10)
Gynecological	5 (8)
Pancreas	3 (5)
Breast	5 (8)
Bladder	4 (7)
Prostate	2 (3)
Other	14 (23)
Distant metastases, n (%)	42 (68)
Liver	21 (34)
Lung	16 (26)
Bone	9 (15)
Brain	3 (5)

SD: standard deviation, GI: gastro-intestinal

Part 2

Table 9.3 details the baseline characteristics of the patients considered for the second part of the study. The mean age was 65 and 62 years in the patients with segmental and subsegmental UPE, respectively, and 60% and 52% of the patients were male, respectively.

In the 30 patients with segmental PE, the two expert radiologists agreed with each other on the most proximal clot location in 24 patients (80%), which resulted in good interobserver agreement (kappa 0.68; 95% CI, 0.46 to 0.90; Table 9.4A). In 3 of 6 cases of disagreement, the radiologists had used a different definition of the most proximal extent of UPE; during the consensus meeting, the most proximal location was based upon the biggest clot burden and number of involved vessels. Overall, the expert radiologist agreed with the original radiologists on the segmental location in 12 cases (40%), whereas the most proximal extent was judged to be central in 1 case (3%), lobar in 14 (47%), and single subsegmental in 3 (10%).

Table 9.2. Most proximal extent of unsuspected pulmonary embolism as adjudicated by the original and expert radiologists

			Result according to the original radiologist				
						Subsegmental	
			Central	Lobar	Segmental	Multiple	Single
Result according to the expert radiologists	Central		**12**	3	1	0	0
	Lobar		2	**8**	12	1	1
	Segmental		0	4	**10**	3	0
	Subsegmental	Multiple	0	0	0	**1**	1
		Single	0	0	0	0	**3**

Table 9.3. Baseline characteristics of all patients with (sub)segmental unsuspected pulmonary embolism (Part 2)

	Segmental UPE* N = 30	Subsegmental UPE* N = 29
Baseline characteristics, *n (%)*		
Mean age, y, (SD)	65 (10)	62 (12)
Male sex, n (%)	18 (60)	15 (52)
Cancer type, n (%)		
Lower GI tract	7 (23)	6 (21)
Upper GI tract	3 (10)	6 (21)
Lung	2 (7)	4 (14)
Gynecological	2 (7)	3 (10)
Pancreas	1 (3)	-
Breast	2 (7)	1 (3)
Bladder	4 (13)	1 (3)
Other	9 (30)	7 (24)
Distant metastases	19 (63)	27 (93)

*Most proximal extent according to original radiologist
UPE: unsuspected pulmonary embolism, SD: standard deviation, GI: gastro-intestinal

In the 29 patients with a subsegmental UPE according to the original radiologist, the two expert radiologists agreed with each other on most proximal extent in 17 patients (61%), resulting in to a moderate interobserver agreement (kappa 0.48; 95% CI, 0.25 to 0.71; Table 9.4B). In 8 of 11 cases of disagreement, the disagreement was the result of the use of different definition of the most proximal extent of UPE. After the consensus meeting, the expert radiologists concluded that UPE was subsegmental in 17 patients (59%), including multiple clots in 9 patients (31%) and a single clot in 8 patients (28%), whereas the most proximal extent was lobar in 2 cases (7%) and segmental in 9 (31%).

Table 9.4. Most proximal extent of unsuspected pulmonary embolism

A. In patients with segmental unsuspected pulmonary embolism according to original reading

			Expert radiologist 1				
						Subsegmental	
			Central	Lobar	Segmental	Multiple	Single
Expert radiologist 2	Central		**1**	1	0	0	0
	Lobar		0	**11**	2	0	0
	Segmental		0	1	**11**	1	0
	Subsegmental	Multiple	0	0	0	**0**	0
		Single	0	0	0	1	**1**

B. In patients with subsegmental unsuspected pulmonary embolism according to original reading

			Expert radiologist 1					
						Subsegmental		
			Central	Lobar	Segmental	Multiple	Single	No PE
Expert radiologist 2	Central		**0**	0	0	0	0	0
	Lobar		0	**1**	3	0	0	0
	Segmental		0	0	**4**	3	0	0
	Subsegmental	Multiple	0	0	1	**5**	0	0
		Single	0	0	2	1	**6**	1
	No PE		0	0	0	0	1	**1**

PE: pulmonary embolism

In one patient (3%), judged by the original radiologist to have a subsegmental UPE, both expert radiologists concluded that no UPE was present.

In none of the segmental and in 5 (17%) of the subsegmental UPE cases, CTPA was performed to confirm the diagnosis. Ultrasonography of the legs was performed in one patient with segmental UPE (3%), which excluded concomitant DVT, and in 3 (10%) of the subsegmental UPE, confirming DVT in one case (33%).

Impact of CT scan characteristics on interobserver agreement

Table 9.5 details the CT scan characteristics for scans for which the original and expert radiologist agreed on the most proximal extent and scans for which no agreement was reached. The image quality and contrast opacification of the subsegmental arteries were better for the scans for which no agreement was reached. There was no difference in confidence of the UPE diagnosis and the arterial contrast score.

Table 9.5. Characteristics of computed tomography scans for scans with agreement on most proximal unsuspected pulmonary embolism location and for scans with no agreement

	Agreement on most proximal UPE location between original and expert radiologists N = 46	No agreement N = 42	P-value
Image quality (scale 0–5), *mean (SD)*	3.9 (0.8)	4.2 (0.8)	< 0.01
Contrast opacification of subsegmental arteries (scale 0–5), *mean (SD)*	3.7 (0.8)	4.1 (0.9)	0.01
Confidence of UPE diagnosis (scale 0–5), *mean (SD)*	4.7 (0.6)	4.8 (0.7)	0.17
Arterial contrast score in HU, *median (IQR)*	156 (141–181)	176 (147–746)	0.16

UPE: unsuspected pulmonary embolism; SD: standard deviation; HU: Hounsfield units; IQR: interquartile range

Discussion

In the present analysis, the agreement between expert radiologists with regard to the most proximal location of UPE in cancer patients was very good, whereas it decreased to good or moderate for segmental and subsegmental clots. Overall, the agreement between original and expert reading was fair, although, once again, concordance decreased substantially for more distally located clots. Over 60% of all UPE in cancer patients that are detected, are proximally located.

For symptomatic PE, several studies have reported very good interobserver agreement regarding the presence of PE, although lower concordance has been observed in segmental and subsegmental PE (20–25,28). In one study the overall agreement as assessed by the kappa statistic was 0.83 (range 0.68 to 0.91) for central and lobar, 0.61 (range 0.40 to 0.80) for segmental, and 0.38 (range 0.0 to 0.89) for subsegmental emboli (20). In another series of 70 cases with subsegmental symptomatic PE, the reviewing radiologist agreed with the subsegmental location in only 36 (51%), whereas a total of 26 cases (37%) were considered to involve more proximal arteries. Importantly, 8 cases (11%) were re-interpreted as without any evidence of PE (10). Our results suggest that, as for symptomatic distal PE, agreement on the diagnosis of subsegmental UPE is modest. Two studies have assessed the interobserver agreement regarding presence of UPE in cancer patients. In one retrospective study, 403 routine CT-scans of cancer patients were independently reassessed by two radiologists (5). In 14 patients, PE was identified by both readers. In another 12 subjects, PE was detected by only one reader. In only two of these patients, PE was detected by consensus (5). Another study found a

high level of agreement between two expert readers on the presence of UPE, but this included only one patient (1.6%) with a subsegmental PE (26).

One potential reason for the significant discrepancy between radiologists regarding the most proximal extent of distal clots may be the use of different definitions. Clots located at the bifurcation from segmental to subsegmental may be classified as segmental (i.e. the most proximal location) or multiple subsegmental (based on the biggest clot burden and number of involved vessels). Indeed, in our study, most of the discrepancies at this level arose from the use of different definitions. In addition, limited visualization of segmental and subsegmental arteries in comparison to the visualization of the more proximal arteries on routine CT scans may play a role in the decreased interobserver agreement on most proximal UPE location. Interestingly, we found that the image quality and contrast opacification of the subsegmental arteries were better for scans for which no agreement was reached, compared to scans for which agreement was reached on the most proximal extent of UPE. We observed no difference in confidence of UPE diagnosis and the arterial contrast score. Although numbers are too small to draw robust conclusions, it seems that CT scan characteristics did not influence the interobserver agreement in our study.

While knowing the exact extent of a proximal PE has relatively limited clinical importance since anticoagulant therapy is indicated in all cases, the distinction between segmental and subsegmental PE may have therapeutic consequences. In a retrospective study, cancer patients with subsegmental UPE had a better survival compared to those with more proximal UPE, and those with isolated subsegmental UPE had a similar survival as matched control patients without UPE (14). Conflicting results were reported in another retrospective study (29). The clinical relevance of isolated subsegmental PE and the possibility to manage these PEs conservatively is currently under investigation in a prospective management cohort study that, unfortunately, excludes patients with cancer (ClinicalTrials.gov; NCT01455818).

A conservative management strategy for isolated subsegmental PE may have an even bigger impact in cancer patients in whom a diagnosis of PE usually implies lifelong exposure to anticoagulant therapy (17), with an associated risk of major bleeding up to 12% during 12 months of treatment, corresponding to 15.7 major bleeding events per 100 patient-years (30–33). In the present study, one patient diagnosed with a subsegmental UPE received therapeutic anticoagulation, but did not have PE according to central reading. Therefore, while a diagnosis of isolated subsegmental UPE may be relatively infrequent, it can have serious consequences as exemplified by this patient who was unnecessarily exposed to the potential harms of anticoagulation. Some authors have recently suggested that compression ultrasonography of the legs may be performed in cancer patients with isolated subsegmental UPE to guide therapeutic decisions (18). Our study suggests that this recommendation is not adopted frequently

in clinical practice, since only in 10% of patient with subsegmental UPE, compression ultrasonography was performed. Similarly, although previous studies have suggested that CTPA may significantly increase the detection rate of UPE and improve the determination of clot extension (34), CTPA was rarely performed to confirm distal PE in the present study which may depend on the costs, technical difficulties, and concerns about contrast and radiation exposure (18).

What are the implications of the current study? The results indicate that for clinical outcome studies on UPE, central reading by an expert radiologist could be valuable to precisely define UPE extension and, therefore, have more reliable imaging for comparison in case of suspected recurrent PE. In clinical practice an extra dedicated reading in patients with UPE may be considered, especially for distal clots, as this may influence diagnostic decisions such as the performance of ultrasonography of the legs or CTPA.

Some limitations deserve to be acknowledged. First, the sample size of the study was relatively modest and the number of patients with subsegmental UPE still relatively small to reach firm conclusions. Second, the expert radiologists were blinded to the extension of the UPE while aware of its presence, which did not allow us to calculate false-positive or false-negative UPE reading rates.

In conclusion, the interobserver agreement between expert radiologists on the most proximal location of these UPE is good, but decreases for more distally located clots. Similarly, concordance between the initial and second reading is only modest for distal PE. Approximately 60% of all UPE in cancer patients involve the proximal pulmonary arteries.

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PART III

Upper extremity deep vein thrombosis

Upper extremity deep vein thrombosis

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10

Published in "Current management of venous diseases" (Book), Springer, 2016.

Abstract

Upper extremity deep vein thrombosis (UEDVT) accounts for up to 10% of all deep vein thrombi. The incidence is increasing, which is mostly due to extensive use of central venous catheters (CVCs). UEDVT often presents with unilateral swelling and pain, but may be asymptomatic. Several factors increase the risk of UEDVT, of which cancer and CVCs are the strongest risk factors. To prevent acute complications and long-term sequelae of UEDVT, such as pulmonary embolism and the post-thrombotic syndrome, a prompt diagnosis and effective and safe therapy is crucial. Objective imaging through venography or compression ultrasonography is at present the cornerstone of diagnosis, despite its moderate efficiency. Current treatment options for UEDVT are anticoagulant therapy, thrombolytic therapy, mechanical catheter interventions, first rib resection in case of thoracic outlet syndrome, and vena cava filter placement. Routine thromboprophylaxis in patients with a CVC is currently not recommended.

Introduction

Upper extremity deep vein thrombosis (UEDVT) is a disease which was first described in the late nineteenth century by Paget and von Schroetter (1,2). The condition accounts for approximately 4% to 10% of all deep vein thrombi, with an estimated incidence of 3.6 per 100.000 patient-years (3). UEDVT is an increasingly frequent clinical problem, mainly due to the widespread use of central venous catheters (CVCs) which carry a substantial risk of thrombosis (3,4). It may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular and brachiocephalic veins, but most often occurs in the subclavian or axillary veins; frequently more than one venous segment is affected (Figure 10.1) (5–11). Deep vein thrombosis (DVT) of the radial, ulnar and brachial DVT are considered distal UEDVT, whereas DVT in the axillary or more proximally located veins is referred to as proximal UEDVT. As UEDVT may lead to loss of venous access or pulmonary embolism (PE) in the acute phase, and is associated with serious long-term complications such as the post-thrombotic syndrome (PTS), prompt diagnosis and treatment is warranted. At present, objective imaging is the cornerstone of diagnosis despite its moderate efficiency. Several diagnostic strategies to improve diagnostic efficacy have been proposed and tested, but which strategy can most safely and effectively exclude UEDVT remains yet to be determined.

In the absence of direct evidence, current treatment recommendations are largely extrapolated from studies on lower extremity DVT, since for UEDVT only small, observational studies are available. In this chapter we discuss the current understanding on the clinical characteristics, risk factors, diagnosis, management, prognosis and prevention of UEDVT.

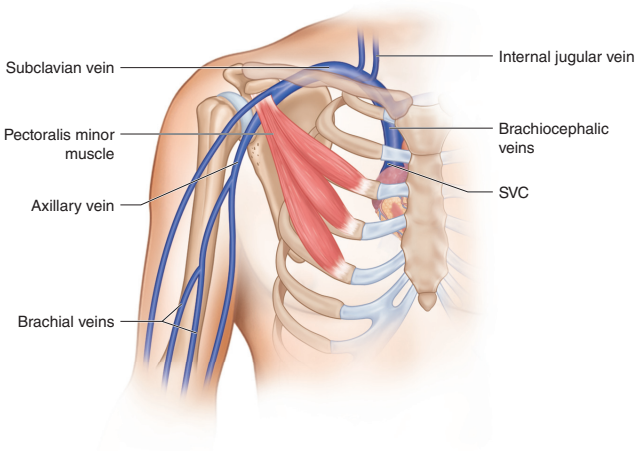

Figure 10.1 Deep veins that may be involved in upper extremity deep vein thrombosis.

Symptoms and signs

Patients with UEDVT most often present with unilateral swelling and discomfort or localized pain (4,8,12–14). Other symptoms and signs that have been described are weakness, paraesthesia, heaviness, low-grade fever, visible collateral veins, erythema, a palpable cord, cyanosis and warmth (Table 10.1) (8,12,15–18). The majority of UEDVT associated with a CVC or pacemaker remain subclinical, as most cases are discovered during the work-up of a dysfunctional catheter or PE (19–21). Concomitant symptomatic PE is present in 3% to 12% of all patients with UEDVT (6,7,22–27), which is less than in patients with lower extremity DVT, in which prevalences of around 30% have been reported (22,27).

Table 10.1 Possible symptoms and signs of upper extremity deep vein thrombosis

	Prevalence in patients with UEDVT
Symptoms	
Unilateral edema or swelling	70%-100% (4,8,12,13,77)*
Discomfort or localized pain	34%-83% (4,8,12,13,77)*
Weakness	NR
Paraesthesia	NR
Heaviness	NR
Signs	
Cyanosis	77% (77)
Warmth	36%-52% (12)
Erythema or skin color change	3%-47% (4,13)*
Visible collateral veins	20%-34% (12)*
Palpable cord	3%-12% (8)*
Low-grade fever	5%*
No symptoms or signs	5% (4)

Abbreviations: UEDVT= upper extremity deep vein thrombosis; NR = not reported
* Including own data from a cohort of 104 consecutive patients with confirmed UEDVT, previously enrolled in a prospective diagnostic management study (7)

Risk factors

UEDVT is subdivided into primary and secondary UEDVT, based on the pathogenesis. Primary UEDVT represents 20% to 50% of all cases, and includes effort-related thrombosis (also known as the Paget-Schroetter syndrome) in combination with the thoracic outlet syndrome (TOS), and idiopathic thrombosis. The majority of UEDVT are secondary to a predisposing risk factor (3,9,28–31). The risk factors most strongly associated with

Table 10.2 Risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (compared to healthy controls)
Cancer	18.1 (28)
Surgery of the upper extremity	13.1 (28)
Central venous catheter	9.7 (4)
Immobilization (plaster cast)	7.0 (28)
Family history of VTE	2.8 (28)
Thrombophilia	2.6–6.2 (28,78–80)
Trauma of the upper extremity	2.1 (28)
Any surgery lasting more than 1 hour	1.7 (81)
Oral contraceptives	1.2–2.9 (28,79,82)

VTE: venous thromboembolism

UEDVT are cancer and the presence of a CVC. Other risk factors include pacemakers, previous venous thromboembolism (VTE), a positive family history of VTE, arm surgery or trauma, immobilization, the use of estrogens, and thrombophilia (Table 10.2).

The Paget-Schroetter syndrome

The Paget-Schroetter syndrome accounts for 10% to 20% of all UEDVT, and mainly occurs in young, otherwise healthy individuals who encounter repetitive or strenuous arm movements (10,31–33). It has been mostly associated with sport activities such as baseball, swimming, weight lifting and wrestling (34,35), but also with playing the violin for prolonged periods of time. The pathogenesis of the Paget-Schroetter syndrome is not entirely elicited, but it is thought that venous TOS plays a key role. Venous TOS is characterized by compression of the subclavian vein, usually caused by either congenital or acquired variations in bone and muscle anatomy (36,37). This renders the subclavian vein more susceptible to trauma. Repeated trauma then leads to intimal hyperplasia, inflammation and perivascular fibrosis, which may eventually cause venous thrombosis (38).

Central venous catheters

Common indications for CVC placement are the administration of chemotherapy, parenteral nutrition and prolonged intravenous antibiotic treatment. It is estimated that over 5 million CVCs are inserted annually in the United States (39). CVC-related UEDVT accounts for up to 70% of all secondary UEDVT (8,24,31). The high risk of CVC-associated UEDVT is mainly due to vessel wall damage following insertion and infusion of irritating substances, and to impeded blood flow through the vein across the catheter. The incidence of symptomatic and asymptomatic CVC-related UEDVT lies around 2% to 6%

and 11% to 19%, respectively (17,40). Baseline factors that increase the UEDVT risk are subclavian vein insertion, improper positioning of the catheter tip, and multiple lumen catheters (Table 10.3) (41). Peripherally inserted central catheters are associated with a higher UEDVT risk than implanted ports (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.54–3.24), especially in critically ill (incidence 13.9%, 95%CI 7.7–20.1) and cancer patients (incidence 6.7%, 95%CI 4.7–8.6) (41,42).

Table 10.3 Central venous catheter-specific risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (95% CI)†
Type of catheter	
• PICC	1*
• Implanted port	0.4 (41)
Number of lumina	
• Single lumen	1*
• Double lumen	1.3–3.5 (41,42,81)
• Triple lumen	3.3–39.5 (41,42,81)
Multiple insertion attempts	1.1‡ (42)
Insertion site	
• Upper arm veins	1*
• Subclavian vein	2.2 (41)
• Internal jugular vein	1.6‡ (41)
Catheter tip positioning	
• Proper positioning	1*
• Improper positioning	1.9 (41)

CI: confidence interval; PICC: peripherally inserted central catheter
† Unadjusted for other risk factors
* Reference category
‡ Confidence interval crosses 1

Cancer

Approximately 40% of all patients with UEDVT have active cancer; it is one of the strongest risk factors for the development of UEDVT (adjusted OR 18.1, 95%CI 9.4–35.1). The presence of distant metastases increases the risk even further, for an OR of 11.5 (95%CI 1.6–80.2) compared to cancer patients without metastases. Cancer and CVCs often coincide (22), as a substantial proportion of cancer patients require a CVC for the administration of chemotherapy (40). The presence of a CVC increases the UEDVT risk in patients with active cancer approximately 2-fold (OR 43.6, 95%CI 25.5–74.6) (28).

Diagnosis

An accurate diagnosis of UEDVT is important, as appropriate treatment can reduce the clinical burden and prevent complications in the acute phase, such as PE. The prevalence of UEDVT in patients with a clinical suspicion of UEDVT varies from 10% to 45% in several cohort studies, which might be explained by differences in study design and the proportions of cancer patients, CVCs and the number of inpatients (Table 10.4) (7,12,43,44). In patients with a CVC, the prevalence of UEDVT was 53% in one study (7), compared to only 18% in patients without a CVC ($p < 0.01$). These figures were 31% and 23% for cancer and non-cancer patients, respectively (p = 0.07; van Es N., submitted data).

Table 10.4 Prevalence of upper extremity deep vein thrombosis and associated risk factors in consecutive patients with a clinical suspicion of upper extremity deep vein thrombosis

	Constans (12)			ARMOUR (7)	Sartori (44,83)	
	Cohort 1	Cohort 2	Cohort 3		Cohort 1	Cohort 2
Patients, n	140	103	214	406	239	483
UEDVT confirmed, n (%)	50 (36)	46 (45)	65 (30)	103 (25)	24 (10)	64 (13)
Study design	Single center			Multicenter	Single center	
Cancer (%)	52	54	NR	34	16	13
CVC (%)	61	65	12	35	6	17
Inpatient (%)	100	100	53	20	0	0

UEDVT: upper extremity deep vein thrombosis; CVC: central venous catheter, NR: not reported

Venography is the gold standard to diagnose UEDVT, as it visualizes the entire deep vein system of the upper extremity, but it is invasive, expensive, and involves the use of contrast, which may cause complications including renal failure and allergic reactions. Due to these disadvantages, venography has been largely replaced in clinical practice by compression ultrasonography, which is non-invasive, relatively cheap, and easy to perform (18). In a systematic review identifying 9 studies on the role of compression ultrasonography in the diagnosis of UEDVT, the overall sensitivity was 97% (95%CI 90–100%), with a specificity of 96% (95%CI 87–100%) (45). The presence of the clavicle may hinder evaluation of the middle part of the subclavian vein, and in case of indeterminate compression ultrasonography results, venography may provide a definitive answer. Other diagnostic options include computed tomography (CT) angiography and magnetic resonance angiography (MRA), which are both non-invasive. However, both have only been evaluated in studies with very few patients with a clinical suspicion of UEDVT, and the diagnostic performance of both modalities is therefore unclear (46,47).

Table 10.5 Constans Clinical Decision Score (12)

Item	Count
Venous material present*	+1
Localized pain	+1
Unilateral edema	+1
Other diagnosis at least as plausible	-1

* Central venous catheter or pacemaker thread
If the total score is ≤ 1, upper extremity deep vein thrombosis is unlikely; if the total score is ≥ 2, upper extremity deep vein thrombosis is likely.

Several attempts have been made to improve the diagnostic process in patients with a clinical suspicion of UEDVT. Constans and colleagues developed a clinical decision rule, incorporating four items (Table 10.5) (12). If the total score is one or less, UEDVT is deemed unlikely, whereas if the total score is two or higher, the diagnosis is likely. The prediction of UEDVT based on this score was consistent in three study samples, with prevalences of 64 to 70% in patients with a total score indicating 'UEDVT likely', and 9 to 13% in those with a total score indicating 'UEDVT unlikely', suggesting that this score can be a valuable tool in a diagnostic algorithm (12).

The diagnostic value of D-dimer has been tested in two studies, one including 52 patients of whom 15 (29%) had UEDVT, and the other including 239 patients, of whom 24 (10%) were diagnosed with UEDVT (43,48). Both studies applied a cut-off value of 500 ng/mL. The sensitivity was high in both studies with 100% (95%CI 78–100%) and 92% (95%CI 73–99%) respectively, whereas the specificity was low (14%, 95%CI 4–29% and 60%, 95%CI 52–67%, respectively). These figures were similar for cancer patients and patients with a CVC (43,48).

Recently, a multicenter, international, prospective diagnostic management study evaluated an algorithm consisting of the Constans score, d-dimer testing and compression ultrasonography in consecutive patients with a clinical suspicion of UEDVT (7). In total, 406 patients were included, and the algorithm was feasible in 390 (96%). UEDVT was confirmed in 103 patients (25%). In 87 patients (21%; 95%CI 17–25%), ultrasonography could be withheld. One patient in which UEDVT initially was excluded, developed a UEDVT during 3 months follow-up, for an overall failure rate of the algorithm of 0.4% (95%CI 0–2.2%). In another study, 483 patients with a clinical suspicion of UEDVT all underwent immediate compression ultrasonography, and were followed for 3 months prospectively. The failure rate, defined as the rate of recurrent VTE, was 0.6% (95%CI 0.2–2.2%) for single ultrasonography and 0.2% (95%CI 0.1–1.7%) for serial ultrasonography. Of note, the prevalence of UEDVT was relatively low in this cohort (13%) (44).

While there have been important improvements in the field, the best diagnostic strategy in patients with a clinical suspicion of UEDVT still remains to be determined. Hence,

at present, objective imaging remains the cornerstone of UEDVT diagnosis. D-dimer testing may help to reduce the number of patients who require imaging, although the efficiency of the test appears moderate in this population with high prevalences of cancer and CVCs. The use of an algorithm has been shown to be efficient and safe, but needs to be validated prospectively before it can be implemented in clinical practice. Furthermore, improvement of the algorithm appears to be desirable, for example by applying age-adjusted d-dimer cut-off values (van Es N., in press). In patients with a CVC and a suspicion of UEDVT direct imaging seems justified, as only two examinations have to be performed to detect one UEDVT.

Treatment

In the acute phase of UEDVT, the goal is to relieve acute symptoms and prevent complications, such as the loss of venous access or development of PE. The long term goals of treatment are mainly the prevention of recurrent VTE, including fatal PE, and the development of PTS. Treatment options for UEDVT are thrombolytic therapy, anticoagulant therapy, mechanical catheter interventions, first rib resection, and vena cava filter (VCF) placement. No randomized controlled trials have evaluated any of these therapies in patients with UEDVT. Therefore, treatment recommendations by the major guidelines are largely extrapolated from studies on DVT of the leg, and are only based on small observational studies in UEDVT patients (49).

Thrombolytic therapy

Thrombolytic therapy may improve early and late venous patency in patients with UEDVT (50–54), but whether it lowers the risk of recurrent VTE or development of PTS remains unknown. The American College of Chest Physicians (ACCP) guideline suggests that thrombolysis is considered only in patients with severe symptoms for less than 14 days with a good functional status, a life expectancy of at least one year, and a low risk of bleeding (49). Data on the use of thrombolytic therapy for UEDVT is limited but suggests a high risk of major bleeding of up to 17% when systemically administered (51,53,54). Therefore, if thrombolysis is applied, catheter-directed thrombolysis is recommended over systemic thrombolysis, based on the assumption that this is associated with lower bleeding risk (49).

Anticoagulant therapy

In patients with lower extremity DVT, low-molecular-weight heparin (LMWH) has a superior efficacy and better safety compared to unfractionated heparin (UFH) for the initial period of treatment (i.e. the first 5 to 10 days) (55). In addition, four observational

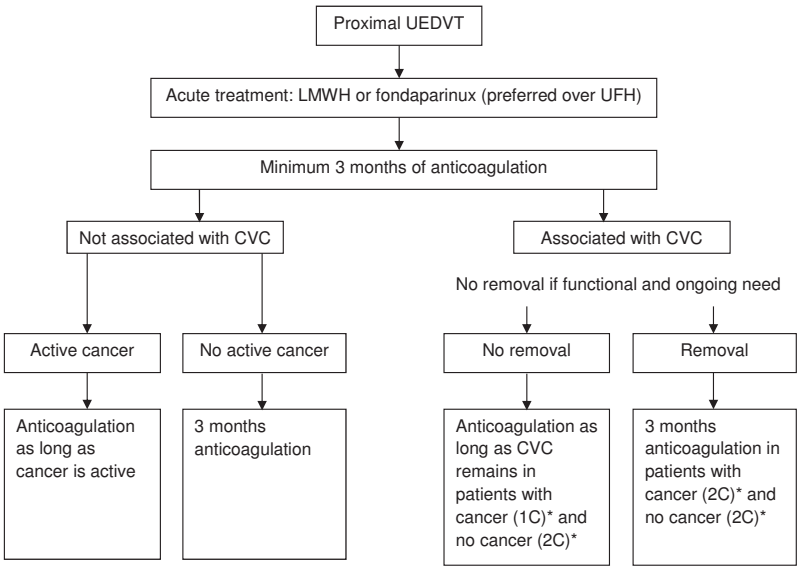

Figure 10.2 Treatment recommendations for upper extremity deep vein thrombosis (49).
UEDVT: upper extremity deep vein thrombosis; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; CVC: central venous catheter
* Grading of Recommendations Assessment, Development and Evaluation (GRADE); 1C: strong recommendation based on low-quality evidence, 2C: weak recommendation based on low-quality evidence

studies that included a total of 209 patients with UEDVT receiving LMWH, reported low recurrence and major bleeding rates (26,56–58). Based on these data, LMWH is the preferred anticoagulant for the initial phase of UEDVT treatment (Figure 10.2). UFH is reserved for patients with contraindications to LMWH such as severe renal failure (49).

For the long-term treatment of UEDVT, i.e. after the initial phase of 5 to 10 days, treatment options besides LMWH are vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). VKA have been the standard method of anticoagulation for decades, but the use of DOACs is emerging since large trials have shown that they are as effective as VKA for the treatment of acute symptomatic lower extremity DVT and PE, with a significant reduction in major bleeding events (59). Extrapolating from trials investigating these drugs for the treatment of DVT of the leg or PE, both can be considered for long-term UEDVT treatment. LMWH may be prescribed but the daily injections are cumbersome and painful for many patients, and hypersensitivity skin reactions are often seen. Despite these disadvantages, the cornerstone of treatment in cancer patients is LMWH, based on a superior efficacy and similar safety profile compared to VKA in cancer patients with lower extremity DVT and PE (60,61).

Treatment duration

All patients with proximal UEDVT (i.e. DVT of the axillary or more proximally located veins) are recommended to be treated with a therapeutic dose of anticoagulants for at least 3 months (Figure 10.2). If UEDVT is not associated with a CVC but is associated with active cancer, patients should receive anticoagulation as long as cancer is active or the patient is receiving chemotherapy. In non-cancer patients with non-CVC associated UEDVT, 3 months of treatment is recommended.

If the UEDVT is CVC-associated, the CVC should not be removed if it is functioning well and there is an on-going need for it. This recommendation is in part based on the fact that many patients still require central venous access, and insertion of another CVC will increase the thrombotic risk as well. Furthermore, an observational study showed no benefit of CVC-removal in 58 of 112 patients (52%) with symptomatic CVC-related thrombosis. In total, 4 patients failed to show resolution of their presenting symptoms, all of whom had their CVC removed at the time of UEDVT (62). In another, prospective study including 74 patients with acute symptomatic CVC-related UEDVT in which the catheter remained in place, there were no recurrent VTE during 3 months of anticoagulant therapy (56). According to the ACCP guideline, anticoagulation should be given as long as the CVC remains in place. This is similar for cancer and non-cancer patients. If the CVC is removed, only 3 months of treatment is recommended, regardless of the presence of cancer. There are no data to guide whether CVC removal should be preceded by anticoagulant therapy (49). There is some debate on the safety of cessation of therapy in patients in whom the CVC is removed, but who still have active cancer after 3 months. In a recent retrospective study the cumulative probability of recurrent VTE was 22.2% in patients with active cancer after cessation of anticoagulant therapy, compared to 2.3% in those in remission ($p = 0.02$ by log-rank test) (63). Another study reported a recurrent VTE rate after 3 months of 7.7% in cancer patients with CVC-related UEDVT, compared to 4.4% in cancer patients with non-CVC related UEDVT (22). These data suggest that patients with active cancer with CVC-related UEDVT in whom the CVC is removed, may benefit from anticoagulation beyond 3 months.

For distal UEDVT, there significant uncertainty on the benefits of anticoagulation, as it is thought that complications occur less often and are less severe in case of distal UEDVT as compared to proximal UEDVT. Therefore, conservative treatment with close surveillance to detect UEDVT extension, a prophylactic dose of anticoagulation, or a shorter course of treatment are options alternative to full therapeutic anticoagulation. If distal UEDVT is symptomatic, associated with a CVC (with the CVC remaining in situ) or with cancer, 3 months of therapeutic dose anticoagulation is favored, unless there is a high bleeding risk (49).

Mechanical catheter interventions

Mechanical interventions include clot aspiration, fragmentation, thrombectomy, percutaneous transluminal angioplasty, and stent placement. These techniques are mostly used in combination with catheter directed thrombolysis. Stents have been associated with high rates of complications such as stent fracture and rethrombosis in the presence of TOS (64,65).

First rib resection

In patients with UEDVT and TOS, surgical decompression through first rib resection has been advocated (49). No randomized trials have evaluated the efficacy and safety of first rib resection in the resolution of acute complaints and prevention of long term sequelae such a recurrent VTE and PTS. This intervention should probably be limited to patients with severe, persistent symptoms and residual subclavian vein stenosis that does not resolve despite adequate anticoagulant therapy, and should be reserved for centers with sufficient expertise (66).

Vena cava filter

In patients with a contraindication for anticoagulant therapy, placement of a VCF may be considered. In a review, reporting on a total of 209 superior VCF placements in patients with UEDVT, complications occurred in 3.8% of the cases, including cardiac tamponade, aortic perforations and a pneumothorax (67). The use of VCF should be limited to experienced centers.

Other therapies

The use of compression stockings to prevent PTS after UEDVT has not been investigated, and the ACCP suggests against its routine use (49).

Prognosis

On the long term, UEDVT can be complicated by recurrent VTE, PTS, bleeding during anticoagulation, and death. To date, mostly small studies with methodological shortcomings have evaluated the long term clinical outcome of UEDVT. A systematic review of all available studies on this topic reported an average incidence of recurrent VTE of 3% to 4% during anticoagulant therapy. After cessation of treatment, the annual incidence of recurrence lies around 4% (68). PTS after UEDVT seems to occur infrequently, and complaints are mostly mild (31,69). Compared to DVT of the leg, the incidences of recurrent VTE and of PTS after UEDVT seem relatively low (26,27,31,69,70).

The recurrence risk in patients with CVC-related UEDVT was reported in two prospective studies; one observed an incidence of 7 per 100 patient-years during anticoagulant therapy, which decreased to 3.4 per 100 patient-years after cessation of treatment (71). Another study observed recurrent VTE in 4.4% of the patients during 3 months of anticoagulant therapy (72). Of note, in both studies no information was available on catheter removal. Cancer patients with UEDVT appear to have a two-fold higher risk of recurrent VTE compared to non-cancer patients (22,31,68), which is comparable to findings from studies on DVT of the leg or PE (73,74).

In patients receiving a therapeutic dose of anticoagulants, the cumulative incidence of major bleeding is approximately 4% after half a year of treatment (22,31,58,68,75). The mortality rate in patients with UEDVT is high and reflects the high prevalence of underlying cancer. To which extent fatal PE adds to this risk is unclear.

Prevention

The prevention of UEDVT has mainly been investigated in patients with indwelling CVCs. A total of six meta-analyses evaluating the efficacy and safety of VKA in the prevention of CVC-related thrombosis showed no overall benefit on the occurrence of symptomatic thrombosis compared to placebo or no treatment (76). Six randomized studies in cancer patients with CVCs found no increased risk of bleeding with LMWH thromboprophylaxis, but also no benefit in preventing CVC-related thrombosis. Routine anticoagulant thromboprophylaxis is therefore not recommended in patients with a CVC by the major international guidelines (49,76). The role of UFH, thrombolytics and heparin-bonded catheters in the prevention of CVC-related thrombosis remains uncertain (41,76). CVCs should only be placed in carefully selected patients in whom the benefits outweigh the risks. As mentioned before, several catheter-specific factors increase the risk of UEDVT, and should be taken into account when placing a CVC (Table 10.3).

Future directions

Several aspects related to UEDVT remain unresolved. Future studies need to evaluate what the most effective and safe diagnostic strategy is to confirm or refute UEDVT. Furthermore, in cancer patients with CVC-related UEDVT in whom the CVC is removed, the efficacy and safety of 3 months of anticoagulant therapy versus prolonged treatment should be assessed. Ideally, future studies would include the use of DOACs for the treatment of UEDVT.

More research is warranted to identify those patients with a CVC in whom the benefits of pharmacological thromboprophylaxis exceed the associated harms, for example by risk stratification. Also, new regimens that are possibly effective and safe in preventing CVC-associated UEDVT, including prophylactic doses of DOACs, should be explored.

Acknowledgments

We would like to acknowledge Marcello Di Nisio for his critical revision of the manuscript for intellectual content.

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Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review

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Thromb Res. 2016 Apr;140 Suppl 1:S81-8.

Abstract

Background: The incidence of upper extremity deep vein thrombosis (UEDVT) is increasing. Information on the clinical course of UEDVT is scarce, especially in cancer patients.

Aim: To summarize the clinical evidence regarding long-term clinical outcomes of UEDVT, in terms of recurrent venous thromboembolism (VTE), mortality, and anticoagulant-related bleeding, in patients with or without concomitant cancer.

Methods: A systematic search of the literature was conducted in MEDLINE, EMBASE and BIOSIS Previews. Incidence rates for all outcome variables were calculated.

Results: In total, 45 studies comprising 4580 patients were included. No randomized controlled trials were identified. In most studies, patients were treated solely with anticoagulants. Among the prospective studies, the incidences of recurrent VTE and bleeding complications averaged 5.1% and 3.1% respectively, during 3 to 59 months of follow-up. In the retrospective studies these figures were 9.8% and 6.7% respectively. Among the prospective studies, the mortality rate was 24% after one year. In the retrospective studies this rate was 35%. Cancer patients were found to have a 2- to 3-fold higher risk of recurrent VTE, an 8-fold increased risk of mortality, and a 4-fold increased risk of bleeding during anticoagulant therapy, compared to non-cancer patients.

Conclusions: Studies were very heterogeneous in terms of study design, study populations and treatment approaches. Follow-up durations varied greatly, hampering combined analyses of average incidence rates. There is a need for large prospective studies to provide information on the best management of this disease, especially in high risk groups such as those with cancer.

Introduction

Upper extremity deep vein thrombosis (UEDVT) may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular, or brachiocephalic veins (1) and accounts for 4 to 10% of all cases of deep vein thrombosis. The incidence of UEDVT is increasing, mostly due to the widespread use of central venous catheters (CVC) for parenteral administration of nutrition or drugs (2,3). Primary UEDVT represents one third of the cases and includes unprovoked UEDVT, effort-related thrombosis (also known as the Paget-Schroetter syndrome), and thrombosis due to the thoracic outlet syndrome. Secondary UEDVT is associated with one or more identifiable triggering factors such as CVCs, pacemakers, or cancer. More than 40% of all patients with UEDVT have concomitant cancer and about 70% of secondary UEDVT are diagnosed in association with the use of a CVC (4).

Acute complications of UEDVT include pulmonary embolism (PE), loss of venous access, arm dysfunction, and CVC-related vein occlusion with or without concomitant infection (4–6). On the long term, patients with UEDVT are at risk of recurrent venous thromboembolism (VTE), fatal PE, post-thrombotic syndrome of the arm and bleeding during anticoagulant therapy. Information about the clinical outcome of UEDVT is derived from few studies with methodological shortcomings. In addition, the efficacy and safety of anticoagulant therapy for UEDVT remains unclear given the lack of randomized controlled studies. As a consequence, recommendations for UEDVT treatment by the major clinical practice guidelines are largely extrapolated from studies on the management of lower extremity DVT and PE (7). Current international guidelines recommend LMWH over VKA in cancer patients with VTE, based on a superior efficacy and similar safety profile (8–11).

The aim of the present systematic review was to evaluate the clinical evidence regarding the long-term clinical outcomes of UEDVT. The results were stratified by cancer status and by the presence of a CVC, given the potential differences in prognosis and treatment of UEDVT in these cases.

Materials and methods

A systematic search of the literature was conducted in MEDLINE, EMBASE and BIOSIS Previews databases from inception to 2 June 2015 to identify all published articles that evaluated the clinical course of UEDVT. BIOSIS was searched for unpublished information from meetings and reports. Full details of the search strategy are provided in the Appendix. Abstracts and full-text articles were screened independently by two authors (S.M.B. and L.G.) to select articles that met the inclusion criteria. In addition, reference

lists of the selected articles were manually screened for potentially eligible studies. Studies were included if they met the following a priori defined criteria: 1) the study was designed as a randomized controlled trial, prospective, or retrospective cohort study, 2) the study included at least 10 adult patients with a first episode of UEDVT, and 3) data were provided on recurrent VTE, mortality or anticoagulant-related bleeding.

The following data were independently extracted by two reviewers (S.M.B. and L.G.) using pre-designed forms: number of patients, study characteristics, follow-up duration, UEDVT etiology, cancer status, presence of a CVC, type of treatment, recurrent VTE, mortality and bleeding complications during anticoagulant therapy. The outcome definitions of the original authors were accepted. All clinical outcomes were extracted for the overall study population and for the subgroups of patients with cancer- and CVC-associated UEDVT. Any disagreements were resolved by consensus or by involving a third reviewer (M.D.N.). An attempt was made to contact the authors in case of missing relevant information.

We assessed the type of study design (prospective, retrospective or unclear), patient enrollment (consecutive, nonconsecutive or unclear), and adjudication of outcome events (yes, no or unclear) as potential sources of bias. A meta-analysis was not performed due to the heterogeneity of the study population and design, and therefore a narrative synthesis of study data is presented. For all outcome variables we described the range and calculated the mean incidence. All statistical analyses were performed in SPSS (IBM SPSS Statistics for Windows, Version 22.0).

Results

Study characteristics

The search yielded 4521 publications, of which 45 studies comprising 4580 patients met the review inclusion criteria (Figure 11.1). The main characteristics of the included studies are summarized in Table 11.1. The number of participants ranged from 12 to 598. No randomized controlled trials were identified. The study design was prospective in 11 studies, retrospective in 29, and unclear in 5. Thirty-two studies (71%) enrolled consecutive patients. Outcomes were centrally adjudicated in one study. The follow-up duration was 3 months or less in 5 studies, between 3 and 12 months in 8 studies, more than 12 months in 22 studies, and not specified in the others. Overall, UEDVT was associated with cancer in 44% (range 0 to 74%) and with CVC in 53% (range 0 to 93%) of the cases.

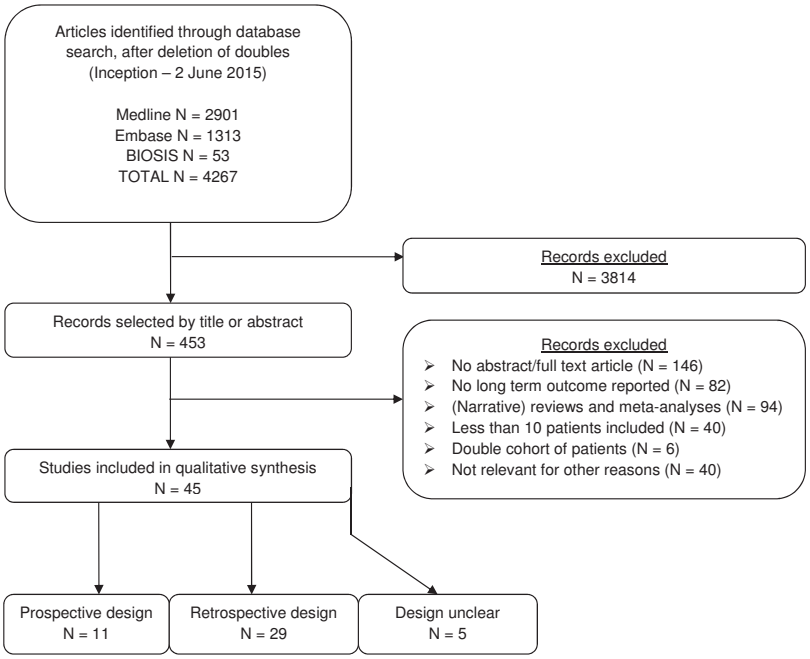

Figure 11.1. Flow chart of study selection

Treatment strategies

Out of 45 included studies, anticoagulant therapy was the mainstay of treatment in 27 (60%; 3271 patients). Initial treatment (i.e. in the first 5 to 10 days) consisted of unfractionated heparin in 13% and low-molecular weight heparin (LMWH) in the remaining 86% of the cases (15 studies, 1781 patients). Among the 24 studies (2636 patients) which reported on long-term treatment, LMWH was used in 32% and vitamin K antagonists (VKAs) in 56% of the patients, for a median duration of 3 to 6 months. In 7 studies, thrombolytic therapy was administered to all patients. In the remaining 11 studies, the treatment strategy was either not reported (2 studies) or heterogeneous (9 studies), including various invasive and non-invasive approaches.

In some of the older studies in this review, VKA were prescribed to all cancer patients (12,13). In the study by Muñoz et al from 2008, 75% of the cancer patients received LMWH and 25% VKA. In three studies after 2006 that included cancer patients with CVC-related UEDVT, LMWH was prescribed in the majority of cases (14–16). In other studies cancer-specific treatment could not be retrieved.

Table 11.1. Baseline Characteristics

Study, year	Number of patients	Consecutive enrollment	Type of UEDVT	Cancer (%)	CVC at baseline (%)
PROSPECTIVE STUDIES					
Savage et al, 1999 (12)	46	Yes	Primary and secondary	74	35
Lee WA et al, 2000* (63)	22	Yes	Primary	0	0
Prandoni et al, 2004 (21)	53	Yes	Primary and secondary	21	11
Karabay et al, 2004 (22)	36	Yes	Primary and secondary	17	36
Lee AY et al, 2006 (16)	19	Yes	CVC-related	100	100
Kovacs et al, 2007 (15)	74	Yes	CVC-related	100	100
Muñoz et al, 2008 (18)	512	Yes	Primary and secondary	38	45
Flinterman et al, 2008 (19)	224	Yes	Primary and secondary	31	25
Lechner et al, 2008 (23)	50	Yes	Primary: idiopathic	0	0
Rathbun et al, 2011 (17)	67	Yes	Primary and secondary	46	-
Baumann Kreuziger et al, 2015 (24)	558	Yes	CVC-related	64	100
RETROSPECTIVE STUDIES					
Kerr et al, 1990* (44)	123	Yes	Primary and secondary	-	-
Marie et al, 1998 (25)	49	Yes	Primary and secondary	33	22
Sakakibara et al, 1999 (45)	12	No	Primary and secondary	42	17
Ellis et al, 2000 (26)	18	Yes	Primary and secondary	6	0
Massoure et al, 2000* (27)	40	Yes	Primary and secondary	65	55
Kreienberg et al, 2001* (48)	23	Yes	Paget-Schroetter syndrome	0	0
Sabeti et al, 2002 (28)	95	No	Primary and secondary	10	9
Martinelli et al, 2004 (29)	98	No	Primary and secondary	0	0
Baarslag et al, 2004 (13)	50	Yes	Primary and secondary	60	50
De Alvarenga Yoshida et al, 2005 (64)	52	Yes	Primary and secondary	33	-

Table 11.1. Baseline Characteristics (continued)

Study, year	Number of patients	Consecutive enrollment	Type of UEDVT	Cancer (%)	CVC at baseline (%)
Ascher et al, 2005 (42)	210	Yes	Primary and secondary	37	60
Lee JT et al, 2006 (30)	35	No	Paget-Schroetter syndrome	0	0
Hingorani et al, 2006 (65)	598	No	Primary and secondary	-	-
Spencer et al, 2007 (32)	69	No	Primary and secondary	44	62
Arnhjort et al, 2007 (31)	32	Yes	Primary	0	0
Vik et al, 2009* (49)	30	Yes	Primary and secondary	-	-
Isma et al, 2010 (2)	63	Yes	Primary and secondary	30	-
Wang et al, 2010* (34)	28	Yes	Primary and secondary	46	-
Belcaro et al, 2010* (33)	211	Yes	Primary and secondary	-	-
Levy et al, 2012* (66)	300	Yes	Primary and secondary	35	80
Lee JA et al, 2012 (43)	94	Yes	Primary and secondary	49	93
Stone et al, 2012* (36)	232	No	Primary and secondary	-	75
Sharifi et al, 2012 (35)	18	No	Primary and secondary	17	50
Chan et al, 2013* (37)	65	Yes	Non-catheter related	37	0
Spivack et al, 2013 (38)	18	Yes	Thoracic outlet syndrome	-	0
Delluc et al, 2014 (14)	89	Yes	CVC-related	100	100
Guida et al, 2014* (41)	19	No	Primary	-	0
DeSancho et al, 2014* (40)	25	Yes	Primary and secondary	0	24
Amira et al, 2014* (39)	17	Yes	Primary and secondary	35	0

Table 11.1. Baseline Characteristics (continued)

Study, year	Number of patients	Consecutive enrollment	Type of UEDVT	Cancer (%)	CVC at baseline (%)
DESIGN UNCLEAR					
Fraschini et al, 1987* (67)	35	Unclear	CVC-related	100	100
Strange-Vognsen et al, 1989* (68)	21	Unclear	Unclear	-	-
Seigel et al, 1993* (47)	38	No	CVC-related	-	100
Machleder et al, 1993* (69)	50	Yes	Paget-Schroetter syndrome	-	0
Burihan et al, 1993* (70)	52	Unclear	Primary and secondary	29	29

*Available as (congress) abstract

UEDVT: upper extremity deep vein thrombosis; CVC: central venous catheter

Recurrent VTE

Eleven prospective studies (1661 patients) reported an average incidence of recurrent VTE of 5.1% (range 0 to 13%; Table 11.2) during a follow-up period ranging from 3 to 59 months. The average incidence of recurrent VTE at 6 months was 3.1% (range 0 to 4.1% in 4 studies) (12,17–19) and 6.5% (range 0 – 13%) in studies with longer observation periods (16,20–24) (Table 11.3). Twenty retrospective studies (1281 patients) reported recurrent VTE in 9.8% (range 0 – 26%) of patients during follow-up varying from 3 to 62 months (2,13,14,25–41) (Table 11.3).

Recurrent VTE was defined as symptomatic, objectively confirmed VTE in 12 studies, and as recurrent VTE detected by routine compression ultrasound in 2 studies. A definition was not provided in the other studies. Eighteen studies described the site of recurrent VTE (12–14,18,19,21,23–26,28–30,32–34,39,40). In 74 (54%) of 138 events, recurrence involved the deep veins of the upper extremities, ipsilateral in 56 (76%), contralateral in 8 (11%), while in 10 cases (14%) the arm was not specified. Twenty-nine recurrent VTE (21%) were PE (including 4 cases of fatal PE) and 10 (7%) were lower extremity DVT. In 25 cases (18%) the exact location of recurrence could not be retrieved.

Two prospective studies evaluated the risk of recurrent VTE in patients with CVC-related UEDVT specifically (18,24) (Table 11.3). Bauman Kreuziger et al followed 558 patients, including 358 (64%) with cancer, for one year (24). All patients were treated with anticoagulants. No information about catheter removal was available. The incidence rates of recurrent VTE during anticoagulant therapy were 7 per 100 patient-years, and 3.4 per 100 patient-years after cessation of treatment. Similarly, in a study by Muñoz et al, the risk of recurrent VTE was 4.4% during anticoagulant therapy among 228 patients with CVC-related UEDVT (of whom 104 with cancer) (18).

The risk of recurrent VTE in cancer patients was evaluated in seven studies comprising 473 patients (13–18,37) (Table 11.3 and Table 11.4). In 4 prospective studies, the average incidence of recurrent thrombosis was 3.8% (range 0 – 6.1%) during follow-up varying from 3 to 13 months, compared to 7.8% (range 0 to 10%) during follow-up periods ranging from 12 to 24 months in 3 retrospective studies. Two studies suggested that the risk of recurrent VTE was two- to three-fold higher among cancer patients compared to those without (18,37).

Four of the seven studies mentioned above addressed the risk of recurrent VTE in cancer patients with CVC-related UEDVT (14–16,18) (Table 11.3). During a follow-up ranging from 3 to 24 months, the average incidence of recurrence was 5.1% (range 0 to 7.1%). In the study by Muñoz et al, 7.7% of cancer patients with CVC-related UEDVT had a recurrence after 3 months compared to 4.4% of cancer patients with non-CVC-related UEDVT (18).

Table 11.2. Clinical outcome after UEDVT: bleeding during anticoagulant therapy, recurrent venous thromboembolism and mortality

Study, year	Number of patients	Bleeding during anticoagulant therapy (%)	Recurrent VTE (%)	Mortality (%)	Follow-up in months (mean or median)
THROMBOLYSIS (with or without additional therapy*)					
Fraschini et al, 1987	35	-	17	-	-
Strange-Vognsen et al, 1989	21	-	0	-	42
Seigel et al, 1993	38	7.9	-	-	-
Lee WA et al, 2000	22	-	4.5	-	-
Kreienberg et al, 2001	23	17	-	-	-
Sabeti et al, 2002	33 / 95**	21	7	-	40
Vik et al, 2009	30	9.0	-	-	-
Spivack et al, 2013	18	-	11	0	19
ANTICOAGULANT THERAPY					
Burihan et al, 1993	52	-	-	19	6
Marie et al, 1998	49	-	14	-	6
Savage et al, 1999	46	4.3	2.2	15	3
Sabeti et al, 2002	62 / 95**	0	8	-	40
Prandoni et al, 2004	53	-	5.9	21	48
Martinelli et al, 2004	98	-	12	-	61
Karabay et al, 2004	36	-	0	25	12
Baarslag et al, 2004	50	-	8	50	21
De Alvarenga Yoshida et al, 2005	52	-	-	29	range 3 – 240
Lee AY et al, 2006	19	-	0	-	13
Hingorani et al, 2006	598	-	-	28	2

Table 11.2. Clinical outcome after UEDVT: bleeding during anticoagulant therapy, recurrent venous thromboembolism and mortality (continued)

Study, year	Number of patients	Bleeding during anticoagulant therapy (%)	Recurrent VTE (%)	Mortality (%)	Follow-up in months (mean or median)
Spencer et al, 2007	69	13	15	20	12
Arnhjort et al, 2007	32	-	0	-	56
Kovacs et al, 2007	74	4.7	0	9.5	3
Muñoz et al, 2008	512	4.1 (cancer)	6.1 (cancer)	22 (cancer)	3
		0.9 (non-cancer)	2.8 (non-cancer)	3.5 (non-cancer)	
Lechner et al, 2008	50	-	4	-	59
Flinterman et al, 2008	224	-	13	25	36
Isma et al, 2010	63	-	13	24	62
Rathbun et al, 2011	67	3.6 (warfarin+dalteparin)	0	11 (warfarin+dalteparin)	3
		0 (dalteparin only)	0	5.3 (dalteparin only)	
Lee JA et al, 2012	94	-	-	9.6	12
Stone et al, 2012	232	8.2	26	-	at least 3
Sharifi et al, 2012	18	0 (dabigatran)	0	-	9
Chan et al, 2013	65	3.1	9.2 (cancer) 2.6 (non-cancer)	-	12
Delluc et al, 2014	99	3.4	7.1	-	24
Guida et al, 2014	19	-	5.3	-	24
DeSancho et al, 2014	25	0	18	0	-
Amira et al, 2014	17	-	5.9	-	6
Baumann Kreuziger, 2015	558	3.9	4.7	19	12

Table 11.2. Clinical outcome after UEDVT: bleeding during anticoagulant therapy, recurrent venous thromboembolism and mortality (continued)

Study, year	Number of patients	Bleeding during anticoagulant therapy (%)	Recurrent VTE (%)	Mortality (%)	Follow-up in months (mean or median)
OTHER					
Machleder et al, 1993	50	-	0	-	37
Sakakibara et al, 1999	12	-	-	33	41
Ellis et al, 2000	18	-	11	-	15
Massoure et al, 2000	40	-	5	40	9
Ascher et al, 2005	210	-	-	42	13
Lee JT et al, 2006	35	-	23	-	13
Wang et al, 2010	28	-	7.1	21	26
Levy et al, 2012	300	5.5	-	-	-
TREATMENT TYPE UNKNOWN					
Kerr et al, 1990	123	-	-	49	24
Belcaro et al, 2010	211	-	3.3	26	36

UEDVT: upper extremity deep vein thrombosis; VTE: venous thromboembolism. *additional therapies included supraclavicular thoracic inlet decompression, percutaneous transluminal angioplasty (PTA), vein stenting and anticoagulant therapy; **in the study by Sabeti et al, 33 of 95 patients received thrombolytic therapy, and 62 patients received anticoagulant therapy.

Table 11.3. Incidence of recurrence, stratified by follow-up duration and subgroups.

	Follow-up duration			
Recurrence rate	**≤ 3 months**	**3 to12 months**	**> 12 months**	**Combined***
All patients				
Prospective studies	22/699 (3 studies)	26/594 (2 studies)	35/346 (4 studies)	84/1661 (11 studies)
Events / total number of patients	3.1 (0–0.1)	4.4 (0–0.7)	10.1 (0–03.4)	5.1 (0–03.4)
% (range)				
Retrospective studies	-	23/241 (5 studies)	58/766 (12 studies)	126/1281 (20 studies)
Events / total number of patients		9.5 (0–04.5)	7.6 (0–03)	9.8 (0–06.1)
% (range)				
Subgroups				
Cancer	12/301 (3 studies)	2/24 (1 study)	10/148 (3 studies)	24/473 (7 studies)
Events / total number of patients	4.0 (0–0.1%)	9.2	6.8 (0–00)	5.1 (0–00)
% (range)				
Central venous catheter (CVC)	10/228 (1 study)	-	26/558 (1 study)	36/782 (2 studies)
Events / total number of patients	4.4		4.7	4.6 (4.5–5.7)
% (range)				
Cancer + CVC	8/178 (2 studies)	-	7/118 (2 studies)	15 / 296 (4 studies)
Events / total number of patients	4.5 (0–0.7)		5.9 (0–0.1)	5.1% (0 – 7.7)
% (range)				

CVC: central venous catheter

*Follow-up ranged from 3 months to 5 years

Table 11.4. Clinical outcome after UEDVT in cancer patients

Study, year	Number of cancer patients	CVC (%)	Bleeding during AC treatment (%)	Recurrent VTE (%)	Mortality (%)
Savage et al, 1999 (12)	34	-	-	-	17
Baarslag et al, 2004 (13)	30	-	-	10	70
Hingorani et al, 2005 (71)	119	-	-	-	28
Lee et al, 2006 (16)	19	100	-	0	47
Kovacs et al, 2007 (15)	74	100	4.7	0	9.5
Muñoz et a, 2008 (18)	196	53	4.1	6.1	22
Isma et al, 2010 (2)	19	32	-	-	47
Rathbun et al, 2011 (17)	31	-	-	0	13
Lee et al, 2012 (43)	46	89	-	-	13
Chan et al, 2013 (37)	24	0	-	9.2	-
Delluc et al, 2014 (14)	99	100	2.0	7.1	-

UEDVT: upper extremity deep vein thrombosis; CVC: central venous catheter; AC: anticoagulant; VTE: venous thromboembolism

Mortality

All-cause mortality was reported in 23 studies, including 8 with a prospective design (Table 11.2). In these studies, the mortality rate was 11% (range 8 to 15%, 4 studies) (12,15,17,18) in the 3 months following UEDVT diagnosis increasing to 19% after 1 year (range 19 to 25%, 2 studies) (22,24). Two studies with follow-up longer than 1 year observed mortality rates as high as 24% (range 21 to 25%) (19,21).

Studies with a retrospective design generally reported higher mortality rates at 1 month (15%, 3 studies) (32,42,43), 3 months (35%, 1 study) (42), 1 year (32%, 3 studies) (32,42,43) and beyond 1 year of follow-up (35%, 5 studies) (2,13,33,44,45).

In cancer patients with UEDVT, the average mortality rate was 18% (range 9.5 to 22%) after 3 months (4 studies) (12,15,17,18) and 47% after 1 year (one study) (16) (Table 11.4). In the study by Muñoz et al, cancer patients with UEDVT had an 8-fold increased risk of dying after 3 months compared to patients with UEDVT without cancer (22% vs. 3.5%, odds ratio 7.8, 95%CI 4.0 to 16) (18).

Bleeding during anticoagulant therapy

In 6 studies, major bleeding was defined according to or very similar to the criteria of the International Society on Thrombosis and Haemostasis (46), and in the other studies the definition was unclear. The incidence of major bleeding was 7.9% and 17% in 2 studies on systemic thrombolysis (47,48) and 9% in another study that used catheter directed thrombolysis (49) (Table 11.2).

The reported major bleeding rates during anticoagulant therapy varied greatly between the studies ranging from 3.1% (range 0 to 4.7%) (12,17,18) in five prospective studies (1257 patients) (12,15,17,18,24) to 6.7% (range 0 – 13%) in 7 retrospective studies (491 patients; Table 11.2) (14,28,32,35–37,40).

Only two studies prospectively reported bleeding complications during anticoagulant therapy in cancer patients (Table 11.4). Cumulative incidences of major bleeding after 3 months of therapy were 4.1% and 4.7%, respectively (15,18). Compared to patients without cancer, those with cancer had a significantly higher risk of bleeding (4.1% versus 0.9%, odds ratio 4.4, 95%CI 1.2 to 21) (18).

Discussion

The findings of this systematic review suggest that patients with a first episode of UEDVT may develop recurrent VTE in 3% up to 10% of the cases. Among cancer patients, the risk of recurrent VTE was 2- to 3-fold higher than in non-cancer patients. Patients with CVC-related UEDVT seem to have a substantial risk of recurrence, especially during anticoagulant therapy. The overall risk of mortality was 24% to 35% after one year, and the incidence of anticoagulant-related bleeding averaged 3.1% to 6.7%.

The reported incidence of recurrent VTE varied greatly across the studies, which may be explained by differences in study design, study populations, treatment approaches, diagnostic tests, and criteria for recurrent VTE. In addition, the duration of follow-up ranged from 3 months to 5 years, hampering the combined analysis and interpretation of the average incidence rates. A more reliable estimate can be obtained from the three large and recent studies with prospective follow-up, in which incidences of 3 to 4% during anticoagulant therapy, usually given for 3 to 6 months, were reported. After cessation of anticoagulation, the annual incidence of recurrent VTE was approximately 4% in two studies (18,19,24). In most instances, studies did not report whether recurrent thrombosis occurred on- or off-treatment which hampers robust conclusions about the trade-off of safety and efficacy of anticoagulant therapy. In contemporary trials the incidence of recurrent VTE during anticoagulant therapy for lower extremity DVT or PE ranges from 2% to 3%, which appears close to the rates after UEDVT observed in the largest studies of this review (50–54). After cessation of anticoagulation, however, relatively high recurrence rates have been reported after lower extremity DVT or PE, especially in those with unprovoked VTE, ranging from 7 to 13% per year (55–60). This risk of recurrence appears lower in patients with UEDVT, but this comparison needs to be interpreted with caution due to indirectness and the limitations of the available evidence discussed above. In the absence of randomized controlled trials on the management of UEDVT, the same treatment as for patients with lower extremity DVT or

PE is advocated by clinical practice guidelines and this approach is supported by the present findings (7).

The two- to three-fold higher risk of recurrent VTE in cancer patients compared to non-cancer patients is in line with findings from studies on lower extremity DVT or PE, in which cancer patients were found to have a three- to four-fold increased risk of recurrence (61,62). These data support the advice of the American College of Chest Physicians (ACCP) guideline which recommends anticoagulant therapy for at least 3 to 6 months in cancer patients with UEDVT, prolonging treatment if the cancer is active or if the patient is receiving anti-cancer therapy. In patients with UEDVT associated with CVC, the guidelines suggest 3 months of anticoagulation over a longer duration of treatment, regardless of the presence of cancer, unless the CVC remains in place (7). The present data suggest, however, that the risk of recurrent VTE is not negligible in cancer patients, questioning the safety of a short course of anticoagulation in these cases. Of note, it was not always clear if the CVC was removed.

The mortality rate after UEDVT was relatively high which likely reflects the presence of underlying cancer in a large proportion of patients with UEDVT. It is uncertain to which extent fatal PE exactly contributed to the overall mortality rate, since it was not consistently reported in all studies.

Major bleeding rates during anticoagulant therapy seem comparable to those found in patients treated for lower extremity DVT or PE (61,62). Similarly, the risk of bleeding complications appear substantially higher in the presence of cancer (61). Data on the safety of thrombolytic therapy were limited to 3 studies with relatively few participants which suggested a high risk of major bleeding, especially with systemic thrombolysis (7). It has been shown that thrombolysis may improve venous patency, but it is unclear whether it reduces post-thrombotic symptoms or the risk of recurrence. It is uncertain which patients are most likely to benefit from thrombolysis, yet the ACCP guideline suggests that it may be beneficial for patients with severe symptoms for less than 14 days, good functional status, a life expectancy of 1 year or longer, and a low bleeding risk (7).

Our systematic review has some limitations that deserve to be acknowledged. First, the analysis was limited to observational studies, mostly with methodological limitations including the absence of a clear definition of outcomes and retrospective design. The significant heterogeneity with respect to patient characteristics, interventions, and outcome assessment precluded a formal meta-analysis. Pooled incidences reported in this review should therefore be interpreted with caution, especially given the variation in follow-up duration. Finally, outcome events were rarely assessed by a central adjudication committee, which may have biased the estimate of recurrent VTE and bleeding rates. Despite these limitations, the results of our systematic review provide the currently best available overview on the clinical course of patients with UEDVT. The

relatively large number of patients included in this review allowed separate analyses on the high risk subgroups with CVC-related UEDVT and cancer patients.

In conclusion, the current review underlines a lack of solid data on the clinical course and treatment of UEDVT. Further studies are needed to inform physicians about the best management of this disease, especially in high risk subgroups such as those with cancer, where they are left with expert opinions based on indirect evidence from studies on lower extremity DVT or PE. A possible way forward could be a large, multicenter, international, prospective registry, with long follow-up duration, in which treatment strategies are closely monitored and outcome events rigorously assessed.

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Appendix. Systematic searches per database.

1. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Search date: 2 June 2015.

#	Searches
1	Upper Extremity Deep Vein Thrombosis/
2	((upper extremit* or upper limb* or arm or arms or forearm* or shoulder*) adj3 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)).ab,kw,ti.
3	uedvt.ab,kw,ti.
4	(no leg deep vein thromb* or no leg deep venous thromb* or non-leg deep vein thromb* or non-leg deep venous thromb* or nonleg or nldvt).ab,kw,ti.
5	((subclavian adj2 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)) or vena subclavia thromb* or brachial vein thromb* or brachial venous thromb* or vena brachialis thromb* or axillary vein thromb* or axillary venous thromb* or vena axillaris thromb*).ab,kw,ti.
6	(((cvc or catheter) adj2 thromb*) and (upper extremit* or upper limb* or arm or arms or forearm* or shoulder*)).ab,kw,ti.
7	(((cvc or catheter) adj2 thromb*) and (oncol* or cancer or neoplasm* or malign* or benign* or chemotherap*)).ab,kw,ti.
8	(((cvc or catheter) adj2 thromb*) and extremit*).ab,kw,ti.
9	(jugular vein? adj3 thrombos*).mp.
10	(paget adj2 schro?tter).ab,kw,ti.
11	or/1–10

2. Embase Classic+Embase 1947 to 2015. Search date: 2 June 2015

#	Searches
1	Upper Extremity Deep Vein Thrombosis/
2	((upper extremit* or upper limb* or arm or arms or forearm* or shoulder*) adj3 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)).ab,kw,ti.
3	uedvt.ab,kw,ti.
4	(no leg deep vein thromb* or no leg deep venous thromb* or non-leg deep vein thromb* or non-leg deep venous thromb* or nonleg or nldvt).ab,kw,ti.
5	((subclavian adj2 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)) or vena subclavia thromb* or brachial vein thromb* or brachial venous thromb* or vena brachialis thromb* or axillary vein thromb* or axillary venous thromb* or vena axillaris thromb*).ab,kw,ti.
6	(((cvc or catheter) adj2 thromb*) and (upper extremit* or upper limb* or arm or arms or forearm* or shoulder*)).ab,kw,ti.
7	(((cvc or catheter) adj2 thromb*) and (oncol* or cancer or neoplasm* or malign* or benign* or chemotherap*)).ab,kw,ti.
8	(((cvc or catheter) adj2 thromb*) and extremit*).ab,kw,ti.
9	(paget adj2 schro?tter).ab,kw,ti.
10	or/1–1

3. BIOSIS Previews 1993 to 2015. Search date: 2 June 2015

#	Searches
1	((upper extremit* or upper limb* or arm or arms or forearm* or shoulder*) adj3 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)).tw.
2	uedvt.tw.
3	(no leg deep vein thromb* or no leg deep venous thromb* or non-leg deep vein thromb* or non-leg deep venous thromb* or nonleg or nldvt).tw.
4	((subclavian adj2 (thrombol* or thromboe* or thrombos* or thrombu* or dvt)) or vena subclavia thromb* or brachial vein thromb* or brachial venous thromb* or vena brachialis thromb* or axillary vein thromb* or axillary venous thromb* or vena axillaris thromb*).tw.
5	(((cvc or catheter) adj2 thromb*) and (upper extremit* or upper limb* or arm or arms or forearm* or shoulder*)).tw.
6	(((cvc or catheter) adj2 thromb*) and (oncol* or cancer or neoplasm* or malign* or benign* or chemotherap*)).tw.
7	(((cvc or catheter) adj2 thromb*) and extremit*).tw.
8	(jugular vein? adj3 thrombos*).tw.
9	(paget adj2 schro?tter).tw.
10	or/1–1
11	or/1–10

Current management strategies and long-term clinical outcomes of upper extremity venous thrombosis

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J Thromb Haemost. 2016 May;14(5):973-81.

12

Abstract

Background: There is scant information on the optimal management and clinical outcome of deep and superficial vein thrombosis of the upper extremity (UEDVT and UESVT).

Objectives: To explore treatment strategies and the incidence of recurrent venous thromboembolism (VTE), mortality, post-thrombotic symptoms and bleeding in patients with UEDVT and UESVT, and to assess the prognosis of cancer patients with UEDVT.

Patients/methods: Follow-up of patients with UEDVT or UESVT, who were enrolled previously in a diagnostic management study.

Results: We followed 102 and 55 patients with UEDVT and UESVT respectively, both for a median of 3.5 years. Anticoagulant treatment was started in 100 patients with UEDVT (98%) and in 40 (73%) with UESVT. Nine patients with UEDVT (9%) developed recurrent VTE, 26 (26%) died, 6 of 72 patients (8%) had moderate post-thrombotic symptoms and 5 (5%) experienced major bleeding. One patient with UESVT had a recurrent VTE, 18 (33%) died, none had moderate post-thrombotic symptoms and none had major bleeding. Of the cancer patients with UEDVT, 18% had recurrent VTE versus 7.5% in non-cancer patients (adjusted HR 2.2, 95%CI 0.6 to 8.2). The survival rate was 50% in cancer patients with UEDVT versus 60% in those without (adjusted HR 0.8, 95%CI 0.4 to 1.4).

Conclusions: The risk of recurrent VTE was low in patients with UEDVT, and negligible for UESVT. Mortality was high for both diseases. Post-thrombotic symptoms were infrequent and mild. Anticoagulant therapy of UEDVT carried a substantial risk of major bleeding. Cancer patients had a significant risk of recurrent VTE.

Introduction

Upper extremity deep vein thrombosis (UEDVT) involves the radial, ulnar, brachial, axillary, subclavian, internal jugular, or brachiocephalic vein, whereas a clot in the cephalic or basilic vein is referred to as upper extremity superficial vein thrombosis (UESVT) (1). The incidence of UEDVT is increasing, mostly due to the more widespread use of central venous catheters (CVC). UEDVT accounts for 4 to 10% of all cases of deep vein thrombosis (DVT) (2–4), and is subcategorized in primary and secondary UEDVT, based on etiology. Primary UEDVT represents one third of UEDVT cases and includes idiopathic UEDVT, effort-related thrombosis, and thrombosis in the setting of a thoracic outlet syndrome. Secondary UEDVT is associated with an identifiable triggering factor such as a CVC, pacemaker, or cancer. More than 40% of all patients with UEDVT have concomitant cancer (5).

No randomized controlled trials have evaluated the treatment of UEDVT or UESVT. Hence, several questions regarding the optimal management of these conditions remain unanswered. In addition, only few studies with mostly small number of patients have prospectively assessed the long-term prognosis of UEDVT (4,6–14). Studies on the clinical outcome of UESVT are lacking. Complications of UEDVT and UESVT may include recurrent venous thromboembolism (VTE), mortality, post-thrombotic syndrome (PTS), and bleeding during anticoagulant therapy. Finally, the risk of recurrent VTE and mortality in cancer patients after a diagnosis of UEDVT is unclear given the paucity of data in this subgroup.

The main objectives of the present cohort study were to (i) explore the current strategies used to manage patients with UEDVT and UESVT and (ii) assess the rates of recurrent thromboembolic events, mortality, post-thrombotic symptoms and anticoagulant-related bleeding. In addition, we assessed the association between cancer and recurrent VTE, and the impact of UEDVT on survival in cancer patients.

Materials and methods

Follow-up data were collected from adult patients with a clinical suspicion of UEDVT and no prior venous thrombosis of the affected arm, who were enrolled from January 2010 to June 2012 in the ARMOUR study, a prospective, international, multicenter, diagnostic management study (15). The informed consent form for the ARMOUR study included the permission which allowed the investigators to contact the patients for future follow-up. All 16 participating centers from 6 countries were asked to collect follow-up data from medical charts and by visit or telephone between August 2014 and January 2015, using a structured questionnaire. In case the patient had died or could

not be reached, data were retrieved from the medical charts only or by contacting the general practitioner. Treatment and outcome data were collected from patients with confirmed UEDVT or UESVT. Finally, outcome data were collected from patients with active cancer at time of enrolment in the ARMOUR study, in whom UEDVT and UESVT were ruled out.

Recurrent VTE was defined as the composite of locally objectively confirmed symptomatic PE or DVT, including recurrent UEDVT and DVT at unusual sites. In addition, analogous to the Villalta score for lower extremity DVT, patients were asked to score the presence of the following post-thrombotic symptoms of the affected arm on a scale from 0 (absent) to 3 (severe): pain, cramps, heaviness, pruritus and paresthesia (16). According to the total score, patients were grouped into having 'no symptoms' (0), 'mild symptoms' (1 to 5), 'moderate symptoms' (6 to 10) or 'severe symptoms' (11 to 15). No physical signs of a possible PTS were recorded. The initial treatment was defined as anticoagulant treatment within the first 5 to 10 days after the diagnosis whereas long-term anticoagulant included anticoagulant treatment provided after this initial phase. According to the criteria of the International Society on Thrombosis and Haemostasis, major bleeding was defined as overt bleeding, associated with a decrease in hemoglobin level of 2 g/dL or more, requiring transfusion of 2 or more units of blood, occurring in a critical site, or contributing to death (17). Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with a medical intervention, contact with a physician, interruption of anticoagulant treatment, or discomfort or impairment in carrying out activities of daily life.

Statistical Analysis

Baseline differences between groups were analyzed with the student's t test for parametric data, the Mann-Whitney U test for nonparametric data, and the Chi-square test or Fisher's exact test for categorical data. The cumulative incidence of recurrent VTE, mortality and bleeding during anticoagulant treatment, were estimated using the Kaplan-Meier estimator. Patients were censored when they died or were lost to follow-up. The absolute incidence of post-thrombotic symptoms was calculated. For the cumulative incidence of bleeding, patients were also censored at cessation of anticoagulant treatment. When the exact treatment duration was unknown, patients were censored after the intended treatment period (this was needed for 6% of the UEDVT and none of the UESVT patients). The difference in the risk of recurrent VTE between cancer and non-cancer patients, and the difference in survival between cancer patients with and without UEDVT, was assessed by the log-rank test. An estimate of the associations was obtained via Cox proportional hazards regression models including age and sex and, if applicable, type of cancer.

Results

Patients

In the ARMOUR study, a diagnostic algorithm consisting of a clinical decision score, D-dimer testing, and ultrasonography was found to be safe and effective in excluding UEDVT. Of the 406 patients with clinically suspected UEDVT who were enrolled in the study, UEDVT was diagnosed in 104 (26%) and isolated UESVT in 57 (14%; Figure 12.1). Follow-up information was complete for 102 UEDVT patients (98%) with a median follow-up duration of 3.5 years (interquartile range [IQR] 2.9 to 4.0). The median follow-up duration was 3.5 years (IQR 3.1 to 4.0) in the 55 patients with isolated UESVT with complete follow-up (97%). Baseline characteristics are shown in Table 12.1.

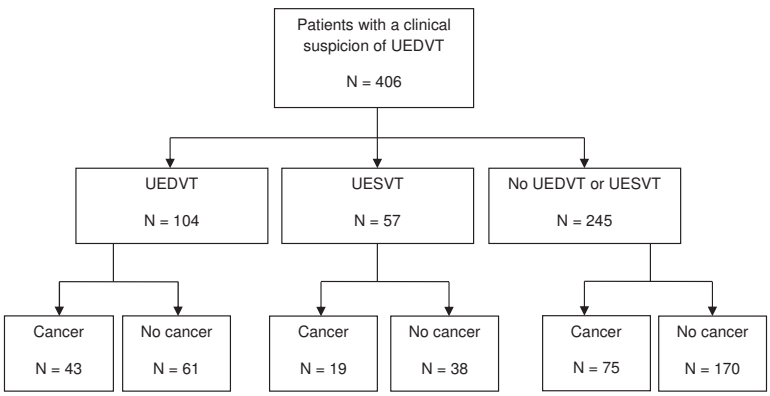


Figure 12.1. Flow diagram of the ARMOUR study.

UEDVT

Management strategies in UEDVT

Anticoagulant treatment was started in 100 patients with UEDVT (98%) and withheld in two. One patient did not receive anticoagulation because he was considered at high risk of bleeding whereas no specific reason for withholding anticoagulant therapy could be identified in the other patient. The median treatment duration was 182 days (IQR 91 to 365). A total of 29 patients (29%) were treated indefinitely. For the initial treatment, low-molecular-weight heparin (LMWH) was most frequently prescribed (88%) with only a few patients treated with unfractionated heparin (UFH) (3%) or fondaparinux (8%). Patients most often received vitamin K antagonists (VKA) for the long-term treatment (56%), whereas LMWH was continued in 41% of the cases (Table 12.2). Seventy-eight percent of cancer patients were managed with LMWH monotherapy for the complete

Table 12.1. Baseline characteristics of the study population

Characteristic	Patients with UEDVT N = 102	Patients with UESVT N = 55
Age in years, mean ± SD	54 ± 17	56 ± 17
Male sex, *n* (%)	44 (43)	31 (56)
Risk factors for venous thromboembolism, *n* (%)		
Cancer	42 (41)	19 (35)
Central venous device	44 (43)	8 (15)
Central venous catheter	3 (7)	1 (13)
Port-a-cath	30 (68)	5 (63)
Pacemaker	11 (25)	2 (25)
Immobilization and/or surgery	12 (12)	10 (18)
Previous venous thromboembolism	5 (5)	5 (9)
Estrogen use	12 (12)	2 (4)
Known thrombophilic defect	6 (6)	7 (13)
Frequent repetitive movements	8 (8)	3 (6)
Unprovoked	27 (27)	17 (31)
Peripheral venous catheter, *n* (%)	10 (10)	22 (40)
Dyspnea or thoracic pain, *n (%)*	10 (10)	3 (6)
Concomitant pulmonary embolism confirmed*	2 (2)	0
Site of thrombosis, *n (%)*		
Brachial DVT	8 (8)	
Proximal DVT	90 (88)	
Unknown	4 (4)	

*Evaluation was not routinely performed, but rather based on clinical judgment
UEDVT: upper extremity deep vein thrombosis; UESVT: upper extremity superficial vein thrombosis; SD: standard deviation; DVT: deep vein thrombosis

treatment period, whereas 81% of patients without cancer were switched to VKA for the long-term treatment. Cancer patients were treated for a median of 182 days (IQR 42 to 339); 38% were treated indefinitely compared to 13% of the non-cancer patients. The use of additional therapeutic measures was uncommon and included systemic thrombolysis, first rib resection, and stent placement (Table 12.2). Thirty percent of patients received elastic compression stockings for the arm, with most of these prescriptions (77%) coming from four of the participating centers. Of the 33 patients with a CVC or port-a-cath present at diagnosis, the catheter was removed within 2 weeks in 2 (6%). Median treatment duration was 182 days (IQR 81 to 361) in patients with CVC- or port-a-cath-related UEDVT, and 240 days (IQR 182 to 730) in patients with a pacemaker.

Table 12.2. Type of initial and long-term treatment for upper extremity venous thrombosis

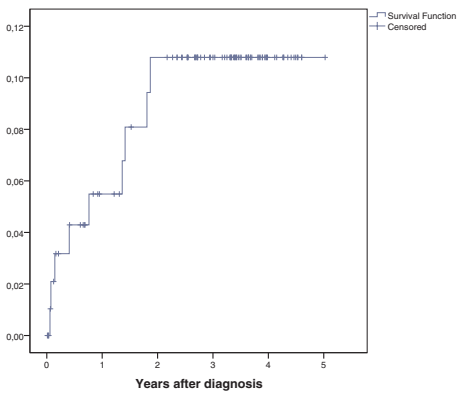
Characteristic	Patients with UEDVT N = 102	Patients with UESVT N = 55
Anticoagulant treatment started, *n (%)*	100 (98)	40 (73)
Initial treatment, *n (%)*		
LMWH		
prophylactic	3 (3)	5 (13)
intermediate	3 (3)	3 (8)
therapeutic	82 (82)	19 (48)
dose unknown	0	1 (3)
UFH	3 (3)	0
Fondaparinux		
2.5mg once daily	0	10 (25)
7.5mg once daily	8 (8)	0
10mg once daily	0	1 (3)
DOAC (rivaroxaban)	1 (1)	0
Unknown	0	1 (3)
Long-term treatment, *n (%)*		
LMWH		
prophylactic	4 (4)	5 (13)
intermediate	9 (9)	14 (35)
therapeutic	28 (28)	7 (18)
dose unknown	0	1 (3)
Fondaparinux		
2.5mg once daily	0	10 (25)
7.5mg once daily	2 (2)	0
VKA	56 (56)	2 (5)
DOAC (rivaroxaban)	1 (1)	0
Unknown	0	1 (3)
Additional treatments, *n (%)*		
Systemic thrombolysis	1 (1)	0
Catheter-directed thrombolysis	0	0
First rib resection	1 (1)	0
Vena cava superior filter placement	0	0
Stent placement	1 (1)	0
CVC removal within 2 weeks	2 (5)	0
Elastic compression stockings	31 (30)	17 (31)

UEDVT: upper extremity deep vein thrombosis; UESVT: upper extremity superficial vein thrombosis; LMWH: low molecular weight heparin; UFH: unfractionated heparin; DOAC: direct oral anticoagulant; VKA: vitamin K antagonist; CVC: central venous catheter.

Clinical outcomes in patients with UEDVT

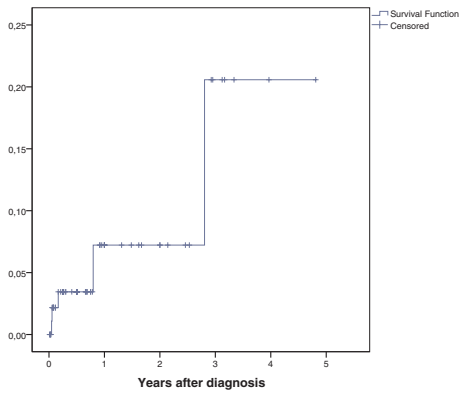
Overall, 9 patients (9%) developed recurrent VTE and 5 events occurred during anticoagulant therapy (Figure 12.2A). Of the 5 patients with a recurrence during anticoagulation, one was receiving a therapeutic dose of LMWH, one an intermediate dose of LMWH, and the other 3 were receiving VKA. Median time to recurrence was 53 days (IQR 24 to 323) during anticoagulant therapy, and 417 days (IQR 261 to 537) after cessation of anticoagulant treatment. Two additional patients (2%) developed UESVT during follow-up. In total, 26 patients (26%) died, which was related to cancer progression in the majority (70%). Data on post-thrombotic symptoms were available in 72 patients (71%) of whom 46 (64%) did not report any post-thrombotic complaints, 20 (28%) had mild and 6 (8%) had moderate symptoms. No patients were classified as having severe symptoms. Of the patients who received elastic compression stockings, 27% developed post-thrombotic symptoms versus 41% of the patients who did not use stockings (p = 0.20). Eleven patients (11%) experienced a bleeding event during anticoagulant therapy of which 5 were classified as major bleeding (5%; Figure 12.2B). Of these 5 patients, 1 was receiving an intermediate dose of LMWH, whilst the other 4 were on VKA.

A



Years	1	2	3	4	5
Number of patients at risk	102	80	73	52	17

B



Years	1	2	3	4	5
Number of patients at risk	100	16	10	4	0

Figure 12.2

A. Cumulative recurrent venous thromboembolism in patients with UEDVT¶

B. Cumulative major bleeding events during anticoagulant treatment in patients with UEDVT†

¶ Y-axis is truncated at 0.12; † Y-axis is truncated at 0.25; UEDVT: upper extremity deep vein thrombosis

UESVT

Management strategies in UESVT

Anticoagulant treatment was started in 40 (73%) patients with UESVT (Table 12.2). Reasons for withholding therapy were a high bleeding risk (N = 1), patient preference (N = 1), and center routine practice (N = 9). In 4 patients the reason was not reported. In the 40 patients who did receive anticoagulants, the median treatment duration was 42 days (IQR 30 to 42). Initial treatment consisted of LMWH in 70% of the patients, mostly in therapeutic doses, and of fondaparinux in 28%. For the long-term treatment, LMWH and fondaparinux remained the preferred anticoagulants with LMWH used in 68%, most frequently at intermediate doses, and fondaparinux in 25% of the patients. No additional therapeutic measures were applied. Elastic compression stockings were prescribed in only two centers, for a total of 31% of the patients. None of the CVCs were removed.

Clinical outcomes in patients with UESVT

One patient with isolated UESVT and metastasized colorectal cancer had a splanchnic vein thrombosis 996 days after stopping anticoagulant therapy. None of 17 patients in whom anticoagulation was withheld experienced recurrent VTE. In total, 18 patients (33%) died during follow-up, and 56% of these deaths were considered cancer-related. Data on post-thrombotic symptoms were available for 34 patients of whom 11 (32%) reported symptoms, all of which could be classified as mild. No patients developed bleeding during anticoagulant treatment.

Cancer patients

Of the 137 cancer patients included in the ARMOUR study, 43 patients (31%) were diagnosed with UEDVT, and thrombosis was ruled out in 75 patients (55%; Figure 12.1). Follow-up was complete for 115 of 118 cancer patients (98%) in these two cohorts. The median follow-up duration was 3.3 years (IQR 2.7 to 3.6 for cancer patients with UEDVT and 2.6 to 4.2 for those without). Table 12.3 depicts the baseline characteristics of all 115 cancer patients included in the present analyses. UEDVT was less often diagnosed in patients with breast or lung cancer than in patients with gastro-intestinal, pancreatic, or hematological cancer. Compared to cancer patients in whom thrombosis was ruled out, cancer patients with UEDVT more often had a CVC (74% vs 40%, $P < 0.01$) or were receiving ongoing cancer therapy at time of clinical suspicion of UEDVT (81% vs 60%, P = 0.02), while the proportion with metastatic cancer was similar.

Two patients with cancer had a recurrent VTE during anticoagulant treatment and 3 after cessation of anticoagulation. The rate of recurrent VTE was approximately two-fold higher than in patients without cancer (18% vs. 7.5%; HR 2.2, 95% CI 0.6 to 8.2 adjusted

Table 12.3. Clinical characteristics of cancer patients with and without UEDVT

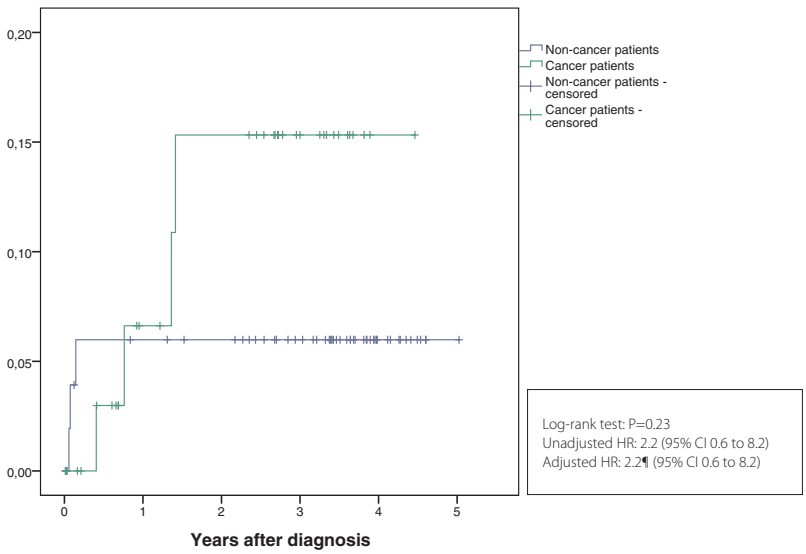
Characteristic	Cancer patients with UEDVT N = 42	Cancer patients without UEDVT N = 73	P-value
Age in years, mean ± SD	57 ± 12	58 ± 12	0.74
Male sex, *n* (%)	18 (43)	26 (36)	0.28
CVC present, *n* (%)	32 (74)	29 (40)	< 0.01
Type of cancer, *n* (%)			0.02*
Breast	12 (29)	38 (52)	
Gastro-intestinal	10 (24)	9 (12)	
Lung	0	8 (11)	
Melanoma	0	3 (4)	
Ovary	1 (2)	0	
Pancreas	3 (7)	1 (1)	
Uterine	1 (2)	1 (1)	
Hematological	7 (17)	6 (8)	
Other	8 (19)	7 (10)	
Distant metastasis, *n* (%)	18 (50)	28 (42)	0.53
Ongoing cancer treatment, *n* (%)	35 (81)	44 (60)	0.02

UEDVT: upper extremity deep vein thrombosis; SD: standard deviation; CVC: central venous catheter
*No cancer types were grouped together for this analysis.

for age and sex; Figure 12.3). After 3.5 years of follow-up, the cumulative survival was 47% in cancer patients with UEDVT compared to 58% in those without UEDVT (HR 0.8, 95% CI 0.4 to 1.4 adjusted for age, sex and type of cancer; Figure 12.4). In contrast, 5 of 60 patients (8.3%) with UEDVT and no concomitant cancer had died at the end of follow-up. None of the cancer patients experienced anticoagulant-related major bleeding. Six patients had a clinically relevant non-major bleeding after a median of 3.6 months (IQR 1.6 to 12) following start of anticoagulant treatment.

Discussion

The present findings provide insight in the current management strategies and long-term outcomes in patients with UEDVT and UESVT. In the absence of randomized controlled trials evaluating the treatment of UEDVT, the American College of Chest Physicians (ACCP) recommends the same initial and long-term treatment as for patients with lower extremity DVT (18). We observed that the majority of physicians who care for patients with UEDVT adhere to these guidelines. Ninety-eight percent of patients

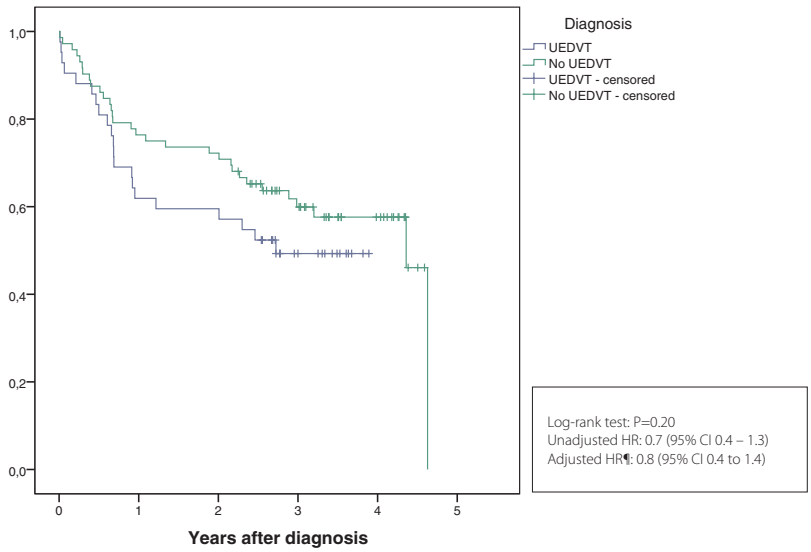


Years		t = 0	t = 1	t = 2	t = 3	t = 4
Cancer patients	Number of patients at risk	42	26	22	10	0
Non-cancer patients	Number of patients at risk	60	52	49	39	12

Figure 12.3. Cumulative incidence of recurrent VTE in patients with or without cancer †
† Y-axis is truncated at 0.2; ¶ Adjusted for age and sex; VTE: venous thromboembolism; HR: hazard ratio

with UEDVT received anticoagulant treatment, mostly VKA, for a median duration of 6 months. A third of the patients received compression stockings, even though the ACCP guideline advices against their use (18). Of note, most of the stocking prescriptions were from a small subset of participating centers. For superficial vein thrombosis of the leg, the ACCP suggests treatment with a prophylactic dose of fondaparinux or LMWH for 6 weeks whereas no specific indications are given for UESVT. A quarter of the patients with UESVT in the present study received fondaparinux in a prophylactic dose, while the majority was treated with an intermediate dose of LMWH, for a median duration of 6 weeks.

The incidence of recurrent VTE in our cohort was somewhat higher than in earlier studies which found rates of 0 to 4% during 3 months of anticoagulant treatment (4,8,13). In a longer term follow-up study by Flinterman and colleagues, the cumulative incidence of recurrent VTE was 7% after 2 years which is consistent with our findings (6). In a recent study from the RIETE investigators including 558 patients with CVC-related UEDVT, the recurrence rate during anticoagulant treatment was 7 per 100 patient-years, decreasing to 3.4 events per 100 patient-years after cessation of treatment (14). In pa-



Years		t = 0	t = 1	t = 2	t = 3
Cancer patients with UEDVT	Number of patients at risk	42	26	24	10
Cancer patients without UEDVT	Number of patients at risk	72	55	51	31

Figure 12.4. Cumulative survival curves of cancer patients with versus those without UEDVT
¶ Adjusted for age, sex and type of cancer; UEDVT: upper extremity deep vein thrombosis; HR: hazard ratio

tients with DVT of the leg, higher rates of recurrence have been reported, ranging from 5 to 13% per year (19–22). The relatively low risk of recurrence observed in patients with UEDVT suggests that a short course of anticoagulation may suffice. Consideration for a longer duration of anticoagulant therapy could be given in patients at high risk of recurrence, but tools to stratify are currently not available for UEDVT. Flinterman et al suggested that women, patients with a first non-subclavian UEDVT and those with a BMI ≥ 25 kg/m^2 had a higher risk of recurrence while CVC-associated UEDVT carried a decreased risk (6). We observed a high mortality rate which was greatly influenced by the large proportion of patients with underlying malignancy, in line with earlier studies (6,23). Post-thrombotic symptoms after UEDVT were infrequent and mostly mild, in agreement with a systematic review by Elman et al (24). After DVT of the leg, relatively high incidences of up to 60% have been reported (25,26). We observed a trend towards a lower incidence of post thrombotic symptoms in patients who received compression stockings compared to those who did not. One explanation for this finding could be that compression stockings indeed prevent development of mild to moderate post thrombotic complaints. However, selection or reporting bias cannot be excluded

entirely in this partly retrospective study. Furthermore, the relatively low numbers of interviewed patients hamper robust conclusions. Thus far, no randomized trials have evaluated the value of compression stockings in preventing PTS after UEDVT. In patients receiving anticoagulant therapy for UEDVT, the cumulative incidence of major bleeding was around 4% after 6 months, which is comparable to earlier studies (4,8,13). All major bleeding events occurred in patients without cancer. Of these, 80% were on VKA treatment, and although we do not have data on International Normalized Ratios, overdosing may have elicited these bleeds. Patients with UESVT had a high mortality rate, mostly due to the high prevalence of malignancy, although other comorbidities may have played a role. UESVT was often provoked by a peripheral catheter, which likely reflects the presence of other diseases. As for the other outcomes, UESVT had a benign course, with only one case of recurrent thrombosis and a low incidence of mild post-thrombotic symptoms. Given the relatively good prognosis, future studies could evaluate the possibility of withholding anticoagulant therapy or reducing treatment duration in these cases.

With regard to cancer patients with UEDVT, the current data suggest a significant risk of recurrent VTE with rates that appear 2-fold higher compared to non-cancer patients. Similar results were reported in the study by Muñoz and colleagues (OR 2.2, 95%CI 0.9 to 5.6) (4), and in cancer patients with DVT of the legs or PE in whom the risk was increased approximately by 3 to 4-fold (27,28). These results support the indication of international guidelines to use anticoagulant treatment for at least 3 to 6 months in patients with active cancer and UEDVT, and to consider prolonging anticoagulant therapy when the cancer is not cured or the patient is still receiving cancer treatment (18). Cancer patients who develop DVT of the legs or PE have a worse prognosis compared to cancer patients without VTE (27,29). In our cohort, cancer patients with UEDVT tended to have a somewhat higher mortality rate after 1 to 2 years of follow-up compared to cancer patients without UEDVT. As autopsy was not mandatory in this study, we cannot exclude that some deaths were related to VTE.

UEDVT was less frequently diagnosed in patients with breast or lung cancer compared to other cancer types. Although this finding may reflect the stronger association between venous thrombosis and pancreatic or gastrointestinal cancer than with breast or lung cancer, we cannot exclude that for UEDVT this result may also be influenced by a different prevalence of CVC in the different cancer populations. In addition, patients with breast cancer often complain of edema of the arm following axillary lymphadenectomy which may raise the clinical suspicion of UEDVT and prompt ultrasonography evaluation.

Our study has some limitations that deserve to be acknowledged. Although our cohort is relatively large in comparison with most previous studies, the absolute number remains modest. The study sample size therefore did not allow to compare recurrence

rates between patients with distal (brachial) versus proximal UEDVT, or between patients with CVC-related versus non-CVC related UEDVT. Second, a part of the follow-up data had to be gathered retrospectively as some patients died or were lost to follow-up. Third, the outcome events were not adjudicated centrally and we relied on the judgment of the local investigators, who used objective testing. Fourth, the centers that participated in the ARMOUR and in the current follow-up study are all specialized in the diagnosis and management of VTE, thus data regarding treatment strategies may not reflect daily practice in other care settings. Fifth, we used a modified Villalta score, evaluating only post-thrombotic symptoms and not clinical signs. However, currently there is no validated scale for the assessment of PTS in the upper extremity, and the evaluation of post-thrombotic signs in the arm is not standardized. Reassuringly, recently it was shown that in patients with lower extremity DVT, a self-reported Villalta score is a valid and sensitive tool for diagnosing PTS (30). Finally, we compared survival in cancer patients with UEDVT to cancer patients in whom UEDVT was ruled out who may, however, not be representative of the general cancer population.

One of the strengths of our study is the long and nearly complete follow-up. In addition, this is the first report on the treatment strategies and clinical outcomes of patients with UESVT. Furthermore, our analysis included separate data for patients with and without cancer.

Conclusions

The overall risk of recurrent VTE during and after anticoagulant treatment was relatively low in patients with UEDVT, and negligible in those with UESVT. The mortality rate was high both in patients with UEDVT and UESVT, although this was largely explained by a high prevalence of underlying cancer. Post-thrombotic symptoms after UEDVT and UESVT were relatively infrequent and mostly mild. Anticoagulant therapy of UEDVT appeared to carry a substantial risk of major bleeding. Cancer patients had a significant risk of recurrent VTE and may benefit of longer anticoagulant treatment.

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PART IV

Bleeding with factor Xa inhibitors and vitamin K antagonists

Clinical presentation and course of bleeding events in patients with venous thromboembolism, treated with apixaban or enoxaparin and warfarin

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2016 Nov 30;116(6):1159-1164.

13

Abstract

Background: Apixaban, a direct acting oral anticoagulant (DOAC), was found to be non-inferior to and safer as enoxaparin followed by warfarin for treatment of venous thromboembolism (VTE) in the AMPLIFY trial.

Objectives: Information is needed on how bleeding events with DOACs present and develop.

Methods: In this post-hoc analysis, the clinical presentation and course of all major and clinically relevant non major (CRNM) bleeding events in the AMPLIFY trial were blindly classified by three investigators, using pre-defined classification schemes containing four categories. Odds Ratios (OR) for classifying as category three or four (representing a more severe clinical presentation and course) were calculated between apixaban and enoxaparin/warfarin.

Results: In total, 63 major and 311 CRNM bleeding events were classified. Of the major bleeds, a more severe clinical presentation occurred in 28.5% of apixaban versus 44.9% of enoxaparin/warfarin related recipients (OR 0.49, 95%CI 0.14–1.78). A severe clinical course was observed in 14.3% and in 12.2%, respectively (OR 1.19, 95%CI 0.21–6.69). Of the CRNM bleeding events, a more severe clinical presentation and extent of clinical care was found in 25% of apixaban recipients compared to 22.7% in the enoxaparin/warfarin group (OR 1.13, 95%CI 0.65–1.97).

Conclusions: The clinical presentation and course of major and CRNM bleeds were similar in apixaban and enoxaparin/warfarin treated patients. This finding should re-assure physicians and patients that even in the absence of a specific reversal agent, apixaban is a convenient and safe choice for VTE treatment.

Introduction

Direct acting oral anticoagulants (DOACs) have been introduced for several indications including treatment of venous thromboembolism (VTE), and are now widely used (1). In the AMPLIFY trial, the direct factor Xa (fXa) inhibitor apixaban proved to be non-inferior to enoxaparin followed by warfarin for treatment of VTE, and was associated with significantly less bleeding (2). Extended treatment of VTE with apixaban reduced the risk of recurrent VTE without increasing the rate of major bleeding (3). In a recent meta-analysis of the phase 3 trials which compared DOACs with vitamin K antagonists (VKAs) for the treatment of acute symptomatic VTE, DOACs were found to be as efficacious in preventing recurrent VTE (risk reduction [RR] 0.90, 95%condidence interval [CI] 0.77 – 1.06), but were associated with a lower risk of major bleeding (RR 0.61, 95% CI 0.45 – 0.83) (4).

Despite clear evidence of less bleeding with the DOACs than with warfarin, the uptake of DOACs for VTE treatment has been slow. Reasons for the slow uptake are manifold but in addition to the higher cost include concerns about management of bleeding and the current lack of specific reversal agents for oral fXa inhibitors, although this may change if andexanet alfa is licensed later this year (5–7). Information is needed on how bleeding events during therapy with DOACs present and develop, and how they are managed, including how often a specific antidote is needed. Although some recent studies have evaluated the severity of major bleeding events in DOAC users, to the best of our knowledge, this has not been done for clinically relevant non major (CRNM) bleeding. In this post-hoc analysis, we blindly classified the seriousness of clinical presentation and course of all episodes of (major and non-major) clinically relevant bleeding in the AMPLIFY trial.

Methods

The AMPLIFY trial

The methodology of the AMPLIFY trial has been published elsewhere (2). Briefly, patients with acute VTE were randomized in a double-blind fashion to either apixaban or conventional therapy (enoxaparin followed by warfarin). The primary safety outcome was major bleeding; the secondary safety outcome was the composite of major and CRNM bleeding. The study was funded by Pfizer Inc. and Bristol Myers Squibb Company.

In the AMPLIFY trial, major bleeding was defined as overt bleeding, associated with a decrease in hemoglobin level of 2 grams per deciliter or more, requiring transfusion of 2 or more units of blood, occurring in a critical site or contributing to death (8). CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding

but associated with a medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life (9). All bleeding events were reported prospectively during the trial by using standardized case report forms.

The current analysis

Classification schemes

Both the major bleeding and CRNM bleeding events were classified. For the major bleeding events, two classification schemes were used; the first assessed the clinical impact of the bleeding event at time of presentation (Table 13.1A), while the second assessed the measures and interventions applied to manage the bleed as well as the clinical course (Table 13.1B). For this assessment, we used our earlier definitions (10). For CRNM bleeding events, one classification scheme was developed, reflecting both the severity of clinical presentation and the extent of clinical care (Table 13.2).

In the first classification of major bleeding, the event was assigned to category one if it presented without any clinical emergency. All bleeding events that could not be classified to any of the other three categories were classified as category two. Category three represented a bleeding event presenting as a medical emergency (i.e. hemodynamic

Table 13.1. Classification of major bleeding events

A. Clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency.
2	All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency.
3	Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability, or cerebral major bleeding presenting with neurologic symptoms.
4	Bleeding events already fatal before or almost immediately upon entering the hospital.

B. Clinical course

Category	Description
1	Bleeding events for which only measures were applied to treat discomfort, without transfusions of erythrocytes.
2	Bleeding events requiring only standard measures such as transfusions of erythrocytes, and straight forward measures.
3	Life threatening bleeding events requiring immediate and elaborate measures to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability.
4	Bleeding events for which death was unavoidable, so that no lifesaving attempts were made.

Table 13.2. Classification of the presentation and course of clinically relevant non major bleeding events

Category	Description
1	Bleeding events which were: - Self-controlled, and/or - Retrospective in nature, and/or - Required no emergency room/medical visit, stop of study medication, procedures or treatment
2	Bleeding events that could not be classified to any of the other three categories (i.e. only requiring temporary interruption of study medication, bleeding events only requiring contact)
3	Bleeding events requiring an emergency room/medical visit and procedures or treatment to control the bleeding, but no hospitalization
4	Bleeding events requiring hospitalization and procedures or treatment to control the bleeding

instability or neurological symptoms), and the bleeding was assigned to category four if it was already fatal before or almost immediately upon entering the hospital.

For the second classification of major bleeding, i.e. the management and clinical course, category one was defined as bleeding events for which measures were only applied to treat discomfort. The bleeding was assigned to category two when it required only standard measures (e.g. blood transfusions). Category three was defined as a life threatening bleeding event requiring immediate and elaborate measures to avoid death, and category four represented bleeding events for which death was unavoidable, so that no lifesaving attempts were made.

CRNM bleeding events were assigned to category one if they had resolved spontaneously, or were reported at scheduled follow-up visits during the conduct of the trial. Category two comprised events that could not be classified to any of the other three categories. The third category represented events requiring an emergency department or medical visit and procedures or treatment to control the bleeding. Category four was reserved for bleeding events requiring hospitalization.

Classification procedure

All bleeding events were classified by three clinicians (AC, HB, SM), first independently and then by discussion to reach consensus, using the pre-defined criteria mentioned above. A fourth clinician (SB) provided all information that was available for each separate classification to AC, HB and SM, including information from emergency room or discharge letters, bleeding narratives, hemodynamic parameters, relevant laboratory results, such as hemoglobin levels, medical treatment and interventions applied to control the bleeding, as well as the outcome of the patient. All adjudicators were blinded as to the administered anticoagulant and outcome of the other classification.

Multiple events were considered as a single event when they occurred during one episode and were treated as one event. Events were also considered as a single event when there was simultaneous bleeding at more than one anatomic site for which uniform measures were taken, or when recurrent bleeding episodes occurred at the same site. Recurrent bleeding events at different time points and distinct anatomic sites were considered more than one event.

Only one event per patient was included in the final analysis. In case of multiple events, the event with the highest category was included and in case of equal categories, the first event was analyzed. Bleeding events were excluded from the classification if 1) the bleeding episode occurred ≥ 10 days after the final dose of study drug, 2) there was insufficient information to classify the event, or 3) the CRNM bleeding event occurred ≤ 10 days before a major bleeding event.

Endoscopic or surgical procedures were only considered interventional measures if they were used in an attempt to stop bleeding (e.g. coiling of a bleeding vessel or surgical evacuation of a hematoma).

Statistical analysis

Results are presented as numbers with percentages. For the analysis, we a priori decided to combine categories 3 and 4, representing a more severe clinical presentation and course. Categories 1 and 2 were combined to represent a less severe clinical presentation and course. Odds ratios (OR) were calculated for category 3 and 4 combined between apixaban and enoxaparin/warfarin.

Results

The AMPLIFY trial

In the AMPLIFY trial, 5244 patients with acute VTE were included and followed for 6 months. A total of 64 major bleeding events were observed of which 15 (0.6%) occurred in the apixaban group and 49 (1.8%) in the enoxaparin/warfarin group (RR 0.31; 95% CI 0.17 to 0.55). There were a total of 318 CRNM bleeding events. Of these, 103 (3.9%) occurred in the apixaban group and 215 (8.2%) in the enoxaparin/warfarin group (RR, 0.50; 95% CI 0.40 to 0.63) (2).

Baseline characteristics of the patients and sites of bleeding are detailed in Table 13.3. For the current analysis, based on the pre-specified exclusion criteria, a total of 63 major bleeding and 311 CRNM bleeding events were adjudicated. One major bleed was excluded because it was unclear whether it occurred within 10 days of the final dose of study drug. Seven CRNM bleeds were excluded; 4 because bleeding occurred within 10

days of a major bleed, and 3 because insufficient information was available to enable classification.

Both major and CRNM bleeding events occurred earlier after start of treatment in the warfarin group than in the apixaban group (Table 13.3).

Major bleeding – clinical presentation

Table 13.4, part A, details the results of the classification of the major bleeding events at presentation for the two treatment arms. Approximately 15% of all major bleeding episodes were classified in category 1, i.e. presenting without emergency. The distribution over the various categories tended to be less severe in the apixaban group. In fact, a severe clinical presentation (i.e. categories 3 and 4 combined) occurred in 4 of 14 (28.5%) of the major bleeding events in the apixaban group, as compared with 22 of 49 (44.9%) of those in the enoxaparin/warfarin group (OR 0.49, 95% CI 0.14 – 1.78).

Table 13.3. Baseline characteristics

A. Patients in the AMPLIFY trial with a major bleeding event

	Apixaban N = 2676	Enoxaparin/warfarin N = 2689
Number of patients with a major bleeding event *(n, %)*	**15 (0.6)**	**49 (1.8)**
History of cardiovascular disease*	12 (80)	39 (80)
On-study medication use		
Antiplatelet agents	5 (33)	17 (35)
NSAIDs	1 (7)	13 (27)
Bleeding site *(n, %)*		
Intracranial	3 (20)	6 (12)
Gastro-intestinal bleed	8 (53)	19 (39)
Retroperitoneal	1 (7)	3 (6)
Vaginal	1 (7)	0
Intra-articular	0	2 (4)
Subcutaneous hematoma	1 (7)	6 (12)
Intraocular	0	2 (4)
Intramuscular	0	6 (12)
Hematuria	0	3 (6)
Other	1 (7)	2 (4)
Median days from randomization to bleeding event (IQR)	67 (15 – 102)	15 (6 – 86)

B. Patients in the AMPLIFY trial with a clinically relevant non major bleeding event

	Apixaban N = 2676	Enoxaparin/warfarin N = 2689
Number of patients with a CRNM bleeding event *(n, %)*	**103 (3.8)**	**215 (8.0)**
History of cardiovascular disease*	62 (62)	124 (59)
On-study medication use		
Antiplatelet agents	18 (18)	53 (25)
NSAIDs	32 (31)	59 (27)
Bleeding site *(n, %)*		
Epistaxis	9 (9)	32 (15)
Gastro-intestinal bleed	25 (24)	35 (16)
Vaginal	28 (27)	24 (11)
Subcutaneous hematoma	16 (16)	38 (18)
Intramuscular	3 (3)	4 (2)
Hematuria	18 (18)	62 (29)
Other	4 (4)	20 (9)
Median days from randomization to bleeding event (IQR)	63 (13 – 109)	28 (10 – 82)
Recurrent VTE	2 (2)	4 (2)

*Includes hypertension, heart failure, heart valve disease, cerebrovascular events, angina pectoris, myocardial infarction, coronary artery disease, peripheral artery disease, cardiomyopathy, congenital heart disease, arrhythmia, aortic disease, and venous thromboembolism. CRNM: clinically relevant non major; NSAIDs: non-steroidal anti-inflammatory drugs; IQR: interquartile range; VTE: venous thromboembolism

Major bleeding – clinical course

A severe clinical course, category 3, was observed in 2 of 14 (14.3%) major bleeding events in the apixaban group and in 6 of 49 (12.2%) major bleeding events in the enoxaparin/warfarin group (OR 1.19, 95% CI 0.21 – 6.69) (Table 13.4B). No major bleeding event from either group met the criteria for the most severe clinical course (category 4). Although the proportion of patients with a less severe clinical course (i.e. categories 1 and 2 combined) in the two treatment groups was comparable, there was a high frequency of category 1 clinical courses in the enoxaparin/warfarin group (26.5%) compared to the apixaban group (7.1%).

Major bleeding – dynamics of presentation and clinical course

In the apixaban recipients, of those major bleeding events presenting in category 1 or 2, none progressed to a severe (i.e. category 3 or 4) clinical course. Conversely, 2 of 4 (50%) of the events with a category 3 or 4 presentation had a mild clinical course (i.e. category 1 or 2).

Table 13.4. Results of the classification of major bleeding events

A. Part 1: Clinical presentation

	Apixaban	Enoxaparin/warfarin
Number of major bleeding events	14	49
Category 1	2 (14.3%)	8 (16.3%)
Category 2	8 (57.1%)	19 (38.8%)
Category 3	3 (21.4%)	22 (44.9%)
Category 4	1 (7.1%)	0 (0%)

	Apixaban	Enoxaparin/warfarin
Number of major bleeding events	14	49
Category 1 or 2	10 (71.4%)	27 (55.1%)
Category 3 or 4	4 (28.5%)	22 (44.9%)

Odds ratio for classifying as clinical presentation category 3 or 4 between apixaban and enoxaparin/warfarin users: 0.49 (95%CI 0.14–4.78)

B. Part 2: Clinical course

	Apixaban	Enoxaparin/warfarin
Number of major bleeding events	14	49
Category 1	1 (7.1%)	13 (26.5%)
Category 2	11 (78.6%)	30 (61.2%)
Category 3	2 (14.3%)	6 (12.2%)
Category 4	0 (0%)	0 (0%)

	Apixaban	Enoxaparin/warfarin
Number of major bleeding events	14	49
Category 1 or 2	12 (85.7%)	43 (87.7%)
Category 3 or 4	2 (14.3%)	6 (12.2%)

Odds ratio for classifying as clinical course category 3 or 4 between apixaban and enoxaparin/warfarin users: 1.19 (95%CI 0.21–1.69)

Of the patients receiving enoxaparin/warfarin who had a bleeding event with a category 1 or 2 presentation, none developed a severe clinical course, whereas 10 of 16 (72.7%) of the patients presenting with a category 3 or 4 bleeding event progressed to a mild clinical course.

CRNM bleeding – clinical presentation and course

In Table 13.5 the results of the CRNM bleeding classification are shown. A more severe clinical presentation and extent of clinical care (i.e. events requiring a medical visit and

Table 13.5. Results of the classification of clinically relevant non major bleeding events

	Apixaban	Enoxaparin/warfarin
Number of clinically relevant non major bleeding events	100	211
Category 1	26 (26.0%)	53 (25.1%)
Category 2	49 (49.0%)	110 (52.1%)
Category 3	9 (9.0%)	25 (11.8%)
Category 4	16 (16.0%)	23 (10.9%)

	Apixaban	Enoxaparin/warfarin
Number of clinically relevant non major bleeding events	100	211
Category 1 or 2	75 (75.0%)	163 (77.2%)
Category 3 or 4	25 (25.0%)	48 (22.7%)

Odds ratio for classifying as category 3 or 4 between apixaban and enoxaparin/warfarin users: 1.13 (95%CI 0.65–5.97)

procedures or treatment to control the bleeding, with or without hospitalization) was observed in 25 of 100 (25.0%) of the CRNM bleeding events in the apixaban group and in 48 of 211 (22.7%) of the events in the enoxaparin/warfarin group (OR 1.13, 95% CI 0.65 – 1.97). The distribution over the categories was comparable for both treatment regimens, although hospitalization occurred slightly more often among the patients who received apixaban as compared with enoxaparin/warfarin recipients (OR 1.6, 95%CI 0.8–3.1).

Discussion

In the AMPLIFY trial, patients treated with apixaban had fewer major bleeding events than those given enoxaparin/warfarin (2). Here we show that in addition, major bleeds with apixaban have a similar presentation and course as those with enoxaparin/warfarin. Although the odds of presenting in category 3 or 4 with apixaban was lower than with enoxaparin/warfarin, this association was not statistically significant. Major bleeds that present as emergencies cause distress for patients, their families and for health care professionals. Furthermore, such bleeds also are likely to be more costly for the healthcare system. Another important finding was the heterogeneity in the presentations and clinical courses of major bleeding events in patients with VTE, regardless of whether they received apixaban or enoxaparin/warfarin. For example, patients with intracranial bleeds can be moribund on admission or can present with mild symptoms and can recover completely without any intervention. This nuance is not captured by solely using the term "major bleeding".

A potential explanation for the non-significant trend towards the less severe clinical presentation of major bleeding events with apixaban that we observed, could be the shorter half-life of apixaban compared with warfarin. Furthermore, the anticoagulant effect of warfarin is less predictable, and International Normalized Ratio (INR) values above the therapeutic range increase the risk of bleeding. Overtreatment may contribute to more severe bleeding. Finally, it needs to be realized that clinicians had the options of administering vitamin K, PCC and FFP for warfarin reversal.

It is reassuring that most major bleeding events appear to have a mild clinical course. Therefore, there is little justification for withholding DOACs because of the fear of bleeding. Nonetheless, idarucizumab, the antidote for dabigatran was recently approved, and andexanet alfa, the antidote for the other DOACs is in an advanced stage of development (5). With the availability of these antidotes, which will be expensive, how often will we need to give them? We found that standard measures were sufficient to manage the vast majority (86% and 88%) of the major bleeding events in the apixaban and enoxaparin/warfarin groups, respectively. Therefore, antidotes are likely to be used infrequently.

In the AMPLIFY trial, CRNM bleeding events occurred about 5 times more frequently than major bleeding events. Therefore, CRNM bleeding represents a relatively frequent problem. We did not find a difference in clinical presentation and subsequent clinical course of CRNM bleeding events in the patients treated with apixaban or enoxaparin/warfarin. Also, for this classification, we observed that about 75% of the bleeds had a mild presentation and course. This is encouraging because a more severe clinical presentation and course implies greater utilization of healthcare resources (i.e. due to interventions and hospitalization), although we did not specifically evaluate this. Even though "mild" CRNM bleeds may utilize fewer healthcare resources, these remain clinically important bleeds because they can cause distress and may lead to temporary or permanent cessation of anticoagulant treatment. The latter carries a risk of recurrent VTE, especially if the index event occurred recently. In the enoxaparin/warfarin group, both major and CRNM bleeding events occurred earlier than in the apixaban group, hence, in the more critical phase of anticoagulant treatment.

Few other studies have analyzed the severity of bleeding events with DOACs versus VKA. In a study by Majeed and colleagues, 1121 bleeding events in 1034 patients in the phase 3 trials that compared dabigatran with warfarin for the treatment of VTE and for stroke prevention in atrial fibrillation (AF), were retrospectively analyzed. A lower 30-day mortality in the dabigatran recipients was reported (9.1% versus 13% in the VKA arm, $p = 0.06$), and the duration of admission to the intensive care unit was shorter in the dabigatran users than the warfarin recipients (an average of 1.6 versus 2.7 nights, respectively, $p = 0.01$) (11). Similar results were obtained by Berger and colleagues. In 15 patients on dabigatran and 25 on warfarin that were admitted to the hospital with

a bleeding event, the admission duration was found to be shorter in the dabigatran group (3.5 versus 6.0 days in the warfarin group) (12). These results imply that bleeding events with dabigatran are also less severe than with warfarin.

Eerenberg et al performed a similar analysis as the present analysis on the major bleeding events in the EINSTEIN studies, in which rivaroxaban was compared to enoxaparin/VKA for the treatment of VTE. They found a milder clinical presentation of major bleeds in patients on rivaroxaban compared with enoxaparin/VKA (OR 0.39, 95%CI 0.16 – 0.96), but also a trend towards a less severe clinical course that was however not significant (OR 0.81, 95%CI 0.30 – 2.13) (10). Brekelmans et al reported on the clinical relevance and management of major bleeding events with edoxaban versus VKA, and reported a comparable clinical presentation and course (13).

One may wonder whether the results of the phase 3 trials such as the AMPLIFY study can be extrapolated to real life practice. It is possible that relatively healthy people were included in these trials, leading to an underestimation of the safety of the DOACs in the general population. However, in a prospective, real life, non-interventional registry of 511 patients on apixaban for the prevention of stroke in AF, after a median follow-up duration of 355 days, 15% experienced a major bleeding event (1.9 per 100 patient-years, 95%CI 1.9 – 5.7). These results are fully comparable to those from the phase 3 trials; hence, the results from these trials seem to be representative for daily practice (14).

Our study has several strengths. The AMPLIFY study was a double blind randomized study, and in the present analysis the adjudicators were blinded for the assigned anticoagulant. Therefore the risk of bias seems negligible. Furthermore, information on bleeding events was prospectively collected during the AMPLIFY trial, and all bleeding events were centrally adjudicated. Finally, this is the first study that gives some insight into the presentation and dynamics of CRNM events.

There are also some limitations that deserve to be acknowledged. First, the number of major bleeding events in the AMPLIFY study was small, hampering statistically robust conclusions. Second, the classification schemes for major bleeding have only been applied in two studies (10,13), whereas the classification scheme for CRNM bleeding was completely novel. Further application of the schemes is needed to prove their reproducibility. Third, we did not have INR values of the patients receiving warfarin at time of bleeding, and therefore it is unclear if overtreatment contributed to the non-significant trend towards the less severe clinical presentation of major bleeding events with apixaban. Finally, although the protocol of the AMPLIFY study pre-specified activities that could be taken in case of bleeding events, the treatment strategy was left to the discretion of the treating physician.

For physicians who see patients with bleeding events during the use of apixaban or one of the other DOACs, it is valuable to know how these bleeding events present and

progress. In conclusion, the clinical presentation and course was similar for apixaban and enoxaparin/warfarin associated major and CRNM bleeding events. The results of this study give insight into the heterogeneity of major and CRNM bleeding events, and should reassure physicians that even in the absence of a specific reversal agent, apixaban is a convenient and safe choice for VTE treatment.

Acknowledgments

We would like to acknowledge John Thompson (Pfizer Inc.) for the provided statistical analysis support.

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Clinical impact and course of major bleeding with edoxaban versus vitamin K antagonists

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Thromb Haemost.
2016 Jul 4;116(1):155-61.

14

Abstract

Background: Edoxaban is a once-daily direct oral anticoagulant (DOAC). The Hokusai-VTE study revealed that, after initial treatment with heparin, edoxaban was non-inferior to and safer than vitamin K antagonists (VKA) in the prevention of recurrent deep vein thrombosis and pulmonary embolism. This is the first report on the clinical relevance and management of bleeding events with edoxaban.

Methods: All major bleeding events were classified blindly by three study-independent adjudicators. Pre-defined criteria were used to classify severity of clinical presentation and, separately, the clinical course and outcome into 4 categories.

Results: Major bleeding occurred in 56 patients treated with edoxaban and 65 patients treated with VKA. The severest categories (3 or 4) of the clinical presentation were assigned to 46% of the major bleeding episodes in edoxaban recipients versus 58% of the major bleeds in VKA recipients (odds ratio 0.62, 95% CI 0.30–1.27, $p = 0.19$). Clinical course was classified as severe (category 3 or 4) in 23% of the edoxaban and 29% of the VKA associated bleeds (odds ratio 0.73, 95% CI 0.32–1.66, $p = 0.46$).

Conclusion: Edoxaban associated major bleeding events have a comparable clinical presentation and course to major bleeds with VKA in patients treated for venous thromboembolism in the Hokusai-VTE study. These results may assure physicians that it is safe to prescribe this medication. If a major bleeding during edoxaban treatment occurs, its clinical presentation and clinical course are not worse than in VKA treated patients.

Introduction

Oral anticoagulants (OAC) are indicated for the treatment and prevention of venous thromboembolism (VTE). For six decades vitamin K antagonists (VKA) were the only available OAC and although VKA are highly effective in prevention of thromboembolism, there are several limitations to their use, such as a narrow therapeutic index, inter- and intra-individual variability, interactions with food and other drugs and a variable dose response which all necessitate frequent monitoring and dose adjustments (1–3). The most important side effect of VKA is an increased risk of bleeding. As such, VKA have been prominent at the top of the list of medications that lead to hospital admission (4).

The direct oral anticoagulants (DOACs) were developed as an alternative for VKA treatment. Advantages of DOACs are a short half-life, few interactions with food and other drugs and a stable pharmacokinetic and pharmacodynamic profile allowing a fixed dose regimen (5). For treatment of VTE, DOACs have been evaluated in large phase III clinical trials with a total of 26872 patients (6–9). A meta-analysis of these studies showed that DOACs are as effective as VKA in the treatment of VTE and reduce the risk of major bleeding. In addition, the risk of intracranial hemorrhage (ICH) was reduced by 30–70% in patients using DOACs compared to VKA (10,11).

Although these large studies show that the absolute number of bleeding events in patients treated with DOACs is low, little is known about the clinical impact of those bleeding episodes. There is a need for information about the severity of presentation and the course of DOAC and VKA associated bleeds. Furthermore insights in optimal management of DOAC associated bleeding and procedures in case of emergent interventions or surgery are wanted (12,13).

The aim of the present study is to assess the clinical relevance and management of major bleeding events associated with edoxaban. We therefore classified all major bleeding events of the Hokusai-VTE study in a blinded fashion with regard to clinical impact at the time of presentation and the clinical course. A comparison was made between edoxaban and VKA treated patients. Additionally, the interventions and treatment strategies used to manage bleeding were described.

Materials and methods

Hokusai-VTE study

In the Hokusai-VTE study, edoxaban was compared to VKA (i.e. warfarin) in a double-blind, double-dummy fashion for the treatment of acute symptomatic DVT or PE. All patients received initial treatment with enoxaparin (LMWH) or unfractionated heparin (UFH) for at least 5 days. After discontinuation of LMWH or UFH, edoxaban (or placebo)

was started at a dose of 60 mg once daily. A lower dose of 30 mg once daily was prescribed in case of a creatinine clearance of 30–50 ml per minute, a bodyweight of ≤ 60 kg or when the patient received concomitant treatment with potent P-glycoprotein inhibitors. Simultaneously, warfarin (or placebo) was started. Target international normalized ratio (INR) was between 2.0 and 3.0 and was measured by point-of-care INR devices at least once a month. The treatment duration was between 3 and 12 months and was a decision of the treating physician. Additional information about the Hokusai-VTE study can be found in the original article (9).

The primary safety outcome was a composite of first major or clinically relevant non-major bleeding. Major bleeding was, according to the ISTH criteria (14), defined as overt and associated with a drop in hemoglobin level of ≥ 2 grams per deciliter or leading to blood transfusion of 2 or more units of red blood cells, appearing in a critical organ or site, or fatal. Patients were followed prospectively and were asked to report symptoms suggestive of bleeding. Appropriate diagnostic investigations were performed when needed.

Classification of presentation and course of major bleeding

All major bleeding events from the Hokusai-VTE study were classified blindly by three independent adjudicators (HB, AC, SM) using pre-defined criteria (Table 14.1). An extensive description of the adjudication process has been described previously (15). Briefly, the first classification assessed the severity of the *clinical presentation* of the bleeding. The second classification assessed the *clinical course* and evaluated applied measures and interventions to treat the major bleed and the outcome of the bleed. When the adjudicators differed in opinion, a thorough debate on the classification followed, taking all relevant information into consideration, in order to reach consensus. If no consensus was reached, the following rule applied: in case of doubt between categories, the more severe outcome was chosen (and the bleeding was adjudicated to the higher category). The investigators were not aware of the assigned treatment regimen at the time of adjudication of both classification schemes.

If a patient had experienced more than one major bleed at different anatomical sites or a recurrent major bleed at the same anatomical site, the first major bleed or the major bleed with the worst outcome was taken into account. Hence, for every patient only one major bleeding episode was considered for the final analysis.

Assessment of treatment of major bleeds

The protocol of the Hokusai-VTE study pre-specified treatment strategies that could be applied for bleeding events (9,16). To assess treatment strategies applied for major bleeds in both treatment groups, the focus was on patients with observed *clinical course* categories 2 and 3. Category 2 of the clinical course was defined as standard

Table 14.1. Classification of clinical presentation and course of major bleeding in the Hokusai-VTE study.

A. Clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency.
2	All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency.
3	Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability; or cerebral bleeding presenting with neurologic symptoms.
4	Bleeding events that are fatal before or almost immediately upon entering the hospital.

B. Clinical course

Category	Description
1	Bleeding events for which only measures were applied to treat discomfort, without transfusions of erythrocytes.
2	Bleeding events requiring only standard measures such as transfusions of erythrocytes, and straight forward interventions.
3	Life threatening bleeding events for which immediate and elaborate measures were used to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability.
4	Bleeding events for which death was unavoidable, so that no lifesaving attempts were made.

measures to treat the bleeding, for example administration of vitamin K, packed cells and/or fresh frozen plasma. Clinical course category 3 was defined as more elaborative measures to avoid serious morbidity and mortality, including administration of prothrombin complex concentrate (PCC) and procedures to stop the bleeding, such as surgical, radiological or endoscopic procedures.

Description of major bleeds included in the analysis

The major bleeds were assessed by means of time-to-first major bleed. Only major bleeds that occurred during the on-treatment period (period in which patients received the study drug or within 3 days after the study drug was stopped or interrupted) were eligible.

Statistical analysis

The results are presented as counts and percentages. Kaplan Meier curves were calculated for the cumulative rates of major bleeds in both treatment groups. Additional information about the statistical analysis in the Hokusai-VTE study is described in the original article (9). A logistic regression model was applied for the analysis of the clini-

cal presentation and course within the major bleeding group. Odds ratios (OR) were computed for the combined categories 3 and 4 between the edoxaban and VKA group for both classifications. In addition, a Cox proportional hazard regression analysis was performed. Outcome was defined as time to onset of major bleedings with combined clinical presentation or clinical course 3 and 4. Patients without clinical presentation or course in categories 3 and 4 were censored. All patients who received at least one dose of study medication were included in the analysis.

Results

Major bleeding in Hokusai-VTE study

A total of 8240 patients were included in the Hokusai-VTE study. Of these patients, 4118 were treated with edoxaban and 4122 patients received standard care with VKA. The primary safety outcome of first major and clinically relevant non-major bleeding occurred in 349 patients treated with edoxaban and in 423 patients assigned to VKA (hazard ratio 0.81, CI 0.71–0.94, p = 0.004). Major bleeds were observed in 56 of the

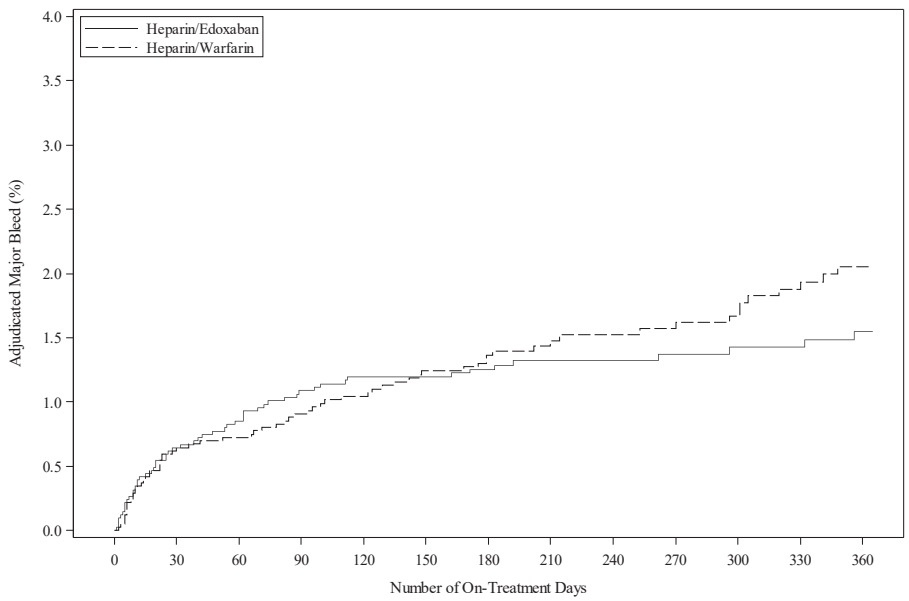

Figure 14.1. Kaplan-Meier cumulative rates of major bleeding.
Kaplan Meier cumulative rates of major bleeding episodes during the on treatment period of the Hokusai-VTE study.

edoxaban treated patients and in 66 of the VKA treated patients (hazard ratio 0.84, CI 0.59–1.21, p = 0.35) (9). Kaplan Meier curves are shown in Figure 14.1.

Descriptive information of major bleeding events

Data of one patient with a major bleed from the VKA group was not available for the current analysis. In total, 56 major bleeds in patients receiving edoxaban and 65 major bleeds in patients treated with VKA were classified. The mean age in the edoxaban group was 64 ± 15 years and in the VKA group 66 ± 14 years and was not statistically different (p = 0.58). The distribution of sex was also not different between the groups (edoxaban group 39% male and VKA group 52% male; p = 0.15). In the edoxaban group 75% of patients had an index DVT compared to 79% in the VKA group (p = 0.65). The median day of presentation was 38 in the edoxaban group (interquartile range (IQR) 9–93) and 77 in the VKA group (IQR 13–176; p = 0.41). In edoxaban recipients, the distribution of bleeding type was 9% intracranial, 48% gastro-intestinal, 16% vaginal, 5% cutaneous/soft tissue and 22% other bleeds. For VKA recipients, 28% intracranial, 26% gastro-intestinal, 5% vaginal, 14% cutaneous/soft tissue and 27% other bleeds were observed.

Results clinical presentation

More than half of the patients with major bleeds in the edoxaban group presented in category 1 and 2 (54%) compared to 42% of the VKA treated group (Figure 14.2A). The distribution of clinical presentation was similar, with a non-significant trend towards a milder presentation for the edoxaban treated patients. The most severe categories of clinical presentation (3+4) were observed in 46% of the edoxaban cases versus in 58%

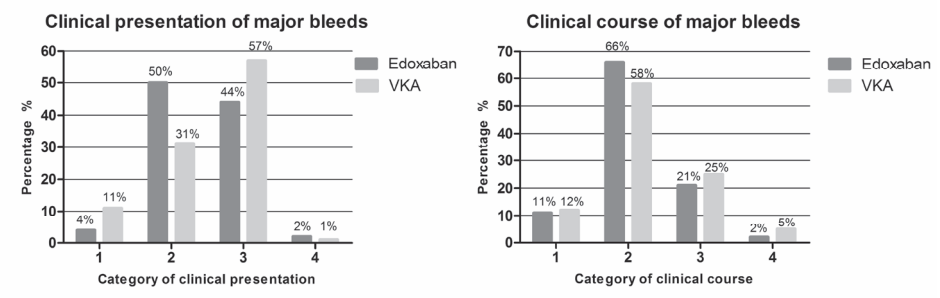

Figure 14.2. Clinical presentation and course of major bleeding episodes.
A. Clinical presentation
B. Clinical course
Clinical presentation (A) and clinical course (B) of all major bleeding events that occurred in the on treatment period with edoxaban or VKA in the Hokusai-VTE study.

of the VKA treated patients (OR 0.62, 95% CI 0.30 – 1.27, p = 0.19). The hazard ratio (HR) for time to onset of major bleeds with clinical presentation 3 or 4 was 0.68 (95% CI 0.41 – 1.12, p = 0.13).

Results clinical course

The clinical course of the major bleeding events in the edoxaban group was categorized as 3 or 4 in 23% of patients and in 30% of VKA related major bleeding events with an OR of 0.73 (95% CI 0.32 – 1.66, p = 0.46) (Figure 14.2B). The accompanying HR for time to major bleeding event with clinical course 3 or 4 was 0.68 with a 95% CI of 0.34 – 1.38 (p = 0.288).

From clinical presentation to clinical course

Table 14.2 shows the clinical course for patients presenting with a major bleeding event classified with categories 2 or 3 for both treatment groups.

Of the edoxaban treated patients who presented with a category 2 major bleeding event (50%), category 1 clinical course was present in 14% of the patients, while 79% was categorized as category 2 clinical course and 7% as category 3. Of the edoxaban

Table 14.2. From clinical presentation to clinical course.

A. Clinical presentation category 2

	Clinical Presentation Category 2	
Clinical course	**Edoxaban**	**VKA**
Category 1	4 (14%)	2 (10%)
Category 2	22 (79%)	17 (85%)
Category 3	2 (7%)	1 (5%)
Category 4	0	0
Total	28	20

B. Clinical presentation category 3

	Clinical Presentation Category 3	
Clinical course	**Edoxaban**	**VKA**
Category 1	1 (4%)	4 (11%)
Category 2	14 (56%)	16 (43%)
Category 3	9 (36%)	15 (41%)
Category 4	1 (4%)	2 (5%)
Total	25	37

Clinical course for major bleeding events classified as clinical presentation 2 (A) and 3 (B), to give an indication of the dynamics in the clinical impact of major bleeding events.

treated patients who had a category 3 bleeding at presentation (44%), clinical course category 1 or 2 was found in 60% of the patients; the remainder of patients had a clinical course 3 (36%) or 4 (4%).

For VKA treated patients presenting with a category 2 major bleed (31%), clinical course were categorized as 1 in 10%, as 2 in 85% and as 3 in 5% of the patients. Of the VKA recipients who had a category 3 bleed at presentation (57%), category 1 or 2 of clinical course was applied in 54% of the patients, while the remaining 46% had a clinical course category 3 or 4.

Treatment of major bleeds

Vitamin K was administered to none of the edoxaban treated patients and to 4 patients (6%) with a VKA associated major bleeding. Thirteen patients (23%) with an edoxaban related major bleed and 19 patients (29%) with a VKA related major bleed received fresh frozen plasma. Packed cells were administered in 34 (61%) versus 27 (42%) patients treated with edoxaban and VKA respectively. Only 1 patient (2%) in the edoxaban and 2 patients (3%) in the VKA treated group received prothrombin complex concentrate (PCC). All three patients receiving PPC had an intracranial bleed. In the edoxaban group, FFP was administered to 13 patients and in the VKA group to 19 patients. FFP was mainly given for retroperitoneal, intracranial and gastro-intestinal bleeds. One (2%) of the major bleeding events in the edoxaban group and 5 (8%) in the VKA group were fatal. Interventions applied to control the bleeding include endoscopy with clip placement for GI bleeds, burr holes for subdural hematomas, drainage of pericardial and joint bleeds and curettage for vaginal bleeds. None of the applied interventions differed significantly between the treatment groups (Table 14.3).

Table 14.3. Interventions to treat the major bleeding.

Prohemostatic intervention	LMWH/Edoxaban N = 56	LMWH/VKA N = 65	P-value (chi square)
Vitamin K	0 (0)	4 (6%)	0.07
Prothrombin complex concentrate	1 (2%)	2 (3%)	0.38
Fresh frozen plasma	13 (23%)	19 (29%)	0.31
Packed cells	34 (61%)	27 (42%)	0.05
Procedure to stop bleeding	18 (32%)	15 (23%)	0.24
Fatality	1 (2%)	5 (8%)	0.13

Applied interventions to treat the major bleeding episodes.

Discussion

The results from our analysis of the major bleeding events from the Hokusai-VTE study suggest that edoxaban associated major bleeding events have a similar presentation and course when compared to major bleeding events with VKA in patients treated for venous thromboembolism, although we observed a non-significant trend towards a milder presentation and a milder course in the edoxaban recipients. Major bleeding events with a presentation in category 2 or 3 had a comparable distribution on the subsequently classified clinical course between edoxaban and VKA. The treatment of major bleeding events did not differ between edoxaban and VKA treated patients; half of the patients in both treatment groups received packed cells and about a quarter of the patients got FFP administered. Other prohemostatic interventions were only applied in a small proportion of the patients in both treatment groups. These results contribute to the insight in severity of presentation, clinical relevance, course or outcome and management of major bleeding episodes. Besides the fact that major bleeding complications occur less often in DOAC treated patients (11), we showed that the clinical presentation and course of those bleeds is in general similar to and potentially less severe than with VKA treatment. It should be realized that at the time of this study, no specific antidote for edoxaban was available. Whether such an antidote would influence the clinical course is speculative.

A possible explanation for the observed trend towards a less severe presentation for the edoxaban group could be the relative unstable anticoagulant effect of VKA (17). Patients using VKA may not be safely and effectively anticoagulated all the time because of unpredictability of VKA anticoagulant properties, interactions with food and concomitant medication and intra- and interindividual variability. Patients therefore may experience episodes of overtreatment, which can contribute to more severe bleeding. Warfarin is a VKA with a longer half-life than edoxaban. Hence, bleeding complications may be prolonged or stimulated when the drug is present in the system for a prolonged period of time (18). Edoxaban has a stable pharmacological profile and is therefore postulated to have a more predictable anticoagulant effect, leading to fewer severe bleeding events. Another possible explanation is the observed higher number of ICH in the VKA group compared to edoxaban in the Hokusai-VTE study (9). There were no fatal ICH in the edoxaban group versus 5 in the VKA group. Nonfatal ICH were observed in 5 edoxaban treated patients and 12 VKA treated patients. This difference in ICH likely plays a role in the observed numbers of major bleeds with severe presentation and course, because ICH are almost always severe and therefore fall in category 3 or 4 of both classifications.

The current observation that edoxaban leads to fewer major bleeds with a possible milder presentation is supported by earlier studies with dabigatran. Dabigatran is an

oral direct thrombin inhibitor and has been shown to cause less intracranial bleeds than treatment with VKA (19,20). Furthermore, bleeding complications with dabigatran had a milder course and were associated with a shorter length of stay in hospital, in a non-randomized comparison (21). Results from the Einstein studies where rivaroxaban was compared to VKA in treatment of VTE, showed that rivaroxaban associated major bleeding events had a less severe presentation and had a milder course than VKA bleeding episodes (15). For the subanalysis of the major bleeds in the Einstein studies, the same classification schemes regarding clinical presentation and course were used as in the present study.

Strengths of our analysis and the previous analysis of the Einstein studies are the use of predefined criteria, the long term follow-up and the fact that information on major bleeds was recorded prospectively on case report forms. Comprehensive medical information was available about symptoms, hemodynamic parameters, laboratory results and interventions to control the bleeding, and could be applied to classify the event according to severity of presentation and course. As a result, our analysis is not just a typical retrospective data collection study. Another strength of the current study is the double blind design, hence the treating physician was unaware of treatment allocation and the bleeding episode was treated using clinical judgment. The findings are robust because all bleeding events were adjudicated by three independent experienced clinicians who were unaware of the assigned treatment regimen at the time of adjudication. A final aspect is that we only adjudicated a single most severe event per patient. From a methodological point of view one should always take one event, since other events are not independent observations in a single patient. Including those latter events could bias the results.

The present analysis has several limitations. One limitation is that the current classification schemes lack in validation and have only been used on data from the Einstein and Hokusai studies. Further research is needed to confirm the results and the quality and reproducibility of the classification schemes. It would be of interest to further validate these scores in other DOAC trials, as well as in other settings, such as in trials of patients with atrial fibrillation. A second limitation is the modest sample size. Although the Hokusai-VTE study included 8240 patients with DVT, PE or both, major bleeding only occurred in 56 edoxaban and 65 VKA treated patients. The results from this study should therefore be confirmed with data from other phase III studies with as a result more major bleeding events. In addition, although the protocol did provide pre-specified guidance for the treatment of bleeding events, the final decision of the applied strategy was made by the treating physician. The limited use of vitamin K, fresh frozen plasma and PCC is remarkable While it is uncertain that PCC work for DOACs and edoxaban in particular, vitamin K and PCC have been shown to be effective for VKA associated bleeding (22,23). The fact that these agents have not been used frequently

is therefore to the disadvantage of VKA treated patients. This may have influenced the results. Another limitation is the potential for overlap and interdependence between the two classification schemes, since presentation is likely to influence clinical course. For example, if all or most category 4 clinical presentations would also have a category 4 clinical course. But as shown in the result section, 56% of the edoxaban treated patients that presented with a category 3 bleeding had a category 2 clinical course. A comparable observation was made for VKA treated patients. So events with a severe presentation can have a mild clinical course, and the other way round. Therefore, the two classifications are largely independent. We also minimized the potential for overlap by first presenting the adjudicators with relevant information to categorize the event for severity of presentation and then, in a separate session and in random order, relevant information about the course was presented. In this way the adjudicators could not be influenced by their own adjudication of the presentation. Finally, the current classification of major bleeding events according to the ISTH criteria (14) has been standardized and used in all phase III DOAC trials. However, we observed that major bleeding events are quite heterogeneous with large variation in clinical severity and course, indicating that all major bleeds do not have the same clinical significance.

In conclusion, edoxaban associated major bleeding events have at least a similar presentation and course as major bleeding events with VKA in patients treated for venous thromboembolism. These results provide insight in the characteristics of bleeding in edoxaban treated patients and may assure physicians that it is safe to prescribe this medication. Should a major bleeding occur, its clinical presentation and clinical course are not worse than in VKA treated patients.

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Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists: an individual patient data meta-analysis

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Accepted for publication in Thrombosis and Haemostasis, 2017.

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Abstract

Background: Factor Xa (fXa)-inhibitors are as effective and safer than vitamin-K-antagonists (VKA) in the treatment of venous thromboembolism (VTE). We previously classified the severity of clinical presentation and course of all major bleeding events from the EINSTEIN, AMPLIFY and HOKUSAI-VTE trials separately. The current aim was to combine these findings in order to increase precision, assess a class effect and analyse presentation and course for different types of bleeding, i.e. intracranial, gastro-intestinal, and other.

Methods: We classified the clinical presentation and course of all major bleeding events using pre-defined criteria. Both classifications comprised four categories; one being the mildest, and four the most severe. Odds ratios (OR) were calculated for all events classified as category three or four between fXa-inhibitors and VKA recipients. Also, ORs were computed for different types of bleeding.

Results: Major bleeding occurred in 111 fXa-inhibitor recipients and in 187 low-molecular-weight heparin (LMWH)/VKA recipients. The clinical presentation was classified as category three or four in 35% and 48% of the major bleeds in fXa-inhibitor and VKA recipients, respectively (OR 0.59, 95% CI 0.36–0.97). For intracranial, gastro-intestinal and other bleeding a trend towards a less severe presentation was observed for patients treated with fXa-inhibitors. Clinical course was classified as severe in 22% of the fXa-inhibitor and 25% of the VKA associated bleeds (OR 0.83, 95% CI 0.47–1.46).

Conclusions: FXa inhibitor associated major bleeding events had a significantly less severe presentation and a similar course compared to VKA. This finding was consistent for different types of bleeding.

Introduction

Factor Xa (fXa) inhibitors are at least as effective as vitamin K antagonists (VKA) in the treatment of venous thromboembolism (VTE), and are associated with less bleeding (1–6). Furthermore, the pattern of bleeding complications has been observed to differ between patients receiving fXa inhibitors and VKA; those receiving fXa inhibitors less often experienced intracranial haemorrhages (ICH) whereas gastro-intestinal (GI) and urogenital bleeds appeared to occur more often in this group (7–10).

The uptake of fXa inhibitors in the treatment of VTE has been slow partly due to concerns about the clinical impact and the best strategies for treatment of bleeding events (11,12). Therefore, there is a need for information about the presentation, development and management of bleeding events during the use of these new agents. Previously, we classified the severity of clinical presentation and course of all major bleeding events in the EINSTEIN, AMPLIFY and HOKUSAI-VTE trials for each study separately (13–15). Although small differences existed amongst the study results, all studies showed at least a trend for a less severe clinical presentation in fXa inhibitor recipients compared to VKA recipients. For clinical course either no or a minimal difference was found in favour of the fXa inhibitors.

In the present individual patient data analysis, we combined the results from these three studies to increase precision and to be able to analyse the effects in different types of bleeding, with a special interest for ICH and GI bleeding. The aim of this study was to assess differences in bleeding pattern and to compare the clinical presentation and subsequent clinical course of major bleeding events associated with fXa inhibitors to those associated with the use of VKA.

Materials and Methods

Study population and design

The EINSTEIN studies randomized patients with acute symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) to rivaroxaban or enoxaparin followed by warfarin or acenocoumarol. Patients were excluded if they received low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin for more than 48 hours in therapeutic dose, if they received more than one dose of a vitamin K antagonist before randomization, if thrombectomy was performed, a vena cava filter was placed, or a fibrinolytic agent administered, or a contraindication existed for enoxaparin, warfarin, or acenocoumarol. Other exclusion criteria are listed in the original publications (2,3). Rivaroxaban was dosed at 15 mg twice daily for the first three weeks, after which the patients continued on 20 mg once daily for the remainder of the therapy duration.

In the standard of care group, enoxaparin was administered for at least five days and either warfarin or acenocoumarol (with a target International Normalized Ratio [INR] of 2.0 to 3.0) was started. The EINSTEIN studies were open-label and funding was provided by Bayer HealthCare and Janssen Pharmaceuticals (ClinicalTrials.gov identifiers: NCT00440193 and NCT00439725) (2,3).

The AMPLIFY trial was a randomized, double-blind study evaluating the efficacy and safety of apixaban versus enoxaparin/warfarin for the treatment of acute symptomatic DVT and PE. Exclusion criteria were, among others, active bleeding, high risk of bleeding, contraindications to treatment with enoxaparin and warfarin; cancer with the need for long-term treatment with LMWH, if DVT or PE event was provoked in the absence of a persistent risk factor for recurrence, dual antiplatelet therapy, aspirin treatment (> 165 mg daily), receiving more than two doses of LMWH, fondaparinux or VKA. Initial treatment with apixaban consisted of one week of 10 mg twice daily, followed by 5 mg twice daily as maintenance therapy for six months. In addition, placebo enoxaparin injections and placebo warfarin were administered. In the conventional-therapy group, patients received enoxaparin for at least five days, and warfarin was begun concomitantly (target INR 2.0 to 3.0). These patients received placebo apixaban tablets. Funding for the AMPLIFY study was received from Pfizer Inc. and Bristol Myers Squibb Company (ClinicalTrials.gov identifier: NCT00643201) (1).

In the HOKUSAI-VTE study edoxaban was compared to warfarin for treatment of acute symptomatic DVT or PE in a double-blind, double-dummy fashion. Exclusion criteria were contraindications to heparin or warfarin, treatment of 48 hours or more with therapeutic dosed heparin, the use of more than one dose of a VKA, cancer with the need for long-term treatment with LMWH, aspirin (> 100 mg daily) or chronic dual antiplatelet therapy, or a creatinine clearance below 30 ml/min. Initial treatment for all patients consisted of enoxaparin or unfractionated heparin (UFH) for at least five days. After discontinuation of initial heparin therapy, edoxaban 60 mg (or placebo) was started once daily. Warfarin (or placebo) was started concurrently with initial heparin therapy, and the parental anticoagulant was stopped when the INR level reached 2.0 or higher (target INR 2.0 to 3.0) (4). Daiichi Sankyo funded the HOKUSAI-VTE study (ClinicalTrials.gov identifier: NCT00986154).

For each study the institutional review board at all participating centres approved the protocol and all patients provided written informed consent.

Definition of major bleeding

In all three fXa inhibitor trials major bleeding was defined according to the ISTH criteria as clinically overt bleeding that was either 1) associated with a decrease of two grams per decilitre or more in haemoglobin level, 2) requiring transfusion of 2 or more units of red bloods cells, 3) occurring in a critical site or 4) contributing to death (16). Major

bleeding events that occurred during the study period were prospectively followed and information about symptoms, signs, diagnostics and interventions were collected on standardized case report forms. All major bleeds in these trials were adjudicated by the same blinded committee.

Current analysis

Classification schemes

For the present analysis we first assessed the *clinical presentation,* i.e. the severity of the bleed at time of presentation (Table 15.1A). The second classification, *clinical course*, evaluated the measures applied and interventions used to treat the major bleed and also took the outcome of the bleed into consideration (Table 15.1B). Both classification schemes were earlier developed and published (13–15).

In short, in the classification of clinical presentation, events were assigned to category 1 if the presentation was without any medical emergency. Category 3 compromised bleeding with great medical emergency, for example hemodynamic instability. The fourth category was applied to bleedings with an immediate fatal or almost fatal presentation, and the remainder of the bleeds were category 2. With respect to the classification of clinical course, category 1 consisted of only measures to treat dis-

Table 15.1. Classification of clinical presentation and course of major bleeding

A. Clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency.
2	All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency.
3	Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability; or cerebral bleeding presenting with neurologic symptoms.
4	Bleeding events that are fatal before or almost immediately upon entering the hospital.

B. Clinical course

Category	Description
1	Bleeding events for which only measures were applied to treat discomfort.
2	Bleeding events requiring only standard measures such as transfusions of erythrocytes, and straight forward interventions.
3	Life threatening bleeding events for which immediate and elaborate measures were used to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability.
4	Bleeding events for which death was unavoidable, so no lifesaving attempts were made.

comfort. Bleedings from category 2 required standard measures of care, for example the administration of red blood cells. Category 3 bleedings required immediate and elaborate measures to avoid death and category 4 was assigned when no lifesaving attempts were undertaken.

Classification procedure

All major bleeding events were blindly classified by the same experienced clinicians (ATC, SM, HRB). Information about each major bleeding episode and items relevant to the classification schemes were presented to the assessors by different clinicians (SMB or MPB). This information included presenting signs and symptoms, laboratory markers such as haemoglobin, applied diagnostic procedures, treatment and interventions to stop the bleeding, and the course and outcome of the patient. At the time of adjudication of either classification scheme, the assessors were not aware of the outcome of the other classification, and the assigned treatment regimen. In case of disagreement a debate followed in order to reach consensus. If no consensus was reached, the highest category was chosen.

For every patient only one major bleeding episode was considered for the final analysis. If a patient experienced more than one major bleeding event at different anatomical sites or a recurrent major bleed at the same anatomical site, the first major bleed or the event with the highest category assigned was included. We excluded bleeding events if 1) the major bleed was observed ≥ 10 days after the last dose of study drug, or 2) if the event could not be classified due to insufficient information.

Analysis of bleeding dynamics

To assess the dynamics of all bleeding episodes, per category of clinical presentation the subsequent clinical courses were analysed for both treatment arms.

Statistical analysis

The results are presented as counts and percentages. We a priori defined severe clinical presentation and course as the composite of category three and four. Categories one and two were also combined and represented a mild presentation and course. A logistic regression model was applied for the analysis of the clinical presentation and course. Odds ratios (OR) were computed for the combined categories three and four between the fXa inhibitor and LMWH/VKA groups for both classifications. If there was a significant difference between both treatment groups in clinical presentation or course, subsequent subgroup analyses were performed. We aimed to perform subgroup analyses in patients with ICH, GI, and other types of bleeding.

In addition, we performed a meta-analysis of the data. Forest plots were visually examined and we measured the proportion of between-study differences not

attributable to chance with the I^2 statistic. We considered values of < 50%, 50–75% and ≥ 75% to indicate low, moderate and high heterogeneity, respectively. In case of low heterogeneity, the ORs were combined across studies using the Mantel-Haenszel procedure which assumes a fixed treatment effect. When heterogeneity was moderate, study data were combined using a random effects model according to the methods of Mantel-Haenszel.

Analyses were performed using SPSS Statistics v 20.0 (IBM Corp., Armonk, NY, USA), and with Review Manager Version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Baseline characteristics and location of bleeding

In the EINSTEIN, AMPLIFY and HOKUSAI-VTE trials combined, major bleeds were observed in 111 of 10.959 (1.0%) fXa inhibitor recipients and in 187 of 10.957 (1.7%) LMWH/VKA recipients ($p < 0.01$). Based on the pre-defined exclusion criteria, 290 (97%) major bleeding events were adjudicated and form the basis for the current analysis (Figure 15.1). Baseline characteristics of the patients with an episode of major bleeding who were included are detailed in Table 15.2. The mean age in the fXa inhibitor group was 64 ± 15 years and in the LMWH/VKA group this was 67 ± 15 years; this difference did not reach statistical significance (p = 0.09). The time from randomisation

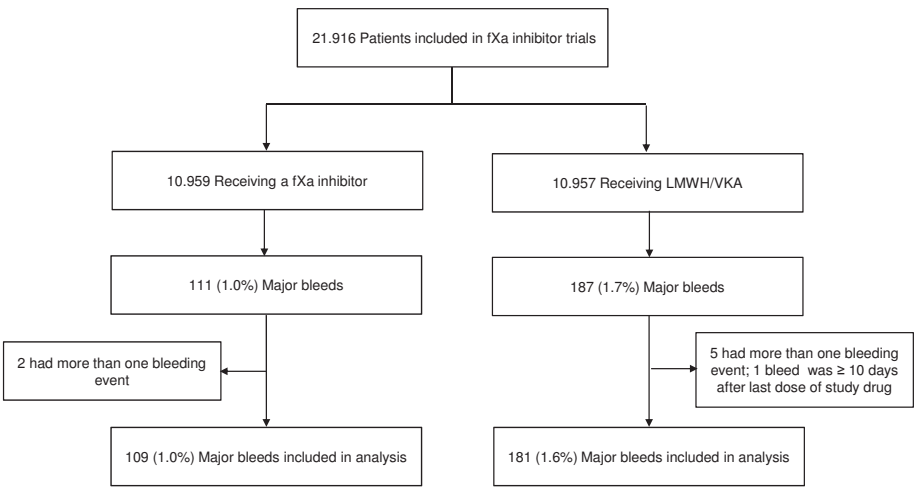

Figure 15.1. Patient flow diagram.
fXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist

Table 15.2. Baseline characteristics and location of bleeding of the patients with a major bleeding event in the Einstein, Amplify and Hokusai studies combined.

	fXa inhibitor	LMWH/VKA	p-value
Total major bleeding events	109	181	NA
Mean age in years ± SD	64 ± 15	67 ± 15	0.09
Male sex, n (%)	48 (44)	91 (50)	0.28
Median days from randomization to major bleeding (IQR)	41 (8–801)	29 (9–921)	0.36*
Location of bleeding, n (%)			< 0.01**
Intracranial	13 (12)	35 (19)	
- Intracerebral	10 (9)	18 (10)	
- Subdural	2 (2)	13 (7)	
- Subarachnoid	1 (1)	2 (1)	
- Unknown	0	2 (1)	
Gastro-intestinal bleed	50 (46)	59 (33)	
Retroperitoneal	2 (2)	10 (6)	
Vaginal	17 (16)	5 (3)	
Intra-articular	4 (4)	10 (6)	
Subcutaneous	5 (5)	17 (9)	
Intraocular	4 (4)	8 (4)	
Intramuscular	3 (3)	14 (8)	
Haematuria	1 (1)	5 (3)	
Other	9 (8)	17 (9)	
30-day case fatality	11 (10)	24 (13)	0.41

* Assessed via non parametric testing of two independent samples (median).
** Comparison of the distribution of all bleeding locations between the two treatment groups.
FXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; NA: not applicable; SD: standard deviation; IQR: interquartile range.

to major bleeding was a median 41 days (interquartile range [IQR] 8–101) in fXa inhibitor recipients, whereas for the VKA group this was 29 days (IQR 9–121; p = 0.36). With respect to the location, a significant difference was found in the distribution of major bleeding events between both groups ($p < 0.01$); GI and vaginal bleeds were more common in patients receiving a fXa inhibitor and in LMWH/VKA recipients intracranial, retroperitoneal, cutaneous and intramuscular major bleedings were more frequently observed. The case fatality was comparable between the treatment groups.

Clinical presentation of major bleeding

Table 15.3A details the results of the classification of major bleeding events at presentation for both treatment arms. Of all bleeding events, 16% to 19% presented without

Table 15.3. Results of the combined classification of major bleeding events

A. Part 1: Clinical presentation

	fXa inhibitor	LMWH/VKA
Total major bleeding events	109	181
Category 1, n (%)	21 (19)	29 (16)
Category 2, n (%)	50 (46)	66 (37)
Category 3, n (%)	35 (32)	83 (46)
Category 4, n (%)	3 (3)	3 (2)

B. Part 2: Clinical course

	fXa inhibitor	LMWH/VKA
Total major bleeding events	109	181
Category 1, n (%)	21 (19)	39 (22)
Category 2, n (%)	64 (59)	96 (53)
Category 3, n (%)	19 (17)	35 (19)
Category 4, n (%)	5 (5)	11 (6)

FXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist

any clinical emergency and were classified as category one. The distribution over the categories was found to be less severe for the fXa inhibitor group. The most severe category of the clinical presentation (i.e. category three or four combined) was observed in 35% of the major bleeds in patients receiving a fXa inhibitor versus 48% in LMWH/VKA recipients (OR 0.59, 95%CI 0.36–0.97). Category 3 or 4 clinical presentation was assigned to 8 of 39 (21%) major bleeds in the rivaroxaban group, 4 of 14 (29%) events in the apixaban group, and 26 of 56 (46%) bleeds in the edoxaban group, compared to 86 of 181 (48%) in the VKA group. The probability of presenting with a severe major bleeding event in fXa inhibitor recipients is 0.3% (38 of 10.959), and in LMWH/VKA treated patients 0.8% (86 of 10.957).

Table 15.4. Clinical presentation of intracranial haemorrhages

	fXa inhibitor	LMWH/VKA
Total major bleeding events	13	35
Category 1, n (%)	0	0
Category 2, n (%)	2 (15)	3 (9)
Category 3, n (%)	10 (77)	29 (83)
Category 4, n (%)	1 (8)	3 (9)

FXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist

Intracranial haemorrhage

In the 48 patients with an ICH, a severe clinical presentation occurred in the 11 of 13 (85%) bleeds in the fXa inhibitor group, as compared with 32 of 35 (91%) of those in the LMWH/VKA group (OR 0.52; 95%CI 0.08–3.5; Table 15.4). The majority of all ICH was classified as category three.

Gastro-intestinal bleeding

In the 109 patients with a major GI bleeding, a severe clinical presentation was observed in 16 of 50 (32%) major bleeding events in the fXa inhibitor recipients and in 28 of 59 (48%) major bleeds in the LMWH/VKA recipients (OR 0.52; 95%CI 0.24–1.14; Table 15.5). Only two patients with a GI bleeding, both receiving a fXa inhibitor, presented in category four.

Table 15.5. Clinical presentation of gastro-intestinal bleeds

	fXa inhibitor	LMWH/VKA
Total major bleeding events	50	59
Category 1, n (%)	6 (12)	6 (10)
Category 2, n (%)	28 (56)	25 (42)
Category 3, n (%)	14 (28)	28 (48)
Category 4, n (%)	2 (4)	0

FXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist

Other types of bleeding

Other types of bleeding included retroperitoneal, vaginal, urogenital, intra-articular, intra-ocular, subcutaneous and intramuscular bleeding, and comprised a total of 133 bleeding events. In 11 of 46 patients (24%) using fXa inhibitors, the clinical presentation was classified as category three or four, in comparison to 26 of 87 (30%) in LMWH/VKA recipients (OR 0.74, 95%CI 0.33–1.67). The same trends were seen for all the different types of bleeding.

Clinical course of major bleeding

The clinical course was classified as category three or four in 22% of the fXa inhibitor and in 25% of the VKA associated bleeding events (OR 0.83, 95%CI 0.47–1.46; Table 15.3B). Category 3 or 4 clinical course was assigned to 9 of 39 (23%) major bleeds in the rivaroxaban group, 2 of 14 (14%) events in the apixaban group, and 13 of 56 (23%) bleeds in the edoxaban group, compared to 46 of 181 (25%) in the VKA group. The probability of a severe clinical course was 0.2% (24 of 10.959) in fXa inhibitor recipients, compared to 0.4% (46 of 10.957) in LMWH/VKA treated patients. Of the 13 patients with an ICH in the

fXa inhibitor group, 2 (15%) were fatal compared to 6 of the 35 (17%) ICH events in the LMWH/VKA group. In patients with GI bleeding, the case fatality rate was 12% (6 out of 50) for patients treated with fXa inhibitors and 19% (11 of 59) for LMWH/VKA recipients.

Meta-analysis

Figures 15.2 and 15.3 show the forest plots for the individual study data for clinical presentation and course, respectively. The results are in line with the findings of the individual patient data meta-analysis. There was no evidence for heterogeneity ($I^2 = 0\%$).

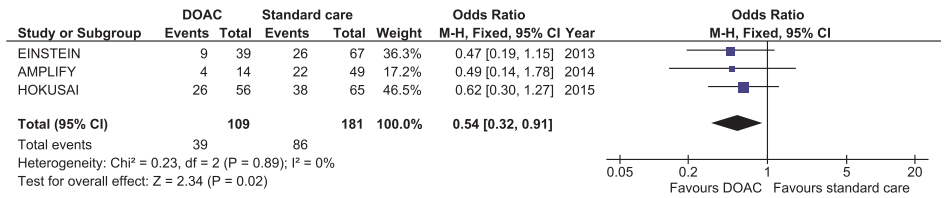

Figure 15.2. Forest plot for a severe clinical presentation of major bleeding in the factor Xa inhibitor trials
CI: confidence interval; DOAC: direct oral anticoagulant

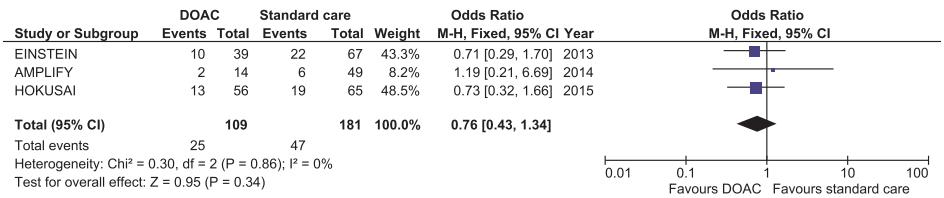

Figure 15.3. Forest plot for a severe clinical course of major bleeding in the fXa inhibitor trials
CI: confidence interval; DOAC: direct oral anticoagulant

Dynamics of major bleeding

Table 15.6 shows the subsequent clinical course per category of clinical presentation for both treatment arms. In the fXa inhibitor group, of the 71 patients with a major bleed presenting as a category one or two, six (9%) progressed to a severe clinical course (i.e. category three or four) whereas 20 of 38 (53%) of the bleeds with a category three or four clinical presentation, moved to a category one or two clinical course (Table 15.6).

Of the 95 patients receiving LMWH/VKA with a major bleeding event presenting as category one or two, six (6%) progressed to a severe clinical course. Conversely, 46 of 86 (54%) of the events with a severe presentation had a mild clinical course.

Patients with a major bleeding event who presented in category one had a milder clinical course in those receiving a fXa inhibitor (100% category 1 or 2 clinical course)

Table 15.6. Dynamics of major bleeding

A. Clinical presentation category 1

Clinical course	fXa inhibitor	LMWH/VKA
Total major bleeding events	21	29
Category 1, n (%)	11 (52)	11 (38)
Category 2, n (%)	10 (48)	16 (55)
Category 3, n (%)	0	2 (7)
Category 4, n (%)	0	0

B. Clinical presentation category 2

Clinical course	fXa inhibitor	LMWH/VKA
Total major bleeding events	50	66
Category 1, n (%)	7 (14)	18 (27)
Category 2, n (%)	37 (74)	44 (67)
Category 3, n (%)	6 (12)	4 (6)
Category 4, n (%)	0	0

C. Clinical presentation category 3

Clinical course	fXa inhibitor	LMWH/VKA
Total major bleeding events	35	83
Category 1, n (%)	3 (9)	10 (12)
Category 2, n (%)	17 (49)	36 (43)
Category 3, n (%)	11 (31)	29 (35)
Category 4, n (%)	4 (11)	8 (10)

D. Clinical presentation category 4

Clinical course	fXa inhibitor	LMWH/VKA
Total major bleeding events	3	3
Category 1, n (%)	0	0
Category 2, n (%)	0	0
Category 3, n (%)	2 (67)	0
Category 4, n (%)	1 (33)	3 (100)

FXa: factor Xa; LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist

than those receiving LMWH/VKA (93% category 1 or 2 clinical course, and 7% category 3), whereas those presenting in category two had a milder clinical course when receiving LMWH/VKA (6% progressed to category 3) compared to fXa inhibitor recipients (12% progressed to category 3). In the patients with a category three clinical presentation, the subsequent clinical course was similar for the fXa inhibitor and LMWH/VKA recipients. Of the six patients with a category four clinical presentation, four (67%) subsequently had a category four clinical course, of which 3 (75%) were using LMWH/VKA.

Discussion

The present study shows a clear difference in the pattern of bleeding complications between patients using fXa inhibitors and VKA for treatment of VTE. We observed that, in addition to a lower absolute frequency of major bleeding events, fXa inhibitor associated major bleeds were associated with a significantly less severe clinical presentation compared to those related to VKA. Hence, there is a clear class effect of fXa inhibitors rather than a single agent effect. This effect appeared to be consistent for different types of bleeding; in patients with ICH, GI bleeds and other types of bleeding the clinical presentation was also milder in fXa inhibitors recipients, albeit not statistically significant in these smaller subgroups. This implicates that the less severe clinical presentation observed in fXa inhibitor users is not a direct consequence of a lower frequency of ICH, which in general presents in a more severe way than for example urogenital or subcutaneous bleeds.

The clinical course of major bleeds was comparable for both treatment strategies. Reassuringly, the majority of major bleeds in both groups had a mild clinical course. The dynamics of major bleeding events were also comparable in both treatment groups. Bleeding events with a mild clinical presentation rarely progressed to a severe clinical course, whereas more than half of the events with a severe clinical presentation had a mild subsequent clinical course. No difference was observed regarding case fatality at 30 days after the bleeds between the two treatment strategies.

The results from this combined analysis provide insight in the clinical presentation and course of major bleeding events in patients receiving fXa inhibitors and VKA. At the time these studies were conducted, no specific antidotes were available for fXa inhibitors. However, with respect to the clinical course of major bleeding events, it appears that standard measures were often sufficient, making the need for a specific antidote somewhat less urgent. Andexanet alpha, a universal antidote for all fXa inhibitors, was recently found to rapidly reverse the anticoagulant effect of apixaban and rivaroxaban (17). A phase 3b-4 study evaluating the efficacy and safety of this compound in patients

with fXa-inhibitor associated major bleeding is currently ongoing (Clinicaltrials.gov identifier: NCT02329327), and the first results have recently been published (18). It is however at present speculation whether the availability of this reversal agent would lead to a milder clinical course of bleeding with fXa inhibitors.

How should our findings be interpreted? A potential explanation may be that bleeding with VKA is prolonged, stimulated or more severe due to the relative unstable and unpredictable anticoagulant effect of VKA. In contrast, direct oral anticoagulants (DOACs) including the fXa inhibitors and direct thrombin inhibitors, are known to have a short half-life and a stable pharmacokinetic profile. This may contribute to the less severe clinical presentation of major bleeds with fXa inhibitors. The present observation that fXa inhibitors cause fewer major bleeding events with a milder presentation is in line with observations for the direct thrombin inhibitor, dabigatran. Dabigatran associated bleeding events were observed to have a lower 30-day case fatality and shorter duration of hospital admission compared to warfarin associated bleeds (19,20).

One of the strengths of the present analysis is the large sample size, allowing for subgroup analysis for different types of bleeding. In addition, the AMPLIFY and HOKUSAI-VTE studies were both double-blind, double-dummy, randomized trials in which data on major bleeds were prospectively collected. In the EINSTEIN studies bleeding events were also recorded prospectively, but since these studies were open-label, information on bleeding events with rivaroxaban may have been recorded more accurately compared to events during the use of VKA. However, the bleeding pattern and effects on clinical presentation were consistent among the three individual studies (13–15). Other strengths are the use of pre-defined classification criteria, and the fact that all adjudicators were blinded for the treatment regimen received by the patient. The classification schemes have now been applied in three separate studies and are easy to use (13–15).

Some limitations deserve acknowledgment. First, the current classification schemes have not yet been used and validated in other populations than patients with acute symptomatic VTE. In addition, the classification schemes have only been applied in three post-hoc analyses of randomized controlled trials. It might be more difficult to use these schemes in real life clinical practice. Further research is warranted to test the quality and reproducibility of the classification schemes in other settings. A second limitation is that no information was available regarding residual morbidity after 30 days following the bleeding event. Although we did not find a difference in 30-day mortality, it is possible that those patients with a severe clinical presentation developed sustaining deficits beyond this initial clinical course.

For those clinicians who treat patients with acute symptomatic VTE it is important to know how bleeding events during use of fXa inhibitors or VKA present and develop. The results of the present analyses implicate that fear of uncontrolled bleeding complications is not a reason to withhold fXa inhibitors in those patients.

In conclusion, in addition to a lower absolute incidence of major bleeding complications, the clinical presentation of major bleeding events is milder in patients receiving fXa inhibitors, as compared to those using VKA. These results were consistent among different types of bleeding, especially in those with ICH and GI bleeds. The proportion of patients in both groups requiring all possible measures to avoid a bad outcome is relatively low. These results provide reassurance in prescribing fXa inhibitors to patients with acute symptomatic VTE.

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Summary

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Summary

This thesis focuses on several clinical aspects of venous thromboembolism (VTE) in special patient populations. In the first part, we address several elements of sex-specific VTE. Part two describes the relationship between cancer and VTE, with a focus on unsuspected pulmonary embolism (UPE). The third part concerns clinical aspects of upper extremity deep vein thrombosis (UEDVT), and the last part focuses on the clinical impact of bleeding with factor Xa (fXa) inhibitors and vitamin K antagonists (VKA).

Part 1: Sex-specific venous thromboembolism

Chapter 2 is a review of the literature describing the pathophysiology and magnitude of risk factors for VTE that are related to female sex, including the use of several types of hormonal contraception, hormone replacement therapy, pregnancy and the postpartum period. Due to these risk factors, during reproductive age women have a two-fold higher risk of developing VTE compared to men. When adjusting for the use of hormonal contraceptives and pregnancy, men seem to have a higher risk of developing VTE than women. The mechanism explaining the intrinsic higher risk of VTE in men has yet to be elucidated.

The presence of thrombophilia, i.e. a genetic variation causing a prothrombotic phenotype interacts with women-specific risk factors for VTE. The clinical implications of the presence of these factors are discussed.

Women with a history of VTE have a 2% to 10% absolute risk of developing a VTE recurrence during subsequent pregnancies. Therefore, the evidence-based guidelines recommend antepartum and postpartum pharmacological thromboprophylaxis for all pregnant women with a history of VTE and a moderate or high risk of recurrent VTE. The optimal dose of low-molecular-weight heparin (LMWH) to prevent a recurrence in these women is unknown. To study which one of two widely used doses of LMWH is most efficacious and safe in preventing pregnancy-related recurrent VTE, we designed the Highlow study, a randomized controlled trial (RCT) of which the protocol is detailed in **Chapter 3. Chapter 4** contains an interim report of the Highlow study, and describes the study status as of June 2016, including baseline characteristics of 181 enrolled patients. This report presents the largest number of pregnant women with a history of VTE participating in a RCT to date. The enrolment rates show that recruitment of these women is feasible. Final outcome results are expected in 2020, and are very likely to impact current clinical practice and modify evidence-based guidelines. In **Chapter 5** we studied the characteristics of vaginal bleeding in women with VTE receiving apixaban, an oral fXa inhibitor, or LMWH followed by VKA. Even though the absolute number of vaginal bleeding events seems comparable between apixaban and VKA recipients, the proportion of vaginal bleeding events is higher in women treated with

apixaban. The characteristics and severity of vaginal bleeding events were comparable in both treatment arms. Our study demonstrates that anticoagulant therapy in women with VTE can be complicated by vaginal bleeding, and physicians should be vigilant of the occurrence of vaginal bleeds in women using anticoagulants, especially in the reproductive phase of life. Future studies should focus on the impact of vaginal bleeding during the use of anticoagulants on quality of life, and preferably validated blood loss scores should be applied to better evaluate the severity of vaginal bleeding events.

Part 2: Cancer and venous thromboembolism

VTE is a common complication in cancer patients. **Chapter 6** reviews the use of anticoagulant drugs for the prevention and treatment of symptomatic and incidental cancer-associated VTE. The use of anticoagulants in cancer patients can be challenging due to concomitant use of antineoplastic drugs, the frequent need of diagnostic or therapeutic interventions, and the susceptibility to nausea and vomiting. LWMH is currently the recommended type of anticoagulant for treatment of cancer-associated VTE because it was found to be superior to VKA in the prevention of recurrent VTE, with a similar risk of major bleeding complications. Ongoing trials are evaluating the effectiveness and safety of direct oral anticoagulants (DOACs) in patients with cancer and VTE. Primary VTE prophylaxis is currently not routinely recommended in ambulant cancer patients due to the high number needed to treat.

In **Chapter 7** several recent studies on UPE in cancer patients are summarized. The reported incidence ranges from 1% to 5% and probably reflects an underestimation. The current evidence on radiologic and clinical characteristics, symptoms and prognosis of UPE is detailed. Major guidelines suggest similar initial and long-term anticoagulant therapy as for cancer patients with symptomatic PE, but direct evidence is scarce. To evaluate current treatment approaches and to prospectively assess the occurrence of major clinical outcomes such as recurrent VTE, bleeding and mortality, we are currently conducting an international, observational, prospective cohort study on cancer patients with UPE. An interim report of the study is provided in **Chapter 8.** Up to June 2016, 490 patients were enrolled in the registry, and this preliminary report demonstrates that cancer patients with UPE have a substantial risk of both recurrent VTE and bleeding during anticoagulant therapy. The risk of recurrent VTE is possibly lower for patients with subsegmental (i.e. most distal) UPE compared to those with more proximal clots. This finding suggests that in cancer patients with subsegmental UPE, the benefits of anticoagulant therapy may not outweigh the risks, but this suggestion needs to be confirmed in larger sample sizes and preferably in a randomized controlled trial. In a substudy, reported in **Chapter 9,** we investigated the interobserver agreement among radiologists on the diagnosis of distal UPE and the actual radiologic extension of UPE. The interobserver agreement between radiologists regarding most proximal location

of UPE in cancer patients appears fair, but decreases for more distally located clots. Following our findings in chapter 8, knowing the extent of UPE may have therapeutic consequences, and extra dedicated reading of CT scans in cancer patients with UPE should be considered.

Part 3: Upper extremity deep vein thrombosis

Chapter 10 provides an overview of the available evidence on the incidence, clinical characteristics, risk factors, diagnosis, treatment and prognosis of UEDVT. UEDVT accounts for 4% to 10% of all DVT and is an increasingly frequent clinical problem which is mainly due to the more widespread use of central venous catheters (CVCs) that carry a high risk of VTE. Several diagnostic strategies have been tested in order to improve the diagnostic efficacy in patients with suspected UEDVT, but they are currently not in use and at present objective imaging is the cornerstone of diagnosis. Treatment recommendations for patients with UEDVT are largely extrapolated from studies on lower extremity DVT. **Chapter 11** summarizes the clinical evidence on long-term clinical outcomes of UEDVT in terms of recurrent VTE, mortality and anticoagulant-related bleeding, with a special focus on patients with or without concomitant cancer. We found that studies were very heterogeneous in terms of study design, study populations and treatment approaches, and we concluded there is a need for large prospective studies to provide information on the clinical outcomes and best management of UEDVT. Subsequently, in **Chapter 12** we assessed the current treatment strategies for patients with UEDVT and upper extremity superficial vein thrombosis (UESVT) in clinical practice and prospectively studied the long-term clinical outcomes for both diseases, including a separate assessment of the prognosis of cancer patients with UEDVT. Anticoagulant therapy was started in 98% and 73% of patients with UEDVT and UESVT, respectively. The risk of recurrent VTE seems low in patients with UEDVT and negligible for UESVT, but cancer patients with UEDVT have a significant risk of developing recurrent VTE. Post-thrombotic symptoms were infrequent and, if present, mild for both diseases.

Part 4: Bleeding with fXa inhibitors and vitamin K antagonists

Oral FXa inhibitors have been introduced for several indications including treatment of VTE and are now widely used. In the AMPLIFY trial, the fXa inhibitor apixaban proved to be non-inferior to enoxaparin followed by warfarin (i.e. the old treatment standard) in preventing recurrent VTE, and was associated with significantly less bleeding. To provide information on how bleeding events with apixaban present and develop, we blindly classified the clinical presentation and course of all major and clinically relevant non major (CRNM) bleeding events in the AMPLIFY trial in **Chapter 13**. The clinical presentation and course of major and CRNM bleeds were found to be similar in both treatment groups. In **Chapter 14** we assessed the clinical relevance and management

of bleeding events with edoxaban, another fXa inhibitor, that was found to be non-inferior and safer than VKA in the treatment of VTE in the Hokusai-VTE study. In a post-hoc analysis of the Hokusai-VTE study we demonstrate that edoxaban associated major bleeds have a comparable clinical presentation and course of major bleeds as with VKA in patients treated for VTE. **Chapter 15** aimed to combine the previously classified severity of clinical presentation and course of all major bleeding events from the major trials comparing fXa inhibitors to VKA for the treatment of VTE. FXa-inhibitor associated major bleeding events were found to have a significantly less severe presentation and a similar course compared to VKA, and this finding was consistent for intracranial, gastrointestinal and other types of bleeding. These findings should reassure physicians and patients that fXa inhibitors are a convenient and safe choice for VTE treatment.

Addenda

NEDERLANDSE SAMENVATTING

Introductie

Bij veneuze trombose raakt een bloedvat dat de terugvoer van zuurstofarm bloed vanuit de organen richting het hart verzorgt ("vene"), verstopt door een bloedstolsel. Zo'n stolsel ontstaat meestal in de benen ("trombosebeen"), en wanneer zo'n bloedstolsel losschiet kan dit via het hart uiteindelijk in de longvaten terecht komen en daar een afsluiting veroorzaken ("longembolie"). Deze twee aandoeningen (veneuze trombose en longembolie) worden samengevat onder de noemer "veneuze tromboembolieën" (afgekort VTE). Zeldzamere locaties van veneuze trombose zijn de aders in de armen, het hoofd, en de buik.

Er zijn vele risicofactoren voor het krijgen van VTE, waaronder zwangerschap en kanker. Dit proefschrift, met de naar het Nederlands vertaalde titel "Klinische aspecten van VTE bij speciale patiëntpopulaties" richt zich op VTE bij (zwangere) vrouwen, bij kankerpatiënten, VTE in de armvenen, en de presentatie en het beloop van bloedingen bij het gebruik van nieuwere ten opzichte van oude antistollingsmiddelen.

Deel 1: Sekse-gerelateerde veneuze tromboembolieën

In **deel 1** komen verschillende onderdelen van sekse-gerelateerde VTE aan bod, met de nadruk op zwangerschaps-gerelateerde VTE, het risico op VTE door gebruik van anticonceptiemiddelen, en het optreden van vaginale bloedingen bij het gebruik van antistollingsmiddelen.

Hoofdstuk 2 geeft een overzicht van de risicofactoren voor VTE bij vrouwen, en de interactie van deze risicofactoren met veelvoorkomende vormen van erfelijke trombofilie (genetische afwijkingen die de bloedstolling bevorderen en daardoor de kans op VTE vergroten). Vrouwen in de vruchtbare leeftijd hebben door veelvuldig gebruik van orale anticonceptiemiddelen en door zwangerschappen een twee keer zo hoog risico op het krijgen van VTE als mannen. Wanneer je corrigeert voor deze sekse-gebonden risicofactoren, lijken mannen juist een hoger risico te hebben voor het ontwikkelen van een VTE. Hoe het komt dat mannen intrinsiek een hoger VTE risico hebben, is nog niet goed onderzocht.

Vrouwen met een VTE in het verleden hebben tijdens zwangerschap een grote kans op het opnieuw ontwikkelen van een VTE (2% tot 10%). Om die reden bevelen de richtlijnen aan dat de meeste zwangere vrouwen met een VTE in de voorgeschiedenis preventief bloedverdunners gebruiken tijdens de zwangerschap en in de 6 weken na de bevalling. Dit gebeurt door middel van bloedverdunners via injecties in de buikhuid ("laag-moleculair-gewicht heparine" [LMWH]). Het is niet bekend wat de beste dosis LMWH is om zoveel mogelijk nieuwe VTE te voorkomen bij deze vrouwen, waarbij tegelijkertijd zo min mogelijk bloedingen worden veroorzaakt. Daarom hebben wij de

Highlow studie opgezet, een gerandomiseerde, gecontroleerde studie die deze vraag probeert te beantwoorden. In **hoofdstuk 3** worden de achtergrond en de opzet van de Highlow studie besproken. In **hoofdstuk 4** geven wij vervolgens een overzicht van de 181 patiënten die tussen maart 2013 en juni 2016 in de studie zijn geïncludeerd. De verwachting is dat eind 2019 alle benodigde patiënten (ongeveer 1000) zullen zijn geïncludeerd en de definitieve resultaten van deze studie zijn naar verwachting in 2020 beschikbaar. In **hoofdstuk 5** onderzochten we vaginale bloedingen bij vrouwen met VTE die behandeld werden met twee verschillende soorten bloedverdunners: apixaban (een factor Xa [fXa] remmer) en warfarine (een vitamine K antagonist [VKA]). Onder de bloedingen die optreden bij het gebruik van apixaban, zijn relatief veel vaginale bloedingen in verhouding tot bij de bloedingen die optreden onder het gebruik van warfarine. De kenmerken en het beloop van vaginale bloedingen lijken hetzelfde te zijn bij vrouwen die apixaban en warfarine gebruiken. Artsen moeten beducht zijn op het optreden van vaginale bloedingen bij vrouwen die bloedverdunners gebruiken, vooral tijdens de vruchtbare leeftijd. Er is meer onderzoek nodig naar de impact (bijvoorbeeld op de kwaliteit van leven) van vaginale bloedingen tijdens het gebruik van antistollingsmiddelen.

Deel 2: Kanker en veneuze tromboembolieën

Deel 2 van dit proefschrift focust zich op de relatie tussen kanker en VTE.

Hoofdstuk 6 bevat een samenvatting van de huidige kennis ten aanzien van het voorkomen en behandelen van VTE bij kankerpatiënten. Het gebruik van bloedverdunners bij kankerpatiënten kan ingewikkeld zijn door interacties met andere geneesmiddelen en voedsel, door misselijkheid en braken waardoor inname van orale bloedverdunners niet altijd mogelijk is, en vanwege het regelmatig onderbreken van de bloedverdunners zoals bijvoorbeeld rondom het ondergaan van operatieve ingrepen. LMWH, via injecties in de buikhuid, is momenteel de soort bloedverdunner van eerste keuze bij kankerpatiënten die behandeld worden voor een VTE. Het geven van bloedverdunners voor het voorkómen van VTE bij kankerpatiënten wordt niet standaard aanbevolen, vanwege het grote aantal kankerpatiënten dat preventief moet worden behandeld om één VTE te voorkomen.

Bij ongeveer 1% tot 5% van alle kankerpatiënten die een CT-scan ondergaat, bijvoorbeeld voor het beoordelen van het effect van chemotherapie, wordt per toeval een longembolie gevonden. In **hoofdstuk 7** geven wij een overzicht van de kenmerken, symptomen en prognose van een onverwacht gevonden longembolie bij kankerpatiënten. Momenteel bevelen alle richtlijnen aan dat een onverwacht gevonden longembolie hetzelfde wordt behandeld als een 'verwacht' gevonden longembolie. Om te onderzoeken hoe dokters wereldwijd een onverwacht gevonden longembolie bij kankerpatiënten behandelen, en wat de prognose is van zo'n longembolie, voeren

wij momenteel een grote internationale studie uit. **Hoofdstuk 8** bevat een samenvatting van de 490 patiënten die tot en met juni 2016 zijn geïncludeerd in deze studie. Hoewel de studie nog niet afgerond is, laten deze voorlopige resultaten zien dat er een relatief hoog risico bestaat op het ontwikkelen van een nieuwe VTE, maar ook op het ontwikkelen van een bloeding tijdens de antistollingsbehandeling. Het lijkt erop dat het risico op een nieuwe VTE kleiner is wanneer de onverwacht gevonden longembolie erg klein is. Of dit inderdaad zo is, moet beter worden onderzocht in een grotere groep patiënten. Als deze bevinding bevestigd wordt, dan zou dat kunnen betekenen dat bij kankerpatiënten met een kleine onverwacht gevonden longembolie de voordelen van antistollingsbehandeling (het voorkomen van een nieuwe VTE) niet afwegen tegen de nadelen (het gebruik van belastende dagelijkse injecties met LMWH en het risico op een bloeding). In **hoofdstuk 9** hebben we onderzocht hoe betrouwbaar de door de radioloog gerapporteerde exacte locatie en grootte van een onverwacht gevonden longembolie is. Wij vonden dat hoe kleiner de onverwacht gevonden longembolie is, hoe minder onafhankelijke radiologen het met elkaar eens zijn over de precieze locatie en grootte van de longembolie. Daarom lijkt een extra gedetailleerde beoordeling van een onverwacht gevonden longembolie op zijn plaats, zeker wanneer dit een kleine longembolie betreft.

Deel 3: Armvene trombose

Verschillende aspecten van armvene trombose, een zeldzamere vorm van veneuze trombose, worden behandeld in **deel 3** van dit proefschrift. **Hoofdstuk 10** bevat een overzicht van het vóórkomen, de klinische kenmerken, risicofactoren, diagnose, behandeling en prognose van dit ziektebeeld. Ongeveer 4% tot 10% van alle diep veneuze tromboses treden op in één van de armvenen. Het is een toenemend probleem ten gevolge van het steeds frequentere gebruik van centraal veneuze katheters (een hol slangetje dat meestal in een groot bloedvat tussen het sleutelbeen en de tepellijn of in de hals wordt ingebracht om zo bepaalde medicijnen te kunnen toe te dienen), welke een relatief hoog risico op armvene trombose met zich meebrengen. Er zijn verschillende diagnostische strategieën getest om zo efficiënt mogelijk armvene trombose te diagnosticeren, maar tot op heden is het verrichten van een echografisch onderzoek van de armvenen de enige gevalideerde methode. De aanbevelingen ten aanzien van de behandeling met antistollingsmiddelen zijn grotendeels overgenomen van de behandeladviezen voor trombose van het been. In **hoofdstuk 11** vatten we de huidige klinische bewijslast samen ten aanzien van de lange-termijn uitkomsten van armvene trombose (het risico op nieuwe VTE, op overlijden, en het optreden van bloedingen bij het gebruik van antistollingsmiddelen). We vonden dat de studies die verricht zijn erg van elkaar verschillen ten aanzien van studie opzet, studie populaties en behandelmethoden. Vervolgens hebben wij in **hoofdstuk 12** onderzocht hoe artsen

in 16 verschillende ziekenhuizen uit 9 landen internationaal patiënten met een diepe en oppervlakkige armvene trombose behandelden. Van de patiënten met een diepe armvene trombose ontving 98% bloedverdunners en bij de patiënten met oppervlakkige armvene trombose was dit in 73% van de patiënten het geval. Daarnaast hebben we onderzocht wat de lange-termijn uitkomsten zijn voor deze patiënten, waarbij we vonden dat het risico op een nieuwe VTE laag is voor patiënten met diepe armvene trombose en verwaarloosbaar voor patiënten met oppervlakkige armvene trombose. Tenslotte bleek dat kankerpatiënten met een diepe armvene trombose wel een grotere kans lijken te hebben op het krijgen van een nieuwe VTE dan niet-kankerpatiënten. Chronische klachten van de arm, ook wel 'post-trombotische klachten' genoemd, kwamen bij beide ziektebeelden nauwelijks voor en waren vaak mild van aard.

Deel 4: Bloedingen bij het gebruik van factor Xa remmers en vitamine K antagonisten

De laatste jaren zijn fXa remmers geïntroduceerd voor onder andere de behandeling van VTE; ze worden inmiddels wereldwijd veelvuldig voorgeschreven. In de AMPLIFY studie die eerder is gepubliceerd werd bewezen dat de fXa remmer apixaban even effectief is als warfarine in het voorkomen van nieuwe VTE, waarbij er onder het gebruik van apixaban significant minder majeure bloedingen optraden. Wij hebben in **hoofdstuk 13** onderzocht hoe klinisch relevante bloedingen onder het gebruik van apixaban en warfarine zich presenteren en ontwikkelen. Daarbij vonden we geen verschil in de klinische presentatie en het verloop van de bloedingen onder beide behandelingen. In **hoofdstuk 14** hebben wij hetzelfde onderzoek verricht maar dan bij majeure bloedingen onder het gebruik van edoxaban, een andere fXa remmer. Ook hier lieten we zien dat de klinische presentatie en het verloop vergelijkbaar zijn ten opzichte van bloedingen onder het gebruik van VKA. Vervolgens hebben we in **hoofdstuk 15** de gegevens over de presentatie en het beloop van majeure bloedingen uit hoofdstuk 13 en hoofdstuk 14 gecombineerd, en daar de resultaten van een andere studie aan toegevoegd waarin dezelfde analyse was verricht bij majeure bloedingen onder rivaroxaban (een andere fXa remmer). In de gecombineerde analyse vonden we vervolgens dat bloedingen bij het gebruik van een fXa-remmer een minder ernstige presentatie hebben en een vergelijkbaar verloop ten opzichte van bloedingen bij het gebruik van VKA, en deze bevinding gold ook voor hersenbloedingen, maag-darm bloedingen en overige bloedingen. Deze bevindingen kunnen artsen sterken in het voorschrijven van fXa remmers voor de behandeling van VTE.

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LIST OF PUBLICATIONS

1. van Es N, **Bleker SM**, Buller HR, Coppens M. New developments in parenteral anticoagulation for arterial and venous thromboembolism. Balliere's Best Practice & Research: Clinical Haematology. Best Pract Res Clin Haematol. 2013 Jun; 26(2):203–13.
2. **Bleker SM,** van Es N, Middeldorp S. Deep vein thrombosis and pregnancy. eBook chapter Future Medicine. www.futuremedicine.com. Published in 2013.
3. Middeldorp S, **Bleker SM**. Women admitted to hospital during pregnancy have increased risk of venous thromboembolism that persists up to 28 days postdischarge. Evid Based Nurs. 2014 Oct; 17(4): 103. *Commentary.*
4. **Bleker SM**, Coppens M, Middeldorp S. Sex, thrombosis and inherited thrombophilia. Blood Rev. 2014 May;28(3): 123–33.
5. Van Es N, **Bleker SM**, Di Nisio M. Cancer-associated unsuspected pulmonary embolism. Thromb Res. 2014 May;133 Suppl 2: S172–8.
6. Wilts IT, **Bleker SM,** van Es N, Büller HR, Di Nisio M, Kamphuisen PW. Safety of anticoagulant treatment in cancer patients. Expert Opin Drug Saf. 2015 Aug; 14(8): 1227–36.
7. Van Es N, Di Nisio M, **Bleker SM,** Segers A, Mercuri MF, Schwocho L, Kakkar A, Weitz JI, Beyer-Westendorf J, Boda Z, Carrier M, Chlumsky J, Décousus H, Garcia D, Gibbs H, Kamphuisen PW, Monreal M, Ockelford P, Pabinger I, Verhamme P, Grosso MA, Büller HR, Raskob GE. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. Thromb Haemost. 2015 Nov 25;114(6):1268–76.
8. Ten Cate-Hoek AJ, Weitz JI, Gailani D, Meijer K, Philippou H, Bouman AC, Whitney Cheung Y, van Mens TE, Govers-Riemslag JW, Vries M, **Bleker S,** Biederman JS, Stoof SC, Büller HR. Theme 3: Non-invasive management of (recurrent) venous thromboembolism (VTE) and post thrombotic syndrome (PTS). Thromb Res. 2015 Sep; 136 Suppl 1: S13–8.
9. Van Es N, **Bleker S,** Sturk A, Nieuwland R. Clinical significance of tissue factor-exposing microparticles in arterial and venous thrombosis. Semin Thromb Hemost. 2015 Sep 26.
10. Van Es N, Di Nisio M, **Bleker SM**, Segers A, Mercuri MF, Schwocho L, Kakkar A, Weitz JI, Beyer-Westendorf J, Boda Z, Carrier M, Chlumsky J, Decousus H, Garcia D, Gibbs H, Kamphuisen PW, Monreal M, Ockelford P, Pabinger I, Verhamme P, Grosso M, Büller HR, Raskob GE. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. Thromb Haemost. 2015 Aug 13; 114(6).
11. Van Es N, **Bleker SM**, Wilt IT, Porreca E, Di Nisio M. Prevention and treatment of venous thromboembolism in patients with cancer: focus on drug therapy. Drugs. 2016 Mar; 76(3):331–41.
12. **Bleker SM,** van Es N, Kleinjan A, Büller HR, Kamphuisen PW, Aggarwal A, Beyer-Westendorf J, Camporese G, Cosmi B, Gary T, Ghirarduzzi A, Kaasjager K, Lerede T, Marschang P, Meijer K, Otten HM, Porreca E, Righini M, Verhamme P, van Wissen S, Di Nisio M. Current management strategies and long-term clinical outcomes of upper extremity venous thrombosis. J Thromb Haemost. 2016 May; 14(5):973–81.
13. Brekelmans MP, **Bleker SM**, Bauersachs R, Boda Z, Büller HR, Choi Y, Gallus A, Grosso MA, Middeldorp S, Oh D, Raskob G, Schwocho L, Cohen AT. Clinical impact and course of major bleeding with edoxaban versus vitamin K antagonists. Thromb Haemost. 2016 Mar 24;116(1):155–61.
14. **Bleker SM,** van Es N, van Gils L, Daams JG, Kleinjan A, Büller HR, Di Nisio M. Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review. Thromb Res. 2016 Apr;140 Suppl 1:S81–8.

15. Schünemann HJ, Ventresa M, Crowther M, Briel M, Zhou Q, Garcia D, Lyman G, Noble S, Macbeth F, Griffiths G, Di Nisio M, Iorio A, Beyene J, Mbuagbaw L, Neumann I, van Es N, Brouwers M, Brozek J, Guyatt G, Levine M, Moll S, Santesso N, Streiff M, Baldeh T, Florez I, Gurunlu Alma O, Solh Z, Ageno W, Marcucci M, Bozas G, Zulian G, Maraveyas A, Lebeau B, Büller HR, Evans J, McBane R, **Bleker SM**, Pelzer U, Akl EA; IPDMA heparin use in cancer patients research group. Use of heparins in patients with cancer: individual participant data meta-analysis of randomised trials study protocol. BMJ Open. 2016 Apr 29;6(4):e010569.
16. **Bleker SM**, Buchmüller A, Chauleur C, Ní Aínle F, Donnelly J, Verhamme P, Jacobsen AF, Ganzevoort W, Prins M, Beyer-Westendorf J, DeSancho M, Konstantinides S, Pabinger I, Rodger M, Decousus H, Middeldorp S. Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomised trial of two doses. Thromb Res. 2016 Jun 3;144:62–68.
17. **Bleker SM**, Cohen AT, Büller HR, Agnelli G, Gallus A, Raskob GE, Weitz JI, Curto M, Sisson M, Middeldorp S. Clinical presentation and course of bleeding events in patients with venous thromboembolism, treated with apixaban or enoxaparin and warfarin. Thromb Haemost. 2016 Nov 30; 116(6):1159–1164.
18. **Bleker SM,** Beenen LF, Di Nisio M, van Es N, Büller HR, Kraaijpoel N, Rutten A. Incidental pulmonary embolism in cancer patients: Interobserver agreement on the diagnosis and extent with a focus on distal clots. Thromb Res. 2016 Nov; 147:46–51.
19. Van Es N, **Bleker SM,** Di Nisio M, Kleinjan A, Beyer-Westendorf J, Camporese G, Aggarwal A, Verhamme P, Righini M, Büller HR, Bossuyt PM. Improving the diagnostic management of upper extremity deep vein thrombosis. J Thromb Haemost. 2017 Jan; 15(1):66–73.
20. Van Es N, **Bleker SM,** Di Nisio M, Kleinjan A, Beyer-Westendorf J, Camporese G, Kamphuisen PW, Büller HR, Bossuyt PM; ARMOUR study investigators. A clinical decision rule and D-dimer testing to rule out upper extremity deep vein thrombosis in high-risk patients. Thromb Res. 2016 Dec; 148: 59–62.
21. **Bleker SM,** Kraaijpoel N, Büller HR. Upper extremity deep vein thrombosis. Book chapter published in "Current management of venous diseases". Springer 2016.
22. Brekelmans MP, Scheres LJ, **Bleker SM,** Hutten BA, Timmermans A, Büller HR, Middeldorp S. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarn. Thromb Haemost. 2017 Apr 3; 117(4):809–815.
23. Van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stépanian A, Smit K, De Tursi M, **Bleker SM,** Bossuyt PM, Nieuwland R, Kamphuisen PW, Büller HR. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica. 2017 May 26. Epub ahead of print.

PORTFOLIO

Name PhD student: S.M. Bleker
PhD period: February 2013 – November 2017

Courses	Year(s) / Credits
Clinical Epidemiology	*2013 / 0.6*
Practical Biostatistics	*2013 / 1.1*
The AMC World of Science	*2013 / 0.7*
Systematic Reviews	*2013 / 0.7*
Project Management	*2013 / 0.6*
Good Clinical Practice (GCP/BROK)	*2013 / 0.9*
Oral presentation in English	*2014 / 0.8*

Seminars, workshops and master classes	Year(s) / Credits
Weekly department journal club, department of Vascular Medicine, AMC, Amsterdam	2013–2016 / 1.0
Weekly department education, department of Vascular Medicine, AMC, Amsterdam	2013–2016 / 1.0
Thrombosis Excellence Course on Cancer and Thrombosis, LeoPharma	2014 / 1.0

Oral presentations	Year(s) / Credits
Highlow study *Internistisch Vascular Genootschap (IVG) Symposium, Zeist, the Netherlands*	*2014 / 0.5*
Antistolling tijdens zwangerschap en kraambed. Waarom en waarmee? *Obstetric Medicine: Pijnstilling en medicatie in de 1e lijn, Ede, the Netherlands*	*2014 / 0.5*
Recurrent venous thromboembolism and mortality in cancer patients with upper extremity deep vein thrombosis *XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Toronto, Canada*	*2015 / 0.5*
The current management strategies and clinical outcome of upper extremity deep vein thrombosis *XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Toronto, Canada*	*2015 / 0.5*
Registry of pregnancy in patients exposed to direct oral anticoagulants (DOACs) *Internistisch Vascular Genootschap (IVG) Symposium, Zeist, the Netherlands*	*2015 / 0.5*
Upper extremity deep vein thrombosis: comparison between cancer and non-cancer patients *8th International Conference on Thrombosis and Hemostasis Issues in Cancer (ICTHIC), Bergamo, Italy*	*2016 / 0.5*
Preventie en behandeling van veneuze tromboembolie in de zwangerschap *Refereeravond Leidse Cluster Gynaecologie en Obstetrie, Haga ziekenhuis, The Hague, the Netherlands*	*2016 / 0.5*

Clinical impact and course of major bleeding events in patients with venous thromboembolism, treated with factor Xa inhibitors or vitamin K antagonists: an individual patient data meta-analysis' *European Society of Cardiology (ESC) Congress, Rome, Italy*	*2016 / 0.5*
Venous thromboembolism prevention in pregnancy *Best Clinical Practices with LMWH organized by ROVI, Valencia, Spain*	*2016 / 0.5*

Poster presentations	Year(s) / Credits
Unsuspected pulmonary embolism in cancer patients: a multicenter, international, prospective, observational study *American Society of Hematology (ASH) Annual Meeting and Exposition, San Francisco, United States of America*	*2014 / 0.5*
Clinical presentation and extent of clinical care of clinically relevant non-major bleeding events with apixaban and warfarin *XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Toronto, Canada*	*2015 / 0.5*
Clinical presentation, impact and course of major bleeding events with apixaban and warfarin *XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Toronto, Canada*	*2015 / 0.5*
Unsuspected pulmonary embolism in cancer patients: an international, ongoing, prospective, observational study *XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Toronto, Canada*	*2015 / 0.5*

Congresses and symposia	Year(s) / Credits
Dutch Society for Thrombosis and Haemostasis (NVTH), Koudekerke, the Netherlands	*2013–2015 / 1.5*
5th Women's Health Issues in Thrombosis and Haemostasis congress (WHITH), Vienna, Austria	*2013 / 0.5*
XXIV congress of the International Society for Thrombosis and Haemostasis (ISTH), Amsterdam, the Netherlands	*2013 / 1.25*
7th International Conference on Thrombosis and Hemostasis Issues in Cancer (ICTHIC), Bergamo, Italy	*2014 / 1.25*
56th American Society of Hematology (ASH) Annual Meeting & Exposition, San Francisco, United States of America	*2014 / 1.25*
Internistisch Vasculair Genootschap symposium (IVG), Zeist, the Netherlands	*2014–2015 / 0.5*
XXV congress of the International Society for Thrombosis and Haemostasis (ISTH), Toronto, Canada	*2015 / 1.25*
7th International Conference on Thrombosis and Hemostasis Issues in Cancer (ICTHIC), Bergamo, Italy	*2016 / 1.25*
European Society of Cardiology (ESC) Congress, Rome, Italy	*2016 / 1.25*

Student monitoring and teaching

Luuk van Gils, Bachelor's research project: 'Treatment and outcome of upper extremity deep vein thrombosis in cancer patients'	*2015 / 1.0*

Awards

Young Investigators Award International Society of Thrombosis and Haemostasis (ISTH)	*2015*
Young Investigators Award European Society of Cardiology (ESC)	*2016*

Other

Consultant coagulation, lipid disorders and hypertension, department of Vascular Medicine, AMC, Amsterdam, the Netherlands

DANKWOORD

Iedereen die op wat voor manier dan ook heeft bijgedragen aan dit proefschrift wil ik ontzettend graag bedanken, waarvan een paar mensen in het bijzonder.

Allereerst wil ik alle patiënten bedanken die hebben meegedaan aan de onderzoeken die zijn gepubliceerd in dit proefschrift.

Mijn promotor, prof. Dr. Middeldorp, beste Saskia. Heel veel dank dat je mij de gelegenheid hebt geboden om bij jou te promoveren, en zo een paar jaar onderdeel te zijn van een fascinerende en inspirerende onderzoeksgroep! Maar bovenal: bedankt dat je zoveel vertrouwen in mij hebt getoond op de cruciale momenten. Ik heb dit promotietraject kunnen afmaken omdat jij me bent blijven stimuleren.

Mijn dank gaat ook uit naar mijn copromotor, prof. Dr. Büller. Beste Harry, jij hebt mij de begeleiding gegeven die ik nodig had en daarvoor ben ik je ontzettend dankbaar. Naast jou zittend tijdens een overlegmoment op jouw kamer leken sommige problemen eigenlijk helemaal niet te bestaan en als mentor tijdens spannende congres presentaties was je voor mij van onschatbare waarde.
Dear Dr. Di Nisio, Marcello, my other copromotor. Thank you so much for your help, patience and super quick and valuable responses to my endless emails!

Ik dank de leden van mijn promotiecommissie, prof. dr. K. Meijer, prof. dr. J.A.M. van der Post, prof. dr. D.P.M. Brandjes, prof. dr. J.A. Reekers, dr. A.M. Westermann en dr. M. ten Wolde, voor het lezen en beoordelen van dit proefschrift en de bereidheid zitting te nemen in de commissie. Ik kijk ernaar uit om met jullie van gedachten te wisselen.

Ik dank ook de stafleden van vasculaire geneeskunde, voor het creëren en in stand houden van een prachtige onderzoeksafdeling, een voedingsbodem voor promovendi zoals ik. Michiel en Erik, jullie wil ik in het bijzonder bedanken voor jullie luisterend oor ten tijde van mijn 'promotiecrisis'.

En dan mijn paranimfen! Zo erg als ik kan twijfelen over dingen, zo zeker weet ik dat jullie naast mij moeten staan tijdens de verdediging van dit proefschrift. Jullie weten als geen ander welk lief en leed er in dit boekje zit!
Lau, van een jeugd samen slapen op dezelfde kamer, vol verkleedpartijen (sorry dat jij altijd de verkleedkist moest halen) en zelfverzonnen liedjes met als muzikaal hoogtepunt het boerenkool-lied, tot beiden in het AMC onder het genot van cappuccino's het

wel en wee van onze promoties doornemen; jij was overal bij en bent mijn eeuwige rots in de branding!
En Laura-Jean, lieve Bill, wat kunnen wij toch altijd heerlijk genieten van alles hè?! (met eten en wijn als rode draad en Bali als toppunt) en elkaar de benodigde schouderklopjes geven ("gut, wat hebben we dit toch weer lekker voor elkaar"). Jij was (en bent) er altijd voor mij, en vice versa.

Ik bedank graag alle mede-auteurs van de artikelen die ik de afgelopen jaren hebben gepubliceerd en die hebben geleid tot dit proefschrift; dank voor de fijne samenwerking!
Dank ook aan de medewerkers van het trialbureau en aan Henriëtte en Joyce voor de hulp bij alle administratieve rompslomp.

Lieve (oud) collega's van F4: bedankt voor de gezelligheid met als hoogtepunten de skiweekenden, promotiefeestjes, spierbal-adjes en congressen met het tromboseclubje (Pau, Nick, Josien, Whitney, Laura, Thijs, Luuk, Marjolein, Mandy, Doortje, en Stefano – mede door jullie waren de WHITH, Koudekerke, Bergamo, de ESC en de ISTH echt een feest!)
Mijn opvolgsters Ingrid en Noémie, wat hebben jullie de nog lopende studies fantastisch opgepakt, ik ben trots op jullie!
Marjet, een speciaal bedankje voor je luisterend oor en interesse. Whitney, wat was het gezellig om ruim 2 jaar lang een kamer met jou te delen! Lieve Merel, ik mis de eindeloze F4-143 koffie sessies! En lieve Soof, wat heerlijk dat we de F4-gezelligheid nog even een jaartje konden doorzetten in Beverwijk (en daar houdt het uiteraard niet op).

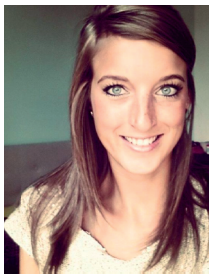
Stafleden en collega assistenten in het Rode Kruis Ziekenhuis, bedankt voor de fijne samenwerking en omgeving waarin ik een groot deel van mijn opleiding tot internist mag volgen. Ik kijk er naar uit om weer terug te komen in mei 2018.

En dan mijn lieve vrienden! Toen ik het promoveren even niet meer zag zitten hebben jullie me er echt doorheen getrokken door naar me te luisteren, met me mee te denken over oplossingen, en simpelweg de vrije tijd buiten mijn promotie zó waardevol te maken door alle gezellige feestjes, etentjes en weekendjes weg. Wat een heerlijk gevoel om nu ook dit hoogtepunt met jullie te kunnen vieren! Lieve Wallies, clubgenootjes, Deventer crew, jullie zijn geweldig en onvervangbaar. Een speciaal woordje voor een paar van jullie: Ireentje, heerlijk mens! Altijd een mooi verhaal, altijd oprecht, je bent de liefste. Lies, als de muren van de Marathonweg toch eens konden praten; promotie dalen en toppen, de liefde, spannende (en succesvolle) sollicitaties voor een opleiding-

splek; niks blijft onbesproken en ongevierd! Veer en Lot, wat fijn dat onze 3-eenheid de studentenjaren heeft overleefd; ik geniet van onze weekendjes in Brussel, Parijs, Rotterdam! Tess, zo heerlijk om eindeloos met jou over van alles te praten, te analyseren, op één lijn te zitten – en ondertussen ook nog eens zo te kunnen genieten van eten.

Aan mijn ooms, tantes, neven en nichten: dank voor jullie interesse en voor de altijd gezellige familiefeestjes!
Mijn lieve familie (pap, mam, Lau, Elien en Ol), jullie zijn mijn grootste geluk. En Jort en Eef, het is zo gezellig dat jullie erbij horen! Elien, van klein zusje tot (steeds meer) vriendin; ik geniet zó van je enthousiasme en (meestal goede) grappen. Ol, je bent zo'n heerlijk en hilarisch individu. Pap, wat lijk ik toch veel op jou, en wat is dat af en toe een geruststelling! Tijdens mijn eerste jaar geneeskunde heb ik kunnen zien wat een fantastische dokter jij bent en hoe patiënten en verpleging naar jou kijken; je bent mijn grote voorbeeld. Mam: zó lief en zorgzaam, slim, vrolijk – mijn optimisme heb ik van jou! Samen met pap altijd stimulerend, begrijpend, betrokken; en er is altijd dat warme bad in Rotterdam. Jullie zijn geweldig en dit boekje is voor jullie. And last but not least, to Simon: thank you for being 'there'.

CURRICULUM VITAE



Suzanne Mariëlla Bleker was born in Rotterdam on the 23rd of September 1986. She grew up with her parents René and Marijke, her two sisters Laura and Eline, and her brother Olivier. After graduating from the Sint Laurens College in Rotterdam in 2004, she moved to Groningen and started medical school at the State University of Groningen. In 2007 she did a rotation abroad in Malawi, Africa. After obtaining her qualifications as a medical doctor in 2011, she started working as an internal medicine resident at the Flevoziekenhuis in Almere. In February 2013 she started a PhD project at the Academic Medical Center, University of Amsterdam, supervised by prof. dr. Saskia Middeldorp, prof. dr. Harry Büller and dr. Marcello Di Nisio which resulted in this thesis. In addition to her work as a PhD student, she worked as a coagulation consultant at the Academic Medical Center.

On the 1st of September 2016 she started her residency in internal medicine at the Rode Kruis Ziekenhuis in Beverwijk (supervisor dr. J.S. van den Broek) and at the Academic Medical Center (supervisor dr. S.E. Geerlings).