Thromboprophylaxis in Hospitalized Medically Ill Cancer Patients

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SECTION 1: Venous thromboembolism in Cancer Patients

INTRODUCTION

Venous thromboembolism (VTE) is the third leading cause of cardiovascular mortality in Canada and 1 in 20 Canadians will experience VTE in their lifetime (1, 2) VTE can present as deep vein thrombosis (DVT), a vein blood clot (usually in the lower limbs) or pulmonary embolism (PE) (a blood clot in the pulmonary arteries of the lungs). VTE can occur in association with a transient risk factor (provoked VTE) or known cancer (cancer-associated VTE). Cancer and other transient risk factors significantly increase the risk of VTE. Transient risk factors include: 1) recent surgery; 2) recent cast; or 3) prolonged immobilization (e.g. during hospitalization). Cancer patients hospitalized for medical illness might be at increased risk of VTE.

VTEs are one of the leading causes of death in patients with cancer. Patients with malignancy not only have increased risk of developing VTEs, but they are also more likely to develop recurrent VTEs and major bleeding during anticoagulant treatment compared to the general population (3). Thrombotic complications can delay or interfere with first-line anticancer therapy, precipitate or prolong hospitalization, and consume health care resources (4).

Hospitalization is in itself a risk factor for VTE and the presence of cancer and its associated intrinsic risk factors, further compounds the risk of developing a VTE (5). Thromboprophylaxis is likely to reduce the risk of VTE in patients hospitalized for medical illness. However, the real impact on VTE reduction and

the associated increase risk of bleeding in hospitalized medically ill patients with cancer is unclear.

In order to counsel hospitalized patients with cancer on the risks and benefits of pharmacological parenteral thromboprophylaxis, clinicians require estimates of the absolute risks of VTE and major bleeding episodes with and without thromboprophylaxis. To address these knowledge gaps, a systematic review of the literature was performed to summarize the efficacy and safety of pharmacological parenteral thromboprophylaxis in cancer patients hospitalized for medical illness. Based on the results of the systematic review, a survey of Canadian Thrombosis Experts was undertaken to assess if clinical equipoise exists regarding the use of thromboprophylaxis for hospitalized medically ill cancer patients and established the best trial design and minimally clinical significant difference required to plan for a randomized controlled trial focussing on determining if pharmacological parenteral thromboprophylaxis is efficacious, safe and cost effective in hospitalized medically ill cancer patients.

BACKGROUND

Venous thromboembolism is a common problem in cancer patients

Venous thromboembolism is common in cancer patients and the second cause of death in cancer patients after cancer progression [10]. Armand Trousseau was the first to describe this link in 1865, when he reported a high frequency of VTE in a series of patients with gastric carcinoma (6). The risk for VTE is estimated to be six to seven-fold higher in cancer patients compared with

a matched population of non-cancer patients (1, 2). Large epidemiologic studies reported an incidence of clinically overt VTE of approximately 1 event per 110–120 cancer-patients (7), (8). In a large population-based study including 235 subjects and 149 cancer patients, a symptomatic VTE episode was diagnosed in 1.6% of the patients in the 2 years following the diagnosis of cancer (9). A recent meta-analysis has also reported the annual incidence rate of cancer-associated VTE to be between 0.5% and 20%, depending on the tumour site and other co-morbidities, with an overall pooled incidence rate of 12.6 per 1,000 person-years (95% CI: 7.0 to 22.6) (10).

Risk Factors for Cancer-Associated VTEs

Cancer patients have a 4 to 7 fold increased risk of VTE compared to the general population (10). Risk factors for cancer-associated VTEs can be related to patients' characteristics, intrinsic to the underlying cancer (tumour type and stage) or its associated treatment (See Table 1). For example, oncologic therapies (e.g. cispatin (11), fluorouracil, doxorubicin, high-dose corticosteroids (12) bevacizumab (13) thalidomide, lenalidomide (14)), hormone therapies (medroxyprogesterone, tamoxifen, aromatase inhibitors (15) and androgen deprivation therapy (16)), use of granulocyte colony-stimulating factor (G-CSF) and erythropoietic stimulant agents (ESAs) (17) have been associated with a heightened risk of VTEs. Additional risk factors include poor Easter Cooperative Group (ECOG) performance status (PS) (18), frequent and prolonged hospitalizations, immobility, older age, thrombocytosis (pre-chemotherapy

platelets ≥350 x 10^9/L), anemia (hemoglobin <100g/L), leukocytosis (leukocytes>11 x 10^9/L) (19), multiple chronic co-morbidities, obesity, pulmonary disease, inherited prothombotic mutations, prior history of VTE, blood transfusion, surgeries, fractures, infections (particularly febrile neutropenia) (19), and insertion of a central catheter (20).

Table 1. Risk factors for VTE in cancer patients

Cancer Related	Patient Related
➢ Tumor site ➢ (Hematologic malignancies, pancreas, brain, stomach, kidney, gynecologic, and lung have the highest incidences) ➢ Stage (higher risk with metastatic disease) ➢ Regional bulky lymphadenopathy with extrinsic vascular compression ➢ Treatments and schedules (chemotherapy, hormonal therapy, anti-angiogenic and immunomodulatory drugs) ➢ Use of erythropoietic stimulant agents (ESAs)(17) ➢ Use of granulocyte colony-stimulating factor (G-CSF) ➢ Radiotherapy ➢ Eastern Cooperative Oncology Group (ECOG) performance status (PS) (18)	➢ Frequent and prolonged hospitalizations, ➢ Co-morbidities (e.g. thrombophilias, etc.) ➢ Immobility ➢ Race (higher risk for African Americans and lower for Asian/Pacific Islanders ➢ Obesity ➢ Prior history of VTE ➢ Older age

Clinical implications of venous thromboembolism in cancer patients

VTEs have been repeatedly identified as a marker of poor outcome in patients with cancer (7, 21, 22). VTEs are also associated with a 2 to 6 fold increased risk of mortality in cancer patients (1-year survival rate 12%, vs. 36% in controls)(22). The impact on survival is more important for patients with localized disease, for which the hazard ratio (HR) for death is 5.1 (95% CI: 3.6 to 7.1) compared to 3.5 (95% CI: 2.5 to 4.8) for patients with metastatic disease

(23). Furthermore, PE is a common cause of death in cancer patients (24-26). Of every seven cancer patients who die in hospital, one dies of PE (27). Therefore, the increased mortality rate observed in cancer patients with VTE may be resulting from a more advanced cancer state but also from VTE-related mortality.

Prevention of VTEs in the oncologic patient population is particularly desirable since the treatment of cancer-associated VTEs with anticoagulation is associated with significant morbidity. Cancer-associated VTE treatment is more commonly complicated by recurrent VTE and major bleeding during anticoagulant treatment than in patients without malignancy (3). The annual risk of bleeding on anticoagulants and of recurrent VTEs, despite anticoagulation, are 12% and 21% respectively among cancer patients receiving anticoagulation compared to 5% and 7% in patients without cancer (3). Finally, cancer-associated VTEs are costly and may impact on ongoing oncologic treatments, including delay or discontinuation of chemotherapy (4, 25).

Thromboprophylaxis in hospitalized patients with a medical illness

VTE remains a frequent cause of preventable morbidity and mortality in hospitalized patients with medical illnesses. More than 15 million medical patients are admitted to hospital in North America annually (28), many who are at risk of developing DVT and PE. It is estimated that 50–70% of all symptomatic inpatient VTEs and 70% of all fatal PEs occur in medically ill patients (29). Hospitalization is in itself a risk factor for VTE and the presence of

cancer, and its associated intrinsic risk factors, further compounds the risk of developing a VTE (5).

Pharmacological parenteral thromboprophylaxis using unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux is recommended in high-risk medically ill patients (30). In hospitalized medically ill patients, VTE occurs approximately in 2.8 to 5.6% of patients receiving thromboprophylaxis compared to 5.0 to 14.9% in patients receiving placebo (29-31). The best studied prophylaxis regimen consists of subcutaneous injections of UFH, LMWH or fondaparinux. Large randomized controlled trials investigating thromboprophylaxis using LMWH or fondaparinux in patients hospitalized for acute medical illnesses have reported clinical benefits in terms of a significant reduction in VTE without increasing the rates of major bleeding (31-33). In a meta-analysis of 8 trials, assessing the effectiveness of UFH or LMWH for thromboprophylaxis in patients hospitalized for medical illness, no significant difference was found in the incidence of VTE or mortality between those receiving UFH and those receiving LMWH (34). However, LMWH reduced the risk of major bleeding by 52% ($p=0.049$). Furthermore, a recent trial demonstrated that LMWH was non-inferior to UFH three times a day (TID) (35). As there is evidence to support all options, UFH (TID and BID), prophylactic doses of LMWH (daily) and prophylactic doses of fondaparinux are all reasonable choices for thromboprophylactic agents in hospitalized medically ill patients. In patients with active bleeding or other contraindications to anticoagulation therapy, mechanical prophylaxis (e.g. graduated compressive stocking, intermittent compressive devices) is recommended (30).

Extending pharmacological parenteral thromboprophylaxis beyond the hospitalization period of medically ill patients is not routinely recommended (30). The EXCLAIM trial (36), looking at extending the duration of enoxaparin from 10 to 28 days in acutely ill medical patients, reported a reduction in VTE rates in comparison to placebo (4.0% to 2.5%), but with increase in major bleeding from 0.3% to 0.8%.

New oral direct Xa inhibitors anticoagulants (rivaroxaban and apixaban) have been evaluated as thromboprophylactic agents in hospitalized medically ill patients (37, 38). A recent trial comparing the efficacy of rivaroxaban 10mg daily for 35 days to enoxaparin 40mg daily for 10 days (placebo afterwards) has shown that rivaroxaban was non-inferior to enoxaparin for 10 days and superior to enoxaparin and placebo at 35 days (38). However, rivaroxaban was associated with an increased risk of major bleeding at both, 10 and 35 days. A subgroup analysis including 592 patients with active cancers found similar conclusions. Similar results were reported using apixaban 2.5 mg BID as a thromboprophylactic agent in hospitalized patients with medical illness (37). Therefore, the risk-benefit ratio of thromboprophylaxis with oral anti-Xa in hospitalized medically ill patients remains uncertain.

Thromboprophylaxis in hospitalized cancer patients with a medical illness

Cancer patients who are hospitalized for an acute medical illness have an increased risk of developing a VTE. The incidence of VTE and PE in

hospitalized cancer patients was reported to be 2% and 0.6%, respectively (39). This represents a two-fold increase risk compared to non-cancer hospitalized patients. Another large study based in databases of hospital discharge has reported an even higher VTE rate of 5.4% in patients admitted to hospital with chemotherapy-induced neutropenia (40). Additionally, the incidence of VTE in the hospitalized oncology population is rising. Possible explanations for this phenomenon are: 1) improvements of diagnostic modalities; 2) greater awareness of the association between VTE and cancer; 3) use of new and more thrombogenic oncologic treatments; and/or 4) increasing use of implanted venous access devices (39, 41).

Unfortunately, data from large randomized trials assessing thromboprophylaxis in hospitalized patients specifically with cancer is not available. Nonetheless, current clinical practice guidelines from the American Society of Clinical Oncology, National Comprehensive Cancer Network, the American College of Chest Physicians and the European Society of Medical Oncology all recommend the use of standard prophylactic doses of UFH, LMWH or fondaparinux for cancer patients requiring hospitalization for acute medical illness in the absence of bleeding or other contra-indications to anticoagulation (42-44). These high-level recommendations are based on extrapolation from large placebo-controlled trials assessing the efficacy and safety of thromboprophylaxis in medically ill hospitalized patients (31-33). However, of the three largest randomized placebo-controlled trials assessing pharmacological thromboprophylaxis in medically ill hospitalized patients, only 4 to 15% of the enrolled patients had a diagnosis of cancer (31-33). Therefore, the risk-benefit

ratio of thromboprophylaxis in cancer patients hospitalized with a medical illness has never been formally assessed.

Despite the strong recommendations from the guidelines, compliance to thromboprophylaxis for hospitalized medically ill patients with cancer is very poor. Additionally, the Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey reported that only 5% of medical oncologists routinely prescribe it (45). In a prospective registry of 5,451 patients with ultrasound (U/S) confirmed DVT from 183 hospitals in the United States, only one-third of patients with cancer received VTE prophylaxis prior to developing DVT (46). These findings are consistent with a study of high-risk hospitalized patients not receiving VTE prophylaxis, of whom 80% were medical oncology patients (47). The lack of Level 1 data showing efficacy and safety in cancer patients is one of the main explanations for the lack of pharmacological thromboprophylaxis use among medical oncologists (48).

Overall Aim

The overall aim of this study is to determine if pharmacologic parenteral thromboprophylaxis is safe and effective to prevent venous thromboembolism (VTE) in cancer patients hospitalized for medical illness. If it is found not to be effective (i.e. reduction in VTE) or safe (i.e. increase in major bleeding), is a study assessing different thromboprophylaxis strategy required? If clinical equipoise exists and a trial needs to be done, which trial design (placebo controlled or different dosing strategy) should be performed? Finally what should

be the minimally clinically important difference used to calculate the sample size?

SECTION 2: Systematic Review

Rationale for the Systematic Review

As previously discussed, there are no randomized clinical trials looking at thromboprophylaxis in medically ill patients with cancer, and the recommendations in guidelines for these patients are based on trials done for the general medically patients, with a small accrual of oncologic patients. Therefore, a systematic review is necessary to determine the efficacy (rate of VTE) and safety (rate of major bleeding) in hospitalized medically ill cancer patients, receiving or not thromboprophylaxis, to look for evidence of benefits and to verify if the benefits outweigh the risks in this setting. In this section, a systematic review of the literature is described to identify those rates in patients receiving different thromboprophylaxis agents (UFH, LMWH and fondaparinux).

Should we have clear evidence of benefit from the use of thromboprophylaxis in this population, without great increase in major bleeding, and with an acceptable balance between risks and benefits as per clinicians involved in the care of these patients, it would be harder to justify the execution of a randomized clinical trial (RCT) in this setting.

A systematic review protocol was designed and approved by the University of Ottawa. The protocol and systematic search strategy of the review is documented on-line (PROSPERO registry - CRD42012002845).

Systematic Review Methods

PICOS Question and Objectives

PICOS Question

Does thromboprophylaxis with anticoagulants decrease the incidence of VTE events and increase the incidence of major bleeding events in medically ill hospitalized cancer patients in observational and randomized controlled clinical trials?

Population: medically ill hospitalized cancer patients

Intervention: thromboprophylaxis with LMWH, UFH, fondaparinux

Comparator: placebo, anticoagulant agents (LMWH, UFH, fondaparinux)

Outcome: VTE (asymptomatic and symptomatic), major bleeding episodes

Study: observational or randomized controlled clinical trial

Objectives

The primary objective of this review is to determine the effectiveness (rates of VTE (asymptomatic and symptomatic)) and safety (major bleeding episodes) of pharmacological parenteral thromboprophylaxis in hospitalized medically ill patients with cancer.

Secondary objectives are to determine the effects of pharmacological parenteral thromboprophylaxis in hospitalized medically ill patients with cancer on: 1) Symptomatic VTE; 2) All cause mortality; and 3) Minor bleeding.

Data Sources and Searches

An electronic search of the following databases using an OVID interface was performed: MEDLINE (1946 to September 2012), EMBASE (1980 to September 2012), the Cochrane Central Register of Controlled Trials, and all evidence based medicine reviews (EBMR). Adjustments were made to the search strategy to account for the differences in indexing between databases. Publications were also sought through a hand-search of journals and of the American Society of Clinical Oncology, European Society of Medical Oncology, and the American Association for Cancer Research, America Society of hematology conference proceedings for the past 5 years (2008-2012). A "grey literature" search was done in OpenSIGLE (opensigle.inist.fr.). Grey literature was also researched on the National Technical Information Service website: www.ntis.gov/ (APPENDIX 1). The reference lists of identified trials were reviewed to identify additional articles. The systematic search strategy is documented in Table 2. There was restriction of language to English, French, Portuguese or Spanish (all languages spoken by the authors). Duplicate references were removed.

Table 2. Systematic Literature Search Strategy
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1	exp "embolism and thrombosis"/pc
2	thromboprophyla$.tw.
3	(thrombo$ adj3 prophyla$).tw.
4	(embol$ adj3 prophyla$).tw.
5	(vte adj3 prophyla$).tw.
6	(dvt adj3 prophyla$).tw.
7	or/1-6
8	Inpatients/
9	inpatient$.tw.
10	(medical$ adj2 ill$).tw.
11	Hospitalization/
12	(hospitalis$ or hospitaliz$).tw.
13	(acute$ adj2 ill$).tw.
14	or/8-13
15	7 and 14
16	exp neoplasms/
17	(cancer$ or neoplam$ or tumor$ or tumour$ or malignan$).tw.
18	16 or 17
19	15 and 18
20	limit 19 to (english or french or portuguese or spanish)
21	remove duplicates from 20

Study Selection

A structured question format was used to select abstracts of observational studies or clinical trials reporting the efficacy and safety of pharmacological parenteral thromboprophylaxis in hospitalized medically ill patients. We reviewed potentially relevant articles that satisfied all of the following criteria: 1)

hospitalized adults with an acute medical illness; 2) receiving pharmacological parenteral thromboprophylaxis; 3) observational studies or randomized controlled trials; 4) one or more of the primary or secondary outcomes were reported according to the cancer status (described below). Articles were excluded if they included: 1) children; 2) post-operative surgical patients; or 3) patients with hematological malignancies.

Outcome Measures

The primary endpoints were VTE and major bleeding episodes. Venous thromboembolism was defined as a composite outcome of: 1) asymptomatic DVT (i.e. detected by protocol scheduled screening studies); 2) symptomatic DVT (distal or proximal); 3) symptomatic PE; 4) fatal PE; or 5) sudden death without another plausible cause. Deep vein thrombosis was defined as: a) non-compressibility of any vein segment from the common femoral vein to the calf veins on compressive ultrasonography and/or b) a persistent intra-luminal filling defect of the iliac, common femoral, superficial femoral, popliteal, posterior tibial or peroneal veins on contrast venography. Pulmonary embolism was defined as: a) high probability ventilation-perfusion (V/Q) scan, b) positive pulmonary angiogram, and/or c) spiral CT demonstrating intraluminal filling defect in a vessel larger than a segmental artery. Major bleeding episodes defined as: a) fatal bleeding, and/or b) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or c) bleeding causing a fall in

hemoglobin level of 20 g/L (1.24 mmol/ L) or more, or leading to transfusion of two or more units of whole blood or red cells (49).

Secondary endpoints included symptomatic VTE (lower limb DVT and PE), all-cause mortality and minor bleeding. Minor bleeding was defined as a bleeding episode not meeting the “major bleeding” definition.

Data Extraction and Quality Assessment

Two reviewers (PM and MC) independently applied the inclusion criteria to the identified articles from the initial search strategy with the aim to minimize bias. Following the first preliminary screening of abstracts, the reviewers acquired copies of all potentially relevant original publications for closer review and final study selection. Decisions about study citations retrieved from the search and inclusion were made independently, and a consensus was achieved to resolve any discrepancies.

Both authors (PM, MC) independently extracted the data from the retrieved articles. Reviewers extracted baseline characteristics, number of cases of VTE, major bleeding and death as well as type and duration of pharmacological parenteral thromboprophylactic regimen. Any discrepancies were resolved by consensus.

The primary authors of any articles with inadequate or missing information were contacted via email (See APPENDIX 2 for example of contact e-mail). A total of 22 study authors were contacted for which we thought that lacking information on cancer patients could be obtained and studies where information

in the outcomes of interest could be better described or clarified. Of the 8 authors that have replied, 7 were not able to provide the information (data no-longer available, studies to be published, data belonging primary funding sources). The last author was agreeable to share the data. However, an agreement between both institutions (Respondent's institution and OHRI) could not be finalized.

The methodological quality of observational studies included should be evaluated using the validated Newcastle – Ottawa Quality Assessment scales and the evaluation of RCT using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials (50, 51). For all eligible studies, 2 reviewers (PM and MC) independently assessed the trial/study quality and extracted the data using a standardized data abstraction form. Any discrepancies were again resolved by consensus.

Data Synthesis and Analysis

Estimates of the weighted rates and its associated 95% confidence intervals (95% CI) were calculated for the review's primary outcomes (rates of VTE and major bleeding) using the Freeman-Tukey variant of the arcsine square root transformed proportion (52). Furthermore, relative risk (RR) (with 95 %CI) from placebo controlled trials using a random effect model was performed to assess the efficacy and safety of pharmacological parenteral thromboprophylaxis in cancer patients hospitalized with medical illness. The I^2 statistic was used to estimate total variation among the pooled estimates across studies. An I^2 of > 50% was considered as a high level of heterogeneity (51) . Analyses were

performed using StatsDirect software version 2.7.3 (StatsDirect Ltd, Cheshire, UK). A priori, subgroup (quality, observational studies vs. randomized trials, etc.) and sensitivity analyses (relevant characteristics) were planned if heterogeneity was detected. Similarly, the impact of publication bias was a priori planned to be explored using funnel plots to assess the relationship between effect size and study precision.

Results of Systematic Review

Baseline Characteristics of Included and Potentially Eligible Studies

A total of 407 citations were identified in our literature search, and 88 papers were fully reviewed. Only 23 studies were considered potentially eligible should the authors provide further information about treatment group to which cancer patients belonged or according to the outcomes of interest. Despite our attempts to contact these authors, we were able to obtain the specific data on cancer patients from only 4 studies. Of these, three placebo-controlled randomized trials included VTE events as a primary outcome and were analyzed according to cancer subgroups (31-33). One trial randomized hospitalized medically ill patients to LMWH or UFH and analysed the data according to cancer subgroups (35). The baseline characteristics of reviewed studies are presented in Table 3 and reviewed in detail below (see also APPENDIX 3). None of the studies reported a definition for cancer status. The characteristics of the included studies are depicted in Table 4. The PRISMA flow diagram can be found in APPENDIX 4.

Table 3. Baseline Characteristics of the Reviewed Studies

Acronym	Authors	Date	Treatment	Dosage	Frequency	Length of treatment-days median and range	Duration of follow up -in-hospital-days-Planned or median	Number of patients medically ill	Cancer patients	Evaluable cancer patients
MEDENOX(31)	Samama	1999	placebo		OD	7 (6-14)	14	371	56	41
(53)	Alikham	2004	enoxaparin	20mg	OD	7(6-14)	14	364	56	n_a
			enoxaparin	40mg	OD	7 (6-14)	14	367	45	31
PREVENT(32)	Leizorovicz	2004	placebo		OD	14 D	21	1833	105	72
(54)	Cohen	2007	dalteparin	5000IU	OD	14D	21	1848	85	65
ARTEMIS(33)	Cohen	2006	placebo		OD	7 (6-14)	15	420	69	51
			fondaparinux	2.5mg	OD	7 (6-14)	15	429	62	47
CERTIFY(35)	Riess	2010	UFH	5000IU	TID	9 (8-20)	90	1624	133	116
(55)	Hass	2011	certoparin	3000Uanti-xa	OD	9 (8-20)	90	1618	141	111
n_a (56)	Perez	1988	none			8 (mean)	8 (mean)	118	5	5
			UFH	5000IU	BID	9	9	39	3	3
			ASA	500mg	OD	10	10	35	1	1
n_a (57)	Harenberg	1990	UFH	5000IU	TID	10	7-12	82	17	n_a
			LMWH	1500 aPTT u	OD	10	7-12	84	23	n_a
n_a (58)	Harenberg	1996	nadroparin	36mg ^^	OD	10 (8-11)	10	810	n_a	57
			UFH	5000iu	TID	10 (8-11)	10	780	n_a	63
n_a (59)	Bergmann	1996	enoxaparin	20mg	OD	10	10	216	11&	n_a
			UFH	5000IU	BID	10	10	223	19&	n_a
THE PRIME	Lechler	1996	UFH	5000IU	TID	7	7	482	71	n_a
(60)			enoxaparin	40mg	OD	7	7	477	96	n_a
THE-PRINCE	Kleber	2003	UFH	5000IU	TID	10	10	333	16	n_a
(61)			enoxaparin	40mg	OD	10	10	332	25	n_a
n_a (62)	Mahe	2005	placebo		OD	21	21	1244	175	NA
			nadroparin	7500anti-Xa	OD	21	21	1230	167	NA
n_a (63)	Lederle	2006	placebo		OD	11(mean)	11(mean)	140	6	NA
			enoxaparin	40mg	OD	13 (mean)	13 (mean)	140	7	NA
n_a (64)	McGarry	2006	UFH	5000IU	OD, BID, TID	10	10	2837	266	NA
			enoxaparin	30-60mg/day	OD-BID	10	10	479	44	NA
IMPROVE(65)	Tapsom	2007	None			NA	5-8	7516	6946	NA

			UFH	n_a	BID, TID, other	5-7	5-8		158	NA
			LMWH	n_a	OD, BID, other	5-7	5-8		530	NA
			Fondaparinux or DTI	n_a	n_a	5-7 (mean)	5-8	7640	30	NA
n_a (66)	Conte	2008	none			NA	9	125	125	NA
			UFH	5000IU	BID, TID	9	9	120	120	NA
			enoxaparin or dalteparin	n_a	n_a	9	9	121	121	NA
n_a (67)	Pandey	2009	none			n_a	14			NA
			LMWH	n_a	n_a	n_a	14	117 total	8 total	NA
GEMINI(68)	Gussoni	2009	none			11 (mean)	n_a	2830		n_a
			LMWH	n_a		11 (mean)	n_a		795 -all	n_a
			UFH	5000IU	BID, TID	11(mean)	n_a	2015	groups	n_a
n_a (69)	Awar	2009	none	Y	NA	NA	8.5 (SD7.5)	n_a	74	NA
			enoxaparin	20mg	OD	n_a	8.5 (SD7.5)	n_a	n_a	NA
			enoxaparin	40mg	OD	n_a	8.5 (SD7.5)	n_a	n_a	NA
			tinzaparin	n_a	n_a	n_a	8.5 (SD7.5)	n_a	n_a	NA
n_a (70)	Reeves	2010	UFH	5000IU	TID	6	28D	94	87	NA
			enoxaparin	40mg	OD	6.5	28D	14	14	NA
			fondaparinux	2.5mg	OD	8	28D	3	3	NA
n_a (71)	Aniwan	2010	none			NA	15.7 (SD 21.7)	7126	1211	NA
ANCIANOS(72)	Manas	2010		2500IU	OD	33 (4-132)	90		0	NA
			bemiparin	3500IU	OD	33 (4-132)	90	507 total	39	NA
CERTAIN(73)	Schellong	2010	UFH	7500IU	BID	10	10	174	14	n_a
			certoparin	3000Uanti-xa	OD	10	10	163	15	n_a
n_a (74)	Rojnuckarin	2011	none			NA	NA	1290	297	NA

Co-interventions: Graduated compression stockings, physiotherapy ,elastic bandages, support stockings; #: lack of outcome confirmation by imaging and exclusion of VTE cases specifically in cancer patients ; &: patients with cancer as a reason for hospitalization. A total of 63 patients had a history of cancer but the distribution on both groups was not described; ^^: as reported; NA: not apply; n_a: not available; $$: 1 PE + 1 DVT; DTI: direct thrombin inhibitor

Medenox trial (31)

This is a multicentre, double-blind, placebo-controlled RCT that was fully published in 1999. A total of 1102 hospitalized patients including 157 (14% of total) patients with cancer (previous or current) were randomized to enoxaparin 20mg, 40mg or placebo groups, once a day (OD), for 6 to 14 days. Co-interventions, such as elastic bandage, support stockings, and physiotherapy were allowed. Randomization was performed centrally, but no description regarding measures to guarantee allocation concealment was available. Two independent and blinded committees performed outcome adjudication and the imaging investigations were analysed by two blinded reviewers. Disagreements were settled by consensus. Finally, a committee reviewed all the outcomes.

The incidence of VTE was significantly lower in the group that received 40 mg of enoxaparin (5.5 %) compared to the placebo group (14.9%) (RR: 0.37 (95% CI 0.22 to 0.63)). During the treatment period, major hemorrhage occurred in 11 patients. The mortality was lower in patients receiving enoxaparin 40mg per day in comparison to placebo (RR: 0.83, 95%CI: 0.56 to 1.21; P=0.31), however it was not statistically significant. There was no significant difference in the incidence of VTE between the low dose of enoxaparin and placebo.

A post-hoc analysis using 118 evaluable patients with cancer reported that the incidence of VTE during hospitalization for medically ill patients with cancer was lower (9.7% (3/31)) in the enoxaparin group compared to the placebo group (19.5% (8/41)) RR, 0.50; 95% CI, 0.14-1.72) (53). In a subsequent logistic regression analyses, the reported odds ratio for VTE in

cancer patients was 1.62 [95% CI: 0.93-2.75] (75). The incidence of bleeding episodes in cancer patients was not reported.

PREVENT trial (32)

This is a multicenter, double-blind, placebo-controlled RCT that randomized 3706 hospitalized medically-ill patients (190 (5% of the total) with cancer (previous or current- not described)) to receive dalteparin 5000 IU or placebo for 14 days. There is no description of the randomization methods or how allocation concealment was guaranteed. The adjudication of outcomes was done by a blinded central committee.

A total of 2991 patients were evaluable for the primary outcome. Overall, the incidence of VTE was 2.77% (42/1518) in the dalteparin and 4.96% (73/1473) in the placebo group [RR 0.55; 95% CI, 0.38-0.80], with the benefit of thromboprophylaxis maintained at 90 days. A higher incidence of major bleeding occurred in patients receiving dalteparin (0.49%) in comparison to placebo (0.16%). No difference in mortality at days 14, 21, or 90 was found.

A post hoc analysis evaluating the risk reduction of VTE with thromboprophylaxis in hospitalized medically ill cancer patients showed that incidence of VTE at 21 days was 8.3% (6/72) in the placebo and 3.1% (2/65) in the dalteparin group. The incidence of major bleeding episodes in cancer patients was not reported. Despite contacting the author, this information was not released (54).

ARTEMIS trial (33)

In this multicenter, double-blind, placebo-controlled RCT, 849 hospitalized medically patients (131 with cancer (15% of the total)) were randomized to fondaparinux 2.5mg OD or placebo until days 6 to 14. Randomisation was done through a central randomization list using blocks of four. Despite a theoretical possibility of communication amongst the centers, and with the group to which the last patient in the block belongs being potentially identifiable, it was deduced not probable to occur. A blinded central committee adjudicated all events.

The primary efficacy outcome could be assessed in 644 patients. Overall, the incidence of VTE was 6% (18/321) in the fondaparinux and 10.5% (34/323) in the placebo group [RR 0.47, 95% CI: 0.08-0.69]. Regarding the primary safety outcome, the incidence of major bleeding was 0.2% in both groups. At one month follow-up, the mortality rate was 3.3 % in the fondaparinux and 6 % in the placebo group (p=0.06). The European Medicine Agency - Scientific Discussion on Arixtra® (fondaparinux) (76) reported event rates for the 98 evaluable patients with cancer enrolled in the trial. The incidence of VTE in the placebo group was 3.9% (2/51) and 17% (8/47) in the fondaparinux group. The bleeding event rates in cancer patients were not reported. Despite contacting the author, this information was not released.

CERTIFY trial (35)

The CERTIFY trial is a multicenter, double-blind, active controlled RCT randomizing 3239 medically-ill hospitalized patients (274 with cancer (8.5% of the total)) to certoparin (3000 U of anti-Xa OD) or UFH (5000 IU TID) for 8 to 20 days. Randomization was done through a central office, with a list being generated by an automated system, with proper allocation concealment .The adjudication of outcomes was done by a blinded central committee and an ultrasound reading centre.

The incidence of VTE during hospitalization was 3.94% (54/1372) in the certoparin and 4.52% (62/1371) in the placebo group [OR of 0.87, 95% CI 0.60-1.26, P = 0.0001 for non-inferiority]. Regarding the safety outcomes, the incidence of any bleeding was 3.2% in the certoparin and 4.58% in the UFH group patients (OR 0.69; 95% CI 0.48-0.99). The overall incidence of major bleeding was 0.43% of certoparin and 0.62% in the UFH group (OR 0.69; 95% CI 0.26-1.83,). Serious adverse events occurred in 5.73% of certoparin group and 6.63% of UFH group, and all-cause mortality was 1.27% in certoparin group and 1.36% in UFH- group. A post-hoc analysis of CERTIFY evaluating the risk of VTE and bleeding in patients with cancer according to the randomization arm was recently published (55). Of the 274 cancer patients available for safety analysis, 227 were available for the efficacy outcome (111 and 116 in the certoparin and UFH groups respectively). In the certoparin group, the incidence of VTE was 4.5% (5/111), major bleeding 0.75%, minor bleeding 0.75%, and use of anti-platelet therapy was of 51%. In the UFH, the incidence of VTE was 6.03%

(7/116), major bleeding 0.71%, and minor bleeding 5.67%. The OR for VTE was 0.73 [95%CI; 0.23-2.39) favouring LMWH. Patients with cancer also experienced more serious adverse events, 10.2%, in comparison to 5.81% on non-cancer patients (OR 1.85; 95% CI 1.21-2.81).

Table 4. Included Studies in the Quantitative Analysis

Acronim		MEDENOX		PREVENT		ARTEMIS		CERTIFY	
Authors	Samama	Alikham		Leizorovicz	Cohen	Cohen	EMA*	Riess	Haas
Date	199(31)9	2004(75)		2004(32)	2007(54)	2006(33)	2005(76)	2010(35)	2011(55)
Treatment	placebo	enoxaparin	enoxaparin	Placebo	dalteparin	placebo	fondaparinux	UFH	certoparin
Dosage		20mg	40mg		5000IU		2.5mg	5000IU	3000Uanti-xa
Frequency	OD	OD	OD	OD	OD	OD	OD	TID	OD
Co-interventions	Y	Y	Y	Y	Y	Y	Y	Y	Y
Length of treatment-days median and range	7 (6-14)	7(6-14)	7 (6-14)	14 D	14D	7 (6-14)	7 (6-14)	9 (8-20)	9 (8-20)
Duration of follow up - in-hospital (days): planned or median	14	14	14	21	21	15	15	90	90
Number of patients medically ill	371	364	367	1833	1848	420	429	1624	1618
Cancer patients	56	56	45	105	85	69	62	133	141
Evaluable cancer patients	41	n_a	31	72	65	51	47	116	111
Total VTE-N	8	n_a	3	6	2	2	8	5	7
Symptomatic DVT-Both	n_a	n_a	n_a	n_a	n_a	n_a	n_a	1	1
Total DVT-N	n_a	n_a	n_a	n_a	n_a	n_a	n_a	n_a	n_a
Total PE-N	n_a	n_a	n_a	n_a	n_a	n_a	n_a	1	0
Death all cause	n_a	n_a	n_a	n_a	n_a	n_a	n_a	2	6
All bleedings	n_a	n_a	n_a	n_a	n_a	n_a	n_a	2	9
Major bleeding	n_a	n_a	n_a	n_a	n_a	n_a	n_a	1	1
Fatal bleeding	n_a	n_a	n_a	n_a	n_a	n_a	n_a	0	0

*European Medicine Agency - Scientific Discussion on Arixtra®

Pooled Proportions of Venous Thromboembolic Events

A total of 534 hospitalized medically ill cancer patients from 4 randomized controlled trials were included in the analyses. Of these, 230 and 395 cancer patients received placebo or thromboprophylaxis respectively. Thromboprophylaxis was done using parenteral LMWH (dalteparin 5000 IU daily; enoxaparin 40 mg daily; certoparin 3000 IU daily), fondaparinux (2.5 mg SC) or UFH (5000 IU TID). All these regimens are approved and recommended as thromboprophylactic agents in medically ill hospitalized patients. Figures 1 and 2 shows the pooled rates of VTE occurring during hospitalization in medically ill patients receiving thromboprophylaxis (Figure 1) or placebo (Figure 2). The rates of VTE for medically ill cancer patients during hospitalization were 7.4% (95% CI: 3.9-11.9%; I^2 51.6%) and 10.2% (95% CI: 3.7-19.4; I^2: 65.3%) in patients receiving thromboprophylaxis and placebo, respectively. However, none of the trials reported the rates of major bleeding episodes according to cancer status and were not made available by either primary authors or primary funding sources.

Figure 1. Forest plot and pooled proportions of the rates of venous thromboembolic events in cancer patients hospitalized for medical illness receiving thromboprophylaxis

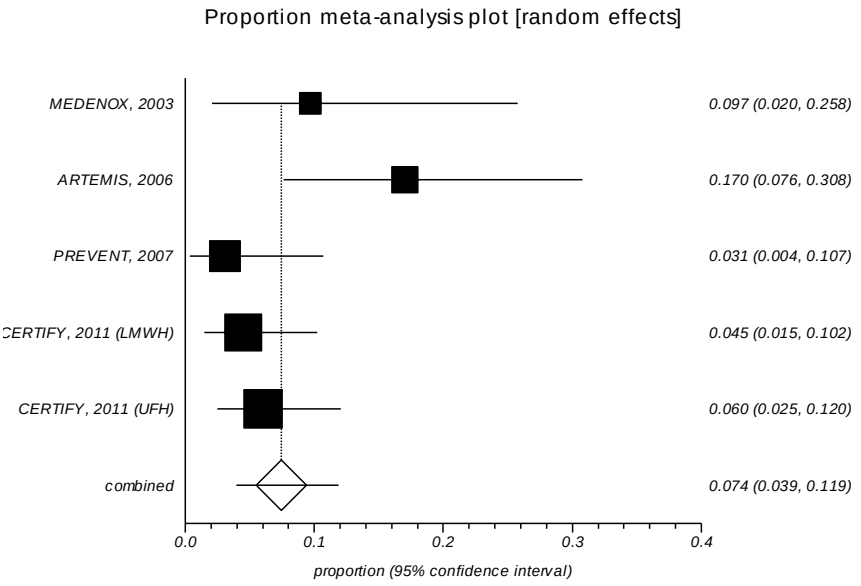
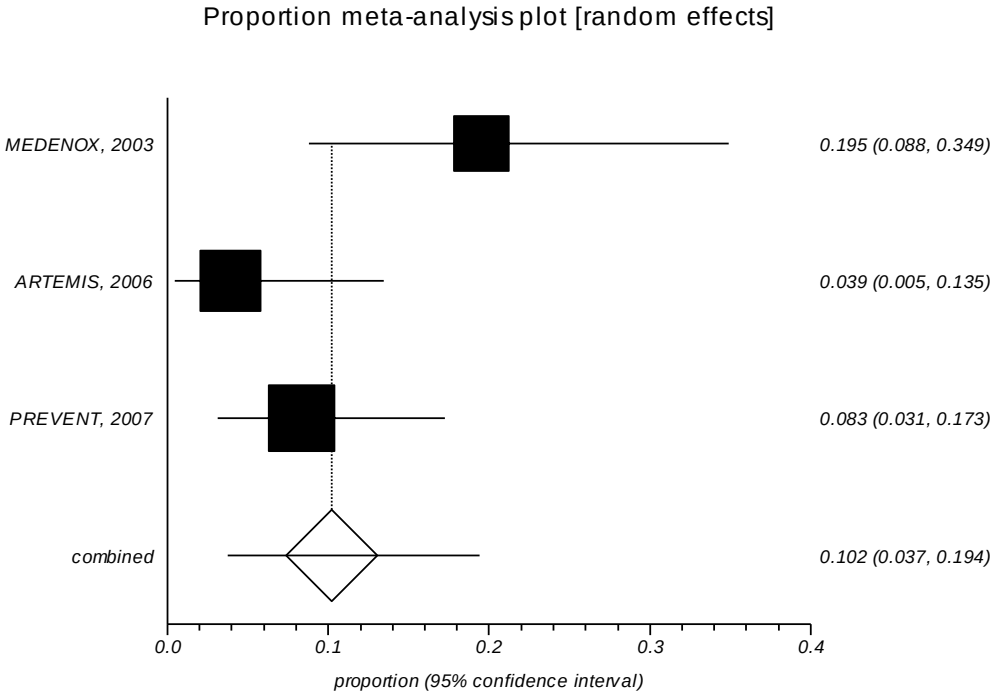


Figure 2. Forest plot and pooled estimates of the proportions of venous thromboembolic events in cancer patients hospitalized for medical illness receiving placebo

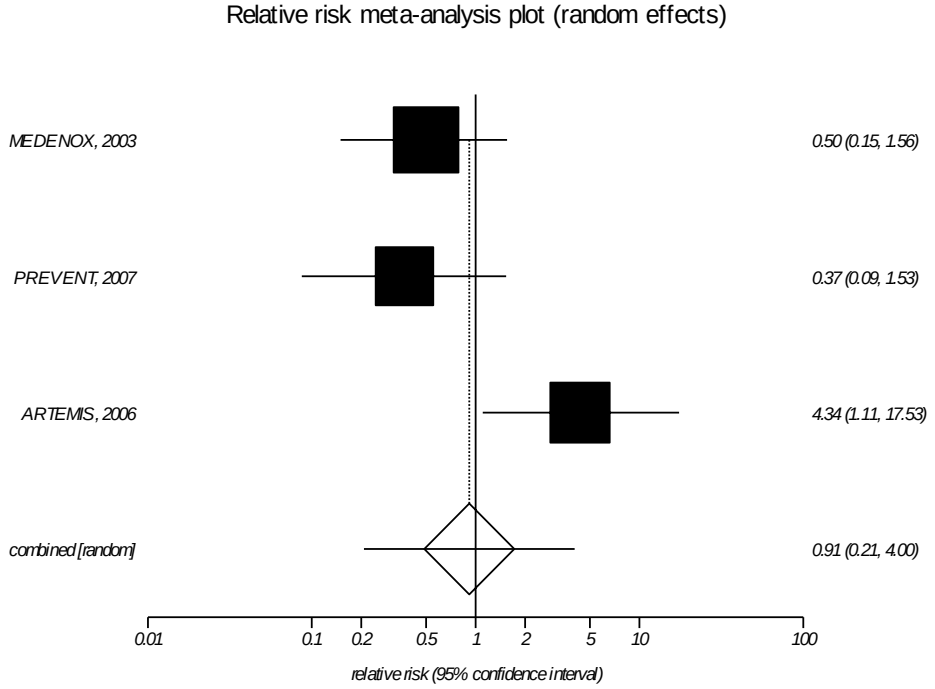


Relative Risk of Venous Thromboembolic Events in Patients Receiving Thromboprophylaxis versus Placebo.

As discussed above, the three major placebo-controlled randomized trials enrolled a total of 307 (n=307/5134, 6%) medically ill hospitalized cancer patients and compared thromboprophylaxis (enoxaparin 40 mg, dalteparin 5000 IU or fondaparinux 2.5 mg daily) to placebo (31-33). The pooled RR of VTE was 0.91 (95% CI: 0.21 to 4.0; I^2: 68%) among hospitalized cancer patients receiving thromboprophylaxis compared to placebo (Figure 3). Again, none of the trials reported the rates of major bleeding episodes according to the cancer status.

A priori, subgroup (quality, observational studies vs. randomized trials, etc) and sensitivity analyses (relevant characteristics) were planned if heterogeneity was detected. Unfortunately, subgroup analyses could not be performed due to the small number of trials meeting our inclusion criteria.

Figure 3: Forest plot and pooled estimates of the relative risk of venous thromboembolic events in cancer patients hospitalized for medical illness receiving thromboprophylaxis versus placebo.



Quality Assessment

As reported above (subsection titled Pooled Proportions of Venous Thromboembolic Events), the study quality of the included randomized controlled trials was adequate (Table 5). All randomized controlled trials reported adequate sequence generation, allocation concealment, blinding and outcome reporting. Only two trials had a study protocol available but all expected outcomes were reported for all other studies (35, 77).

Table 5. Quality Assessment

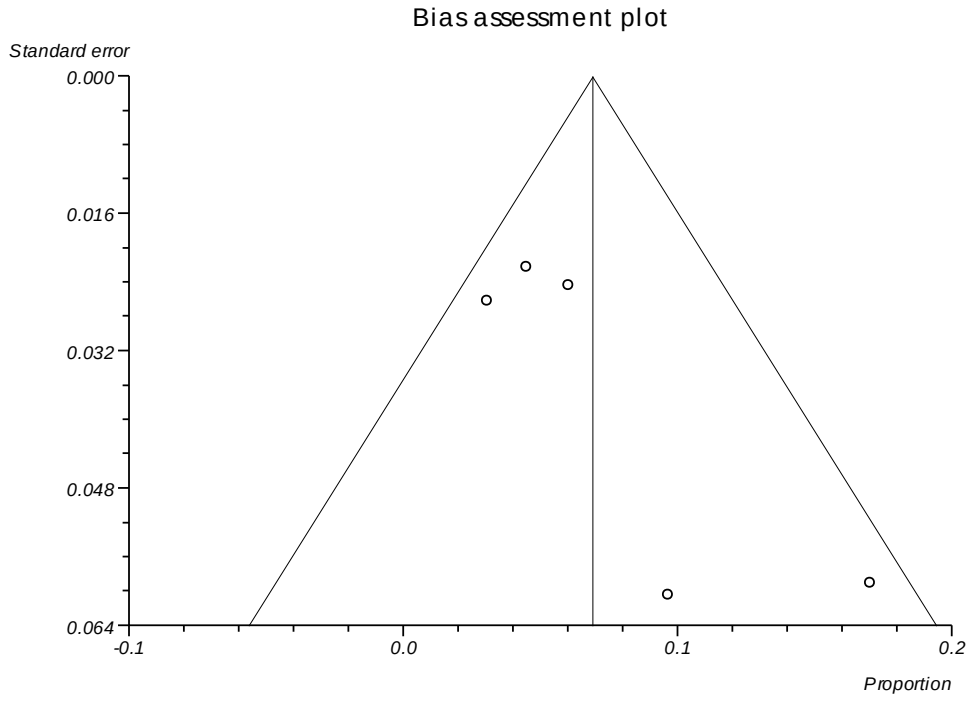
	Selection bias				Performance bias		Detection bias		Attrition bias		Reporting bias	
	Random sequence generation.		Allocation concealment.		Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).		Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).		Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).		Selective reporting.	
	Support for judgement	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement	Review authors' judgement
MEDENOX (31,53)	Randomization was performed centrally	No further information provided.	No description regarding measures to guarantee allocation concealment	Can't evaluate due to lack of inormation	Blinded, study medications were packaged in prefilled, single-dose syringes	Proper blinding	The outcomes were reviewed by two independent, blinded, committees, and the imaging investigations were analysed by two blinded reviewers.	Proper blinding	Primary outcome could be assessed in 866 patients, since not all patients had the screening immaging.	Pitfail of studies with screening for assymptomatic DVT. Similar loss of patients due to death, refusal, investigator's decision and lost to follow up in the study groups*.	Positive and negative findings were reported	No evidence of reporting bias
PREVENT (32, 54, 77)	Randomized trial	No further information provided.	regarding measures to guarantee allocation concealment	Can't evaluate due to lack of inormation	Blinded	Proper blinding	Adjudicated by a blinded centraL committee	Proper blinding	8 patients randomized to the dalteparin group and 17 to the placebo group did not receive a study medication and were not included in the analysis, as well as the patients without the screening immaging.	Pitfail of studies with screening for assymptomatic DVT. Similar loss of patients in the study groups (18% for dalteparin and 21 % for the placebo group).	Positive and negative findings were reported	No evidence of reporting bias
ARTEMIS (33)	Predefined central randomisation list, balanced in blocks of 4	Proper randomization	As described in randomization	The central randomization in a multicenter trial, despite of being on blocks of 4 only, could still garantee proper allocation	Blinded	Proper blinding	Adjudicated by a blinded centraL committee	Proper blinding	Primary outcome could be assessed in 644 patients, since not all patients had the screening immaging.	Pitfail of studies with screening for assymptomatic DVT. Similar loss of patients not treated in both groups.	Positive and negative findings were reported	No evidence of reporting bias
CERTIFY (35, 55)	"Validated system automated the random assignment of treatment arms to randomization numbers in the specified ratio. This was reviewed and approved by a biostatistics quality assurance group"	Proper randomization	As described in randomization	This should garantee poper allocation	Blinded	Proper blinding	Adjudicated by a blinded centraL committee and and compression ultrasonography reading center	Proper blinding	Primary outcome could be assessed in 2743 patients, since not all completed the core study	Pitfail of studies with screening for assymptomatic DVT. Similar loss of patients not treated, consent withdraw, subject's condition no longer required study drug, death, other in both groups.	Positive and negative findings were reported	No evidence of reporting bias

* However,in the safety analysis , where mortality was an outcome, data on subjects who had not received any study medication (3 in the placebo group and 5 in the 20-mg group) were not included.

Publication Bias Assessment

Assessment of publication bias was also planned a priori in order to assess the relationship between effect size and study precision. Unfortunately, only one funnel plot could be generated due to the small number of included studies (Figure 4). Qualitative assessment of the funnel plot depicted in Figure 4 does not reveal any evidence of significant publication bias. However, the interpretation of the funnel is limited.

Figure 4. Publication bias assessment plot for the pooled proportions of the rates of venous thromboembolic events in cancer patients hospitalized for medical illness receiving thromboprophylaxis.



Discussion

This is the first systematic review and pooled analysis assessing the efficacy of parenteral thromboprophylaxis among cancer patients hospitalized for medical reasons. In this analysis, only 4 randomized trials were used. There was a lack of apparent significant benefit for the use of LMWH or fondaparinux to prevent VTE in hospitalized medically ill cancer patients.

The apparent lack of efficacy of thromboprophylaxis in hospitalized cancer patients might be explained by a number of reasons. First, heterogeneity between studies was apparent and the I^2 showed high level of heterogeneity (51 to 68%) for all pooled estimates (both pooled proportions and RR). In Figure 3, it appears fondaparinux might be less efficacious compared with dalteparin or enoxaparin in cancer cohorts. However, in patients undergoing cancer-related major abdominal surgery, fondaparinux was as effective as dalteparin in the prevention of post-operative venous thromboembolic events (78). Similarly, fondaparinux seems to be as effective and safe as LMWH or unfractionated heparin for the acute treatment of cancer patients with acute venous thromboembolic events (79). Based on the results from these studies and its pharmacological properties, it is biologically reasonable to pool fondaparinux with the other LMWH. Furthermore, removing the ARTEMIS trial from the analyses does not significantly alter the pooled VTE rates or its associated heterogeneity. The pooled rates of VTE during hospitalization of medically ill cancer patients were 8.5% (95% CI: 4.3 to 14.1%; I^2 55%) and 13.5% (95% CI: 4.6 to 26.3; I^2: NA) for patients receiving thromboprophylaxis (excluding fondaparinux) and

placebo respectively. Although the RR was lower (0.44; 95% CI: 0.17-1.17% I^2: NA), it remained non-statistically significant. Second, the recommended thromboprophylactic doses might not be optimal for hospitalized cancer patients. Previously published studies assessing higher doses of LMWH as primary thromboprophylaxis agents in ambulatory cancer patients undergoing chemotherapy reported higher relative risk reduction of venous thromboembolic events compared to studies using standard dosing (80-82). Third, none of the included studies randomized patients according to their cancer status or stratified patients according to their underlying risk of venous thromboembolic events, which was shown to be influenced by biomarkers, tumour type and body mass index for chemotherapy associated venous thromboembolic events in outpatients (19). Finally, a relatively small number of patients were included in the four studies (N=534) reflecting inadequate power to detect a small relative benefit. The population of cancer patients enrolled in clinical trials assessing mortality as the primary endpoint could not be included in this analysis. However, the low rates of VTE reported in these trials and the concern regarding the lack of accuracy as a secondary endpoint are unlikely to significantly change our conclusions.

The risk of bleeding for hospitalized cancer patients receiving thromboprophylaxis remains unknown as none of the included trials reported rates of major bleeding episodes among cancer patients nor was the data accessible for further analysis. Therefore, it is currently impossible to accurately assess the risk benefit ratio of thromboprophylaxis in cancer patients hospitalized for medical reasons.

Limitations

The intent was to do an individual patient data systematic review and meta-analysis in order to perform a subgroup analysis (cancer patients) of previously published studies for thromboprophylaxis in medically ill patients. However, not all authors provided individual level data from the published reports initially obtained as a result of the systematic search. Therefore, analysis was restricted to only 4 out of 22 potential studies, which were accepted at face value. In this case, the data available came from good quality RCTs. Further analysis to explain the heterogeneity (age groups; performance status; active cancer vs. history of cancer in the past; and patients who were considered not evaluable in the different trials) was not possible. The analyzed studies reported symptomatic and asymptomatic VTEs. Still the analysis of the impact of thromboprophylaxis on each of these outcomes separately or on different points in time was not possible. Therefore, assessment of the efficacy for more clinically relevant outcomes, such as symptomatic VTE, was also not possible. Additionally, we were not able to evaluate the risk of bleeding, and important safety outcome in this setting, as it was reported for cancer patients.

Publication bias is always a concern, as negative trials are more commonly not published. As stated above, due to the small number of trials analyzed, the interpretation of the funnel plot was limited. The languages considered for searching studies included English, French, Spanish and Portuguese, but a large majority of the identified potentially eligible studies were

in English. Therefore, it is unlikely that language limitations were a significant source of bias.

Conclusion

We acknowledge that the limited amount of data included in the pooled analysis is problematic; however it is this same data that guides the formulation of clinical practice guideline recommendations. Hospitalized cancer patients constitute a unique population with increased risks for both venous thromboembolic events and major bleeding. Our analysis highlights the fact that the risk benefit ratio of current doses of thromboprophylaxis administered to all cancer patients admitted for medical illness is unclear and additional randomized trials are necessary to establish which cancer cohorts' benefit from the routine administration of LMWH.

SECTION 3: Cross-sectional Survey of Thrombosis Expert Physicians

Rational for the Survey

As discussed above, the decision to use thromboprophylaxis in medically ill hospitalized cancer patients is based on and extrapolations from studies evaluating thromboprophylaxis in all hospitalized medically ill patients (i.e. not necessarily with active cancer). Evidence from the systematic review suggests that the risks and benefits of primary thromboprophylaxis with anticoagulant therapy in hospitalized cancer patients are not known.

Before conducting a randomized controlled trial evaluating the efficacy and safety of primary pharmacological thromboprophylaxis, it was necessary to assess the following questions: 1) What is the most common strategy for primary thromboprophylaxis in hospitalized medically ill cancer patients ; 2) Is there perceived clinical equipoise regarding the use of pharmacological thromboprophylaxis in cancer patients hospitalized for medical illness; 3) What is the absolute accepted decrease in the rate of VTE or increase rate of major bleeding episode caused by thromboprophylaxis to determine the minimal clinically important difference (MCID)? Lastly, if a study evaluating pharmacological parenteral thromboprophylaxis in hospitalized medically ill cancer patients was conducted, will physicians participate in the study?

Aims of the Survey

The principal aim of this survey was to define the MCID (recurrent VTE and major bleeding episodes) for the sample size calculations needed for the future study.

The secondary goals of the survey were:

1. Evaluate clinical practice and gain knowledge about clinical equipoise
2. Assess the potential participation rate in the study
3. Assess current practices for thromboprophylaxis (including selection of the comparator)

Methods

Sample

We initially aimed to survey both Medical Oncology and Thrombosis experts. However, following the results from the pilot survey (see results below), it was noticed that medical oncologists had limited knowledge regarding the different types of parenteral thromboprophylaxis and did not feel comfortable establishing accepted rates of VTE and major bleeding associated with parenteral thromboprophylaxis. Therefore, we focussed on targeting Canadian Thrombosis Physicians Experts. These experts were identified through the Thrombosis Canada and VECTOR member roster (54 members identified), which also comprehend personal contacts from individual thrombosis centers. Our subjects were limited to physicians that are actively involved in the management and prevention of thrombosis in adult patients. Physicians who

treat children only were excluded because the clinical issues associated with pediatric thrombosis are different from that of adults.

Survey Design and Implementation

This survey was conducted using a web-based program, Survey Monkey, an easy-to-use tool for survey creation, distribution and data analysis. Survey Monkey also helped improve response rates with custom invitations.

Its primary strength is its intuitive Web interface, which makes it easy for most individuals to create surveys and export collected data. It has advanced features, like the ability to branch questions based on response and exporting to different formats, including HTML, CVS and SQL. Furthermore, the software has a free limited account that can store 100 responses, enough for the purposes of this survey. Survey Monkey also helped improve response rates with custom invitations. The results were stored on the web and the descriptive analysis was obtained through the site.

A pre-survey letter introducing the survey was sent prior to the individually addressed e-mail to each physician containing a link for the survey. The participation in the survey was interpreted as consent, and confidentiality was guaranteed for the participants. A total of two reminders were also sent out at 1-week intervals.

Survey Content

Prior to the dissemination of the survey, a pre-survey letter was sent to all potential respondents. This letter served to introduce the survey and make the potential respondents aware of its intent. In cases where the survey monkey was blocked by the firewall, should the potential respondent be interested, they could contact the principal investigator (PI) and the survey could be sent to another e-mail or in a PDF format. The goals and importance of the survey were also communicated at that time.

The survey questionnaire is depicted in Appendix 5. Subjects were first asked general questions about pharmacological parenteral thromboprophylaxis in cancer patients, followed by the use or not of established guidelines. The description of the most commonly used guidelines was provided. The PI proceeded to ask about the risk /benefit ratio in this population and the clinical equipoise around the subject. Questions regarding the willingness in enrolling patients in a clinical trial, schedules, doses, comparators and MCID were asked. We decided to simplify the questionnaire and ask only about the MCID in terms of absolute risk reduction in order to make it simpler, shorter and avoid redundancy. Finally, questions about demographic data were asked.

Pilot

Comprehensiveness, acceptability and validity of the survey questions were assessed by disseminating a preliminary draft of the survey instrument to the supervisors and to assess the comprehensiveness, redundancy and clarity of

the survey instrument. A focus group of 8 Ottawa hospital physicians (medical oncology, radiation oncology, and thrombosis) assessed the survey's face and content validity. After both phases, the survey was reviewed based on the feedback obtained and minor changed were made to the survey to account for the received feedback.

Test-retest reliability was initially planned but was not possible as the oncology group (both medical and radiation oncology) was not familiar with all the available options for thromboprophylaxis in medically ill non-oncologic or oncologic patients or to what could be a reasonable reduction on VTE rates or expected bleeding rates with thromboprophylaxis. Test-retest reliability could not be formally calculated, as many medical oncologists and radiation oncologists in the focus group could not complete the initial survey. Consequently, an Internet based survey was carried out to all Thrombosis Canada and VECTOR physicians who are actively involved in the management and prevention of thrombosis in adult patients.

Analysis

Descriptive survey data (%, 95% CI) was analyzed and summarized. Analytic comparisons were made among relevant demographic subgroups regarding practice patterns and willingness to conduct future trials of thromboprophylaxis in hospitalized cancer patients.

Results

After the first submission the response rate was 44 % (24/54). After the initial e-mail with the link for the survey was sent, two reminders were sent, one week apart. After the first and second reminders, the response rates were 50% (27/54) and 67% (36/54), respectively.

The majority of responders were hematologists (68.6%), followed by internists (25.7%) and medical oncologists (5.7%). The majority of responders were male (57.1%), young adults (51.4%), practicing for more than 10 years (60%). All respondents practiced in academic centers, and, despite the fact that for the majority (54.3%) spent less than 25% of their practice working with cancer related VTE, for 17% of the surveyed doctors it represented more than 50%. The majority of responders were from Ontario (65.7%), followed by Quebec (20%).

The majority of doctors (75%; 95% CI: 60.3 to 85%) always recommend the use of thromboprophylaxis in adult patients with active cancer (non-hematological malignancies) hospitalized for acute medical illness (not due to surgery) who are neither actively bleeding nor at high risk of bleeding. The type and dose regimens used for thromboprophylaxis are depicted in Table 6.

Table 6. Drugs/dose/schedules usually used for thromboprophylaxis in medically ill adult hospitalized patients with active cancer

Options	Response (N=36)
UFH 5,000 units, SC, twice a day (N, %)	0 (0)
UFH 5,000 units, SC, three times a day (N, %)	0 (0)
Enoxaparin 30mg, SC, twice a day (N, %)	0 (0)
Enoxaparin 40mg, SC, daily (N, %)	13 (36.1)
Dalteparin 5,000 units, SC, daily (N, %)	20 (55.6)
Tinzaparin 4,500 units or 75 units/kg, SC, daily (N, %)	0 (0)
Fondaparinux 2.5mg, SC, daily (N, %)	0 (0)
None (N, %)	1 (2.8)
*Other (please specify) (N, %)	2 (5.6)

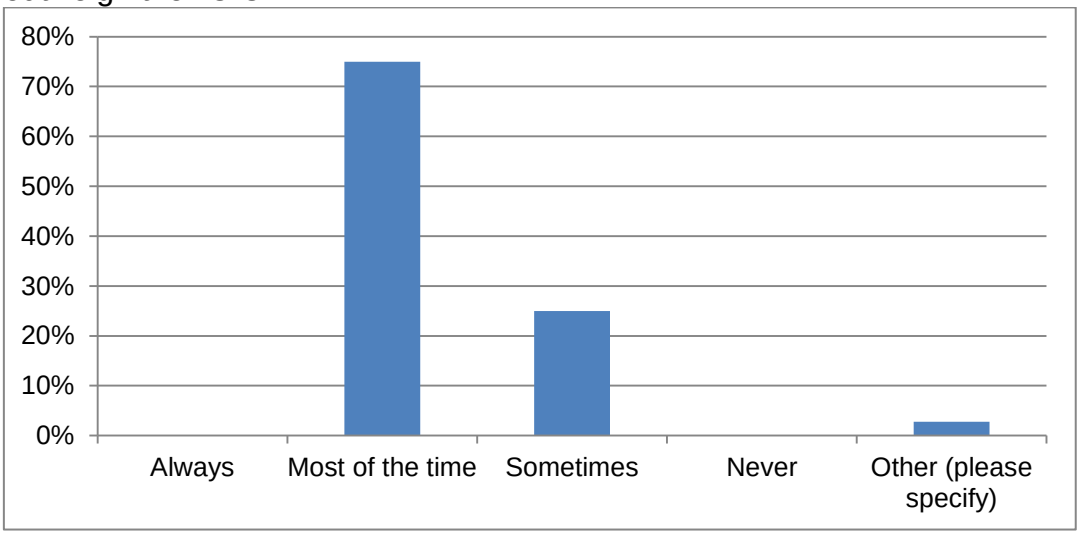
SC: subcutaneous; UFH: unfractionated heparin.
*Other; Enoxaparin 40mg SC, daily, Dalteparin 5000, SC, daily or Tinzaparin 75u/kg/SC

More than 90% (95% CI: 79.7 to 96.9%) of doctors follow the recommendations of one or more guideline when deciding about thromboprophylaxis for adult patients with active cancer, hospitalized for medical illness. The most common guidelines for decision-making on thromboprophylaxis for hospitalized cancer patients were ACCP (30) (87.0%), followed by ASCO (42) (33.3%) or guidelines from their own institution (24.2%). Medical oncologists (n=2) follow the NCCN guidelines (43).

The majority (75%; 95% CI: 60.3-85%) of responders indicated that the benefits of pharmacological parenteral thromboprophylaxis outweigh the risks in

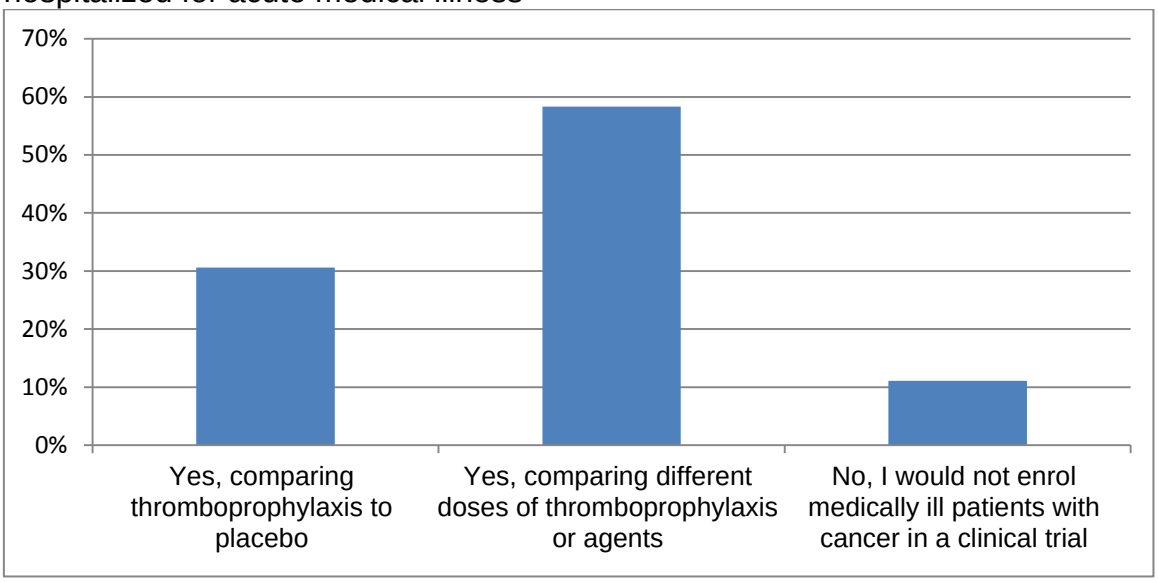
adult patients with active cancer hospitalized for acute medical illness (see Figure 4). However, 63.9% (95% CI: 50.6 to 77.3%) believe there is still clinical equipoise around the use of thromboprophylaxis for this group of patients and 88.9% (95% CI: 77.3 to 95.8%), and would consider participating in a randomized trial (30.6% and 58.3% in a placebo controlled or comparing different agents/dosing randomized trial, respectively) (See Figure 5).

Figure 4: Responders who believe the benefits venous thromboprophylaxis outweigh the risks



Other: “need to know the risks of course.”

Figure 5: Response to consideration for enrolling patients in a randomized trial assessing the use of thromboprophylaxis in adult patients with active cancer hospitalized for acute medical illness



For the responders that would consider participating in a placebo-controlled trial, the absolute reduction in symptomatic VTE reported as the MCID was 2% (63.6%) (See Figure 6), while the absolute "acceptable" increase in major bleeding events was 1% (63.6%) (See Figure 7). The most common drug and doses of choice to compare against placebo were enoxaparin 40mg, SC daily (22%) dalteparin 5000 unit SC daily (22%), fondaparinux, 2.5mg SC daily (22%) and tinzaparin 4,500 units or 75 units/kg SC daily (19.5%) (See Table 7).

Figure 6: Minimal absolute reduction in symptomatic proximal DVT and PE required for placebo-controlled trial

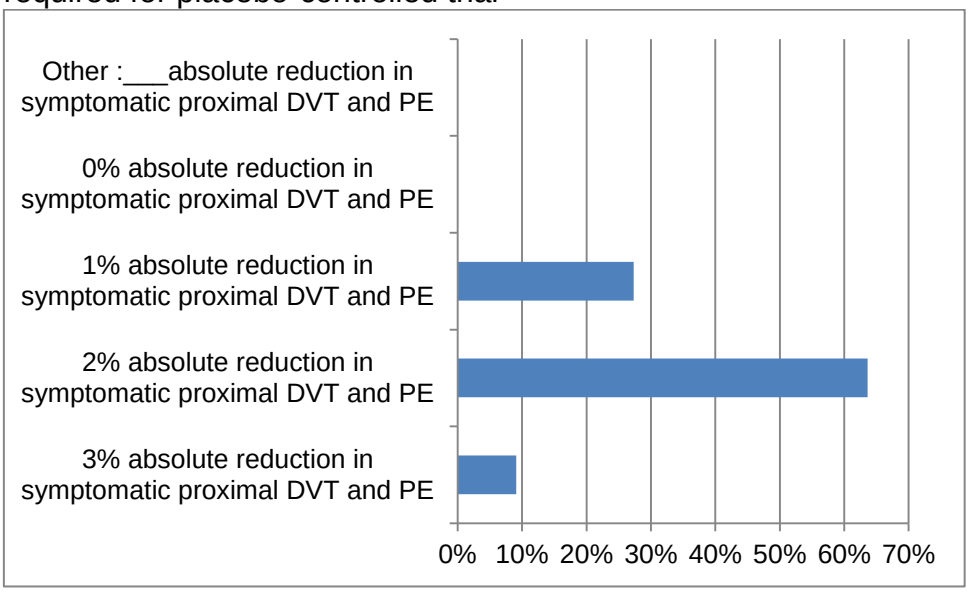


Figure 7: Maximal acceptable absolute increase in major bleeding for placebo-controlled trial

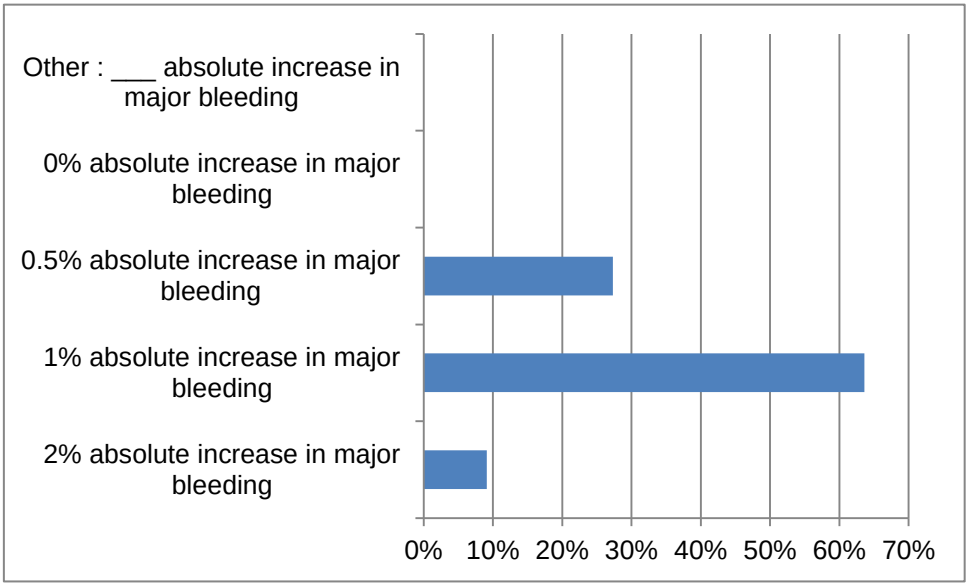


Table 7. Drugs/doses chosen to compare to placebo in a clinical trial to study the role of thromboprophylaxis in medically ill adult hospitalized patients with active cancer

Options	Response (N=41^)
UFH 5,000 units, SC, twice a day (N, %)	0 (0)
UFH 5,000 units, SC, three times a day (N, %)	2 (4.8)
Enoxaparin 30mg, SC, twice a day (N, %)	1 (2.4)
Enoxaparin 40mg, SC, daily (N, %)	9 (22)
Dalteparin 5,000 units, SC, daily (N, %)	9 (22)
Tinzaparin 4,500 units or 75 units/kg, SC, daily (N, %)	8 (18.5)
Fondaparinux 2.5mg, SC, daily (N, %)	9 (22)
*Other (please specify): (N, %)	3 (7.3)

SC: subcutaneous; UFH: unfractionated heparin.
*Other: "Rivaroxaban, new oral agents, time to move away from injected therapy"
^ Respondents could choose more than one answer. Total of 11 respondents.

For the responders that would consider participating in a randomized controlled trial comparing different doses of thromboprophylaxis or agents, the absolute reduction in symptomatic VTE between the two arms reported was 1% and 2% for 47.6% of the respondent (for each option) (See Figure 8). One respondent reported an absolute reduction of 5%. The mean of the response was 1.67% (95% CI: 1.25-2.1) for an MCID of 2%. The absolute "acceptable" increased in major bleeding events between the two arms was 1% (42.9%) (See Figure 9). The most common drug chosen to be compared was enoxaparin (17/65 (26%)). Two different doses were suggested for enoxaparin: 30 mg twice daily and 40 mg SC OD.

Figure 8: Minimal absolute reduction in symptomatic proximal DVT and PE required for different dosing/agents randomized-controlled trial

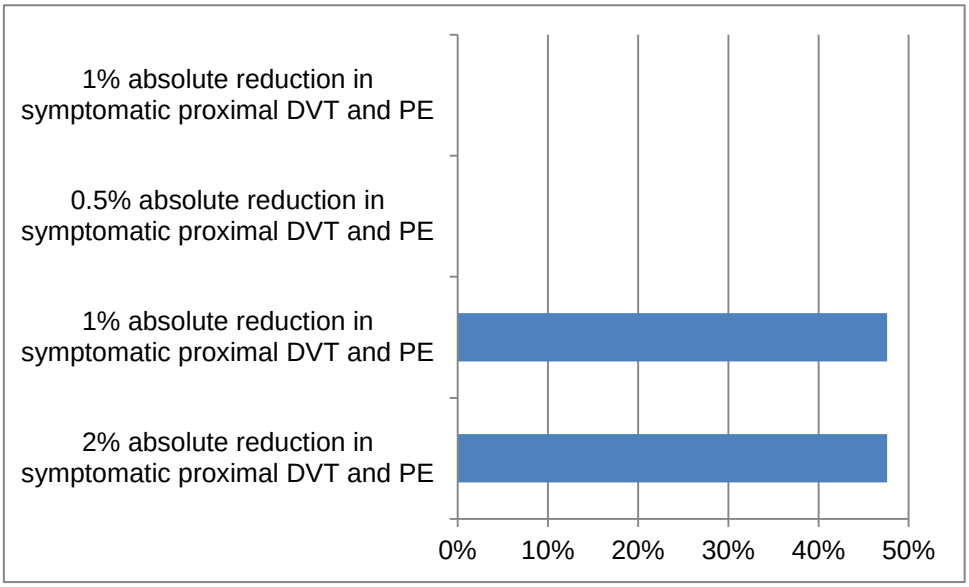


Figure 9: Maximal acceptable absolute increase in major bleeding for different dosing/agents randomized-controlled trial

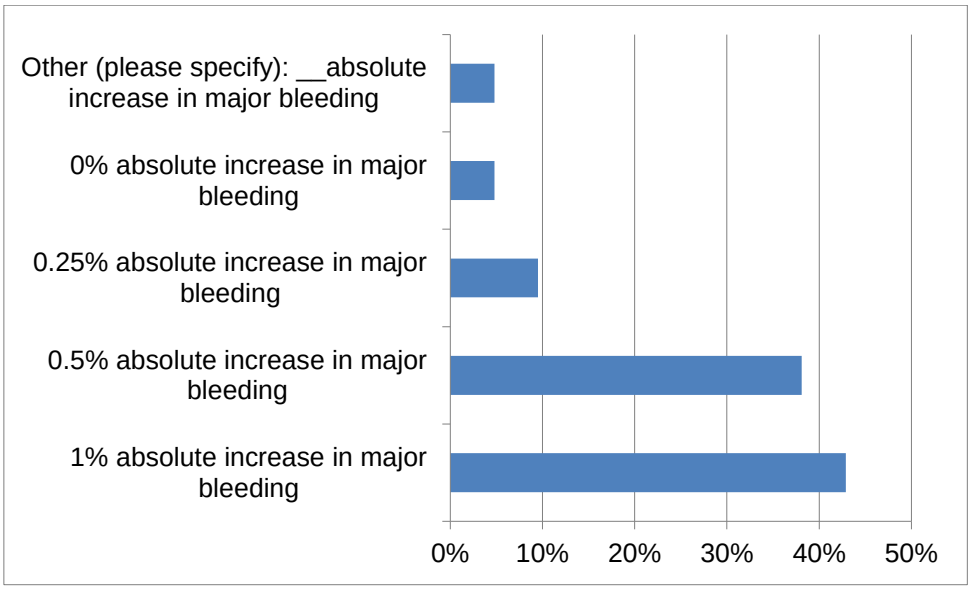


Table 8. Drugs/doses chosen to be compared in a clinical trial to study the role of thromboprophylaxis in medically ill adult hospitalized patients with active cancer

Options	Response (N=65)
UFH 5,000 units, SC, twice a day (N, %)	8 (12.3)
UFH 5,000 units, SC, three times a day (N, %)	4 (6.1)
Enoxaparin 30mg, SC, twice a day (N, %)	5 (7.7)
Enoxaparin 40mg, SC, daily (N, %)	12 (18.4)
Dalteparin 5,000 units, SC, daily (N, %)	15 (23)
Tinzaparin 4,500 units or 75 units/kg, SC, daily (N, %)	12 (18.4)
Fondaparinux 2.5mg, SC, daily (N, %)	7 (10.8)
*Other (please specify) (N, %)	5 (7.7)

SC: subcutaneous; UFH: unfractionated heparin.
*Other: "LMWH at half-therapeutic dose; Rivaroxaban; 10 mg, daily; Apixaban; Dalteparin 7500 SC,daily; Enoxaparin 40 mg SC,BID"
^ Respondents could choose more than one answer. Total of 21 respondents.

Discussion

This clinical survey of thrombosis experts confirms that there is equipoise regarding the use of parenteral pharmacological thromboprophylaxis in medically ill cancer patients. A majority of physician would participate in a randomized controlled trial on this topic. The respondents favored a dose/agent finding trial compared to a randomized controlled trial. An RCT where different doses of enoxaparin would be used was the most frequent option selected by the respondents. The MCID chosen by the majority of respondents for this particular study was 2% for absolute reduction in symptomatic VTE and 1% for the absolute "acceptable" increased in major bleeding events between the two arms.

Survey Population

The population frame was composed of subjects with expertise in thrombosis, capable of interpreting the literature, with both clinical and research experience. Canadian thrombosis expert physicians were identified through the Thrombosis Canada and VECTOR collaborative groups. These groups were easily accessible and we expected a high response rate due to the collegial nature of the thrombosis experts in Canada. A survey of Thrombosis Canada and VECTOR physicians was considered a more "accurate" measure of effect than a sample from another larger group (e.g. American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO)). Moreover, the potential number of physicians with expertise in thrombosis is small in these other medical associations (ASCO, ESMO). This became more evident during the pilot phase of this survey, when it appeared that oncologists lack the expertise required to answer important clinical questions regarding thromboprophylaxis. Furthermore, all thrombosis experts reported having significant experience in caring for cancer-related thrombosis issues and more than 45% of them stated that caring for cancer patients with thrombotic issues represented more than 25% of their clinical practice. This allowed us to establish a more clinically relevant MCID for the clinical trial (See Section 4)

Response Rate

Our survey response rate was good (67%). Response rates for physician's surveys have been previously reported at around 58% (83). Survey response is dependent on 3 major factors: 1) the importance of the survey to the people who receive it, 2) the design of the survey and 3) the length of the survey. We believe our response rate was good partly because we used a select group of respondents who have close links with other thrombosis centers. We sent reminders to all non-respondents and we believe that the survey addressed an important question. The survey was succinct and clear, and Survey Monkey is an easy-to-use format.

Survey Results

Current Standard of Care

As expected, the majority (75%) of responders recommend thromboprophylaxis in adult patients with cancer hospitalized for acute medical illness. This agrees with recent guidelines (30, 42-44). A large majority of respondent (75%) reported that the risk of parenteral pharmacological thromboprophylaxis outweighed the risk of bleeding in a majority of cancer patients. The ACCP guidelines (30) were the most frequently (87.9%) selected guidelines. These guidelines are prepared by hematologists and are a common reference for thrombosis doctors, as 1) they cover several different scenarios and indications for anticoagulation/ thromboprophylaxis, and 2) they are transparent and evidence based. Note that medical oncologists usually follow the

NCCN guidelines (43), a choice by only 3 responders, 2 of whom were medical oncologist. Nonetheless, all guidelines have similar recommendation regarding the use of parenteral pharmacological thromboprophylaxis in cancer patients hospitalized with medical illness.

Clinical Equipoise and Need for a Study

Interestingly, the lack of evidence from randomized controlled trials supporting the efficacy of thromboprophylaxis the risk of bleeding in this population is generating significant clinical equipoise (63.9%). The clinical equipoise seems to center on dosing of parenteral pharmacological thromboprophylaxis used in this population.

A large majority of respondents selected LMWH (67.8%) compared to UFH (18.4%) or fondaparinux (10.8%). This is not surprising given that LMWH has a better safety profile compared to UFH. Low molecular weight heparin is easier to use, is associated with higher risk of heparin-induced thrombocytopenia (0.1 for LMWH compared to 1% for UFH) and is associated with lower risk of a major bleeding among hospitalized medically ill patients (34). Similarly, LMWH was preferred over fondaparinux (indirect Factor Xa inhibitor) or other the direct oral Factor Xa inhibitors (rivaroxaban or apixaban). Two respondents selected rivaroxaban or apixaban as comparators. Indirect, post-hoc data from trials comparing fondaparinux or rivaroxaban with LMWH suggest that specific factor Xa inhibition might be less efficacious than LMWH inhibition in cancer patients

(38, 79). The MAGELLAN trial (38) assessed the efficacy and safety of rivaroxaban in medically ill patients. The supplemental data showed that patients with active cancer randomized to 35±4 days of rivaroxaban had more asymptomatic proximal or symptomatic VTE than patients receiving only 10±4 days of enoxaparin (9.9% (20/202) *vs.* 7.4% (15/203)) (38). Although this difference was not statistically significant due to the small number of cancer patients enrolled, there was a statistically significant increase in major and clinically relevant non-major bleeding episodes with rivaroxaban compared with enoxaparin (5.4% *vs.* 1.7%). Therefore, parenteral pharmacological thromboprophylaxis using LMWH seems to be the optimal choice.

More respondent have selected that they would favor a trial assessing different doses of enoxaparin (40 mg *vs.* 30 mg, SC BID or 40 mg, SC BID). Currently, a dose of 40 mg would be the recommended dose for thromboprophylaxis of hospitalized cancer patients who are medically ill Previous biomarkers studies have shown that higher doses of LMWH (i.e. higher than 40 mg once daily) might increase its efficacy in cancer patients. For example, D-dimer levels and prothrombin fragments(F1+2) are recognized indicators of thrombin generation and are elevated in cancer patients (84, 85). Enoxaparin has been shown to decrease the level of D-dimer and F1+2 in hospitalized medically ill patients (85, 86). Furthermore, higher doses of enoxaparin (80 mg) has been reported to significantly decrease the peak thrombin levels compared to lower dose (40 mg) in hospitalized cancer patients, suggesting that the heightened pro-thrombotic state related to cancer might be

attenuated by higher doses of LMWH (86). Furthermore, previous clinical studies in other high-risk cancer populations assessing the use of higher doses of LMWH have demonstrated significant benefits (80, 82, 87) without increasing the risk of bleeding. For example, weight adjusted dalteparin was shown to significantly decrease VTE and VTE-related death among ambulatory advanced pancreatic cancer patients receiving gemcitabine chemotherapy (87). Similar results were reported in a trial assessing enoxaparin at a dose of 1 mg/kg daily in pancreatic cancer patients (80). Therefore, assessing different doses of LMWH has a strong biological and clinical rational. Given that most respondents selected different doses of enoxaparin, we are proposing to compare enoxaparin 40 mg once daily to enoxaparin 30 mg twice daily.

Minimal Clinically Significant Difference

Most respondents selected a MCID of 2% for recurrent VTE and an MCID for major bleeding of 1%. However, there is not data from published trials for rates of bleeding specific to cancer patients,. Therefore, a trial with an MCID of 2% for recurrent VTE as primary endpoint instead of a composite endpoint would be recommended.

Limitations

Although we met some problems with the Internet survey such as the firewalls which prevented some doctors from receiving the survey through the monkey link, participants contacted us for the monkey link to be sent to another

address. The survey was limited to Canadian doctors, specifically from university centers, and, therefore, may not reflect the worldwide opinion on the subject. Nonetheless, experts on the subject and leaders in the field provided the most relevant opinion on the matter. Additionally, some questions should have allowed more than one answer, such as “Which drugs/dose/schedules do you usually use for thromboprophylaxis in medically ill adult hospitalized patients with active cancer”, and this was pointed out by some responders. This, however, did not influence on our primary endpoint, MCID. The responses were based not only in the available literature, but also on their experiences and availability of anticoagulants (the anticoagulants funded by the government). Having said that, this still reflects the available literature for thromboprophylaxis in a non-cancer medically ill patient population.

Conclusion

There is clinical equipoise regarding the use of parenteral pharmacological thromboprophylaxis in cancer patients hospitalized with medical illness. Based on the survey results from thrombosis experts, we propose to perform a double blind randomized controlled trial comparing enoxaparin 40 mg SC once daily to enoxaparin 30 mg SC twice daily using a MCID of 2% for the decrease in the rate of VTE. Before embarking into a multi-center double blind randomized controlled trial, a pilot study is necessary to ensure feasibility (See Section 4).

SECTION 4: Design of a Pilot Study

We describe the design of a pilot study in this section. The study aims to evaluate the feasibility of a multicenter randomized controlled trial where the arms of interventions and MCID were delineated by the systematic review and clinical survey findings in this study. The systematic review highlighted the clinical equipoise around the efficacy of parenteral pharmacological (LMWH or fondaparinux) thromboprophylaxis in hospitalized medically ill patients with cancer. Unfortunately, the incidence of bleeding in cancer patients was not reported and safety of thromboprophylaxis could not be evaluated. Based on the results from the Thrombosis Expert Survey, it was confirmed most physicians were of the same opinion that there is no one superior intervention. Thrombosis physicians would be willing to enrol medically ill patients with cancer in a clinical trial evaluating the efficacy and safety of thromboprophylaxis. However, given the high risk nature of VTE in cancer patients, the majority of physicians would prefer to enrol patients in a randomized controlled trial comparing higher doses (e.g. enoxaparin 30 mg SC BID) to standard doses (e.g. enoxaparin 40 mg daily) of thromboprophylaxis. The MCID most elicited by the survey was an absolute reduction in VTE by 2% (i.e. from 7 to 5% absolute event rates during hospitalization).

Based on this information, we propose to perform a double blind, multicenter, randomized, controlled trial comparing enoxaparin 40 mg SC once daily to enoxaparin 30 mg SC twice daily, using an MCID of 2% for the decrease

in the rate of VTE. Before embarking into a multi-center double blind RCT, a pilot study is necessary to ensure feasibility.

Pilot studies are an important step in the research process, providing an opportunity to identify and prepare for the challenges of evaluating an intervention. One of the advantages of conducting a pilot study is that it might give advanced warning about where the main research project could fail, where research protocols may be breached, or whether proposed methods or instruments are inappropriate or too complicated (88). In general, the term pilot study has been used to describe a feasibility study intended to guide the planning of a large-scale investigation (89). It is also used to assess the safety of treatment or interventions, to assess recruitment potential, to assess the feasibility of international collaboration or coordination for multicentre trials, to evaluate surrogate marker data in diverse patient cohorts, to increase clinical experience with the study medication or intervention, and identify the optimal dose of treatments for the phase III trials (90). Problems with feasibility (e.g., ineffective delivery) or acceptability (e.g., ineffective uptake) rather than ineffectiveness of the intervention itself can lead to misleading results of a trial (91).

Reasons to conduct a pilot study include (88):

1) To determine the acceptability of the study design by the participants by obtaining estimates of the recruitment rates and rates of patients screened and eligible (92)

2) To estimate the expenses related to conducting an RCT
3) To provide estimates of outcome rates to more precisely estimate sample size
4) To obtain an approximation of sample size prior to embarking on the main study

Aside from determining feasibility and acceptability, this pilot study would also serve to obtain estimates of loss to follow-up and withdrawals, obtain a precise estimate of the primary outcome event rate (VTE and major bleeding episodes), and have a preliminary idea of effect size for the interventions. The sample population for this pilot study would be representative of the target study population, and the same inclusion/exclusion criteria as the main study will apply.

Objectives

Pilot study

The criteria for success of this pilot study will be based on the primary feasibility objectives, providing the basis for interpreting the results of the pilot study and determining whether it is feasible to proceed to a main study (93). The recruitment rate over a 6 month period will be assessed and evaluated according to the following success criteria: 1) at least 70% of all eligible patients can be recruited; 2) complete follow-up in at least 95% of all recruited subjects;

and 3) 98% of patients had to receive study drug within 24 hours of randomization.

Main RCT

To assess the efficacy and safety of higher dosing (enoxaparin 30mg, SC, twice a day) thromboprophylaxis among hospitalized medically ill cancer patients in comparison to enoxaparin 40mg, SC, daily.

Methods

Study Design

Study Design–Pilot

A prospective, active-controlled, double-blinded, randomized clinical trial study, including consecutive medically ill cancer patients admitted to the Ottawa General Hospital over a 6-month period. Patients will be randomized, in the first 48 hours of admission, to thromboprophylaxis with enoxaparin 30mg,SC, BID vs. enoxaparin 40mg, SC, OD (and associated placebo), beginning at randomization or the following day and continuing for the duration of the hospitalization.

Study Design–Main RCT

A prospective, active-controlled, double-blinded, multicenter randomized clinical trial study, including consecutive medically ill cancer patients admitted to the Ottawa General Hospital. Patients will be randomized, in the first 24

hours of admission, to thromboprophylaxis with enoxaparin 30mg, SC, BID vs. enoxaparin 40mg, SC, OD, beginning at randomization or the following day and continuing for the duration of the admission.

Study Participants for the Pilot and Main RCT

Consecutive medically ill cancer patients admitted to the hospital, who fulfil the inclusion and exclusion criteria and sign the consent form, will be enrolled. A research coordinator will contact the coordinator of the medical oncology ward daily to ensure that all potential patients are recruited.

Inclusion Criteria

- Medically ill cancer patients (solid malignancy, with evidence of disease or on oncological treatment) admitted to the Ottawa General Hospital
- Estimated survival > 1 month
- Age ≥18 years
- Hemoglobin ≥ 80g/L
- Able and willing to sign Research Ethics Board (REB)-approved written consent form
- Able and willing to comply with study procedures and follow-up examinations contained within the written consent form.

Exclusion Criteria

- Admitted to the intensive care unit or acute monitoring area

- Major surgical or invasive procedure within the last month
- DVT, PE, or major bleeding within 3 months
- Platelet count of less than 30 x 109/L;
- Contraindication to heparin therapy;
    - History of heparin induced thrombocytopenia (HIT);
    - Actively bleeding;
    - Uncontrolled arterial hypertension (systolic blood pressure of more than 200 mm Hg, diastolic blood pressure of more than 120 mm Hg, or both); on more than one reading;
    - Documented peptic ulcer within 6 weeks;
    - Severe hepatic failure (INR >1.8;)
    - Creatinine clearance of < 30 ml/min as calculated by the Cockcroft-Gault formula;
    - Heparin or pork allergy
- Other contraindication to anticoagulation;
- Acute stroke within 3 months
- Recent hemorrhage in brain metastases;
- Active bacterial endocarditis, or other conditions that could increase the risk of hemorrhage;
- Requiring therapeutic anticoagulation or already on anticoagulation (LMWH, warfarin (Coumadin), rivaroxaban (Xarelto), dabigatran (Pradaxa), apixaban (Ellquis)

- Receiving any type of anticoagulant therapy for more than 48 hours prior to admission;
- Geographic inaccessibility (less likely to comply with required follow-up visits and care);
- Participating in another interventional trial that may result in co-intervention or contamination;
- Pregnant or within 6 weeks postpartum;
- Unable or unwilling to provide informed consent.
- Any other medical, psychological, and/or social reason which, in the opinion of the investigator, would prohibit the understanding of the informed consent and/or make administration of the study drug hazardous.

Study Interventions

Arm A: Enoxaparin 40mg, SC, OD

Subjects in arm A will receive a daily subcutaneous injections of 40mg of enoxaparin and placebo, 12 hours apart, beginning at randomization or the following day, and continued for the duration of hospitalization.

Arm B: Enoxaparin 30mg, SC, BID

Subjects in arm B will receive a subcutaneous injection of 30mg of enoxaparin twice a day, beginning at randomization or the following day, and continued for the duration of hospitalization.

After obtaining informed consent, patients who fulfill the inclusion criteria will then be randomized to Arm A or B by telephone, using a central location (OHRI). A set of random numbers will be generated and the results communicated to the study coordinator. The study pharmacist would dispense previously numerated packages containing study medications (pre-filled syringes).

The use of mechanical thromboprophylaxis will not be allowed. The use of concomitant low dose aspirin, ticlopidine and clopidogrel would be allowedIf during the admission the subjects need to receive UFH, direct thrombin inhibitors, warfarin or thrombolytic therapy, the study medication would be stopped and patients removed from the protocol.

This would allow assessing on how randomization will be received by potential participants since the acceptability of clinical equipoise can be crucial in determining whether participants consent to randomization and accept their group allocation (94). Once randomization is done, the intervention should start in the same day. Patients, ward staff, ultrasound technologists, and research personnel will all be blinded to drug allocation.

Outcomes

Primary Outcome or the Pilot Study

- Recruitment rate

Secondary Outcomes for the Pilot Study

- Refusal rate
- Rate of complete follow up
- Rate of patients who received the drug within 24 hours of randomization
- Variance estimate Rate of patients excluded due to each exclusion criteria
- Rate of exclusion due to failure to screening patients in 24 hours of hospital admission
- Rate of patients who received at least 90% of doses
- Rate of drop outs in each arm
- Reasons and time for the dropouts
- Work load: money spent for patients, number of hours, per study nurse per patient, spent in identifying potential candidates, screening and enrolment.
- Rate of thromboembolic events in each arm.
- Rate of major bleeding in each arm.

Primary Outcome for the Main RCT

- VTE –composite outcome of proximal DVT and/or PE

Secondary Outcomes for the Main RCT

- Each component of the primary outcome (symptomatic DVT, asymptomatic DVT, fatal-PE, non-fatal PE), major bleeding, thrombocytopenia, HIT and allergic reactions.

DVT would be defined as:

- Lower extremity US revealing non-compressibility at the trifurcation of the popliteal vein or above;
- Venography demonstrating a constant intraluminal-filling defect above the trifurcation of the popliteal vein;

PE would be defined as:

- Pulmonary angiography demonstrating a new constant intraluminal filling defect or a cut off of a vessel;
- Ventilation/perfusion scanning with a high probability of PE; OR CT pulmonary angiography (CTPA) demonstrating new intraluminal filling defect in a segmental or greater sized pulmonary artery;
- PE discovered at autopsy.

HIT would be defined as defined:

- **Thrombocytopenia, positive** ELISA for antibodies directed against the PF4/heparin complex, and compatible clinical scenario (4T)(95)

Major bleeding would be defined according to previously published criteria (96):

- Fatal bleeding;
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome;
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

All suspected primary or secondary outcomes during follow-up will be blindly and independently adjudicated by an adjudication committee. The committee will be composed of 3 experts in clinical research and thrombosis and will meet monthly during the active phase and follow-up phase. Detailed clinical information, laboratory and imaging results will be provided to the committee for review.

Schedule

Baseline Investigations

Prior to randomization and receiving the first dose of enoxaparin, patients will have undergone the following investigations to qualify for enrolment. The following reports would have to be available for assessment of eligibility:

- Blood work including hematology (hemoglobin and platelet count within 14 days), serum creatinine, and coagulation (PTT, INR)
- Proximal bilateral lower extremity compression US exam in the first 24 hours of admission
- CXR (or CT Chest) (≤ 90 days)
- Patients with symptoms compatible with PE should have a CTPA or ventilation-perfusion scan

Investigation Schedule

- Follow-up hematology and biochemistry (haemoglobin, platelet count, creatinine) will be done on day 2, and once a week until discharge from hospital.
- Screening Doppler ultrasound will be done at days 7 and 14.
- Any suspicious episode of DVT should be confirmed by U/S
- Any suspicious episode of PE should be confirmed with CTPA, ventilation-perfusion scan or autopsy.

6.3 Follow-up

- Subjects would be contacted on days 21, 30, and 90 (personally or over the phone).
- Any suspicious episode of DVT should be confirmed by U/S or venography

- Any suspicious episode of PE should be confirmed with CTPA, ventilation-perfusion scanning, pulmonary angiography or autopsy.

Sample size

Pilot Study

The pilot study would be done over a fixed period of 6 months. This will ensure proper assessment of the recruitment rate and other feasibility criteria (refusal rates, loss to follow-up, etc). Approximately 4 cancer patients are hospitalized every day for medical illness at the Ottawa Hospital (Medical Oncology, Radiation Oncology, Gyne-oncology). It is estimated that a conservative accrual rate of 40 patients per month, 240 patients can be recruited over 6 months.

Main RCT

As discussed previously, the systematic review showed that approximately 7% of hospitalized medically ill cancer patients would have a VTE complication during hospitalization despite pharmacological thromboprophylaxis with standard doses LMWH. The survey of Canadian Thrombosis Experts identified the MCID to be approximately 2%. In order words, if it is demonstrated that higher doses of thromboprophylaxis (enoxaparin 30 mg SC BID) can decrease the absolute risk of VTE by 2%, physicians would likely change practice and use enoxaparin 30 mg SC BID for hospitalized medically ill cancer patients.

The null hypothesis would be that enoxaparin 30 mg SC BID does not decrease the rate of VTE by 2% compared to enoxaparin 40 mg SC OD. As such, a 5% chance of falsely rejecting the null hypothesis (i.e. two tailed alpha = 0.05) would be accepted. A 20% chance of falsely not rejecting the null hypothesis (i.e. power = 80%) would be accepted. To achieve these standards a sample size of 5918 (n=2959 per arm) is required. The total sample size would need to be adjusted for loss to follow-up and dropouts based on the estimates from our pilot study.

Data Analysis

Pilot Study

The rates of the primary and secondary outcome measures will be reported and 95% confidence intervals will be provided.

Main RCT

Descriptive statistics would be used to examine the baseline characteristics of included patients. Standard deviations would be reported for all characteristics expressed as continuous variables. Medians and ranges will be presented for discrete data.

Analyses would be performed by intention to treat (ITT). Safety analysis would be done in a ITT safety population (all patients from the ITT population who received at least one dose of the study drug). The incidence of VTE during

hospitalization would be reported and compared by an unadjusted Fisher's exact test of proportions. Ninety five percent confidence intervals would be provided.

The proportions of patients with secondary outcomes would also be compared in the control and intervention groups by an unadjusted Fisher's exact test of proportions. Kaplan Meier analysis to examine time to VTE would be conducted over the follow-up period for both groups.

Feasibility

If the pilot is successful and demonstrate feasibility of the main RCT, the protocol will be presented to the Canadian VECTOR (Venous Thrombosis Clinical Trials Organization) network. A multi-center trial design would be required to enrol the total sample size within 5 years. The VECTOR group is a large multicenter (Ottawa, London, Montreal, Halifax) collaborative research group in venous thrombosis. This group has an excellent track record for completing thromboprophylaxis-related clinical trials. All centers within the VECTOR group are managing primary thromboprophylaxis in their centers. If feasible and endorsed by the VECTOR collaborative group, it would be uniquely positioned to answer this important research question.

All VECTOR centers have similar medical oncology hospitalization rates as the Ottawa Hospital. If the trial is deemed feasible locally, the total sample size could be achieved within 5 years by including patients at all VECTOR sites

1. Trial Coordinating Centre; Ottawa Hospital - Ottawa, Ontario
2. London Health Sciences Centre – London, Ontario
3. SMBD Jewish General Hospital – Montréal, Québec
4. St-Mary's Hospital – Montréal, Québec
5. Montreal General - Montréal, Québec
6. Winnipeg Health Centre – Winnipeg, Manitoba
7. QEII Halifax Health Science Centre – Halifax, Nova Scotia

Recruitment Strategies

Specific recruitment strategies would vary from site to site; however, the main sources of potential participants for this study are new admissions to hospital on the different oncology wards. Attending physicians and hospitalists will identify potentially eligible patients. They would briefly describe the study and ask if the patient was willing to meet with the study nurse to receive further information. If the patient was interested, the nurse reviews the study objectives, procedures, risks, and benefits as well as the voluntary nature of participation and the right to withdraw consent. The consent form would be provided in English or French, as the patient prefers, and sufficient time would be given for the patient to review it. The nurse answers the patient's questions about the study or refers the patient to the physician if more information is requested. Once the consent form is signed, a copy would be provided to the patient

Safety

A Data Safety and Monitoring Board (DSMB) would be created. The DSMB would be independent and is composed of 3 members (one statistician, one medical oncologist and one thrombosis expert). All members of the DSMB would remain at arms-length from the study. All adverse and severe adverse events would be reported to and reviewed by the DSMB. The DSMB would meet after the completion of the pilot study and every 500th participant is enrolled during the Main RCT. Should safety issues arise that the DSMB feel compromise participant safety, a meeting would be convened for all co-investigators to consider amending or stopping the study.

Ethics

This study would be conducted in accordance with the ethical principles of the current Declaration of Helsinki and would be consistent with the International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. The study would be conducted in compliance with the protocol. The protocol, any amendments as well as the subject informed consent would be reviewed by the Ottawa Hospital Research Ethics Board and Health Canada.

The doctors, nurses and the study coordinator would give all the appropriate scientific information to patients, plus a written consent form to make sure that their consent is informed. Given the pilot nature of this study, patients would be informed that the main objective is to assess the feasibility of a main

RCT. Patients would be able to participate or not in this study without any interference in their care.

Trial Management

The pilot study would be conducted in Ottawa whereas the main RCT would be coordinated from the Ottawa Hospital Research Institute's (OHRI) Clinical Epidemiology Unit, where the PI is based. The Multi-Centre Trial Coordinator, supervised by the PI, would be responsible for the day-to-day running of the study and conduct in the different centres. Study coordinators at each site would carry out patient screening, recruitment, case report form completion, initiation of study interventions, patient education, blood drawing and arranging follow-up visits.

Data management would be overseen by the OHRI CEP-Data Management Services (DMS) and the trial statistician. The DMS group would be responsible for database administration, data entry, and data management, including quality assurance activities. The cleaned database would be provided to the biostatistician for analysis, conducted under the supervision of PI and trial's statistician.

1) Roles of the principal applicant and co-applicants

The research team would be composed of experienced researchers and clinicians with expertise in thrombosis and clinical trials. Dr. P. Moretto is the

Principal Investigator of this study. She would regularly review the progress of the trial and, after consultation with co-investigators, give final approval to any changes to study procedures. Each co-investigator would be responsible for conduct of the study at their respective sites. One of the co-applicant's would be an expert in cost-utility analysis and a clinical trialist will provide methodological support for this trial.

2) Steering committee

A Steering Committee comprising all of the study's co-investigators would manage the overall conduct of the trial and would meet regularly via teleconference to ensure ongoing enthusiasm, for the trial and review the conduct of the trial. The first Steering Committee meeting would be scheduled before the initiation of the pilot study.

Anticipated results and conclusions

The results of this study, whether positive or negative, would be highly relevant to the clinical practice of medical oncologist, internists, family physicians and thrombosis specialists who manage hospitalized cancer patients with medical illness. Numerous recently published peer-reviewed narrative reviews and editorials have highlighted the importance of this clinical question. If our trial was feasible and successful, it would directly inform decision making regarding management of thromboprophylaxis in medically ill patients with cancer.

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Appendix 1: Grey Literature Search

We did a search for grey literature in OpenSIGLE, at opensigle.inist.fr.

- Search for thrombosis: 57 findings
- Search for thromboprophylaxis: 0 findings,
- Search for thrombosis and prophylaxis: 3 findings
- Kudma K. Optimization of thrombosis and embolism prevention after hip fractures treated by surgery. Thesis. Univerzita Karlova Praha, Czech Republic, 2001. Language: Czech
- Scottish Intercollegiate Guidelines Network. Prophylaxis of venous Thromboembolism: A national clinical guideline. Miscellaneous. United Kingdom, 2002.Language: English.
- Harrison J. Deep vein Thrombosis after total hip replacement: A review of the incidence, prophylaxis, diagnosis and economic impact of thromboembolic disease in lower limb joint replacement. A comparison of low molecular weight heparin and pneumatic plantar compression. Thesis. United Kingdom, 2000.Language: English.

None met our inclusion criteria (papers related to thromboprophylaxis in hospitalized medically ill patients or medically ill patients with cancer.

Grey literature at National Technical Information Service (NTIS) was also researched. This particular site gives us access to government-sponsored research.

www.ntis.gov/

- Search for thrombosis: 100 findings
- Search for thromboprophylaxis: 0 findings
- Search for thrombosis and prophylaxis: 6 findings

- Sauter RD. Clinical trial of aspirin, sulfinpyrazone or placebo for the prevention of deep vein thrombosis in patients undergoing total rip replacement. Technical report for National Heart and Lung Institute, United Stated, 1978.
- Hamilton MT. Case Study: The Venous Thromboembolism Collaborative Team at the Johns Hopkins Hospital. Technical report for Johns Hopkins Hospital, Baltimore, MD, 2009.
- McCormick JG, et al. Sudden Hearing Loss Due to Diving and Its Prevention with Heparin. Journal article. United States Navy, 1975.
- Author: N/A. Healthcare Inspection: Alleged Quality of Care Issues in the Geriatrics and Extended Care Service VA North Texas Health Care System Dallas, Texas. Technical report for Texas. Department of Veterans Affairs, 2010
- Rue LW, et al. Thromboembolic Complications in Thermally Injured Patients. (Renouncement with New Availability Information). Journal Article. Army Inst. of Surgical Research, Fort Sam Houston, TX, 1992.

- B. Holley C, et al. Difference Finite Durations of Anticoagulation and Outcomes Following Idiopathic Venous Thromboembolism: A Meta-Analysis. Journal article, Walter Reed Army Medical Center, Washington, DC, 2010.

APPENDIX 2: Example of Contact e-mail

Dear Professor X:

My name is Dr. Patricia Moretto and I am a clinical fellow in medical oncology, pursuing my master's degree at the University of Ottawa under the supervision of Dr Marc Carrier. We are in the process of performing a systematic review on thromboprophylaxis in acutely ill medical patients with cancer, and we would appreciate your collaboration by sending us individual data from your paper "XXXX" published in XX in XX.

Please let us know if you are able to help. We recognize that this means extra work for a previous project, but your help would be most appreciated. In return, we offer you authorship in our publication.

Specifically, we need information on patients with cancer:

- Median age and range for patients with cancer in each group, enoxaparin and unfractionated heparin (UFH), if available
- Any information on performance status, localized vs advanced disease, active treatment or not--- in each group, enoxaparin and UF, if available
- For each subgroup of cancer patients receiving enoxaparin or UFH : Total number of VTE, number of patients who had screening for DVT, total number of DVT, total number of symptomatic DVT and number of symptomatic proximal DVT, total number of asymptomatic DVT and number of asymptomatic proximal DVT. Number of PE, number of fatal PE, number of death of all causes, total number of bleedings, number of major bleedings, number of fatal bleedings.

Thank you for your help which is very much appreciated.

Best wishes,

Dr Patricia Moretto

APPENDIX 3: Other Potentially Eligible Trials

Perez et al (56)

Perez et al (56) published in 1988 singe center, open-label, active controlled RCT. Patients ≥ 40 years hospitalized due to lung diseases in a tertiary center in Mexico were enrolled (ICU patients included). A total of 192 patients were enrolled, 18 with cancer (9.4%), and after allocating the first 46 patients in the control group (passive exercises and massage), they randomized the remaining patients to graded compression stockings (39), elastic bandages (33), UFH 5000 IU, SC,BID (39), or ASA 500mg, PO, BID(35), until patients became ambulatory. The randomization and concealment method was not described. Co-interventions were not described.

The primary outcome was the incidence of DVT in patients bedridden for three consecutive days or more, according to the specific group (control or other mechanical/pharmacological interventions). The fibrinogen scan was performed daily until patients became ambulatory and, if positive, venography was done to confirm the presence of DVT. Fibrinogen test was considered the standard for distal DVT in the study; and U/S and strain gauge plethysmography were considered the standard for proximal DVT. Interestingly, PE was a secondary outcome, and symptomatic PE was confirmed with ventilation/perfusion scan. Outcome adjudication was not described.

The mean age and hospital stay for all patients were 62 years and 10 days, respectively. The incidence of VTE was: 33% (15 /46) in the control (12 DVT, 3 PE), 0% in the graduated compression stoking (0/39), 15% (5/35) in the

elastic bandages (4 DVT 1 PE), 2.5% (1/39) in UFH (1 DVT), and 6% (2/35) in ASA groups. Regarding DVT incidence, there was a statistically significant difference between all interventions versus control group, except for elastic bandages (P > 0.10). Amongst the 15 cancer patients, 2 were mechanically ventilated and developed a DVT. Their allocation was not described.

Of the 5 patients in the control group, 2 developed a DVT. In the interventions groups, the occurrence of DVT was described as the following: 0-graduated compression stockings (5 patients), 3-elastic bandages (4 patients), 0-UFH (3 patients) and 1-ASA (1 patient). Bleeding in cancer patients was reported as 7 episodes in the UFH group (4 gastrointestinal bleeds and 3 minor) and 4 episodes in the ASA group (2 gastrointestinal and 2 minor). There were various reasons for not including this study in the quantitative analysis: the poor quality of this study; the lack of clarification about the intervention group for patients with mechanical ventilation and for those who had cancer who and developed a VTE; the poor definition of bleeding events; the use of 4 different methods to diagnose DVT; and the lack of outcome adjudication.

Harenberg et al (57)

Harenberg et al. published in 1990 (57) single center, double-blind, active controlled RCT of thromboprophylaxis with 1,500 aPTT units of LMWH vs. UFH 5000 IU, TID for 10 days. Patients with a previous history of VTE were included. A total of 200 patients, between 50 and 80 years of age, were randomized to LMWH or UFH for 10 days. However, 34 were treated for less than 7 days and

excluded of the analysis. From the remaining 166 patients, 40 (24% of the total) had cancer. Co-interventions such as antiplatelet therapy and compression stockings were not allowed. Randomization and concealment methods were not described.

The primary outcome for efficacy was the incidence DVT during treatment. Screening with U/S, and impedance plethysmography were performed. Positive tests, in addition to clinical signs of DVT, were an indication for venography. Secondary outcomes were hematoma size, and laboratory abnormalities. Patents were followed until discharge from hospital (range 7-12 days). Outcome adjudication was not described

The primary efficacy outcome could be assessed in 166 patients, median age 66 year. The incidence of DVT was 4.9% (4/82) in the UFH and 3.6 % (3/84) in the LMWH (p value not provided). The mean subcutaneous hematoma size was smaller in the LMWH group. Bleeding incidence was not properly described. Among the patients with cancer, 23 were randomized to LMWH and 17 to UFH. The incidence of DVT or bleeding in each group was not available despite contacting the author. The imaging methods utilized were outdated and differed from the included studies. This study could not be included in the quantitative analysis.

Harenberg et al (58)

Harenberg et al. published in 1996 (58) a multicenter, double-blind, active controlled RCT of thromboprophylaxis with nadroparin 25mg OD vs. UFH 5000U

TID. The study included postoperative patients. A total of 1968 patients between 50 and 80 years of age were randomized to receive nadroparin or UFH for 10 days. However, 378 patients were excluded after randomization since they were actually not eligible for the trial. From the remaining 1510 patients, 120 (8% of the total) had cancer as main diagnosis at admission, but 189 had a history of cancer. There was no description of co-interventions or randomization and concealment.

The primary outcome for efficacy was the composite of proximal DVT or PE occurring during the treatment, with a screening U/S on day 10. Venography was performed if the U/S was nondiagnostic. Ventilation/perfusion lung scan or angiography was used to confirm PE. Secondary outcomes were thrombosis at other sites, arterial embolism, myocardial infarction and mortality. Patients were followed until discharge from hospital (mean 8 days). Safety was assessed through bleeding (major or minor) and adverse effects. A blinded central committee did the outcome adjudication.

The primary efficacy outcome could be assessed in 1436 patients. The incidence of VTE was 0.82% (6/726) in the nadroparin and 0.56 % (4/710) (p=0.012 for equivalence). The incidence of bleeding was 1% for the nadroparin (3 minor + 5 major) and 1.4% (7 minor and 4 major) for the UFH group. For the patients with cancer as a main diagnosis at admission, 57 were randomized to nadroparin and 63 to UFH. The incidence of DVT in each group was not available despite of contacting the author. Amongst the 189 patients with a history of cancer, 1 fatal PE in each group was described There were no details

for the bleeding rate in cancer patients, despite of contacting the author. The imaging modalities were also outdated.

Bergmann et al. (59)

Bergmann et al. published in 1996 (59) a multicenter, double-blind, active controlled RCT of thromboprophylaxis with enoxaparin or UFH. In this study there were a total of 442 patients, 30 with cancer (6.8% of the total) as a reason for hospitalization (but 63 with a history of cancer. Patients were 65 years of age or older. They were randomized to enoxaparin 20mg OD vs. UFH 500IU BID for 10 days. Co-interventions were not allowed. Randomization was performed centrally, though a computer systems, balanced by center, using blocks of 4. The primary outcome was VTE, as a composite outcome of DVT diagnosed by a daily fibrinogen uptake test, or PE as diagnosed by lung ventilation/perfusion scans, angiogram or autopsy. The fibrinogen scans could be confirmed with venography, but this was not mandatory. Safety outcomes were death, bleeding and thrombocytopenia. The follow up was done during the treatment period only. The fibrinogen test was interpreted centrally by and blinded independent expert.

The median age was 83 years old. The primary outcome could be assessed in 423 patients, with an incidence of VTE of 4.6% (10/216, 10 DVTs) in the UFH group and 4.8% (10/207), 9 DVTs and 1 PE) in the enoxaparin group (p=0.005 for equivalency). During the treatment period, major bleeding occurred in 2 patients, one in each group. From the 30 patients with cancer as reason

from hospitalization, 11 were randomized to enoxaparin and 20 to UFH. In total, 63 had a history of cancer. Despite our attempts to contact the authors we could not obtain description of VTE or bleeding by treatment group in cancer patients. Therefore, it could not be included in the quantitative analysis. . Fibrinogen uptake scans are no longer used to diagnose DVT and are considered an obsolete test.

PRIME study (60)

The PRIME study (60), published in 1996, was a multicenter, double–blind, active controlled RCT on thromboprophylaxis in hospitalized medical patients. A total of 959 patients, 167 with cancer, ≥ 18 years of age, were randomized to enoxaparin 40mg, OD or UFH 5000 IU TID for 7 days. Patients with previous VTE were included. However, only 774 received the treatment as per protocol. Co-interventions were not described, but anti-platelet agents were not allowed. Randomization and methods to guarantee proper allocation concealment were not described.

The primary outcome for efficacy was the incidence of VTE. DVTs diagnosed on U/S were confirmed with venography. PE was diagnosed with ventilation/perfusion scan, angiography or autopsy. The secondary outcomes included death, symptoms compatible with VTE but not confirmed by imaging methods, and bleeding. Outcome adjudication was not described.

The primary efficacy outcome could be assessed in 203 patients. The incidence of VTE 0.2 % (1/481) in the enoxaparin group and 1.4% (6/443) in the

UFH group, a non-statistically significant difference (p=0.1235). The incidence of major bleeding was 0.4% (2/477) in the enoxaparin and 1.45 % (7/482) in the UFH group. Eighteen patients died during the study, 7 in the enoxaparin group and (2 due to bleeding from erosive gastritis and aortic rupture) in the UFH group. Ninety six patients with malignancy received enoxaparin and 71 UFH. No description of VTE or bleeding by treatment group in cancer patients was reported despite contacting the authors. This study could not be included in the quantitative analysis.

The PRINCE (61)

The PRINCE (61) was a multicenter, open label, active-controlled RCT of thromboprophylaxis in patients with heart failure or severe respiratory disease, and was published in 2003. A total of 665 patients, 41 (6% of the total) with cancer (previous or current- not described), ≥ 18 years of age were randomized to receive enoxaparin 40mg, OD or UFH 5000IU, TID, for 10 days. Co-interventions such as graduated compression stockings were allowed. Patients were randomised in blocks of 6 and stratified according to the disease group, with proper allocation concealment.

The primary efficacy outcome was the incidence of VTE up to 1 day after the end of treatment. A screening with fibrin monomer and D-dimer in the blood on days 2 and 5, and 1-2 days prior to the end of treatment was done. The positive tests, as well as symptoms compatible with DVT, were confirmed with bilateral venography (standardized at all centers) or autopsy. For PE additional

ventilation/perfusion lung scan or pulmonary angiography was performed. Secondary outcomes were the composite endpoint of VTE and death. For safety outcomes, bleeding, and injection-site hematoma were evaluated. Outcome adjudication was done by a blinded central committee for the evaluation of the screening test and VTE.

The mean age was 70 year. Only 451 patients were evaluable for the primary outcome including: 239 in the enoxaparin and 212 in the UFH groups. Overall, the incidence of VTE was 8.4% (20/239) in the enoxaparin group and 10.4 % (22/212) in the UFH group (p=0.0146 for equivalence). For the secondary outcomes, death occurred in 9 and 15 patients in the enoxaparin and UFH groups, respectively (not statistically significant). Fewer side effects and less bleeding occurred in the enoxaparin group, with one major bleed in each group. However, again the difference was not statistically significant. Twenty five cancer patients were randomized to the enoxaparin and 16 to the UFH group. There was no description of VTE or bleeding on cancer patients despite contacting the author. This study could not be included in the quantitative analysis.

Mahe et al. (62)

Mahe et al. (62) published in 2005 a multicenter, double-blind, placebo-controlled RCT. A total of 2474 patients, 342 (13.8% of the total) with cancer, ≥ 40 years, were randomized to nadroparin (7,500 anti-Xa units) OD vs. placebo, for 21 days (or less according to the hospitalization duration). Patients with

previous VTE were included, but conditions that required full dose anticoagulation were not. Co-interventions were not reported. Randomization was done through a central office, with a list being generated by an automated system using random number tables, generating blocks of 16. The sealed envelopes with the randomization code were placed in each participating center, to be returned to the central office at the end of the study.

The primary outcome was 21 day mortality rate.. The secondary efficacy outcome was the incidence DVT or PE, confirmed by venography, angiography, or autopsy. Outcome adjudication was not described. The primary efficacy outcome, overall mortality, was not statistically significant, 10.08% vs. 10.29%, (relative risk reduction 0.02, p=0.89). The incidence of symptomatic DVT was 1.5% in the nadroparin group and 1.7% in the placebo group. On autopsy, 9 DVTs and 10 PEs were reported in the nadroparin group and 11 DVTs and 17 PEs in the placebo group (p=0.130). The incidence of bleeding was 2.8% in the napdroparin group (1 severe) and 2% in the placebo (3 severe) groups. For the patients with cancer 167 were randomized to nadroparin and 1175 to placebo. The incidence of VTE or bleeding in each group was not available in spite of contacting the author. This study could not be included in the quantitative analysis

Lederle et al. (63)

Lederle et al. (63) published in 2006 a pilot study of a multicenter, double-blind, placebo-controlled RCT of thromboprophylaxis in medically ill patients. A

total of 280 patients, 13 with cancer (4.6% of the total), ≥ 40 years, were randomized to enoxaparin 40mg, OD vs. placebo during the hospital admission. Co-interventions were not described. Randomization was done through a central office, with a list being generated by an automated system, stratified according to medical center, with proper allocation concealment.

Although a pilot study was done, the feasibility outcomes were not clearly described. The primary outcome of the proposed RCT was, however, all-cause mortality in 90 days of randomization. The secondary outcomes included VTEs; major bleeding; and all-cause mortality at 1 year. Outcome adjudication was not described.

The mean age was 72 years, with a mean hospital stay of 13.4 and 11 days in the enoxaparin and placebo groups, respectively. During the first 90 days, 14 patients in the enoxaparin and 14 in the placebo group died (RR= 0.93, 95% CI 0.26-1.59). For the secondary outcomes, overall, the incidence of VTE was 3.6% (5/140) in the enoxaparin and 6 % (8/140) in the placebo group, with only one event occurring after the 90 days follow-up period. There were more deaths in the enoxaparin group (36) in comparison to placebo (RR: 1.13, 95% CI 0.66-1.60). Less major bleeding occurred in the enoxaparin group (2) in comparison to the placebo group (5 7 cancer patients were randomized to the enoxaparin and 6 to the placebo group. However there were no details of VTE or bleeding in cancer patients despite contacting the authors. This study could not be included in the quantitative analysis.

McGarry et al. (64)

McGarry et al. (64) published in 2006 an observational, retrospective, cohort study of a multi-hospital U.S database. Medically ill patients were selected, in order to evaluate clinical and economical outcomes related to thromboprophylaxis. A total of 7,907 patients received enoxaparin or UFH prophylaxis. 310 had cancer (3.9%), all were over 40 years of age, with an inpatient stay ≥6 days. The prophylactic doses of enoxaparin were 30-60mg/day and 5000 to 15,000IU/day for UFH. Co-interventions were not described. In this case, the group assignment was not randomized.

The primary outcome for efficacy was the VTE (DVT and/or PE), incidence as recorded by ICD-9-CM codes. The secondary outcomes included side effects, length of hospital stay and costs. Outcome adjudication was not described. The incidence of VTE was 1.7 % (8/479) in the enoxaparin group and 6.3% (180/2873) in the UFH group, (RR = 0.26; $p < 0.001$). In the enoxaparin group, all VTE occurred in patients who receive 50-60mg/day of enoxaparin (8/293), and the highest incidence of VTE in the UFH group was found with 5,000-10,000U UFH (52/414). Side effects, length of stay and total costs were similar between the groups. The incidence of major bleeding was 2.5% in both treatment groups. Forty four cancer patients received enoxaparin and 266 received UFH. No description of the dose/schedule, VTE or bleeding by treatment group in cancer patients were reported. This information was not released by the authors. This study could not be included in the quantitative analysis

IMPROVE 2007 (65)

This multicenter, observational, prospective study was fully published in 2008. The primary objective was to describe physician practices for providing VTE prophylaxis to acutely ill hospitalized medical patients. A total of 15156 patients were enrolled, 7735 with current cancer (11% of the total), ≥ 70 years, and grouped according to thromboprophylaxis and non- thromboprophylaxis. Thromboprophylaxis included LMWH, UFH, warfarin, acetylsalicylic acid, other anticoagulants (fondaparinux and direct thrombin Inhibitors), elastic stockings (ES), and intermittent pneumatic compression (IPC). The information was collected at discharge and 90 days thereafter. It was recorded on standardized case report forms, and analysed in the study coordinating centre.

Of the 7735 cancer patients, 789 received any thromboprophylaxis, 530 (31%) received LMWH, 158 (9%) UFH, 113 (7%) IPC, 76 (4%) ASA, and 30 (2%) received other drugs. The doses and schedules were not published. The rates of VTE and bleeding in cancer patients were not published. In 2011 Decousus et al. (97) published a sub-analysis to determine factors at admission associated with bleeding risk. Of the 10,866 patients with available information and no bleeding at admission, 1166 (11%) had active cancer. Major bleeding occurred in 16 patients, but 27 patients had clinically significant but non-major bleedings. In a multiple logistic regression model, the OR for bleeding in cancer patients was 1.78 [95% CI: 1.2-2.63]. Despite attempts to contact the authors it was not possible to obtain the description of the number of VTE or bleeding

episodes by each treatment group for cancer patients. Therefore, this study could not be included in the quantitative analysis.

Conte et al. (66)

Conte et al. published in 2008 (66) a single center, observational, retrospective study of oncologic patients. A total of 366 hospitalized patients in a tertiary center in Chile, ≥18 years of age, were classified in groups according to no thromboprophylaxis (125 patients), use of UFH-5000IU BID or TID (120 patients) or use of LMWH (enoxaparin or dalteparin, doses and frequencies not described,121 patients), during hospital admission. The use of antiplatelet drugs was not described, but no patients received pneumatic compression. The primary outcome was VTE (DVT or PE), and the secondary outcome was bleeding. The methods to evaluate the outcome were not described. There was no outcome adjudication.

The median age of patients was 63 years old, with a median hospitalization period of 9 days. The incidence of VTE was 6.4% (8/125) in the no thromboprophylaxis group and 1.2% (3/241) in the thromboprophylaxis group (p=0.014)(all DVTs). During the hospitalization, major bleeding occurred in 2 patients (1.6%) in the non-thromboprophylaxis group and in 4 patients (2%) in the thromboprophylaxis group. Despite all attempts to contact the authors we could not obtain description of the diagnostic methods used or the primary outcome, the number of VTE or bleeding by each treatment group. This study could not be included in the quantitative analysis.

Pandey et al. (67)

Pandey et al. (67) published in 2009 a single center, prospective, observational study of medically ill patients, admitted to the wards or ICU of a tertiary center in India. A total of 117 patients were enrolled, 8 with cancer (7%), 49 (42%) from intensive care unit (ICU) and 68 (58%) from the medical wards. All admitted patients were enrolled within one week of hospital admission. Patients with contra-indications to thromboprophylaxis or who had been on DVT prophylaxis in the previous months were not eligible. Patients were evaluated for risk factors for VTE according the Caprini's score (98) and the use of pharmacological thromboprophylaxis. Other forms of thromboprophylaxis, such as mechanical, were not used. The primary outcomes were the percentage of patients in each risk score group (no risk, low risk, moderate risk, high risk and highest risk) and the related frequency of thromboprophylaxis. The definition of pharmacological thromboprophylaxis was not given. Patients were followed for the first 2 weeks of hospital admission. No outcome adjudication was described. The incidence of symptomatic VTE was a secondary outcome, confirmed by U/S or CTPA.

The mean age was 44 years. The majority (75%) of patients were very high risk, followed by high (8%), moderate (7%), low (5%) and no risk (5%) groups. Thromboprophylaxis was given to 11 patients only, all in the highest risk group. After 2 weeks, only 62 patients were alive, 72% belonging to the very high risk group. The incidence of VTE confirmed by imaging was 8% (3 DVTs

and 2 PEs). However, from the 22 patients with VTE symptoms, only 13 were further investigated, 19 belonged to the very high risk category, and none had received thromboprophylaxis. Drug dose/schedules were not described. No major bleeding occurred in patients receiving thromboprophylaxis. Cancer patients were allocated 2 points in the score system and were classified as at least moderate risk. Further details were not provided despite contacting the authors. This study could not be included in the quantitative analysis.

GEMINI (68)

This multicenter, prospective observational study was fully published in 2009. A total of 4846 patients, 795 of whom had cancer (16% of the total), were evaluated. History of previous VTE was not an exclusion criterion. The primary outcome was symptomatic VTE, with onset of symptoms occurring after 2 days of hospital admission, confirmed according to the centre-specific procedures. The secondary objective was to assess the physicians' attitude to thromboprophylaxis. Thromboprophylaxis was grouped in the following: low doses of LMWH (3,400 antiXa/, OD), low doses of UFH (5,000 IU BID, high doses of LMWH (>3,400 antiXa IU, OD), high doses of UFH (5,000 IU TID) .Patients were followed for three months. Outcome adjudication was not described.

The median age of patients was 71 years. The incidence of symptomatic VTE was 0.55 % (26/4846) overall, 4 PEs, 4 concomitant PEs and DVTs, and18 DVTs. Sixty five percent (17/26) of those patients did not receive

thromboprophylaxis. Four VTEs occurred in cancer patients (3 DVTs and 1 PE all without a previous history of VTE), but only one of those patients received thromboprophylaxis. There were no further details despite contacting the authors. This study could not be included in the quantitative analysis.

Awar et al. (69)

Awar et al. (69) published in 2009 a single center, observational, retrospective study of oncologic or hematologic patients. Surgical patients were included. A total of 130 hospitalized patients in a tertiary center in Lebanon were classified into groups according to any contra-indication (35 patients) or no contra-indication to pharmacological thromboprophylaxis. The use of antiplatelet drugs was not described, and patients could have received pneumatic compression. The primary outcome was the number of patients who received DVT prophylaxis in the absence of bleeding or other contraindications to anticoagulation. The methods to evaluate the outcome were not described. There was no outcome adjudication.

The median age of patients was 54 years old, with a median hospitalization period of 8.5 days. The majority of the patients (71.5%) were on active chemotherapy. Of the 130 patients included, 40 had a hematological malignancy. Of the 95 patients who qualified for thromboprophylaxis, 6 underwent surgery. Therefore, it was not clear how many patients had solid malignancies and were medically ill. Of the 21 patients who received pharmacological thromboprophylaxis only 10 out of 21 patients had proper

doses, 5 had tinzaparin and 16 had enoxaparin. In the enoxaparin group, 2 were surgical cases. The incidence of VTE was 2.3% (3/130), all DVTs: 2 patients did not receive thromboprophylaxis and 1 had low dose (20mg of enoxaparin). No further details were available. This study could not be included in the quantitative analysis.

Reeves et al. (70)

Reeves et al. (70) published in 2010 a single center, observational, retrospective study of oncologic patients on pharmacologic thromboprophylaxis. A total of 193 patients between the ages of 18 and 89 were included. Post-operative status was not an exclusion criterion, and 78 patients underwent surgery. Patients were grouped according to the thromboprophylaxis agents (UFH=154; enoxaparin= 26; fondaparinux=9, 4 excluded as received multiple agents). The majority of patients on UFH (80%) received 5000 IU TID. With enoxaparin 84.6% had 40 mg OD. All patients on fondaparinux received 2.5 mg OD. However, of the 154 patients who received UFH, 60 had surgery and17 had hematologic malignancies. Of the 26 patients who had enoxaparin, 12 had surgery; and of the 9 who received fondaparinux 6 had surgery. Mechanical thromboprophylaxis and anti-platelets agents were not described.

The primary outcomes for efficacy were symptomatic VTE during hospitalization and within 4 weeks of hospital discharge. Safety (bleeding – major and minor) was a secondary outcome. The methods to evaluate the outcome or outcome adjudication were not described. During hospital

admission, 2 patients experienced DVTs, but none had a PE. One patient did not receive treatment for the DVT and developed a second DVT in the 4 weeks follow up period. All VTEs occurred in the UFH group with an incidence of 1.3% (2/154). 25 patients in the UFH experienced a bleeding episode (22 minor and 3 major), in comparison to 3 minor bleedings in the enoxaparin and 2 minor bleedings in the fondaparinux groups. The author was contacted to clarify the post-operative status of patients who developed a VTE or bleedings, but no response was obtained. This retrospective study also differs from the previous studies on the definition of primary outcome, with only symptomatic VTEs identified. Therefore, it could not be included in the quantitative analysis.

Aniwan et al. (71)

Aniwan et al. (71) published in 2010 a single center, prospective, observational study. A total of 7126 hospitalized patients in a Asian tertiary (medical wards, intensive care and stroke unit), were included. 1211 had cancer (17 % of total) and no patient was given thromboprophylaxis. Other antiplatelet drugs were noted. The primary outcome was the composite of symptomatic DVT or PE. DVT was confirmed with U/S, venography, or by thrombus removed at surgery or autopsy.PE was confirmed on ventilation/perfusion lung scan, CT, magnetic resonance imaging (MRI), angiography, or pathologic examination of thrombus removed at surgery or autopsy. There was no outcome adjudication.

The median follow up in hospital was 15.7 (SD 21.7) days. The mean age of all patients was 59 years. The incidence of VTE was 0.59% (42/7126

patients). DVT or PE alone occurred in 19 patients each, and 4 patients developed both (PE and DVT). CTPA confirmed the 19 PEs. Of the 1211 patients with a history of cancer, 22 patients developed a VTE. No more details were provided and it could not be included in the quantitative analysis.

ANCIANOS (72)

ANCIANOS (72) was published by Manas et al in 2010. This was a prospective, multicenter, open-label, single arm observational study of thromboprophylaxis with bemiparin in elderly patients with acute medical illnesses and reduced mobility, admitted to geriatric centres or nursing home., Patients received bemiparin 2500 IU OD or 3500IU OD according to their VTE risk. Cancer patients were classified as high risk, and therefore received the higher dose. A total of 507 patients over the age of 65, 39 with cancer (7.7% of total were enrolled. Concomitant medications with potential anticoagulant effect were noted. The primary outcome for efficacy was the composite of symptomatic DVT, PE or both, assessed at 7 days and 90 days follow up. The primary safety outcomes were major bleeding. No outcome adjudication was done.

The median duration of treatment was 33 days. The incidence of VTE overall was 0.6% (3/503), all DVTs. The incidence of major bleeding was 0.4%, and minor bleeding was 1.6%. No description of bleeding in cancer patients was reported or obtained when contacting the author. Therefore, this study could not be included in the qualitative or quantitative analysis.

CERTAIN (73)

This multicenter, open-label, active controlled RCT was fully published in 2010. A total of 342 patients over the age of 40, were randomized to certoparin (3000 U of anti-FXa OD) or UFH (7500 IU BID) for 10 days. Only 337 received at least one dose of treatment and only 203 had their screening ultrasound as per protocol. 29 patients had cancer. Co-interventions were not described. Randomization was done through a central office, with a list being generated by an automated system, with proper allocation concealment.

The primary outcome was the incidence of VTE during treatment period. The secondary outcomes included DVT, PE and the incidence of bleeding (major and minor) during the treatment period and at the 3 months follow up (telephone call) period. The outcome adjudication was centrally done by two independent radiologists.

The primary efficacy outcome could be assessed in 203 patients. The incidence of VTE was 11% (11/103) in the certoparin group and 18% (18/100) in the UFH group, (absolute difference -7.3; 95%CI -16.9 to 2.3; p = 0.1353). During the follow up period, the incidence of VTE was 2.6% in the UFH group and 2.0% in the certoparin group (absolute difference -0.6; 95%CI -4.0 to 2.8; p = 0.7150). The incidence of major bleeding was 0.43% for certoparin and 0.62% in the UFH group (OR 0.69; 95% CI 0.26–1.83,). During the treatment period, 3 bleeding events occurred in the UFH group (2 major and 1 minor) and 3 in the certoparin group (1 major and 2 minor). There was no description of VTE or

bleeding by treatment group in cancer patients. Despite contacting the author, this information was not released. This study could not be included in the quantitative analysis.

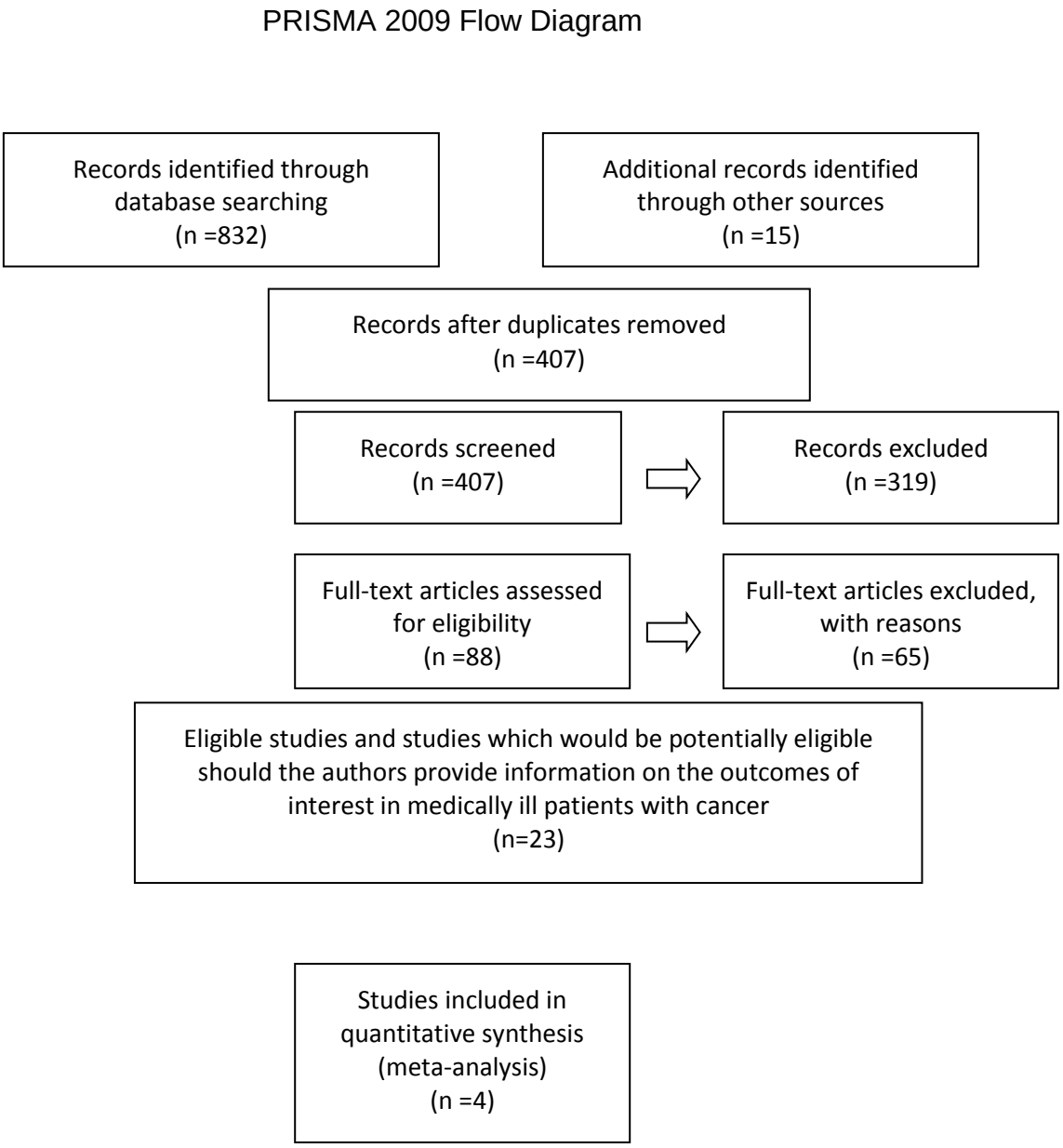
Rojnuckarin et al. (74)

Rojnuckarin et al. (74) published a single enter, prospective observational study in 2011. Medically ill patients admitted to a tertiary centre, in Thailand, classified as at high risk for VTE were followed during the hospital admission to identify very high-risk patients. No thromboprophylaxis was provided (mechanical or pharmacological). A total of 1335 patients were identified as high risk for VTE. High risk patients were described as having the following: congestive heart failure - New York Heart Association functional class III or IV, chronic respiratory disease with acute exacerbation, hemiparesis or paraparesis, a bedridden or vegetative state, active cancer (hematologic or solid malignancy), active systemic lupus erythematous, respiratory failure (on assisted ventilation), compression fracture, arthritis, previous VTE or family history of VTE, prior history of cancer, varicose veins, estrogen use, thrombophilia, thrombocytosis, obesity and nephrotic syndrome. After excluding 45 patients who died or who were lost to follow up after admission, 1290 patients were enrolled, 657 of them with active malignancy, including 297 (23% of the cohort) with a solid malignancy

The primary outcome was symptomatic VTE, and secondary outcomes were length of hospital admission and mortality. The occurrence of the above mentioned risk factors was captured by the attending physician and confirmed by

the investigators according the medical records. Patients were followed up to discharge, and symptomatic VTE were confirmed by U/S and CTPA, ventilation/perfusion scan, or autopsy. However, some VTE cases in dying cancer patients were not investigated. These patients were excluded from the analysis reported. Not only was there no outcome adjudication but also no image confirmation of these VTE cases. A follow up call was done at 6 weeks after discharge. The mean age of patients was 60 years. The incidence of symptomatic VTE was 2.1% (27/1290), 95% CI: 1.3–2.9. The majority, 23 cases, occurred during the hospital admission. Symptomatic PE occurred in 9 patients, 2 were fatal. Eleven VTE occurred in cancer patients. The number of DVT or PE in cancer patients was not specified. The presence of other important risk factors such as previous VTE, mechanical ventilation and fracture in the solid malignancy group was not specified. Despite contacting the author, this information was not released. The study could not be included in the quantitative analysis.

APPENDIX 4: PRISMA 2009 Flow Diagram



The papers were excluded due to:

1) Non-medically ill patients (surgical patients; patients in the intensive care unit; lack of clear distinction about the patient's enrolled-surgical *vs.* non-surgical; patient on rehabilitation –post-acute care) and lack of information on cancer patients
2) Lack of description about the intervention: use of thromboprophylaxis, or lack of description of method used for thromboprophylaxis, or the study was evaluating extended-duration of venous thromboprophylaxis.
3) Enrolment of patients with indications for anticoagulation
4) The outcomes of interest were present at the start of study (diagnosis of VTEs)
5) Lack of information about the outcomes of interest (VTE or bleeding) in the paper.
6) Irrelevant studies (the study objective was only to describe the methodology of a future paper; description only of opinions or use of guidelines; studies of modeling of potential reduction in VTE with prophylaxis)
7) Studies of administrative hospital databases with no clear data description.

Appendix 5: Survey

A survey for thrombosis experts evaluating practices and opinions regarding venous thromboprophylaxis in patients with active cancer hospitalized with an acute medical illness.

1. Do you recommend the use of thromboprophylaxis in adult patients with active cancer (non-hematological malignancies) hospitalized for acute medical illness (not due to surgery) that are not actively bleeding or at high risk of bleeding?

- Always
- Most of the time
- Sometimes
- Never
- Other (please specify)

2. Which drugs/dose/schedules do you usually use (weight = 70 kg and normal renal function) for thromboprophylaxis in medically ill adult hospitalized patients with active cancer?

- Unfractionated Heparin (UFH) 5,000 units, subcutaneous (SC), twice a day
- UFH 5,000 units, SC, three times a day
- Enoxaparin 30mg, SC, twice a day
- Enoxaparin 40mg, SC, daily
- Dalteparin 5,000 units, SC, daily
- Tinzaparin 4,500 units or 75 units/kg, SC, daily
- Fondaparinux 2.5mg, SC, daily
- None
- Other (please specify)

3. Do you usually follow the recommendations of one or more guideline(s) when deciding about thromboprophylaxis for adult patients with active cancer hospitalized for medical illness?

- Yes
- No

4. If you use a guideline for decision making on thromboprophylaxis for hospitalized cancer patients, which of the following do you use (please mark all that apply):

- ASCO
- ESMO
- ACCP
- NCCN
- From your own institution

5. In your opinion, do you think that the benefits of venous thromboprophylaxis outweigh the risks in adult patients with active cancer hospitalized for acute medical illness?

- Always
- Most of the time
- Sometimes
- Never
- Other (please specify)

6. Do you believe there is clinical equipoise around the use of thromboprophylaxis in adult patients with active cancer hospitalized for acute medical illness (please choose only one answer)?

- Yes
- No

7. Would you consider participating in a randomized trial assessing the use of thromboprophylaxis in adult patients with active cancer hospitalized for acute medical illness (please choose only one answer)?

- Yes, comparing thromboprophylaxis to placebo (Please answer questions 8, 9, and 10)
- Yes, comparing different doses of thromboprophylaxis or agents (Please answer questions 11, 12 and 13)
- No, I would not enrol medically ill patients with cancer in a clinical trial (go directly to Question 14)

8. What would you consider to be the minimal clinically important difference (MCID) for VTE among two arms (active drug vs. placebo)?

- 3% absolute reduction in symptomatic proximal DVT and PE 9.1%
- 2% absolute reduction in symptomatic proximal DVT and PE
- 1% absolute reduction in symptomatic proximal DVT and PE
- 0% absolute reduction in symptomatic proximal DVT and PE
- Other (please specify): _____absolute reduction in symptomatic proximal DVT and PE

9. What would you consider to be the minimal clinically important difference (MCID) for bleeding between two arms (active drug vs. placebo)?

- 2% absolute increase in major bleeding
- 1% absolute increase in major bleeding
- 0.5% absolute increase in major bleeding
- 0% absolute increase in major bleeding
- 0.0%
- Other (please specify): _____ absolute increase in major bleeding

10. In a clinical trial to study the role of thromboprophylaxis in medically ill adult hospitalized patients with active cancer, which of the drugs/doses listed below do you think should be compared to placebo? (Please select all that apply)

- UFH 5,000 units, SC, twice a day
- UFH 5,000 units, SC, three times a day
- Enoxaparin 30mg, SC, twice a day
- Enoxaparin 40mg, SC, daily
- Dalteparin 5,000 units, SC, daily
- Tinzaparin 4,500 units or 75units/kg, SC, daily
- Fondaparinux 2.5mg, SC, daily
- Other (please specify):

11. What would you consider to be the minimal clinically important difference (MCID) for VTE among two doses (comparison between two active drugs)?

- 2% absolute reduction in symptomatic proximal DVT and PE
- 1% absolute reduction in symptomatic proximal DVT and PE
- 0.5% absolute reduction in symptomatic proximal DVT and PE
- 1% absolute reduction in symptomatic proximal DVT and PE
- 0% absolute reduction in symptomatic proximal DVT and PE
- Other (please specify):_____ absolute reduction in _____

12. What would you consider to be the minimal clinically important difference (MCID) for bleeding among two doses (comparison between two active drugs)?

- 1% absolute increase in major bleeding
- 0.5% absolute increase in major bleeding
- 0.25% absolute increase in major bleeding
- 0% absolute increase in major bleeding
- Other (please specify): _____ absolute increase in major bleeding

13. In a clinical trial to study the role of thromboprophylaxis medically ill adult hospitalized patients with active cancer, which of the drugs/doses listed below do you think should be tested? Please mark the all that apply. If none apply, please fill in use the answer “other” to explain the drug, dose and schedule you think should be tested.

- UFH 5,000 units, SC, twice a day
- UFH 5,000 units, SC, three times a day
- Enoxaparin 30mg, SC, twice a day
- Enoxaparin 40mg, SC, daily
- Dalteparin 5,000 units, SC, daily
- Tinzaparin 4,500 units or 75 units/kg, SC, daily
- Fondaparinux 2.5mg, SC, daily
- Other (please specify): drug_____units_____SC, frequency_____a day.

14. Profession:
- Medical Oncologist
- Hematologist
- Internist

15. What is your gender?
- Female
- Male

16. Which category below includes your age?
- 25-35
- 36-45
- 46-55
- 56-65

17. You have been in independent practice for _____years.
- 1 to 5 years
- 6 to 10 years
- 10 to 15 years
- >than 15 years

18. You practice >50% of your time in the following providence/territory:
- NF
- NS
- NB
- PEI
- QC
- ON
- MB
- SK
- AB
- BC
- YT/NT /Nunavut

19. You practice >50% of your time at:
- A non-academic (community) hospital
- An academic (teaching) hospital
- Private Practice Office
- Other (please specify):

20. Approximately what proportion of your clinical practice is related to the care of VTE in cancer patients?
- Less than 25%
- Between 25-50%
- More than 50%