12.

A worldwide survey to assess the current approach to the treatment of patients with cancer and venous thromboembolism

Ankie Kleinjan
Anita Aggarwal
Annemarie van de Geer
Charles Faselis
Harry R. Büller
Marcello Di Nisio
Frederick R. Rickles
Pieter W. Kamphuisen

Accepted for publication in Thrombosis and Haemostasis
ABSTRACT

Introduction

Low-molecular-weight heparin (LWMH) is recommended as the preferred anticoagulant treatment over vitamin K antagonists (VKA) for venous thromboembolism (VTE) in patients with cancer. However, there is uncertainty about the duration and dose of LMWH treatment. Therefore, we designed this multinational survey to assess the current approach to the treatment of patients with cancer and VTE.

Methods

An electronic survey tool was used to disseminate a survey containing 49 questions on different aspects of the treatment of patients with cancer and VTE, among both thrombosis and non-thrombosis specialists.

Results

A total of 229 invitations were sent, and 141 completed the survey (60% of the total). Fifty-eight percent of the respondents were from Europe, 35% from the US and the remaining 7% from other countries. Respondent’s specialties included haematology (23%), oncology (18%), pulmonology (15%) and general internal medicine (15%). LMWH was indicated as the first choice for the long-term treatment by 82% of the respondents, of whom 60% used full therapeutic doses and 40% chose a dose reduction. When continuing anticoagulants after the long-term treatment period, 44% of respondents preferred LMWH, 10% VKA, while the remaining 45% chose per individual patient for either LMWH or VKA.

Conclusions

We observed a relatively high observance rate of the guidelines with respect to the use of LMWH for the long-term treatment of VTE in cancer. In contrast, the dose of LMWH and the type of anticoagulant chosen after the initial 3 to 12 months varied substantially, probably reflecting the limited available evidence.
INTRODUCTION

Venous thromboembolism (VTE) complicates the clinical course of 10-20% of cancer patients (1-3). Risk factors for VTE are the cancer itself, patient-related factors such as immobility and increasing age, and factors related to the treatment for cancer such as chemotherapy, radiotherapy and surgery (4-6). Most frequently VTE presents as deep venous thrombosis (DVT) of the legs and/or pulmonary embolism (PE), whereas upper extremity DVT is increasingly encountered as catheter related (7).

VTE constitutes a serious threat for patients with cancer, increasing the risk of death by two to three fold (8) and carries a significant morbidity risk due to a higher rate of recurrent VTE and bleeding complications when compared to patients without cancer (9). Thus, the development of VTE in patients with cancer often poses a therapeutic dilemma, particularly in those patients with end-stage disease in whom anticoagulant treatment may impact significantly on quality of life.

In the CLOT study, the largest randomised trial in cancer patients with acute VTE, low molecular weight heparin (LMWH) decreased the risk of recurrent VTE by almost 50% relative to the standard treatment with vitamin K antagonists (VKA) (10). A few smaller studies and meta-analyses have subsequently confirmed these findings (11-14). Bleeding rates appear to be similar for LMWH and VKA, however, studies have been largely under powered to detect differences in (major) bleeding (10;15). Based on the available evidence, international guidelines recommend or suggest LMWH treatment for at least 3 to 6 months in cancer patients with VTE (16;17).

Several questions remain unanswered regarding the treatment of VTE in patients with cancer. First, it is unknown to what extent different specialists adhere to the guidelines with respect to using LMWH as the sole agent for both the initial and long-term phases of treatment. In fact, experts in the field, suggest that VKA could be used in selected cases (18). A recent study on a single cohort of cancer patients with pulmonary embolism showed that in practice adherence to the guidelines might be far from complete, as only 51% of the patients are receiving LMWH (19). Furthermore, the American College of Chest Physicians (ACCP) has recently down-scaled the strength of their recommendation on the long-term treatment of patients with LMWH which may cause confusion among the different specialists involved in the care of these patients, and, as a consequence, a decrease in the use of LMWH (17).

Second and importantly, guidelines do not provide clear indications about the dose of LMWH to use in the acute as well as the long-term phase. Therefore, it is currently unclear whether physicians should switch from full therapeutic to lower doses after a certain period of time. The rationale behind lowering the dose of LMWH is that the risk of recurrent VTE decreases with time from the initial event, while the risk for bleeding stays the same or might even increase (9). The CLOT study investigators reduced the dose of LMWH after 1 month to 75% of the therapeutic dose (10). However, not all physicians may be aware of or agree with this approach, as normally, the anticoagulant dose is not changed during treatment.
Another major issue is the duration of anticoagulant treatment. The CLOT study evaluated a 6 month course with LMWH. However, no study has assessed longer durations of LMWH nor compared 6 months with shorter treatment periods. As a consequence, physicians can only rely on expert-based recommendations which suggest to continue anticoagulants after 6 months in case of active tumour load or ongoing chemotherapy. Whether treatment should be continued with LMWH or switched to VKA as an alternative has not been investigated. Lastly, it is not clear how recurrent VTE, upper extremity DVT and unsuspected VTE diagnosed on staging imaging should be approached.

To summarize, the lack of solid evidence and clear recommendations leave physicians with substantial uncertainty concerning the treatment of cancer patients with VTE. Therefore, this multinational survey was designed to assess the current approach to the treatment of patients with cancer and VTE around the world.

| MATERIALS AND METHODS |

An electronic survey tool (surveymonkey.com) was used to build a questionnaire containing 49 questions on different aspects of the treatment of VTE in patients with cancer. The survey was tested before the distribution by approx. 10 different physicians in Europe and the US, in order to prevent ambiguous questions. Physicians were asked to answer the questions visualising how they had treated the last 3 cancer patients with VTE. The questionnaire contained mainly multiple-choice questions, and the survey and the definitions used in the survey are available as an online supplement. Importantly, the initial treatment involves the first 5-10 days of anticoagulant treatment; whereas long-term treatment period was defined as the time frame between the initial treatment and the first evaluation moment 3-12 months after VTE.

Both in-hospital physicians specialised on thrombosis as well as physicians with other specialisations (if they treated patients with cancer associated VTE) were invited to participate in this survey. Thrombosis experts were defined as being either members of the International Society on Thrombosis and Haemostasis (ISTH) or as having one or more publications on thrombosis within the last decade. Thrombosis experts were recruited principally from the network of two multicenter thrombosis trials (the Longheva study, clinical trials.gov number NCT01164046 and the Armour study, number NCT01324037). These experts were asked to propose two or more colleagues from the same hospital, preferably non-thrombosis experts working in another discipline, to join the survey. In the United States, the survey was spread among different specialists from the Veterans Affairs Hospital DC Medical Center (VADCMC) and The George Washington University, both in Washington, DC. Physicians were always given the choice to opt out, in which case they did not receive any further emails. All other physicians were sent two reminders in case they did not respond to the first invitation. In the United States, the Institutional Review Board and the Research and Development Committee of the VADCMC approved the protocol, whereas in Europe, ethical approval was not required.
Statistical methods
All results were directly exported from surveymonkey to PASW statistics version 18 (Inc., 2009, Chicago, IL) for analysis. Distributions were expressed as percentages and the corresponding confidence intervals were calculated with the programme Confidence Interval Analysis version 1 (20). Differences between groups were analysed with the Student’s t-test or with the Mann-Whitney U-test, whichever was appropriate for the specific continuous variable, whereas differences in categorical variables were tested using the 2-sided Fisher’s exact test. Factors associated with the choice of LWMH for the treatment of VTE in cancer patients in the first 6 months, were assessed in a multivariate logistic model.

RESULTS
A total of 229 invitations for the survey were sent between December 2010 and March 2012. One hundred forty one (141) surveys (60%) were completed and available for the analysis. Fifty-eight percent of the respondents were from Europe, 35% from the US and the remaining 7% from other countries around the world. Of the 88 non-respondents, 53% were from Europe, 43% from the US, and 3.4% from other continents, which was not significantly different from the responders (p=0.32; Figure 1). Respondent’s specialties (self-identified) included haematology (23%), oncology (18%), pulmonology (15%) and general internal medicine (15%). Nearly half of the respondents (46%) were considered thrombosis experts, compared to 26% of the non-respondents (p=0.003).

Initial and long-term treatment (Figure 2)
LMWH was indicated as the anticoagulant of first choice for the long-term treatment of VTE in cancer patients by 82% (95% CI 76 – 89%) of the respondents. The remaining 18% switched from initial treatment with LMWH to long-term VKA. A minority (0.7%) chose for initial treatment with unfractionated heparin, followed by long-term use of VKA.

In univariate analyses, the long-term use of LMWH was significantly higher among European respondents (90%) compared to respondents from the United States (69%), an odds ratio (OR) of 4.1 (95% CI 1.6-11; p=0.004). Moreover, 95% of the experts in thrombosis prescribed LMWH, an unadjusted OR of 5.8 (1.8-18; p=0.001), when compared to non-experts. Similarly, physicians treating more than 10 patients with cancer and VTE per year were more likely to prescribe long-term LMWH (86%), an unadjusted OR of 3.1 (1.2-8.0; p=0.022) compared to physicians who treat less than 10 patients per year. These variables, however, did not remain as independent predictors for LMWH prescription in a multivariate logistic model; for Europe vs. US, experts vs. non-experts and more vs. less than 10 patients per year, respectively, adjusted ORs (95% CI) decreased to 2.5 (0.9-7.2), 3.7 (0.9-15) and 2.4 (0.84-7.1).

Of all specialists for whom LMWH was the first or second choice anticoagulant for long-term treatment, 60% used full therapeutic doses throughout the treatment period.
Figure 1. Characteristics of respondents and non-respondents. The self-reported country of origin (A) and specialties (B) of respondents (grey bars) and non-respondents (black bars).
The other 40% chose a dose reduction after a variable amount of time following the initial treatment, in most cases (93%) the dose was reduced to 75% of therapeutic doses (as utilized in the CLOT study (10)), while in the remaining cases (7%) the dose was lowered to half of the therapeutic dose after 1 month. Dose reduction of LMWH was more frequently adopted by thrombosis specialists (59%) than non-thrombosis specialists (24%; p<0.001).

After 3-12 months, 32% of the respondents indicated they would continue anticoagulant treatment in every patient, 49% would do it in most cases, 17% in some, and 2% would never continue anticoagulation beyond 1 year. Reasons to continue included metastatic disease (86%), local unresectable disease (59%) and use of chemotherapy (52%). When continuing anticoagulants after the long-term treatment period, 44% of respondents preferred LMWH, 10% VKA, while the remaining 45% chose per individual patient for either LMWH or VKA.

Recurrent VTE during treatment
In patients developing recurrent VTE during treatment with LMWH, 42% of the respondents continued LMWH with a higher dose, 8.2% gave combination therapy with LMWH and
VKA, and 4.3% switched from LMWH to VKA. Lastly, 30% inserted a vena cava filter, most often (90%) together with anticoagulants, whereas the remaining 15% consulted a vascular / haematology specialist or did not know what to do.

In patients with recurrent VTE during VKA treatment, the large majority of the respondents (84%) switched to LMWH, while another 8.6% chose a vena cava filter and 3.6% for dual therapy with LMWH and VKA, whereas 4.2% continued VKA with a higher INR target range or had another approach.

Side-effects and monitoring of VKA and LMWH

In general, long-term use of VKA in cancer patients was often regarded as problematic, when compared to LMWH (respectively 48% and 14%, absolute difference 34%; 95% CI 24-44%). With VKA use, most important problems reported were monitoring (89%), poor compliance (30%), side-effects (30%), costs/reimbursement (2.1%), and other (11%; drug interactions most often mentioned). Most frequently reported problems with LMWH use were: difficulty in administration (55%), poor compliance (26%), costs/reimbursement (38%) and side-effects (26%). Of the respondents who answered ‘side-effects’ to these two questions, bleeding was indicated by 7 of the 37 respondents (19%) as an important side-effect of LMWH and in 33 of the 42 respondents (79%) as an important side-effect of VKA. Respondents from the USA more often reported problems with reimbursement (63% of all US respondents), as did respondents from other continents (50%), when compared to European respondents (21%). With regard to patients with frequent hematomas on LMWH use, the approaches chosen were changing to VKA (29%), switching to another brand of LMWH (22%), lowering the dose (21%), changing injection technique (24%), nothing/reassurance (3.6%) and in one case switching to fondaparinux.

Of all specialists using long-term treatment VKA routinely or as second choice, 89% used a target INR of 2.0 to 3.0, while the remaining 11% indicated a target of 2.5 to 3.5. The majority of all patients on VKA (63%) were monitored via a specific anticoagulation clinic.

### Table 1. Characteristics of the respondents

<table>
<thead>
<tr>
<th>Cancer patients with VTE per year (estimated)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 10</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>10-50</td>
<td>92 (65%)</td>
</tr>
<tr>
<td>50-100</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>More than 100</td>
<td>7 (5.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expertise on VTE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Membership of ISTH</td>
<td>22 (16%)</td>
</tr>
<tr>
<td>At least one publication on thrombosis in last decade</td>
<td>63 (45%)</td>
</tr>
<tr>
<td>Expert on VTE by study definition*</td>
<td>65 (46%)</td>
</tr>
</tbody>
</table>

ISTH: International Society for Thrombosis and Haemostasis; *Expert on VTE was defined as either being a member of the ISTH or having at least one publication on thrombosis in the last decade.
Management of cancer-related venous thrombosis

20% via a primary care or general practitioner and 9.9% via the hospital with 7.0% via other ways or by self-measurement.

In patients on long-term LMWH use, physicians routinely monitored renal function (87%), platelet count (75%), anti-Xa levels (32%) and bone density (9.2%). In patients with cancer and moderately impaired renal function (estimated glomerular filtration rate (eGFR) of 30-60 ml/min), 46% of the physicians did not make any dose adjustments, 53% decreased the dose and 1.4% stopped LMWH. In patients with severe renal disease (eGFR below 30 ml/min), 48% would decrease the dose and 48% would stop LMWH, while 4.3% would continue LMWH without changing the dose. In these hypothetical cases, respectively 48% (eGFR 30-60) and 65% (eGFR < 30) of the respondents, who continued LMWH (full or reduced dose), measured anti-Xa levels.

In case of thrombocytopenia, physicians stopped anticoagulants when the platelet count dropped below the following margins: below $8 \times 10^9$/L (8.6%), $5 \times 10^9$/L (50%), $2 \times 10^9$/L (25%), $10^9$/L (6.5%), or other (8.6%). In this latter group, reasons indicated to decide on whether to stop anticoagulants, included: the time elapsed since the thrombotic event, cause of the thrombocytopenia, the estimated bleeding risk and another margin, namely a platelet count below $30 \times 10^9$. A small group of respondents (2.8%) indicated they would not stop anticoagulant treatment at any value of the platelet count.

Upper extremity DVT and unsuspected pulmonary embolism

In case of catheter-related upper extremity DVT in cancer patients, 12.5% chose for thrombolysis as the primary treatment approach, while 68.4% chose LMWH, and 19.1% VKA. Half of the respondents removed the catheter. The duration of the treatment was variable ranging from 3 months (49%) to 6 months (25%) to 12 months (0.7%). Twenty-six percent reported that the decision depended on various factors including whether the cancer was still active and whether the catheter remained in situ.

Patients with unsuspected pulmonary embolism diagnosed on a staging CT-scan were treated by respondents with LMWH (77%), VKA (20%) or no anticoagulant treatment (2.2%), for a duration of 3 months (7.4%), 6 months (33%), 12 months (13%), or, as with symptomatic PE, indefinitely in patients with active malignancy (46%). Respondents specified that there is ‘a lack of specific data’ and therefore ‘the attitude to unsuspected PE is the same as to symptomatic PE’, as they assumed that ‘this is the same process as symptomatic VTE’.

| DISCUSSION |

In this worldwide survey, we observed a relatively high observance of the guidelines, with respect to the type of anticoagulant used for the long-term treatment of VTE in cancer patients, as 82% used LMWH. In contrast, the dose and duration of LMWH treatment as well as the type of anticoagulant chosen after the initial 3 to 12 months varied substantially,
which may reflect the limited available clinical evidence. Several aspects and findings of the present study require comment.

When compared to the results of the large Frontline survey, conducted in 2001, the reported use of LMWH has dramatically improved from 11% in North-America and 22% in Western Europe to respectively 69% and 90% in the present study (21). Interestingly, both in 2001 as well as in the current dataset, a lower percentage of the physicians in the US chose LMWH for use in patients with cancer compared to their European colleagues, possibly because of problems with the reimbursement of LMWH for the long-term use, an issue reported by over 60% of the US respondents. Not surprisingly, experts in the field of thrombosis were more aware of the superior efficacy of LMWH and therefore had the highest rates of LMWH use for long-term treatment. The lower proportion of non-experts using LMWH, while they frequently treat these patients, stresses the potential importance of the centralisation of VTE treatment within the hospital or, alternatively, hospital-wide recommendations on this topic which are available and known to all specialists who treat these patients.

Potential limitations of our study include the sample size, which was modest when compared to the large Frontline study, but was somewhat larger than a survey on thromboprophylaxis among oncologists in the United Kingdom (21;22). Strengths of our present study, however, are that we chose for individual invitations rather than providing the survey at a central easy accessible side. We wanted to be able to monitor the response rate, as this type of study is susceptible to inclusion bias (23). Furthermore, we took care to assess practices from all parts of the world, and from different specialists, experts on thrombosis as well as non-experts. We approached non-experts via thrombosis-experts in the same hospital to reach an optimal response rate among non-experts; however, this might also have lead to selection bias. Our current response rate of 60% is comparable to the survey on prophylaxis use among UK oncologists, whereas the method of the Frontline survey did not allow for the calculation of response rate (21;22). Although no scientifically proven acceptable margin of response rate is available in the survey literature, 60% is usually considered reasonable (23). Lastly, inherent to assessing treatment approaches in a survey is that answers might not always resemble actual clinical practise.

The heterogeneous responses on the optimal dose of LMWH to be used for long-term treatment reflect the paucity of the evidence. Given the serious consequences of under-treatment (recurrent VTE) and over-treatment (bleeding) (8;9;15;24), new data is urgently needed to inform the discussion of this subject. A related topic is the monitoring in patients on long-term LMWH, especially, anti-Xa measurements in patients with severely reduced kidney function, and monitoring of platelet levels. The results of our survey suggest that, in these vulnerable patients, monitoring of platelet counts, anti-Xa levels or kidney function is far from standard practice.

Of interest, almost half of the respondents chose to continue LMWH treatment after the initial 3-12 months (most often for life-long), whereas the remaining physicians considered VKA and LMWH equal and chose one of the alternatives on an individual patient basis. In
fact, no studies have assessed the efficacy and safety of LMWH versus VKA beyond 6 months and ongoing studies will hopefully provide an answer to this important question (25).

While most participants agreed on switching to LMWH in patients who experienced recurrent VTE while on VKA treatment, the approach to recurrent VTE in patients on LMWH treatment varied significantly. A substantial percentage (33%) of physicians chose placement of a vena cava filter in this group of patients, despite the lack of evidence for such an approach in patients with cancer and recurrent VTE. A randomised comparison in this field may be very difficult since these patients are rare, however, valuable information is expected from an ongoing registry (26).

Only 1 respondent reported on using fondaparinux, i.e. one of the newer anticoagulants, as an alternative to LMWH for initial and long-term treatment of VTE in patients with cancer. After publication of the CLOT study, the proportion of cancer patients in studies of new anticoagulants has decreased steadily, making it more difficult to ask physicians to consider these agents in the absence of an adequate subset of cancer patients in the studies. For example, in the most recent studies (e.g. Hokusai, using edoxaban) active malignancy is even among the exclusion criteria (10;27-29). Thus, the efficacy and safety of these agents in cancer patients, who often present with relevant co-morbidities and multiple concurrent treatments, is presently unknown.

Our study illustrates that most physicians feel comfortable in stopping anticoagulant treatment in patients with cancer and (catheter-related) upper extremity DVT after 3-6 months, also when the catheter is not removed. Whether or not this confidence is justified, is a question to which presently no definitive answer is possible, as only small studies are available (30-32).

Asymptomatic PE is often treated as if symptomatic, while the increasingly sensitive CT-scans currently available, detect also very small thrombi of which the clinical significance and natural history are unknown (19;33;34). Randomized trials are needed to determine if anticoagulant treatment of patients with unsuspected and truly asymptomatic PE – especially in those patients with subsegmental PE - is superior to watchful waiting.

In conclusion, the first decade of this century has been important for establishing and implementing the use of LMWH in the long-term treatment of patients with cancer and VTE. However, the results of this survey underscore the many challenges that still remain and calls attention to the need for additional studies on these various topics, to guide physicians where, at present, they are often adopting a highly heterogeneous empirical approach.

**REFERENCE LIST**


SUPPLEMENTARY INFORMATION: SURVEY TEXT

Used definitions & abbreviations

1. Initial treatment = first 5-10 days
2. Long-term treatment = first 3-12 months after VTE, the period during which all patients are treated (i.e. the time frame between initial treatment and first evaluation moment)
3. Recent VTE = within 1-2 months of the initial thrombotic event
4. Non-recent VTE = within 2-6 months of the initial thrombotic event

VTE = Venous Thrombo-Embolism
VKA = Vitamin K antagonists (e.g. warfarin or marcoumar)
LMWH = low molecular weight heparin
UFH = unfractionated heparin
GFR = glomerular filtration ratio
IVC = Inferior Vena Cava filter

General information

1. Country
   City/town: ..............................................................
   State/province: ......................................................
   Country: ..............................................................

2. Specialty:
   Oncologist    ☐
   Hematologist  ☐
   Vascular specialist ☐
   Pulmonologist ☐
   If other, please specify: .................................

3. How many cancer patients with thrombosis do you see annually (estimation)
   <10 ☐
   10-50 ☐
   50-100 ☐
   >100 ☐

When answering these questions, please keep in mind how you treated your last 3 cancer patients with thrombosis.
Management of cancer-related venous thrombosis

Long-term treatment period (including initial treatment (1))

4. How do you treat patients with active malignancy and a first episode of acute DVT or PE preferably?
   - Entire long-term treatment period (including initial treatment) with LMWH
   - Initial treatment with LMWH, followed by VKA
   - Initial treatment with UFH, followed by VKA
   - Thrombolysis

5. What is your second choice for the treatment of cancer patients with DVT or PE?
   - Entire long-term treatment period (including initial treatment) with LMWH
   - Initial treatment with LMWH, followed by VKA
   - Initial treatment with UFH, followed by VKA
   - Thrombolysis

6. In case of LMWH treatment, what is the usual dosage?
   - Full therapeutic
   - CLOT regimen (reduction of dose to 75% after 1 month)
   - Other
   - If other, please specify: .................................................

7. In case of VKA treatment, what is the target INR?
   - 2-3
   - 5-3.5
   - Other
   - If other, please specify: .................................................

8. What is the minimum duration of the anticoagulant treatment in cancer patients? (time until re-evaluation; decide to stop or continue)
   - 3 months
   - 6 months
   - 12 months
   - Other
   - If other, please specify: .................................................

Continuation of treatment after long-term treatment period (2)

9. Do you continue anticoagulant treatment in case of active malignancy or chemotherapy, after the long-term treatment period has been completed?
   - Always continue
   - Mostly continue
   - Sometimes continue
   - Never continue ➔ question 12
10. What are reasons to continue anticoagulant treatment after the long-term treatment period has been completed in patients with cancer? (multiple options possible)
   - Metastatic disease
   - Local unresectable disease
   - Use of all chemotherapy
   - Use of chemotherapy in association with anti-angiogenesis Rx
   - Use of hormonal therapy
   - Patient's preference
   - Low bleeding risk
   - Other
   If other, please specify: ................................................

11. Which medication do you prescribe if the anticoagulant therapy is continued after the long-term treatment period has been completed?
   - LMWH
   - VKA
   - Sometimes VKA, sometimes LMWH
   Please specify dose and/or target INR: ................................................

Recurrent VTE

12. For patients with a recurrent VTE during VKA treatment, what is your policy?
   - Continue VKA
   - Continue VKA, with higher INR target
   - Switch to LMWH, therapeutic dose
   - IVC* filter, go to 13
   - Double treatment with LWMH and VKA, go to 14
   - Other
   If other, please specify: ................................................

13. In case of IVC filter, do you give anticoagulant treatment?
   - Yes
   - No

14. In case of double treatment with LMWH and VKA, please specify duration:

15. For patients with a recurrent VTE during LMWH treatment, what is your policy?
   - Continue same dose LMWH
   - Continue LMWH, with a higher dose > go to 16
   - Switch to VKA
   - Double treatment with LMWH and VKA > go to 17
   - IVC filter > go to 18
   - Other
Management of cancer-related venous thrombosis

If other, please specify: .........................................................

16. If you continue LMWH with a higher dose, please specify exact dose:
 .................................................................

17. In case of double treatment with LMWH and VKA, please specify duration:
 .................................................................

18. In case of IVC filter, do you give anticoagulant treatment?
 Yes ☐
 No ☐

Problems for patients

19. LMWH:
   Problematic ☐
   Acceptable ☐
   Easy to use ☐

20. Most important problem(s):
   Problems with the administration ☐
   Problems with the monitoring ☐
   Compliance ☐
   Costs/Reimbursement ☐
   Side-effects >21 ☐
   Other, please specify: ......................................................... ☐

21. In case of side-effects, please specify:
 .................................................................

22. VKA:
   Problematic ☐
   Acceptable ☐
   Easy to use ☐

23. Most important problem(s):
   Problems with the administration ☐
   Problems with the monitoring ☐
   Compliance ☐
   Costs/Reimbursement ☐
   Side-effects >21 ☐
   Other, please specify: ......................................................... ☐

24. In case of side-effects, please specify:
 .................................................................
Chapter 12

Side effects and monitoring

25. What is your action in patients with frequent hematomas or induration of the skin because of LMWH treatment?
   - Switch to another brand of LMWH
   - Lower the dose of LMWH
   - Change to VKA
   - Other, please specify

26. How do you monitor vitamin K antagonist treatment (INR)?
   - Hospital
   - General practitioner
   - Specific anticoagulant clinic
   - Self measurement by the patient
   - Other, please specify

27. What is your action in patients with frequent INR values out of the therapeutic range?
   - Switch to other VKA (not an option in U.S.)
   - Insertion of IVC filter
   - Change to LMWH
   - Other, please specify

28. Is there a difference in treating major bleeding in oncology patients compared to other patients, if yes, explain?

29. What do you generally monitor in cancer patients on LMWH treatment? (multiple options possible)
   - Renal function
   - Platelet count
   - Osteopenia
   - Anti – Xa levels
   - If so, please specify frequency and timing of blood draw

30. What do you do in case of an estimated GFR of 30-60 ml/min during LMWH treatment?
   - No alteration in treatment
   - Decrease the dose
   - Stop LMWH
31. Do you check anti-Xa levels?  □

32. What do you do in case of an estimated GFR of < 30 ml/min during LMWH treatment?
   - No alteration in treatment  □
   - Decrease the dose  □
   - Stop LMWH  □

33. Do you check anti-Xa levels?  □

34. At which platelet count do you stop anticoagulant treatment?
   - Never  □
   - Below 10 x 10⁹  □
   - Below 20 x 10⁹  □
   - Below 50 x 10⁹  □
   - Below 80 x 10⁹  □
   - Other  □
   - If other, please specify: ...

35. What is your preferred action in cancer patients with a recent VTE (3) using LMWH, who need surgery?
   - Stop temporarily without bridging  □
   - Bridge with unfractionated heparin  □
   - Insertion of an IVC filter  □

36. What is your preferred action in cancer patients with a non-recent VTE (4) using LMWH, who need surgery?
   - Stop temporarily without bridging  □
   - Bridge with unfractionated heparin  □
   - Insertion of an IVC filter  □

37. What is your preferred action in cancer patients with a recent VTE (3) using VKA, who need surgery?
   - Stop temporarily without bridging  □
   - Bridge with unfractionated heparin  □
   - Bridge with LMWH  □
   - Insertion of an IVC filter  □

38. What is your preferred action in cancer patients with a non-recent VTE (4) using VKA, who need surgery?
   - Stop temporarily without bridging  □
   - Bridge with unfractionated heparin  □
   - Bridge with LMWH  □
   - Insertion of an IVC filter  □
Specific situations

39. What is your preferred type of treatment in a patient with cancer who develops a catheter related upper extremity DVT?
   - Thrombolysis
   - Unfractionated heparin followed by VKA
   - Unfractionated heparin followed by LMWH
   - LMWH followed by VKA
   - LMWH monotherapy

40. What is your second choice of treatment in a patient with cancer who develops a catheter related upper extremity DVT?
   - Thrombolysis
   - Unfractionated heparin followed by VKA
   - Unfractionated heparin followed by LMWH
   - LMWH followed by VKA
   - LMWH monotherapy

41. Do you remove the catheter?
   - Yes
   - No

42. Usual duration of treatment
   - 3 months
   - 6 months
   - 12 months
   - Other
     - If other, please specify: ..................................................

43. Please specify reasons for duration:
    ........................................................................................................
    ........................................................................................................

44. What is your preferred type of treatment of patients with cancer and asymptomatic pulmonary emboli on CT-scan?
   - No treatment
   - Thrombolysis, eventually followed by anticoagulants
   - Unfractionated heparin followed by VKA
   - Unfractionated heparin followed by LMWH
   - LMWH followed by VKA
   - LMWH monotherapy
45. Usual duration of treatment
   3 months
   6 months
   12 months
   Other
   If other, please specify: ..............................................................

46. Please specify reasons for duration:
   ........................................................................................................

Case
Woman, 62 years of age, presents at the vascular department with an idiopathic deep
vein thrombosis of the leg. Initial treatment is given with LMWH and VKA (until twice INR
value >2), with a duration of 6 months.

After she has been treated with a VKA for 3 months, she discovers a small nodule in her
breast, which turns out to be a breast carcinoma. Stage: T4N1M1. Oncological treatment:
palliative chemotherapy.

47. Would you change the type of treatment, after the underlying malignancy has become
   apparent?
   Yes
   No

48. Would you change the duration of treatment, after the underlying malignancy has
   become apparent?
   Yes
   No

49. Depending on what variables; please specify
   ........................................................................................................