Venous thromboembolism, coagulation and cancer
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CHAPTER 3

Development in anticoagulant treatment

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ABSTRACT
Venous thromboembolism is an important clinical problem. Cancer patients have a higher risk to develop venous thrombosis and vice versa. The treatment consists of heparin followed by vitamin K antagonists. Both agents have several limitations. Especially in cancer patients vitamin K antagonists cause bleeding or recurrence of VTE because of a small therapeutic window. Monotherapy with low molecular weight heparin seems to cause less of these complications in cancer patients compared to vitamin K antagonists. Besides, the drug is thought to have anti-cancer properties. Several novel anticoagulants are being developed and are undergoing clinical evaluation. New anticoagulants should also be evaluated on the effect on progression of cancer and cancer related survival.
INTRODUCTION
Venous thromboembolism is an important clinical problem with an incidence of 1-2 per 1000 persons. The consequences can be life threatening. Cancer is an important risk factor. Active cancer has been recognized as an independent predictor of recurrent VTE [1]. Conversely, of all VTE patients, almost 25% have active cancer [2], and in approximately 10% of the patients with an idiopathic VTE an occult cancer will be found in the following two years [2]. Survival after VTE is lower than expected in cancer patients [3]. Currently, VTE is treated with vitamin K antagonists (VKA) and heparin, but both agents have several limitations. In cancer patients, treatment of VTE with VKA compared with treatment with low-molecular-weight-heparin (LMWH) is more often complicated by bleeding and the risk of recurrent thrombosis is higher than in non-cancer patients [4,5]. Besides, heparin not only benefits treatment of VTE, but appears to also have anti-cancer properties [6,7].

The aim of this overview is to outline the treatment of symptomatic VTE in general, as well as in cancer patients. Subsequently, we will review the potential beneficial effects of anticoagulants on the survival of cancer patients, regardless of the presence of VTE, and discuss the suggested mechanisms of action. Because of limitations of the currently available anticoagulants, new agents are being developed and will be discussed.

COAGULATION SYSTEM
Thrombosis can occur in veins or arteries. Venous thrombi, which are formed under low shear conditions, are predominantly composed of fibrin and red blood cells. The process can be triggered by injury to the vessel wall, disturbances of the pro- and antithrombotic balance and low flow conditions [8]. Arterial thrombi develop under high shear conditions and mainly consist of platelet aggregates held together by fibrin strands. Most arterial thrombi are superimposed on disrupted atherosclerotic plaques. Rupture of the plaque exposes thrombogenic material in the lipid-rich core to the blood [9]. In venous thrombosis as well as in arterial thrombi platelets adhere to subendothelial collagen and to von Willebrand factor, where they become activated and release thromboxane A2, adenosine diphosphate and serotonin, substances that activate ambient platelets. Platelet activation induces conformational changes in glycoprotein (GP) IIb/IIIa; once activated, GP IIb/IIIa ligates fibrinogen and, under high shear, von Willebrand factor. These adhesive
molecules mediate platelet aggregation by linking adjacent platelets together. At the same time at sites of vascular injury, tissue factor (TF) is exposed which triggers coagulation and induces the formation of fibrin strands that stabilize the platelet-rich thrombus [10]. This is the first of three overlapping stages in coagulation at sites of vascular injury, namely initiation of the activation of the coagulation system, propagation of the cascade and finally fibrin formation.

The initiation of the coagulation cascade is triggered by TF (Figure 1). Tissue damage causes exposition of TF which binds factor VIIa, and forms the TF/factor VIIa complex. This complex activates factor X [11]. Activated factor X (factor Xa) then converts small amounts of prothrombin to thrombin. Such low concentration of factor Xa is sufficient to amplify coagulation by activation of factors V and VIII, platelets and platelet bound factor XI. The TF/factor VIIa complex activates factor IX as well. In the propagation stage factor IXa binds to factor VIIIa on the surface of activated platelets, and this complex effectively activates more factor X. Activation of platelet bound factor XI by thrombin also promotes factor Xa generation [11]. The final step of coagulation involves the conversion of fibrinogen to fibrin by thrombin. Thrombin also activates factor XIII, which cross-links and stabilizes the fibrin network.

Procoagulant activity is regulated by three important anticoagulant pathways. Activated protein C downregulates coagulation activation by the cleavage of the essential cofactors Va and VIIIa. Binding of thrombin to thrombomodulin located on the endothelial cell membrane results in a strong increase of activated protein C. Antithrombin is another anticoagulant protease, and it is the main inhibitor of thrombin and FXa. Tissue factor pathway inhibitor (TFPI) inhibits the activity of the TF/factor VIIa complex.
Development in anticoagulant treatment

Fig. 1. Regulation of blood coagulation

Legend fig.1: Tissue factor (TF)-factor VIIa complex activates factor IX or factor X, the coagulation is initiated. Factor X is mainly activated by the TF-VIIa complex. The Factor IXa-factor VIIIa complex enhances the activation of factor X. Coagulation is maintained through the activation by thrombin of factor XI. The coagulation system is regulated by the protein C pathway. Thrombin activates protein C by binding with thrombomodulin located on the endothelium. Together with protein S, activated protein C (APC) is capable of inactivating factors Va and VIIIa, which results in a down-regulation of thrombin generation and consequently in an up-regulation of the fibrinolytic system. The activity of thrombin is controlled by the inhibitor antithrombin. The solid arrows indicate activation and the broken arrows inhibition.

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), manifested as deep venous thrombosis (DVT), pulmonary embolism (PE) or both is a frequent clinical problem. The annual incidence of objectively confirmed episodes of VTE is 1-2 per 1000 inhabitants and this rate appears to be similar in different parts of the world [12]. Traditionally, DVT and PE were considered separate diseases, but increasing evidence indicates that there is much overlap in their etiology, occurrence, prognosis and treatment [13]. The main risk factors are increasing
age, thrombophilia, surgery, immobility, central venous catheters, hormone replacement therapy, oral contraception and cancer. The natural history of untreated symptomatic VTE is not well known, but the study by Barritt and Jordan in patients with clinically diagnosed PE showed that if patients do not receive anticoagulant therapy, approximately 25% will have a fatal recurrence, whereas another quarter of the patients will experience recurrent disease that is not fatal [14].

**VTE in cancer patients**
In cancer patients VTE is the second leading cause of death [15;16]. The incidence differs between studies [17-19]. A large population-based study showed that in the first three months after diagnosis of cancer the incidence of VTE was highest, with an odds ratio of 54 declining to an odds ratio of 4 after 1 to 3 years [20].

Tumor depending risk factors are stage and histology, with metastatic disease associated with a higher incidence of VTE than local cancer stages. It is clear that the VTE risk differs between various types of cancer but conflicting data exist about the estimated relative risks [15]. Treatment of cancer is also an important risk factor. Surgery, radiotherapy and chemotherapy all contribute to the risk of VTE [15;21;22]. Also the risk of recurrent VTE is approximately 3-fold higher in cancer patient compared to VTE patients without cancer [18;21].

**CURRENTLY USED ANTICOAGULANT THERAPY**
Traditionally, anticoagulant therapy is used for prevention and treatment of venous and arterial thromboembolism. The currently used oral anticoagulants are vitamin K antagonists (VKA). By inhibiting the metabolism of vitamin K the synthesis of clotting factors (prothrombin, factor VII, IX and X) is inhibited. This therapy requires regular monitoring of the level of anticoagulation by the International Normalized Ratio (INR) [23].

Heparins are the more commonly used parenteral anticoagulants. Unfractioned heparin (UFH) inhibits fibrin formation indirectly by binding to antithrombin catalyzing the activity of approximately 1000-fold. It is given intravenously. The antithrombotic dose depending effect of UFH differs in and between patients. Consequently, frequent monitoring by coagulation tests is necessary. LMWH is a derivate of UFH, which binds far more strongly to FXa than to thrombin. LMWH is given subcutaneously in
Development in anticoagulant treatment

a weight adjusted dose once or twice daily. Besides the injections, heparin induced thrombocytopenia can be a hurdle.

ANTICOAGULANT THERAPY IN CANCER PATIENTS

VTE treatment

Especially in cancer patients the anticoagulant effect of VKA is unpredictable. Various reasons such as drug interactions, malnutrition, liver dysfunction, vomiting and diarrhoea can cause changes in vitamin K status. Because VKA have a delayed onset of action and prolonged clearance of the anticoagulant effect, they are difficult to manage in patients who require invasive procedures or who experience frequent episodes of chemotherapy-induced thrombocytopenia [4;5]. Cancer patients treated with VKA frequently have recurrent episodes of VTE as well as a high risk of bleeding. In prospective studies, the annual risk of recurrent VTE is 21-27% in cancer patients treated with VKA [4;5], which is 2-3-fold higher than in patients without cancer. On the other hand cancer patients treated with VKA also have a high risk of major bleeding of 13.3%, as compared to 2.1% (per 100 patient years) for patients without cancer [4].

The first study in which the efficacy and safety of LMWH has been compared with that of VKA in preventing recurrent thrombosis in patients with cancer is the study of Meyer et al [24]. In this open label trial enoxaparin (1.5 mg/kg once daily subcutaneously) was compared to warfarin for 3 months in 146 patients with VTE and cancer. Of the patients assigned to warfarin 21.1% (95% CI 12.3-32.4%) experienced major haemorrhage or recurrent thromboembolism versus 10.5% (95% CI 4.3-20.3%) of the patients assigned to enoxaparin (p=0.09). The authors concluded that enoxaparin was as effective as VKA in the prevention of recurrent VTE, and provoked less bleeding.

In the CLOT study patients with cancer who had acute, symptomatic proximal deep vein thrombosis (DVT) in the leg, pulmonary embolism (PE), or both, were randomly assigned to receive LMWH (dalteparin) at a dose of 200 IU per kilogram of body weight subcutaneously once daily for five to seven days followed by VKA for six months (target INR, 2.5), or dalteparin alone for six months (200 IU per kilogram of body weight once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for the remaining five months). In the dalteparin group 9% had recurrent VTE, as compared to 17% of the patients in the VKA group (hazard ratio 0.48, 95% CI; 0.30-0.77). No significant difference was observed in the rate of major bleeding [25]. The prevention of DVT and PE is outside the scope of this contribution.
Cancer treatment

Since decades there has been interest in the influence of anticoagulants on the progression of cancer. In a systematic review of 9 studies on the treatment of VTE, post-hoc analyses showed that administration of LMWH improved the three months survival of cancer patients when compared to UFH, with an odds ratio of 0.61 (95% CI 0.40-0.93), whereas in VTE patients without cancer the survival was similar [7]. This reduction of mortality was present in various types of cancer and was not the result of differences in death related to VTE, bleeding or other known prognostic variables. It is also unlikely that these differences in survival were the result of a detrimental effect of UFH, as was shown by Smorenburg et al [26]. These results have led to randomised clinical trials that evaluated the effect of (LMW) heparin on survival in cancer patients without thrombosis.

Figure 2 shows a meta-analysis of five studies on the effect of (LMW) heparin on death at 12 months after study entry [27-31]. There is a 12% decrease in death in patients treated with LMWH, in the absence of statistical heterogeneity (relative risk 0.88, 95% CI; 0.80-0.96). However, these studies differ considerably in design. In one study, UFH was administered, in the others LMWH [27]. In two of the studies only patients with small cell lung cancer were included [27,28], whereas patients with different cancer types were enrolled in the other studies. The duration of heparin therapy ranged between studies from 5 to 52 weeks, and in one study a therapeutic dose of LMWH was given [30]. Three studies a priori defined a subgroup consisting of patients with a prognosis of at least 6 months at study entry (also referred to as limited disease) [27,28,30]. These patients have a significant survival benefit if they are treated with (LMW) heparin (relative risk 0.66, 95% CI; 0.52-0.84). Furthermore, post hoc analyses of the other studies are in agreement with these positive findings in those with limited disease [25,29,31].

Fig. 2A. A meta-analysis of 5 randomized controlled studies on the survival effect of (LMW) heparin in cancer patients
Fig. 2B. A Meta-analysis of 3 randomized controlled studies on the survival effect of (LMW) heparin in cancer patients with a prognosis of more than 6 months at study entry.

The knowledge about mechanisms of the heparin effect on cancer progression is mainly based on in vitro and animal studies.

One of the mechanisms is based on the anticoagulant effect. Tumour cells are capable to produce procoagulant molecules such as tissue factor, cancer procoagulant and hepsin. These initiate the clotting cascade activating the protease-activated receptors [32;33]. Stimulation of the receptors by these coagulation factors may change the tumour phenotype, and enhance growth, invasion, metastasis, and angiogenesis in experimental models [34;35]. LMWH's are also effective in releasing endothelial tissue factor pathway inhibitor (TFPI), the natural inhibitor of tissue factor [36]. Besides its coagulant effects, heparin is thought to have other properties. This is illustrated by the anti-metastatic effects of non-anticoagulant heparins [37].

The first non-anticoagulant mechanism of heparin is interfering with the interaction between cancer cells and platelets. Specific oligosaccharide structures in heparin can bind to P-selectins exposed on activated platelets [38] and show minimal anticoagulant activity [39]. Ludwig and colleagues tested the impact of UFH, LMWH (nadroparin and enoxaparin), and fondaparinux on P-selectin-dependent tumour interactions in vitro and metastasis formation in vivo. These agents differ widely in their potential to interfere with P-selectin-mediated cell binding. The ability strongly correlates with the potency in inhibiting experimental lung metastasis in vivo [40;41]. Selectins are expressed on leukocytes (L-selectin) and the vascular endothelium (E- and P-selectin). Heparin can inhibit L-selectin binding to its ligands resulting in inhibition of the inflammatory response. Also extravasation of cancer cells is hindered by binding of heparin to selectins. [38;42;43].
The second non-anticoagulant property of heparin is inhibition of cancer cell heparanase [44]. In humans, elevated heparanase expression by the tumor has been correlated with a more aggressive behaviour in breast, colon, ovary, pancreas, non-small lung cancer, acute myeloid leukaemia, and myeloma tumors [45-52]. Heparanase is an enzyme that breaks down the polysaccharide barrier on the endothelium, which enhances cancer-cell invasion is enhanced [53]. Heparanase also cleaves the growth factor that bears heparan sulphate groups from heparan sulphate proteoglycans which are localized in the extracellular matrix and cellular membranes [54-56]. Heparins can directly inhibit the effect of growth factors as well. LMWH hinders binding of growth factors to high-affinity receptors to a greater degree than UFH [57].

Finally, heparin, especially LMWH, is thought to increase apoptosis in cancer cells. In heparin knockout mice LMWH resulted in a four fold increase in the apoptosis index with LMWH as compared to controls [58]. Heparin probably enters the cell by endocytosis and induces apoptosis by interfering with transcription factors [59].

NEW ANTICOAGULANTS
Because of the limitations of both VKA and LMWH, new anticoagulants are being developed. New anticoagulants target specific steps in the coagulation cascade. Initiation of coagulation can be inhibited by targeting the TF/factor VIIa complex, whereas in the propagation stage thrombin generation can be blocked by drugs that target factor IXa or Xa, or by inactivation of factor Va or VIIIa. In the final stage, an inhibitor of thrombin prevent fibrin formation, block thrombin-mediated feedback activation of factors V, VIII, and XI, and attenuate thrombin induced platelet activation.

Inhibitors of initiation
Agents at the most advanced stage of development are recombinant TFPI, nematode anticoagulant peptide (NAPc2) and the active site-blocked factor VIIa (factor VIIai).

Animal studies demonstrated that TFPI attenuates the coagulopathy and improves survival in sepsis models [60;61]. A recombinant form of TFPI (tifacogin) has been evaluated for these indications in humans. In 1754 patients with severe sepsis, the effect of TFPI on all-cause 28-day mortality was compared with placebo. The INR was determined in all patients within 24 hours before the start of drug infusion and a prolongation was based on severe sepsis and not attributable to medications or other
Fig. 3. New antithrombotics

conditions. For patients with a high baseline INR, the all cause mortality at 28 days did not differ in both groups (34.2% and 33.9% with tifacogin and placebo, respectively) and the rate of bleeding was significantly higher with tifacogin than with placebo (6.5% and 4.8%, respectively). For patients with a low INR the overall mortality was lower in the tifacogin group (12%) as compared to placebo (22.9%). The rate of bleeding was higher in the tifacogin group compared to the placebo group (6.5% tifacogin and 4.8% placebo for those with high INR; 6.0% tifacogin and 3.3% placebo for those with low INR) [62]. Currently, TFPI is being evaluated in patients with community-acquired pneumonia.

NAPc2 is a protein which is isolated from the nematode, Ancylostoma caninum. It binds to a non-catalytic site on both factor X and factor Va and inhibits factor VIIa within the TF/factor VIIa complex. NAPc2 can be given on alternate days, because it has a half-life of almost 50 hours after subcutaneous injection. In a phase II study, NAPc2 showed promise in preventing VTE after elective knee replacement surgery [63]. Phase III randomised controlled trials are needed to compare the efficacy and safety of NAPc2 with the currently used anticoagulants.
Inhibitors of propagation

F Xa inhibitors

Factor Xa is an attractive target for anticoagulants because of its pivotal ‘upstream’ location in the coagulation cascade. It is the rate-limiting component in the generation of thrombin. The response of drugs targeting the effects of factor X is predictable and routine coagulation monitoring is unnecessary.

Indirect factor Xa inhibitors are active by binding to antithrombin which then inhibits free factor Xa. Direct factor Xa inhibitors are active by binding to factor Xa. Fondaparinux and idraparinux, both indirect factor Xa inhibitors, are two new synthetic pentasaccharides. They are analogous to the pentasaccharide sequence of heparin that exert the same effect on FXa.

Currently, only fondaparinux is licensed for prophylaxis of venous thromboembolism in high-risk orthopaedic surgery and as an alternative to heparin or LMWH for the initial treatment of VTE. Fondaparinux has a half-life of approximately 17 hours and can be administered subcutaneously once daily [64]. It is not metabolized and it is cleared almost exclusively by the kidneys. Idraparinux is a hypermethylated derivate of fondaparinux, with a very high affinity to antithrombin which results in a plasma half-life of 80 hours, similar of that of antithrombin [65]. Consequently, idraparinux can be given subcutaneously once weekly. Like fondaparinux, idraparinux is not metabolized and is cleared by the kidneys. Fondaparinux has been evaluated for the treatment of VTE in two phase III clinical trials. In the MATISSE-DVT study, a randomized, double-blind controlled study, 2205 patients received either fondaparinux or enoxaparin for at least 5 days, followed by treatment with VKA. At 3-months, the rates of recurrent symptomatic VTE with fondaparinux or enoxaparin were 3.9% and 4.1% respectively, whereas rates of major bleeding were 1.1% and 1.2% respectively [66].

The MATISSE PE trial was an open-label trial, in which 2213 pulmonary embolism (PE) patients were randomized to receive either fondaparinux or UFH by continuous infusion for 5 days, followed by VKA. At 3 months, the rates of recurrent symptomatic VTE with fondaparinux or heparin were 3.8% and 5.0%, respectively, with an absolute difference of -1.2% (95% CI -0.3-0.5%) in favour of fondaparinux. Rates of major bleeding were 1.3% and 1.1% respectively, absolute difference of 0.2%, (95% CI -0.7-1.1%). The results of both MATISSE trials indicate that fondaparinux is as effective as LMWH or UFH for the initial VTE treatment. Furthermore, fondaparinux is easier to administer than UFH [66].
Idraparinux was compared with warfarin in patients with proximal DVT in a phase II, dose-finding trial [67]. Patients were treated for 5 to 7 days with enoxaparin (2.5, 5.0, 7.5, 10 mg) and then randomized to idraparinux, once weekly subcutaneously, or VKA for 12 weeks. The primary efficacy outcome, changes in compression ultrasound and perfusion lung scan findings, was similar in all idraparinux groups and did not differ from that in the VKA group. However, there was a strong dose dependent increase in bleeding in the idraparinux group, with an acceptably high rate in the 10 mg group; however in the 2.5 mg group the bleeding rate was lower than in the VKA group (p=0.029). Recently completed trials have compared subcutaneous idraparinux monotherapy (at a dose of 2.5 mg once weekly) with 5 to 7 days of enoxaparin, followed by at least 3 months of VKA therapy for the treatment of patients with DVT or PE. Regarding the recurrence of VTE, the pre-specified non-inferiority criterion was met at 3 months and maintained at 6 months in the 6 month stratum for patients with DVT. In the PE patients, however, the non-inferiority criteria were not met due to a higher recurrence rate in the idraparinux recipients. The incidence of clinically relevant bleedings was statistically lower at 3 months but similar at 6 months in the 6-month stratum. Idraparinux has also been studied in patients with atrial fibrillation. In patients with AF at risk for thromboembolism, idraparinux (2.5 mg/wk) was at least as efficacious as VKA therapy, but associated with more bleeding. A different dosing regimen, adjusted to patient characteristics to improve the safety while preserving efficacy, will be considered for future trials in AF.

One parenteral (DX9065a) and several oral direct factor Xa inhibitors (BAY 59-7939, LY-51, 7717, BMS-562247 and DU-176b) are currently undergoing phase II or phase III evaluation.

DX-9065a is a synthetic non-peptidic low-molecular-weight inhibitor that binds reversibly to the active site of factor Xa. The drug half life is 45 minutes after bolus i.v. injection and it is cleared by the kidneys. Phase I and II studies in patients undergoing percutaneous coronary intervention are promising but confirmation is required by phase III clinical trials.

BAY 59-7939, LY-51, 7717, BMS-562247 and DU-176b are orally active, direct factor Xa inhibitors that are currently undergoing phase II/III testing for thromboprophylaxis in patients undergoing elective hip or knee arthroplasty. A phase III study in treatment with BAY 59-7939 of DVT and PE is ongoing.
**Protein C**
Activated protein C inactivates factor Va and factor VIIIa. Strategies to enhance the action of protein C include administration of recombinant protein C, activated protein C, or soluble thrombomodulin. Protein C is not only a strong natural anticoagulant but also has anti-inflammatory properties [68]. Recombinant activated protein C (drotrecogin alpha), was compared to placebo in a trial in 1690 patients with severe sepsis and showed a 6% absolute reduction in the 28 day mortality at a cost of more major bleeding (3.5 percent vs. 2.0 percent; p=0.06) [69]. This benefit was not found in a recent study in sepsis patients at a low risk of death [70]. An exploratory randomized, placebo-controlled, double blind, dose escalation study comparing a standard therapy for submassive pulmonary embolism (enoxaparin sodium) to a combined therapy of drotrecogin alfa plus enoxaparin sodium is ongoing.

**Soluble thrombomodulin**
Like membrane-bound thrombomodulin, soluble thrombomodulin binds thrombin and converts it from a procoagulant enzyme into a potent activator of protein C. In a phase II trial examining the utility of soluble thrombomodulin for VTE prophylaxis after elective hip arthroplasty, the primary outcome (a composite of venographically detected DVT and symptomatic VTE) occurred in 3.4% (95% CI 1.3-8.5%) of 116 evaluable patients in the 0.3 mg/kg group and in 0.9% (95% CI 0.2-4.9%) of 111 patients in the 0.45 mg/kg group [71]. Major bleeding occurred in 1.4% (95% CI 0.4-5.1%) of the patients receiving the low dose of soluble thrombomodulin and 6.3% (95% CI 3.3-11.5%) in the high dose group.

**Inhibitors of fibrin formation**
Thrombin can be blocked indirectly, by blocking its generation (i.e. antithrombin stimulation by heparins) or directly. Direct thrombin inhibitors bind to thrombin and block its interaction with substrates, thus preventing fibrin formation, thrombin mediated activation of factor V, VIII, XI or XIII, and thrombin induced platelet aggregation. Direct thrombin inhibitors possibly attenuate thrombus formation more effectively than the indirect inhibitors, because they also inactivate fibrin-bound thrombin. Hirudin, argatroban and bivalirudin are parenteral direct thrombin inhibitors. Hirudin and argatroban are approved for therapy in case of heparin induced thrombocytopenia in North America. Bivalirudin is registered in North America for use during percutaneous
Development in anticoagulant treatment

coronary interventions [72]. Ximelagatran is the first orally available direct thrombin inhibitor. However a phase III trial in which patients were undergoing orthopaedic surgery was stopped and the agent was withdrawn by its manufacturer because of an adverse event report of serious liver injury. Dabigatran is another direct IIa inhibitor. Currently, phase III studies are testing dabigatran in atrial fibrillation and treatment of acute symptomatic venous thromboembolism.

DEVELOPMENT IN ANTICOAGULANT THERAPY IN CANCER
Currently, several trials are studying the effects of anticoagulant therapy in cancer patients. One study is recruiting cancer patients with VTE to test the optimal duration of treatment of VTE with LMWH (cancer-DACUS study). Another study is investigating the prevention of thromboembolic events with an FXa inhibitor (apixaban) in patients with metastatic cancer. At least eight studies are ongoing in cancer patients without VTE to determine the effect of different LMWH's on survival.

Furthermore the effect of NAPc2 and fondaparinux on survival is being studied in cancer patients without VTE. Recombinant NAPc2 is given in up to 100 patients with metastatic colon cancer. The aim is to identify a safe and effective dose of twice-weekly, subcutaneous rNAPc2 for the second-line treatment of metastatic colorectal carcinoma in combination with contemporary 5-FU-based chemotherapy. Non-small cell lung cancer patients are treated with fondaparinux in a phase I study.

CONCLUSIVE REMARKS
Despite the ongoing development of new anticoagulant drugs that overcome limitations of currently used agents, (low-molecular-weight) heparins and VKA are still the drugs of choice in the treatment and prevention of VTE. Using LMWH for long term treatment of VTE in cancer patients should be considered. Furthermore, anticoagulants, in particular LMWH, appear to prolong survival in patients with cancer, although five randomized clinical trails have not reached a firm conclusion yet. This potential effect may be due to various modes of action in the coagulation system as well as inhibition of cancer cell-platelet interaction during intra-vascular dissemination, inhibition of cancer cell adhesion to the endothelium, and inhibition of angiogenesis, and increasing the apoptosis rate in cancer cells.
Chapter 3

In the development and evaluation of new anticoagulants it is essential that the effect on progression of cancer as well as cancer-related survival is being monitored. Finally the effect of LMWH on survival of cancer patients should be finally established in currently ongoing trials.
REFERENCE LIST


