The role of a malignancy in the treatment of a venous thromboembolism and superficial thrombophlebitis

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Tiivistelmä – Referat – Abstract

Cancer patients have a manifold risk of suffering from both thrombotic events and anticoagulation-related bleeding complications. For this reason, knowledge of their adequate medication is crucial. The aims of this study were to find out are guidelines being followed regarding the treatment of venous thromboembolisms. The emphasis was on the anticoagulation therapy of cancer patients, but also non-cancer patients were analyzed as controls.

Data was collected from the clinical information system Uranus CGI. All patient records (with the diagnostic codes I26.0, I67.6, I74.3, I80*, I81*, I83*, K55, N28.0, 022.3) in the hospital district of Helsinki and Uusimaa (Jorvi, Meilahti, Peijas, Lohja, Porvoo, Tammisaari and Hyvinkää hospitals) during the time period 1.1.2014- 29.4.2016 were reviewed. Statistical analysis was performed using the IBM SPSS Statistics and Microsoft Excel computer softwares. The study included 1667 patients, out of whom 163 (9.8%) had active cancer.

The recommendation of using low molecular weight heparins as the primary anticoagulants for patients with malignancies has been practiced. More research is necessary in order to find the optimal duration for treatment of, especially, isolated calf muscle venous thromboses and cancer patients' superficial thrombophlebitides.

Avainsanat – Nyckelord – Keywords
venous, thromboembolism, thrombophlebitis, cancer, anticoagulation, treatment

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1. Introduction

The term venous thromboembolism (VTE) covers both the deep vein thrombosis (DVT) (where blood clots inappropriately in the deep veins), and its potentially lethal consequence – the pulmonary embolism (PE) (where a clot breaks free and travels into the pulmonary arteries) (1). VTE is a major health concern, as it is estimated to affect up to 5% of people during their lifetimes (2), and 1-2 people out of a thousand annually (3).

Even though currently many of the risk factors have been identified (table 1), a significant portion of the cases are idiopathic. Approximately 50% of the patients have no identifiable acquired risk factors, and around 10%-20% of the patients have no distinguishable acquired or genetic risk factors. This shows us VTEs etiology is not yet fully understood. (1)

GENETIC	ACQUIRED	TRANSIENT ACQUIRED
Family history	Advanced age	Pregnancy
Factor V Leiden	Antiphospholipid antibodies	Oral contraceptives
Prothrombin G20210A	Cancer	Hormone therapy
Protein C deficiency	Chronic disease	Hospitalization
Protein S deficiency	Obesity	Surgery
Antithrombin deficiency		Trauma
Sickle cell trait		Immobilization

Table 1. Risk factors for venous thromboembolisms (1)

1.1. Diagnostic Process

The diagnosis of a DVT is usually based on the anamnesis, clinical examinations, laboratory results and a Doppler ultrasound. Symptoms include swelling, pain, warmth, redness, fever and walking-related tenderness. Nevertheless, many of the VTEs are un-symptomatic, and roughly 10% are hence incidental findings. (3)

Symptoms often occurring with PE include tachypnea, shortness of breath, a pleural rub, pleuritic chest pain, hypoxia, hemoptysis, tachycardia, syncope together with accompanying symptoms, DVT symptoms and right heart failure. PE can be diagnosed using a ventilation/perfusion scan or, nowadays predominantly, a spiral computed tomography scan. (3,4) If PE causes right ventricular strain it may be seen through elevated levels of P-ProBNP and P-TNT in the blood samples (3).

The D-dimer is a predictive tool, used to exclude a VTE in cases with a small or moderate clinical probability (3) (appendices 2 and 3). However, the D-dimer can be elevated for multiple reasons unrelated to VTE (5).

The simplified pulmonary embolism severity index (sPESI) (appendix 1) is a tool designed to help predict a 30-day outcome for PE patients. Those with a sPESI outcome of 0 are considered to be low-risk patients and could be considered for early discharge and outpatient treatment. Approximately a third (13% to 51%) of PE patients fit into this category. However, also other factors such as patient compliance and social backgrounds must be taken into consideration before discharge. (6)

1.2. Anatomic locations

Most VTEs occur in the lower extremity, which is generally divided into two regions. The proximal veins of the lower extremity are the popliteal vein and those cranially from it, while consequently those caudally are considered as its distal veins. The soleus and gastrocnemius veins are part of the deep distal venous system of the lower extremity. (3)

Isolated distal deep vein thrombosis (IDDVT) is a common manifestation of a VTE, yet it remains to be a topic which requires more research. Even though there is an insufficient amount of studies focusing on IDDVTs treatment and association with PE, they are, nonetheless, known to be related with fewer recurrences than other VTEs. Alongside with IDDVTs, another question of interest is whether or not isolated calf muscle veins (ICMV) should actually be categorized as deep veins – therefore leading to uncertainty concerning their treatment. (7)

Somewhat 4% of the DVTs occur in the upper extremity, where the thrombus can be classified as primary or secondary. Secondary thrombi are results of central venous catheters, pacemakers or cancer, and they represent 75% to 80 % of the cases. Effort-induced thrombosis is most common in males under the age of 45. (8)

In addition, thrombotic events can occur in other unusual sites. Even though these locations are less frequent, they are often more challenging due to the severe outcomes and lack of clinical trials. Cerebral vein thrombosis often affects young females, with headache being the most common symptom. (9) Portal vein thrombosis can occur in both childhood and adulthood (10), with abdominal pain as the most frequent syndrome. (9)

The most significant superficial veins of the lower extremity include the great and small saphenous vein. The former travels from the medial ankle anteromedially through the calf up into the thigh and joins the common femoral vein at the saphenofemoral junction. The latter travels from the lateral foot to the posterior side of the lateral malleolus, continues posteriorily through the calf into the popliteal vein through the saphenopopliteal junction at the popliteal fossa. Variations in the anatomy occur amongst patients. (11)

1.3. Association between cancer and VTE

Studies show that patients with active cancer have somewhere between a four to eight times greater risk of developing a VTE than those who are cancer-free (5,12-15). Even though the exact risk cannot be precisely estimated, it is clearly a significant issue, as approximately 20% to 30% of the primary VTEs occur in cancer patients (12,14,16).

Cancer patients with VTEs have twice the mortality rate of cancer patients without VTEs (14), and currently VTEs are the second leading cause of death in cancer patients – coming second to only cancer itself (12,16). Thrombotic events are most likely to occur during the initial three months following the cancer diagnosis. The risk remains rather high until the 12th month, and decreases to almost no elevated risk only after 10 years (12).

Although different studies have slight variations when it comes to which cancer types have the highest association with VTEs, some malignancies appear to repeatedly stay on top of the list. At least lung cancer, gastrointestinal cancer and hematological malignancies have been accepted as cancers with high risks of VTEs rather unanimously (12,13,17). In addition the following are mentioned: brain, ovarian, and kidney cancer (12,17).

Especially metastasized cancers seem to be associated with a higher risk of a VTE (13), as approximately half of those patients with cancer during the diagnosis of a VTE also have metastases (14). When it comes to the location of the thrombus, cancer has been associated with arm or intra-abdominal DVTs, but not with PEs (14).

1.3.1. Cancer-related challenges

Cancer patients have not only a greater incidence of thrombotic events, but also a higher risk of developing anticoagulation-related bleeding problems. Therefore thromboprophylaxis isn't recommended unless the patient has such a high risk of a VTE, that it surpasses the risk of bleeding.(12)

Cancer patients possess more than twice the risk of developing recurrent venous thromboembolic events despite the use of adequate doses of low molecular weight heparin (LMWH), than non-oncologic patients receiving anticoagulation therapy (LMWH followed by warfarin). If cancer patients are treated with vitamin K antagonists (VKA), there are often problems with keeping the international normalized ratio (INR) within the therapeutic range. (5)

In addition to the challenges mentioned above, cancer patients are a difficult group to treat due to multiple other issues such as chemotherapy, hormonal agents, invasive procedures, long-term central venous catheterization and short life expectancy (18) – the one year survival rate being only circa 40% (3).

1.4. Treatment

The duration of the anticoagulation treatment can be divided into three subcategories. The acute treatment counts for the first 5-10 days. Following this comes the long-term treatment lasting up until 3-6 months, and treatment after this is called extended. (15)

Generally VTE patients are treated for 3 months with one of the following options: LMWH, VKA, novel oral anticoagulants (NOAC) or fondaparinux (table 2). As there are multiple options regarding the choice of anticoagulants, the used treatment should be based on risk, benefit, etiology, cost and patient preference. (2)

ANTICOAGULANT	ACTIVE INGREDIENT	STRENGTHS	WEAKNESSES	SOURCE
Vitamin K antagonist (VKA)	Warfarin	-Taken orally -Inexpensive	-Requires regular INR monitoring -Fluctuating INR levels can result in recurrent thrombosis or excessive bleeding -Must be stopped days before invasive procedures	(18)
Low molecular weight heparins (LMWH)	Dalteparin Enoxaparin Tinzaparin	-Routine monitoring not required -Rapid onset of action -Outpatient treatment is safe	-Subcutaneous injections may cause discomfort	(18)
Novel oral anticoagulants (NOAC)	Dabigatran Apixaban Rivaroxaban	-Taken orally - Routine monitoring not required	-Unpredictable absorption and drug interaction -Lack of an antidote (apixaban and rivaroxaban) -Higher risk of GI-bleeding	(17)
Others	Fondaparinux	-Routine monitoring not necessary -Low risk for heparin induced thrombocytopenia (HIT)	-Subcutaneous injections may cause discomfort	(19)

Table 2. Most frequently used anticoagulants

The duration of treatment should be decided based on several individual factors, such as previous VTEs, risk factors (Table 1), location, magnitude, bleeding risk, and patient compliance (3). The decision to continue extended treatment is based on evaluating the etiology of the VTE, the risk of recurrent VTEs and the risk of major bleeding (2). Anticoagulation is often used for indefinitely when there is an irremovable risk factor for the time being. Permanent treatment is preferred for patients with a genetic risk factor for VTE (table 1) already after the first thrombus. It is also used for patients with repeating idiopathic DVTs. (3)

It is common policy in Finland to treat IDDVTs with anticoagulation, even though this approach varies internationally (3). Most guidelines recommend a three month anticoagulation period, even though 6 weeks could be just as effective (7).

Studies show that recurrence amongst untreated IDDVTs is rare – suggesting that their anticoagulation treatment may be unnecessary. (7) However, according to the Käypä hoito -recommendation (3) anticoagulation treatment should be used at least if the IDDVT is symptomatic, or if the patient has significant risk factors (Table 1).

Upper extremity DVTs are treated in the same manner as lower extremity DVTs (3) as especially veins from the axillary vein proximally are associated with a high risk of PE (2). PEs have been reported in anywhere between 0% to 36% of patients with upper extremity DVTs (9).

1.4.1. Treatment of cancer-related VTEs

The Cochrane study (20) shows that cancer-related long-term anticoagulation with LMWH significantly reduces the risk of VTE recurrence when compared to treatment with warfarin. In addition, LMWH treatment doesn't increase the amount of bleeding complications or affect the mortality rate. Be that as it may, it appears that LMWH doesn't significantly reduce recurrent VTEs in patients without cancer for reasons yet unclear. (20)

Although it isn't fully understood why LMWH is superior to warfarin in the anticoagulation treatment of cancer patients, it has been suggested that they are less responsive to warfarin treatment (instead of reacting better to LMWH treatment) (18,21). Some studies propose that LMWH could actually inhibit angiogenesis, and in that manner restrict tumor growth and metastasis. This claim is supported by evidence that the use of dalteparin (compared to oral anticoagulants) reduces the risk of 12-month mortality in cancer patients with solid tumors, if they weren't known to have metastases. (22)

Even though NOACs and warfarin are efficient in treating VTEs unrelated to cancer, LMWH is recommended for both the acute and the long-term treatment for patients with malignancies (in the absence of contraindications). (5,17,23)

1.4.2. Cancer and duration of treatment

The duration of anticoagulation should be at least 3-6 months for patients with active cancer, and extended treatment should be considered (5,15-17). Whether the optimal treatment period is 3 or 6 months remains uncertain, as so far no study has compared these two (16). Patients with active cancer include, inter alia, those with metastatic disease and those with ongoing chemotherapy (4).

According to the Cancer-DACUS Study (23), the lack of a residual vein thrombosis (RVT) after a six-month anticoagulation period with LMWH indicates a low risk for recurrent thrombotic events. This calls in question the practicality of extended treatment, as it is a burden economically, may cause discomfort, and increases the risk of bleeding (16,23).

Extended treatment reduces the risk of recurrent thromboembolisms as the anticoagulation is ongoing. However, the risk increases as soon as the therapy ends, and returns to the same level as without extended treatment after two years. (5) This shows us, that prolonging the treatment doesn't seem to produce long-term benefits.

Even though extended treatment is often practiced for patients with active cancer, this protocol is not based on randomized trials (4,23), and the topic requires further research and clinical trials. The extended treatment can be performed by LMWH or warfarin (3).

It is safe to say, that currently extended treatment should be decided on a case-by-case basis, considering the benefits, risks, tolerability, patient preference and cancer activity (16). As cancer patients differ in their types, stages and histologies of the cancer, generalization of the required treatment is near impossible (23).

1.4.3. Cancer screening in idiopathic VTE

It is not uncommon to find an underlying malignancy after the diagnosis of an idiopathic VTE. As studies suggest, up to 10% of these patients are diagnosed with cancer in the following year, and over 60% of occult cancers are diagnosed as a result of unprovoked VTEs. (24) This ought to be kept in mind as dealing with first unprovoked VTEs. Screening can be performed through history taking, basic blood testing, physical examinations, chest radiography and age- and sex-specific screening. Nonetheless, it is not recommended to perform extensive screening (including CT [computed tomography]) for occult cancers without symptoms pointing at it, as it doesn’t appear to reduce cancer-related mortality. (5)

1.5. Thrombolysis

Thrombolysis can be used in a high-risk pulmonary embolism, or in a DVT extending above the inguinal ligament with prominent symptoms and signs. The criteria for use of thrombolysis related to the upper extremity are similar. The bleeding risk accompanying thrombolysis must always be taken into consideration. (3) There is, however, no evidence of thrombolysis reducing the rate of VTE-recurrence, PE, or mortality (2).

1.6. Superficial thrombophlebitides

Superficial thrombophlebitis (STP) is an inflammatory process, often associated with blood clots affecting the superficial veins. Symptoms include localized pain, tenderness, itching, redness of the skin, and hardening of the neighboring tissue (25)

Studies suggest there is an association between STP and VTE. It has been estimated, that STP's incidence is higher than DVT's. (25) Of the STPs extending to the length of over 5cm, over 20% progress into a DVT (3) and both DVT and PE are their possible complications (26). As there isn't research concerning the incidence of STPs in cancer patients, it is yet unclear should it be interpreted as a possible sign of occult cancer (12).

There is limited evidence regarding the treatment of STPs. Fondaparinux has been recorded to be associated with a significantly reduced amount of symptomatic VTEs, STP-extension and recurrent STPs without increasing bleeding relative to placebo. Also LMWHs and NSAIDs have been demonstrated to reduce extension and recurrence of STPs, however, without significant effect on symptomatic VTEs. (25) Currently, recommendations suggest the use of LMWH for the minimum of one month in the treatment of STPs (26).

1.7. Bleeding

Before the development of adequate anticoagulants, untreated VTEs were fatal in approximately 30% of cases. Despite offering better starting points for treatment nowadays, they do not come risk-free: anticoagulation therapy increases the risk of major bleeding – being fatal in up to 25% of cases. (2)

The highest risk of bleeding in cancer patients is during the first month. If treatment is extended beyond six months, months 6 to 12 have similar rates of recurrence and bleeding as months 2 to 6. (15) The reported rates of severe bleeding are 2% - 5% with warfarin, 1,2% with LMWHs and 3%-6% with NOACs (3).

2. Aims

The primary aim of this study was to find out whether venous thromboembolism is treated according to the current recommendations in the HDHU-area. Patients without active cancer were included as controls. The complete list of aims was:

1. to find out the choice of anticoagulant and the planned duration of the anticoagulation in cancer patients and control.
2. to find out the frequency of different locations of thrombotic events, in order to see if cancer patients were more prone to certain types of thrombi.
3. to assess the prevalence of bleeding complications due to anticoagulation.
4. to describe the characteristics of the patients, and to analyze the associations between VTEs and age, sex, and malignancies.
5. to analyze the duration from cancer diagnosis to VTE discovery
6. to evaluate the possibility for home treatment of PE in control group by calculating the sPESI-score.
7. to analyze the 6-month mortality-rate.

3. Materials and methods

3.1. Materials

Data was collected from patient records in the Oberon software. All patient records (with the diagnostic codes I26.0 pulmonary embolism with acute cor pulmonale, I67.6 nonpyogenic thrombosis of intracranial venous system, I74.3 embolism and thrombosis of arteries of the lower extremities, I80* phlebitis and thrombophlebitis, I81* portal vein thrombosis, I83* varicose veins of lower extremities, K55 vascular disorders of intestine, N28.0 ischemia and infarction of kidney, 022.3 anthrax septicemia) in the hospital district of Helsinki and Uusimaa (Jorvi, Meilahti, Peijas, Lohja, Porvoo, Tammisaari, Hyvinkää hospitals) during the time period 1.1.2014-29.4.2016 were reviewed.

The original registry included 2833 patients. In the present study, only patients with a VTE or STP (in any given location) were included. Patients with a VTE/STP –suspicion which was, after further examination, confirmed wrong were excluded. Each patient was only analyzed once per VTE/STP. After this 1667 patients were left suitable for the study.

Excel was used for collecting the required data of the patients. The patients' gender, age, duration of treatment and choices regarding hospitalization versus outpatient treatment were reviewed. If the patient has passed away, time and cause of death were searched as far as it was possible.

It was planned to find out how many of the pulmonary embolism patients could have been suitable for outpatient management, and hence information required for the sPESI-evaluation (appendix 1) was collected.

Regarding the patients with active or previous cancer, data was collected about the type of the cancer, whether or not it has metastasized, and when it has been diagnosed. The practiced cancer treatment during the time of the VTE/STP was also recorded. According to the treatment, the cancer was classified as active or non-active in the following manner:

NON-ACTIVE CANCER	ACTIVE CANCER
Recovered	Active care
In partial remission	Palliative care
In complete remission	Recently discovered malignancy (care hasn't started yet)
	Patient has cancer but refuses further research/treatment
	End-of-life care

Table 3. Classification of active cancer

Information was collected on the location of the VTE/STP and whether it was a primary symptom or an incidental finding. Were the patient to have a pulmonary embolism, reports were checked to see was there right ventricular strain or an embolism within the heart.

The choices of anticoagulants regarding the used long-term and extended treatment were collected, while also tracking the durations of the medication. Previous VTEs or genetic factors contributing to the prolongation of the prescribed treatment were also marked down. Finally, hemorrhages due to the anticoagulation treatment were searched. Only the cases with sufficient information have been included in the tables.

3.2. Methods

Statistical analysis was performed using the IBM SPSS Statistics and Microsoft Excel computer softwares. The Chi-Square test was used for data analysis with 0.05 probability level as the critical value.

Often patients had thrombi in multiple locations. Since the results would have been hard to interpret if every single VTE and STP were to have been listed separately in each case, locations were classified in the following manner (Figure 1): First, patients with either a portal vein (and possibly mesenteric vein) thrombosis or cerebral vein sinus (and possibly jugular and/or cortical vein) thrombosis were divided into their own categories.

Next, categories were formed of the thrombi affecting the pulmonary arteries and limbs in the hierarchical manner described above, favouring always those closest to the heart. This way no thrombus was counted twice, and the result could be analysed and presented in a comprehensible manner. The aim was to have the choice of treatment reflect the location of the thrombus as precisely as possible.

After this 16 thrombi were left, not fitting into the categories above. The locations of these mainly included veins of the neck (jugular veins) and the abdominal region (mesenteric veins, splenic vein). In addition, thrombi were identified in the ovarian vein, the brachiocephalic vein and the inferior and superior vena cava. These were all grouped in to the “others” category.

The classification “permanent treatment” applies to cases, where treatment is planned to be continued permanently, if no contraindications appear. The classification “indefinite treatment” applies to cases, where the duration of the treatment hasn’t yet been decided. Often these patients had transient acquired risk factors (table 1), during which anticoagulation was planned to be continued.

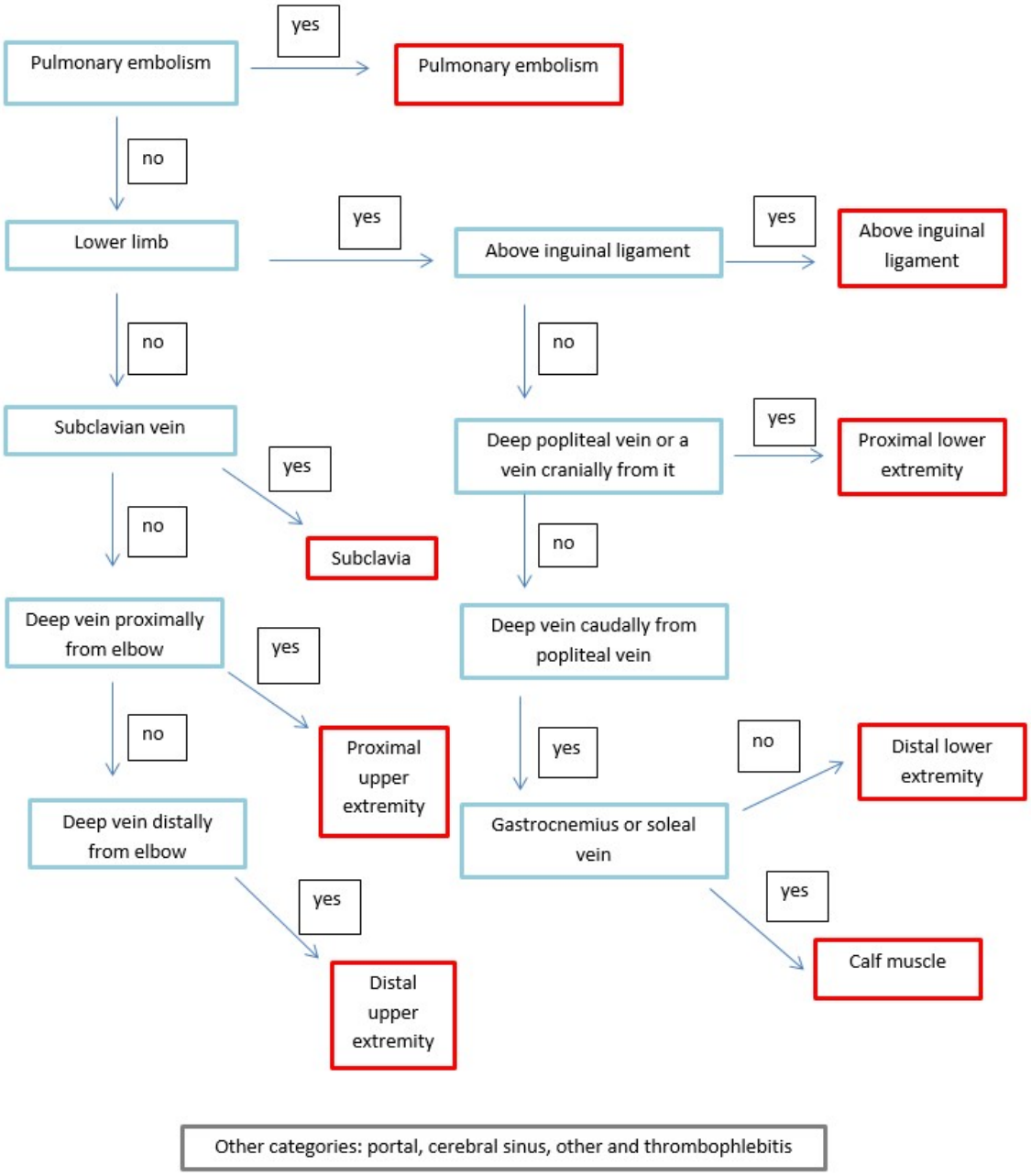

Figure 1. Classification of anatomical location of venous thromboembolisms and superficial thrombophlebitides

3.3. Limitations

The data was based completely on the clinical information system database Uranus CGI. Many of the entries were incomplete due to the lack of their content regarding the recorded variables, or written in a manner that couldn't be interpreted in and adequately unequivocal way. The content of such data was therefore incomplete. Only patients with sufficient treatment-related information are included in the results-section.

Other possible reasons for the durations of the hospitalization and anticoagulation could not be excluded. Patients could have an extended time spent in the ward due to diseases unrelated to the VTE/STP, and medication could last for longer than expected because of other underlying conditions (e.g. atrial fibrillation).

Too many assumptions regarding whether or not the treatments are appropriate cannot be made, as we have not collected all the background information leading to these decisions. These could include factors such as contraindications, underlying diseases, patient preferences and co-operation.

One of the original aims was to find out the percentage of patients who suffered from severe bleeding complications due to each group of anticoagulants. Due to the vast number of patients treated with combinations of different anticoagulants, this became impossible to accurately describe.

We had no access to the official death certificates, and the information related to the causes of death was limited.

4. Results

After excluding the patients unrelated to our study, 1667 patients from ages 16 to 102 (mean 59.0, SD 16.9) were left, out of whom 760 (45.6%) were male and 907 (54.4%) female (table 4). There were 28 incidental VTE-findings (1.7%) in the whole group, out of which 11 appeared in cancer patients ($p < 0.001$). In other words, 6.7% of the thrombotic events in cancer patients were incidental findings. 15 new malignancies were found in the courses of the VTE treatment periods. Out of the 163 patients with active cancer, 90 (55.2%) had metastases.

	VTE* (n=1185)	STP** (n = 482)
Male	583 (49.2 %)	177 (36.7 %)
Female	602 (50.8 %)	305 (63.3 %)

Table 4. Frequencies of VTEs and STPs

* VTE = venous thromboembolism

** STP = superficial thrombophlebitis

The following tables represent the choices in treatment in relation to the thrombus's location.

Location of thrombosis		All patients	Patients without active cancer	Patients with active cancer	P-value
Pulmonary embolism		204 (17.2 %)	175 (16.6 %)	29 (22.0 %)	0.023
Lower extremity, proximal		388 (32.7 %)	349 (33.1 %)	39 (29.5 %)	0.836
Lower extremity, distal	Calf muscle	127 (10.7 %)	117 (11.1 %)	10 (7.6 %)	0.639
	Other	275 (23.2%)	257 (24.4 %)	18 (13.6 %)	0.048
Above inguinal ligament		95 (8.0 %)	75 (7.1 %)	20 (15.2 %)	< 0.001
Upper extremity, proximal		12 (1.0 %)	9 (0.9 %)	3 (2.3 %)	0.075
Upper extremity, distal		3 (0.3 %)	3 (0.3 %)	0 (0.0 %)	0.568
Subclavia		18 (1.5 %)	17 (1.6 %)	1 (7.6 %)	0.544
Portal vein		21 (1.8 %)	18 (1.7 %)	3 (2.3 %)	0.484
Cerebral sinus		27 (2.3 %)	24 (2.3 %)	3 (2.3 %)	0.814
Other		15 (1.3 %)	9 (0.9 %)	6 (4.5 %)	< 0.001
All		1185 (100.0%)	1053 (100.0%)	132 (100.0%)	-

Table 5. Locations of deep venous thromboembolisms

Location of thrombosis	All patients	Patients without active cancer	Patients with active cancer	P-value
Thrombophlebitis	482 (100.0 %)	451 (93.6 %)	31 (6.4 %)	0.023

Table 6. Amount of thrombophlebitides

Anticoagulant	Portal vein/Cerebral sinus/Other, no cancer (n=50)	Portal vein/Cerebral sinus/Other, cancer (n=12)
Warfarin	19 (38.0 %)	-
LMWH	22 (44.0 %)	12 (100.0 %)
NOAC	2 (4.0 %)	-
combination of anticoagulants	7 (14.0 %)	-

Table 7. Anticoagulant choices of thrombi in portal veins, cerebral sinuses and other locations

Duration of treatment (months)	Portal vein/Cerebral sinus/Other, no cancer (n=45)	Portal vein/Cerebral sinus/Other, cancer (n=11)
<3	1 (2.2 %)	-
3	4 (8.9 %)	-
3-6	1 (2.2 %)	1 (9.1 %)
6	27 (60.0 %)	4 (36.4 %)
6-12	1 (2.2 %)	-
12	1 (2.2 %)	-
>12	1 (2.2 %)	-
permanently	4 (8.9 %)	3 (27.3 %)
indefinitely	5 (11.1 %)	3 (27.3 %)

Table 8. Duration of portal vein, cerebral sinus and other thrombi's anticoagulation

Anticoagulant	Above inguinal ligament, no cancer (n=74)	Above inguinal ligament, cancer (n=20)	Lower extremity, proximal, no cancer (n=348)	Lower extremity, proximal, cancer (n=37)	PE*, no cancer (n=174)	PE*, cancer (n=29)
Warfarin	44 (59.5 %)	-	172 (49.4 %)	6 (16.2 %)	88 (50.6 %)	-
LMWH**	20 (27.0 %)	16 (80.0 %)	55 (15.8 %)	27 (73.0 %)	31 (17.8 %)	27 (93.1 %)
NOAC***	8 (10.8 %)	-	101 (29.0 %)	-	49 (28.2 %)	-
fondaparinux	-	1 (5.0 %)	-	2 (5.4 %)	3 (1.7 %)	-
combination of anticoagulants	2 (2.7 %)	3 (15.0 %)	20 (5.7 %)	2 (5.4 %)	3 (1.7 %)	2 (6.9 %)

Table 9. Anticoagulant choices of thrombi above the inguinal ligament, in the proximal lower extremity and pulmonary embolisms

* pulmonary embolism

** low-molecular-weight heparin

*** novel oral anticoagulant

Duration of treatment (months)	Above inguinal ligament, no cancer (n=67)	Above inguinal ligament, cancer (n=17)	Lower extremity, proximal, no cancer (n=333)	Lower extremity, proximal, cancer (n=34)	PE, no cancer (n=165)	PE, cancer (n=27)
<3	1 (1.5 %)	-	6 (1.8 %)	1 (2.9 %)	4(2.4 %)	-
3	3 (4.5 %)	-	44 (13.2 %)	4 (11.8 %)	8 (4.8 %)	-
3-6	2 (3.0 %)	-	6 (1.8 %)	-	1 (0.6 %)	-
6	28 (41.8 %)	4 (23.5 %)	150 (45.0 %)	9 (26.5 %)	75 (45.5 %)	10 (37.0 %)
6-12	1 (1.5 %)	-		1 (2.9 %)	1 (0.6 %)	-
12	2 (3.0 %)	1 (5.9 %)	4 (1.2 %)	1 (2.9 %)	6 (3.6 %)	3 (11.1 %)
>12	-	-	-	-	2 (1.2 %)	-
permanently	16 (23.9 %)	9 (52.9 %)	82 (24.6 %)	11 (32.4 %)	48 (29.1 %)	5 (18.5 %)
indefinitely	14 (20.9 %)	3 (17.6 %)	41 (12.3 %)	7 (20.6 %)	20 (12.1 %)	9 (33.3 %)

Table 10. Duration of anticoagulation of thrombi above the inguinal ligament, in the proximal lower extremity and pulmonary embolisms

Anticoagulant	Subclavia, no cancer (n=17)	Subclavia, cancer (n=1)	Upper extremity, no cancer (n=12)	Upper extremity, cancer (n=3)
Warfarin	9 (52.9 %)	-	9 (75.0 %)	-
LMWH	3 (17.6 %)	1 (100.0 %)	3 (25.0 %)	2 (66.7 %)
NOAC	5 (29.4 %)	-	-	-
combination of anticoagulants	-	-	-	1 (33.3 %)

Table 11. Anticoagulant choices of thrombi in the subclavian vein and upper extremity

Duration of treatment (months)	Subclavia, no cancer (n=14)	Subclavia, cancer (n=1)	Upper extremity, no cancer (n=11)	Upper extremity, cancer (n=3)
<3	-	-	1 (9.1 %)	-
3	5 (35.7 %)	-	1 (9.1 %)	1 (33.3 %)
6	7 (50.0 %)	1 (100.0 %)	1 (9.1 %)	-
12	1 (7.1 %)	-	1 (9.1 %)	-
permanently	1 (7.1 %)	-	3 (27.3 %)	1 (33.3 %)
indefinitely		-	4 (36.4 %)	1 (33.3 %)

Table 12. Duration of anticoagulation of thrombi in the subclavian vein and upper extremity

Anticoagulant	Lower extremity, distal no cancer		Lower extremity, distal, cancer		STP**, no cancer (n=352)	STP**, cancer (n=25)
	ICMV* (n=110)	other (n=257)	ICMV* (n=10)	other (n=18)		
Warfarin	26 (23.6 %)	125 (48.6 %)	2 (20.0 %)	1 (5.6 %)	20 (5.7 %)	-
LMWH	43 (39.1 %)	27 (10.5 %)	5 (50.0 %)	15 (83.3 %)	312 (88.6 %)	25 (100.0 %)
NOAC	40 (36.4 %)	98 (38.1 %)	2 (20.0 %)	-	13 (3.7 %)	
fondaparinux	-	-	-	-	2 (0.6 %)	-
combination of anticoagulants	1 (0.9 %)	7 (2.7 %)	1 (10.0 %)	2 (11.1 %)	5 (1.4 %)	-

Table 13. Anticoagulant choices of thrombi in the distal lower extremity and STP
* Isolated calf muscle vein
** Superficial thrombophlebitis

Duration of treatment (months)	Lower extremity, distal no cancer		Lower extremity, distal, cancer		STP, no cancer (n=349)	STP, cancer (n=24)
	ICMV (n=107)	other (n=251)	ICMV (n=11)	other (n=18)		
<3	36 (33.6 %)	5 (2.0 %)	2 (18.2 %)	-	292 (83.7 %)	16 (66.7 %)
3	41 (38.3 %)	86 (34.3 %)	4 (36.4 %)	2 (11.1 %)	12 (3.4 %)	2 (8.3 %)
3-6	3 (2.8 %)	12 (4.8 %)	1 (9.1 %)	-	3 (0.9 %)	2 (8.3 %)
6	12 (11.2 %)	83 (33.1 %)	2 (18.2 %)	5 (27.8 %)	10 (2.9 %)	-
6-12	-	1 (0.4 %)	-	1 (5.6 %)	-	-
12	-	3 (1.2 %)	-	-	1 (0.3 %)	1 (4.2 %)
>12	-	-	-	-	1 (0.3 %)	-
permanently	11 (10.3 %)	38 (15.1 %)	2 (18.2 %)	5 (27.8 %)	13 (3.7 %)	-
indefinitely	4 (3.7 %)	23 (9.2 %)	-	5 (27.8 %)	17 (4.9 %)	3 (12.5 %)

Table 14. Duration of anticoagulation of thrombi in the distal lower extremity and STP

All in all 100 (20.7 %) of the patients with STPs had either been treated only by topical treatments, or then been left untreated. In addition, seven (5.5 %) of the patients with ICMV thrombi had been treated only by topical treatments.

Choice of anticoagulant		Cancer (n=130)	No cancer (n=1039)	P-value
LMWH		105 (80.8 %)	205 (19.7 %)	< 0.001
Warfarin		10 (7.7 %)	506 (48.7 %)	< 0.001
NOAC		2 (1.5 %)	303 (29.2 %)	< 0.001
Fondaparinux		3 (2.3 %)	4 (0.4 %)	N.A.
Combination of anticoagulants	Initial 3 months LMWH	10 (7.7 %)	16 (1.5 %)	N.A.
	Initial 3 months NOAC	-	5 (0.5 %)	N.A.

Table 15. Cancer's effect on the choice of anticoagulant of VTE-patients

Duration of treatment (months)	LMWH (n=289)	NOAC (n=299)	Warfarin (n=479)	Fondaparinux (n=5)	Combination of anticoagulants (n=22)
<3	46 (15.9 %)	10 (3.3 %)	1 (0.2 %)	-	-
3	30 (10.4 %)	98 (32.8 %)	76 (15.9 %)	1 (20.0 %)	-
3-6	5 (1.7 %)	11 (3.7 %)	10 (2.1 %)	-	-
6	71 (24.6 %)	142 (47.5 %)	200 (41.8 %)	-	1 (4.5 %)
6-12	1 (0.3 %)	-	4 (0.8 %)	-	1 (4.5 %)
12	4 (1.4 %)	7 (2.3 %)	11 (2.3 %)	-	1 (4.5 %)
permanently	49 (17.0 %)	26 (8.7 %)	131 (27.3 %)	3 (60.0 %)	18 (81.8 %)
indefinitely	83 (28.7 %)	5 (1.7 %)	46 (9.6 %)	1 (20.0 %)	1 (4.5 %)

Table 16. Durations of VTE-treatment according to anticoagulant

Anticoagulant	Enoxaparin	Tinzaparin	Dalteparin	Warfarin
Bleeding cases (n=11)	3	3	1	4

Table 17. Amount of severe anticoagulation-related bleeding complications

There were eleven cases of severe bleeding complications in this study (table 17). However, none of them were fatal. All in all the bleeding rate of this study's patients was 0.7 %.

The patients with histories of malignancies had different cancer types in the following proportions:

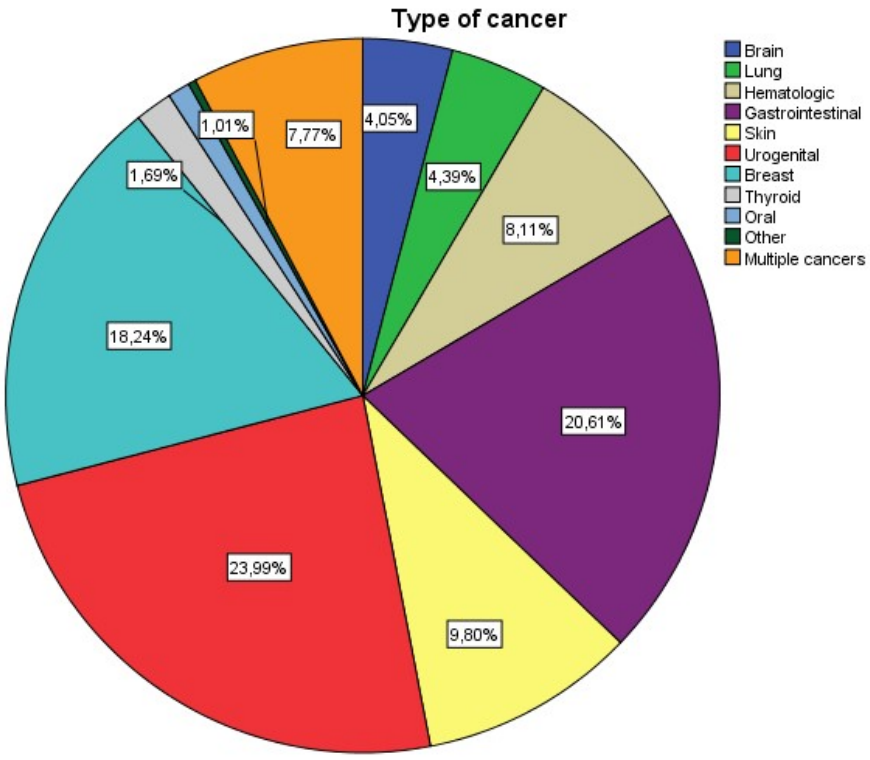

Figure 2. Types of cancers in patients with a history of malignancies

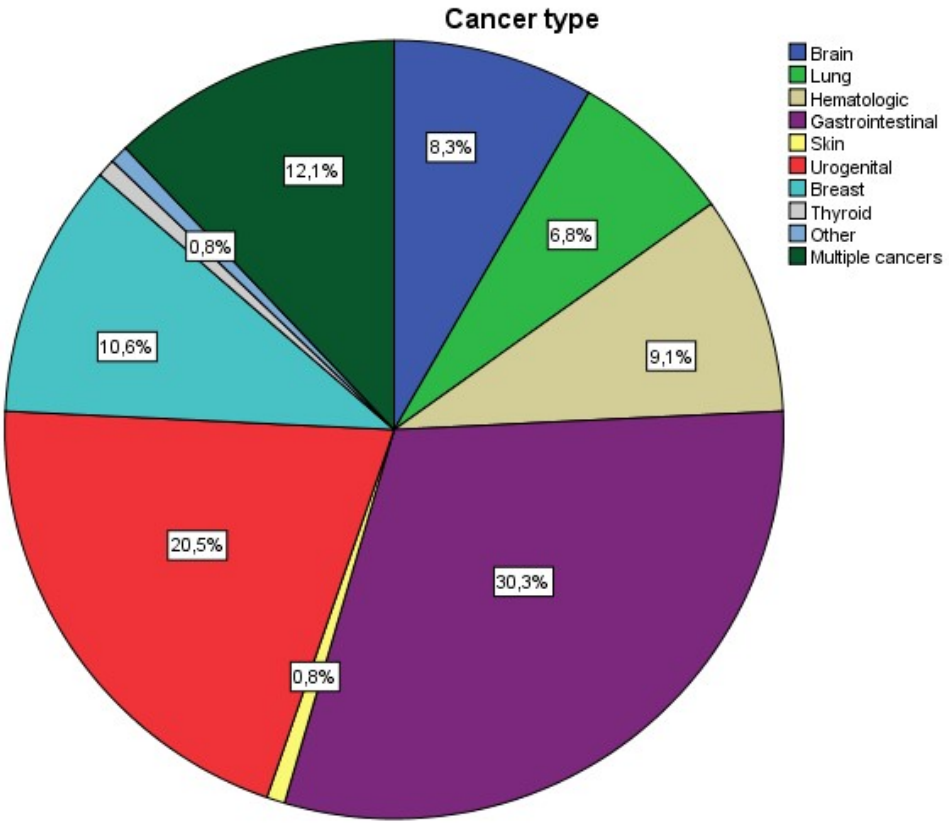

Figure 4. Types of cancers in patients with active malignancies

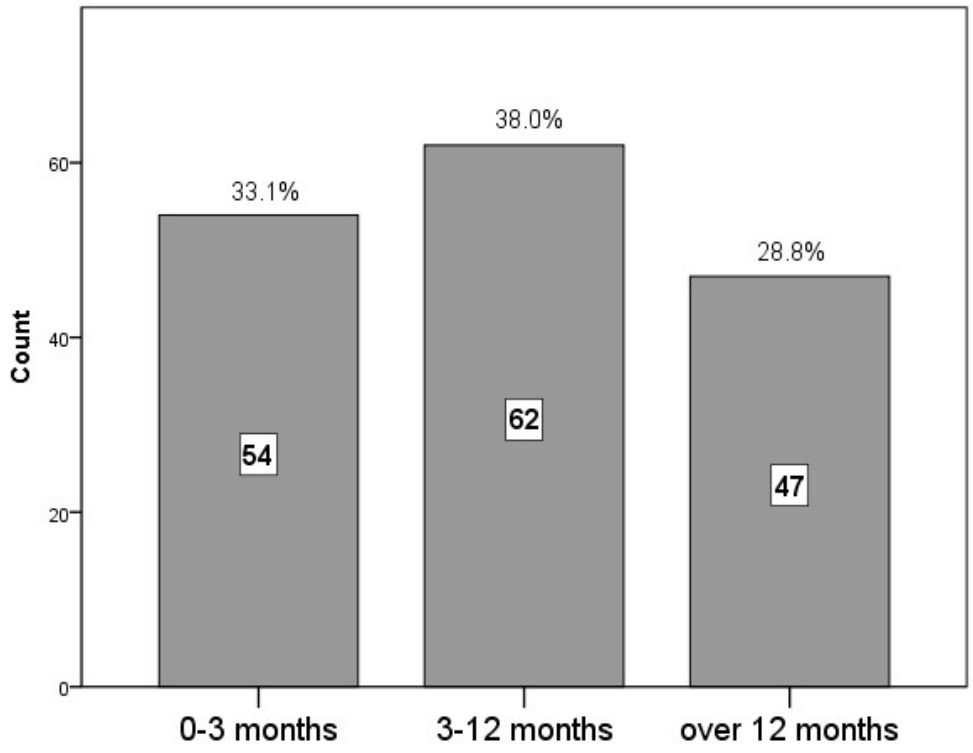

Figure 3. Duration from cancer diagnosis to VTE/STP diagnosis

The data included 204 PE patients. Out of them 76 (37.3%) scored a 0 in the sPESI, 106 (52.0%) got 1 or more points, and from 22 (10.8%) all the necessary information required for the sPESI couldn't be found. In other words, out of those from who all the information could be collected 41.8% could have been considered for early discharge.

Out of the 76 low-risk PE patients 6 were discharged immediately and 5 were transferred into another location, from where no further information could be found. Therefore, they are not included in the following statistics. 65 patients with clear treatment periods were left. Out of them, 24 (36.9%) had a short hospitalization duration lasting for only 1-2 days. The range varied from 1 to 31 days, with a mean of 4.2 days.

	Active cancer (n=163)	No active cancer (n= 1504)	P-value
6-month mortality	64 (39.3 %)	60 (4.0 %)	< 0.001

Table 18. Six-month mortality-rates after VTE diagnosis

The 6-month mortality rate after VTE/STP diagnosis was 7.4 %. Out of the 124 patients who died during this time period, 64 (51.6 %) had active cancer. It appears, that four of these patients' causes of deaths were related to thrombotic events – none of them had active cancer.

5. Discussion and conclusions

There were all in all 132 patients with active cancer in this study. The results show that recommendations regarding the usage of LMWH as primary anticoagulants have been adequately taken into consideration. It seems like patients with malignancies are more likely to suffer from VTEs in locations with worse outcomes (pulmonary embolism, above inguinal ligament) and less likely to suffer from the more minor clots (distal lower extremity, thrombophlebitis).

The cancer types matched rather well with the previously reported data (12,13,17), as cancer patients had high frequencies of gastrointestinal, hematological and lung cancers. One difference appears to be the high portion (18.1%) of patients with breast cancer in our study. In this study the portion of cancer patients with a metastasized cancer was notably high. Previous studies (14) suggest that approximately half of the cancer patients with thrombotic events would have metastases – harmonizing well with this study's 55.2%.

There were 19.3% more females than males suffering from a VTE/STP. The difference is mostly do to to STPs. Women had STPs 72.3% more frequently than men, whereas VTEs occurred only 3.3% more in females than in males.

Thrombotic events in the upper extremity occurred amongst 32 (1.9%) of the patients – a result which is slightly less than the 4% presented in previous studies (8).

The results regarding VTE location in cancer patients are somewhat controversial with the literature (14). Even though both studies recognized a correlation between cancer and VTE in an abnormal location (intra-abdominal/other), the current study additionally showed a significant correlation between cancer and pulmonary embolism, yet no significant correlation between cancer and DVT of the upper extremity.

A significant amount of thrombotic events occurred within one year of the cancer diagnosis being in line with earlier studies (12). This could be partially due to the fact that cancer patients have such high mortality rates – without the early deaths more VTEs and STPs would most presumably occur also after longer time periods. (12).

Previous studies (2) suggest that major bleeding could be fatal in up to 25% of cases (appendix 4). Nonetheless, in this study no case of severe bleeding lead to death.

The choices in treatment seem adequate, and follow the present guidelines (3). Most cancer patients have received LMWH for appropriate time periods.

However, one unexpected uncertainty that came up in this study was the ICMV – related treatment. When it comes to the cancer patients, 40.0% percent of them were treated by anticoagulants other than LMWHs. Also the durations of the treatments vary so notably, that the reason for this is more likely to be inconsistency in treatment protocols than sporadic differences between individual patients. There was notable variance in regarding the calf muscle vasculature as either deep or superficial, thereby leading to significant diversity in the durations of treatments. Many radiology statements referred to the ultrasound findings saying there was no coagulation in the deep veins of the low extremity, but some could be found in the veins of the isolated calf muscles. This naturally leads to confusion in whether or not the ICMV thrombi should be treated in the same manner as other DVTs. As a result, treatment periods of ICMVs ranged from just few weeks up to 6 months (with both cancer and non-cancer patients), with no clear majority focusing around any decided duration. In addition, 7 patients were treated using only topical treatment.

Another aspect that came up in this study, was the confusion related to the anatomy of the superficial femoral vein. Unlike the name may suggest, it belongs to the deep venous system of the proximal lower extremity. However, one study (27) suggests that 75% of clinicians don't recognize its correct anatomical location or, thereby, realize its need for anticoagulation. Treating it as a superficial vein may result in potentially unsafe consequences.

The portion of the non-cancer PE patients scoring 0 from the sPESI fit well in with the results of previous studies. As over a third of them were discharged within two days of PE diagnosis, it may be concluded that the sPESI results (or otherwise appropriate clinical judgment) have been taken into consideration in these cases.

The six-month mortality-rate of patients without cancer was only 4.0 %. As also patients with only STPs were included, it appears rational that the rate is not bigger.

However, the mortality-rate of cancer-patients during the same time period is ten-fold higher. Previous studies (3) suggest that cancer-patients have a one-year mortality-rate of 60% after VTEs. Even though the results of this study cannot be directly compared to those, it appears, roughly speaking, that results related to cancer patients' mortality-rates correspond with previous studies.

5.1. Conclusions

Overall, the designated treatments have been adequate, and cases of severe bleeding have been rare. In this study, it appears that cancer patients are more likely to suffer from thromboembolisms in more severe locations than non-cancer patients.

Warfarin and LMWHs caused all of this study's anticoagulation-related severe bleeding complications. However, these were by far the most used anticoagulants, making the results reasonable.

What became evident is that further research regarding the optimal treatment of ICMV thrombi and cancer patients' STP is required for the sake of creating a unified treatment protocol. Also, physicians ought to be made aware of the anatomical location of the superficial femoral vein to in order to avoid potentially harmful treatment-related consequences.

There is still room for improvement in using the sPESI routinely. Embracing it as a standard tool could help save time and money, and most importantly improve the patients' qualities of life.

List of abbreviations

VTE – venous thromboembolism

DVT – deep venous thrombosis

PE – pulmonary embolism

IDDVT – isolated distal deep vein thrombosis

ICMV – isolated calf muscle vein

STP – superficial thrombophlebitis

sPESI – simplified pulmonary embolism severity index

VKA – vitamin K antagonist

LMWH – low molecular weight heparin

NOAC – novel oral anticoagulant

INR – international normalized ratio

NSAID – nonsteroidal anti-inflammatory drug

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Appendices

CLINICAL CHARACTERISTIC	POINTS*
Age over 80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Heart rate ≥ 110/min	1
Systolic blood pressure < 100 mmHh	1
Oxygen saturation < 90%	1

Appendix 1. Evaluating the 30-day mortality rate using sPESI (3)

*Those with a score of 1 or more have a 30-day mortality rate of up to 11% (6)

CLINICAL CHARACTERISTIC	SCORE*
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of lower extremity	1
Recently bedridden for more than three days or major surgery within four weeks	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	-2

Appendix 2. Wells model for predicting the clinical pretest probability of deep vein thrombosis (28)

If both legs are symptomatic, the more symptomatic leg is used

**0 or less = Low risk*
**1 or 2 = Moderate risk*
**3 or more = High risk*

CLINICAL CHARACTERISTIC	SCORE*
Clinical signs and symptoms of DVT (minimum of leg sweeling and pain with palpation of deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100	1,5
Immobilization or surgery in previous four weeks	1,5
Previous DVT/PE	1,5
Hemoptysis	1
Malignancy (on treatment, treated in last six months or palliative)	1

Appendix 3. Wells model for predicting the clinical pretest probability of pulmonary embolism (29)

**< 2 = Low risk*
**2-6 = Moderate risk*
**> 6 = High risk*

	Fatal bleeding n = 135	Non-fatal major bleeding n = 411	Total major bleeding n = 546
Gastrointestinal, n (%)	54 (40)	140 (34)	194 (36)
VTE to major bleeding (days)*	10, 6-25	12, 5-33	12, 5-29
Major bleeding to death (days)*	1.5, 0-4		
Intracranial, n (%)	34 (25)	37 (9.0)	71 (13)
VTE to major bleeding (days)*	20, 10-51	32, 7-68	23, 9-54
Major bleeding to death (days)*	1, 0-2		
Genitourinary, n (%)	7 (5.1)	51 (12)	58 (11)
VTE to major bleeding (days)*	11, 9-13	20, 4-48	13, 4-44
Major bleeding to death (days)*	7, 3-13		
Hematoma, n (%)	22 (16)	133 (32)	155 (28)
VTE to major bleeding (days)*	9, 7-19	10, 4-18	10, 5-18
Major bleeding to death (days)*	2.5, 1-9		
Other, n (%)	18 (13)	50 (12)	68 (12)
VTE to major bleeding (days)*	22, 5-43	12, 4-32	12, 3-31
Major bleeding to death (days)*	1, 0-4		

Appendix 4. Sites and timing of major and fatal bleeding in a study based on findings from the RIETE registry (30)

VTE, venous thromboembolism. Some patients died after repeated episodes of major bleeding.

*Median, interquartile range.