Primary Thromboprophylaxis for Inpatients with Advanced Cancer

by

Breffni Hannon

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for the degree of Master of Science
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Abstract

Introduction: Thromboprophylaxis (TP) is recommended for acutely hospitalised cancer patients; little is known about its use on palliative care units (PCUs).

Methods: First, we conducted a systematic review to explore the landscape of TP use, venous thromboembolism (VTE) and bleeding rates on PCUs. We then administered a fractional factorial survey to Canadian medical oncologists and palliative care physicians exploring their attitudes towards TP using a series of vignettes.

Results: The systematic review revealed heterogeneity in TP use, VTE and bleeding rates. The survey revealed heterogeneity in decision-making around TP between the two physician groups. We identified a number of patient factors that contributed to TP use; oncologists were at higher odds of prescribing TP compared with palliative care physicians (OR 2.09 [95%CI 1.56-2.8]).

Conclusions: True rates of TP use, VTE and bleeding on PCUs remain unclear. Greater exploration of the drivers and barriers to TP use, and physician group differences, are warranted.
Acknowledgements

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List of abbreviations

AACP – American Association of Chest Physicians

ASCO – American Society of Clinical Oncology

BMI – Body Mass Index

CSPCP – Canadian Society of Palliative Care Physicians

DVT- Deep vein thrombosis

ECOG – Eastern Cooperative Oncology Group

ESA – Erythropoiesis-stimulating agents

ESMO – European Society for Medical Oncology

INR – International Normalised Ratio

ISTH – International Society on Thrombosis and Hemostasis

KI – Karnofsky Performance Scale Index

LMWH – Low-molecular weight heparin

NICE – National Institute for Health and Clinical Excellence

NHS- National Health Service

NNT – Number needed to treat

NOAC – Novel oral anticoagulants

NSAIDs- Non-steroidal anti-inflammatory drugs

OBRI- Outpatient Bleeding Risk Index

PE- Pulmonary embolus
PCU – Palliative Care Unit

RCT – Randomised controlled trial

REB – Research Ethics Board

SDM – Substitute Decision Maker

TED – Thromboembolic disease

TP – Thromboprophylaxis

UHN – University Health Network

VTE – Venous thromboembolic disease
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Chapter 1 Thesis Organisation
Introduction

Thesis organisation

This thesis is organised in a 'multiple paper' format rather than a 'continuous design', using in part unaltered peer-reviewed content. This structure best reflects the sequential nature of this research and its evolution over the course of the Master's program.

Chapter 2 contains a broad introduction to the area of venous thromboembolism in cancer, discussing the clinical significance, pathophysiology, risk factors and international guidelines around the use of thromboprophylaxis (TP) for inpatients with cancer. We discuss the associated risk of bleeding on anticoagulation, along with a specific section focusing on patients admitted to palliative care units and residential hospices. Chapter 3 outlines the research aims and hypothesis while Chapter 4 describes the methods used for the original research component of this thesis.

Chapter 5 is a systematic review of the literature around the use of TP on palliative care units or residential hospices, largely derived from a peer-reviewed manuscript submitted to the journal 'Palliative Medicine' in April 2018. Chapter 6 presents original research addressing the objectives outlined in Chapter 3 and is largely derived from a manuscript planned for submission to the journal ‘Supportive Care in Cancer’ in November 2018. The discussion and future directions sections of Chapters 5 and 6 are complemented by Chapter 7, which summarises the key findings and general conclusions of the thesis, along with an expansion of the ongoing future directions of this work.
Chapter 2 Literature Review
Literature Review

2.1 Venous thromboembolic disease and cancer

The association between venous thromboembolic disease (VTE) and cancer is thought to have been first described by Armand Trousseau in 1865 in France (Trousseau, 1865), although it has been suggested that it may date back even further, to 1823, and an earlier observation by Bouillard (Bouillard, 1823).

2.2 Clinical significance

It is estimated that 18-20% of thromboses are attributable to cancer. Compared with age and sex-matched controls without a cancer diagnosis, there is a six-fold increased risk of VTE in cancer patients, and it is the second most common cause of death among cancer patients, after the cancer itself (Geerts et al. 2008).

There is a bidirectional relationship between cancer and thrombosis. Metastatic disease or greater tumour burden confers a higher risk of VTE; VTE is itself a marker for cancer aggressiveness and is a poor prognostic indicator. Patients with both cancer and VTE have been found to have a 2.2-fold increased risk of death compared with matched cancer patients without VTE (Sørensen et al. 2000).

Thromboembolic events are also associated with significant morbidity. Pulmonary hypertension and post-thrombotic syndrome as a consequence of VTE can have an important negative impact on wellbeing and quality of life (Noble & Pasi 2010). Pulmonary hypertension can occur in up to 5% of patients within two years of a pulmonary embolus (PE) (Pengo et al. 2004); post-thrombotic syndrome (characterised by lower limb pain, swelling, and occasionally ulceration and reduced mobility) occurs in up to 30% of patients following a deep-vein thrombosis (DVT) and can be severe in up to 8% (Prandoni et al. 1997). VTE can disrupt and complicate cancer treatment plans, with approximately 25% of patients with cancer cited as requiring admission for either VTE recurrence or bleeding, carrying an important economic burden within cancer care (Donnellan & Khorana 2017). Despite this, it is widely considered
that physicians generally underestimate the risk and significance of VTE among patients with cancer (Cohen et al. 2008; Gerotziafas et al. 2017). TP may be under-prescribed in patients with cancer; a cross-sectional study of hospitalised patients with cancer found that only 50.6% were prescribed TP (31.9% had contraindications to TP however). Of those without contraindications, 74.2% received TP (Zwicker et al. 2014).

2.3 Pathophysiology of venous thromboembolic disease and cancer

Both direct and indirect mechanisms are implicated in the pathophysiology of the prothrombotic effect exerted by cancer cells. Virchow’s triad, characterised by hemostasis, vessel injury, and hypercoagulability, leads to a prothrombotic state among patients with cancer. Hemostasis is influenced by immobility such as bed rest, and vascular compression caused by tumour masses. Vessel injury can be caused by systemic therapies provided as part of cancer treatment, intravascular devices, and intravasation of cancer cells. Hypercoagulability can occur as a result of interplay between the tumour cells themselves, the host response, and additional clinical risk factors (Zwicker et al. 2007).

Patients with cancer are commonly found to have elevated coagulation factors and increased levels of coagulation activation markers such as thrombin-antithrombin and D-dimers (Hoffman et al. 2001). Cancer cells release procoagulants (such as tissue factor and cancer procoagulant) which can directly influence the formation of thrombin and fibrin, activating procoagulant pathways. Indirectly, cancer cells release cytokines such as TNF-α and interleukin-1β; these can influence the activation of leukocytes, platelets and endothelial cells through the production of mucinous glycoproteins, factor X-activating cysteine proteases, and circulating tissue factor-bearing microparticles (Donnellan et al. 2014).

There is growing evidence to suggest a role for genetic factors in the pathophysiology of cancer-associated VTE. It has been postulated that some of the same genetic mechanisms responsible for malignant transformation of cells and oncogene activation (such as RAS), and inactivation of tumour suppressor genes (such as p53 and PTEN) may have a role to play, at
least in certain cancer types such as primary brain tumours (glioblastomas) and non-small cell lung cancer (Rong et al. 2005; Regina et al. 2009).

In combination, these factors all facilitate the development of a fibrin scaffold which may confer a selective advantage for cancer cells and allow for tumour cell adherence and activation (Boccaccio & Comoglio 2009).

2.4 Risk factors for venous thromboembolism in cancer

VTE risk factors can be broadly classified in patient-, cancer-, and treatment-related factors (see Table 1). Patient-related factors include advanced age, increased body mass index (BMI), race (black race is associated with a higher risk of VTE, Asian-Americans appear to have a lower risk), presence of renal or pulmonary disease, concurrent infection, and the presence of anemia, thrombophilia, or leukophilia (Khorana et al. 2007; Lyman et al. 2013; Simanek et al. 2010; Khorana et al. 2008).

Cancer-related factors include both the primary site and histology of the cancer. Primary brain tumours have been shown to have rates as high as 47%; upper gastrointestinal tumours such as pancreas (19.2%) and stomach (15.8%); and lung cancers (13.9%) appear to have the highest rates of VTE (Khorana et al. 2013; Petterson et al. 2015). Some hematological malignancies such as lymphoma (4.6-4.8%) and multiple myeloma (5%) also incur an increased risk (Khorana et al. 2007; Donnellan & Khorana 2017a; Knight et al. 2006; Zangari et al. 2001), as do primary cancers of the kidney and ovary (5.6% each) (Khorana et al. 2007; Heit et al. 2000; Chew et al. 2006). Patients appear to be at particularly high risk of developing VTE within the first three months after initial diagnosis (Blom et al. 2005; Sallah et al. 2002; Park et al. 2012); in one study, the risk was 54-fold higher up to three months after diagnosis, dropping to 14-fold from three to 12 months after diagnosis (Blom et al. 2005). Cancer stage has also been linked to VTE risk; with adjusted relative risks of 2.9, 2.9, 7.5, and 17.1 cited for patients with Stage I-IV cancers, respectively (Cronin-Fenton et al. 2010).

Treatment-related factors include the insertion of central venous catheters (Verso & Agnelli 2003); surgery confers a 90-day post-operative risk of VTE twice that of patients without
cancer (White 2003); and systemic chemotherapy increases the risk of VTE two-to six-fold (Heit et al. 2000; Blom et al. 2005). For patients with multiple myeloma receiving drugs such as lenalidomide and thalidomide combined with dexamethasone, there is an increased risk of VTE (Knight et al. 2006; Zangari et al. 2001). Hormonal therapies such as tamoxifen have been shown to significantly increase the frequency of VTE (5.4 vs 1.6%, p=0.0002) compared with patients undergoing active surveillance (Saphner et al. 1991). Aromatase inhibitors may be associated with a reduced risk of VTE compared with tamoxifen however (Howell et al. 2005). The use of drugs such as erythropoiesis-stimulating agents (ESA), as well as packed red cell or platelet transfusions, also increases the risk of VTE (Khorana et al. 2008a; Bohlius et al. 2006). Other drugs associated with thrombosis that are commonly utilised by patients with advanced cancer include non-steroidal anti-inflammatory drugs (NSAIDs), cortisone, antipsychotic drugs (sometimes used as anti-emetics for patients receiving chemotherapy), and herbal preparations. In the majority of cases, decreased fibrinolysis is considered the most plausible mechanism for these drug-induced hypercoagulable states (Girolami et al. 2017). Hospitalisation, including post-operative recovery periods (where patients with cancer have a 2-to 3-fold higher risk of VTE compared to those without cancer (White 2003), is another factor known to increase the risk of VTE (Khorana et al. 2013).

### Table 1: Risk factors for venous thromboembolism among patients with cancer

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>FACTORS</th>
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<tr>
<td>Patient factors</td>
<td>- Increasing age</td>
</tr>
<tr>
<td></td>
<td>- High BMI</td>
</tr>
<tr>
<td></td>
<td>- Ethnicity (Black race increased risk; Asian-Americans reduced risk)</td>
</tr>
<tr>
<td></td>
<td>- Medical comorbidities: renal disease, pulmonary disease, anemia, thrombophilia, leukophilia</td>
</tr>
<tr>
<td></td>
<td>- Heritable prothrombotic mutations</td>
</tr>
<tr>
<td>Cancer-related factors</td>
<td>- Primary site of cancer</td>
</tr>
<tr>
<td></td>
<td>- Cancer stage (increased risk with metastatic disease)</td>
</tr>
</tbody>
</table>
| Treatment-related factors | -Indwelling central venous catheters 
-Systemic therapies 
-Some hormonal therapies 
-Blood or platelet transfusions 
-Erythropoiesis stimulating agents 
-Following major surgery 
-Other drugs (e.g. NSAIDs, cortisone, antipsychotics, herbal preparations) |
|---------------------------|------------------------------------------------------------------|
| Histological subtype (adenocarcinoma) 
-Time from diagnosis |

### 2.5 Risk assessment tools

Several international bodies, including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) all recommend the use of risk assessment tools rather than individual risk factors to guide TP decision-making (Lyman et al. 2015; Mandala et al. 2011; Khorana 2007). The Khorana score is widely used for patients prior to initiating chemotherapy; the COMPASS-CAT risk assessment model can be used after initiation of anti-cancer treatment; while for patients with advanced cancer whose treatment is primarily palliative, TP guidelines have been developed by the Pan-Birmingham Cancer Network.

#### 2.5.1 The Khorana score

The Khorana score is a validated tool that uses five patient characteristics (cancer site, platelet count, leukocyte count, hemoglobin or use of ESA, and BMI) to identify patients with solid tumours at high-risk of chemotherapy-associated thrombosis (score ≥3), see Table 2 (Khorana et al. 2008). It is typically used at the initiation of chemotherapy (Gerotziafas et al. 2017). It can be used for patient education (Lustig et al. 2015), to screen for occult VTE (Khorana et al. 2014), and to aid with decision-making around TP (Verso et al. 2012); all in relation to the risk of VTE in patients undergoing chemotherapy (Donnellan & Khorana 2017). It has also been shown to be
predictive for the development of symptomatic VTE during hospitalisation for medical reasons (Parker et al. 2018). It has been shown to have low accuracy when used in certain patient subgroups, however, including patients with lung, colon and ovarian cancers (Verso et al. 2012).

**Table 2: The Khorana predictive model for chemotherapy-associated VTE**

<table>
<thead>
<tr>
<th>PATIENT FACTOR</th>
<th>RISK SCORE</th>
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<tbody>
<tr>
<td>Cancer site: very high risk (pancreas, stomach)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>High risk (lung, gynecological, bladder, testicular, lymphoma)</td>
<td></td>
</tr>
<tr>
<td>Platelet count (pre-chemotherapy) ≥350x10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Use of erythropoiesis stimulating agents OR Hemoglobin level &lt;100g/L</td>
<td>1</td>
</tr>
<tr>
<td>Leukocyte count (pre-chemotherapy) &gt;11x10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥35kg/m²</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL SCORE</strong></td>
<td><strong>Max 6, high risk considered ≥3</strong></td>
</tr>
</tbody>
</table>

Modified from Khorana et al, 2008

**2.5.2 The COMPASS-CAT risk assessment model**

This model was developed for use in outpatients with breast, colorectal, lung, and ovarian cancers. It includes cancer-related risk factors (such as time from diagnosis, stage of cancer and certain treatment types such as hormonal therapies or anthracyclines for breast cancer), predisposing risk factors (such as cardiovascular disease or recent hospitalisation), and biomarkers (elevated platelet count) to stratify patients into low/intermediate (score >4.7) or high (score ≥7) risk of VTE. For high-risk patients, the rate of VTE has been shown to be as high as 13%; it was 1.7% for low/intermediate scores (Gerotziadas et al. 2017). This model has not been extensively validated however, and its utility in hospitalised patients remains unclear (Table 3).
Table 3: COMPASS-CAT Risk Assessment Tool

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>SCORE</th>
</tr>
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<tbody>
<tr>
<td>Breast cancer patients receiving hormonal therapies or anthracyclines</td>
<td>6</td>
</tr>
<tr>
<td>Cardiovascular risk factors (at least 2 of previous stroke, peripheral vascular disease, coronary artery disease, hypertension, dyslipidemia, obesity)</td>
<td>5</td>
</tr>
<tr>
<td>Recent acute medical illness requiring hospitalisation</td>
<td>5</td>
</tr>
<tr>
<td>Time from diagnosis ≤6 months</td>
<td>4</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>3</td>
</tr>
<tr>
<td>Advanced/metastatic disease</td>
<td>2</td>
</tr>
<tr>
<td>Platelets ≥350x10⁹</td>
<td>2</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1</td>
</tr>
</tbody>
</table>

Modified from Gerotziafas et al. 2017

2.5.3 Pan-Birmingham Cancer Network Guideline for the primary prophylaxis for Venous Thromboembolism in palliative patients with malignancy whose treatment is primarily palliative

This guideline and its accompanying flowchart were developed to support the care of patients with advanced cancer admitted to either acute or palliative care settings. It suggests that all patients admitted to either setting should have an assessment of their VTE risk to guide decision-making about whether they might benefit from TP. Through a three-step process of general assessment, assessment of the benefits of TP, and palliative team decision-making, these guidelines present a structured framework within which to consider TP. The guidelines highlight patient groups who may particularly benefit from TP. These include patients who have undergone recent major surgery or who are admitted with an acute medical illness from which the patient is expected to recover, as well as recently and acutely bedbound patients; those with newly-diagnosed spinal cord compression with an expectation of functional recovery; or pathological fracture with an expectation of functional recovery. It also provides contra-indications to treatment (actively dying patient, active bleeding, already receiving
anticoagulation, platelet count <50, previous intolerance to heparin). The authors suggest that there is insufficient evidence to treat all inpatients with TP, and that decisions should be made on a case-by-case basis, taking into consideration the individual risks and burdens of treatment. See Appendix 1 (Lock et al. 2011).

2.6 Current recommendations around the prevention of venous thromboembolism in patients with cancer

Consensus guidelines have been developed by several international bodies around the use of TP for hospitalised patients with advanced cancer. These include ASCO, ESMO, the American College of Chest Physicians (ACCP) and the National Institute for Health and Clinical Excellence (NICE).

2.6.1 American Society of Clinical Oncology guidelines

ASCO has published clinical practice guidelines around VTE prophylaxis and treatment in patients with cancer; these were most recently updated in 2014. In terms of TP, the key recommendations are that most hospitalised patients with active cancer require TP throughout their hospitalisation. There are insufficient data to support patients admitted for minor procedures or for administration of chemotherapy. Routine TP is not recommended for ambulatory patients, although may be appropriate for certain high-risk groups. There are specific recommendations around the use of TP for patients with multiple myeloma undergoing active anticancer treatment, as well as patients undergoing major surgery in both the pre- and post-operative periods. Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications. Patients with cancer should be assessed for VTE risk periodically, and healthcare professionals should educate patients about the signs and symptoms of VTE. The recommended treatment is low-molecular weight heparin (LMWH); use of novel oral anticoagulants (NOACs) is not currently recommended (Lyman et al. 2015).


**2.6.2 European Society for Medical Oncology guidelines**

ESMO has also published clinical practice guidelines to improve awareness of the magnitude of the risk of VTE among patients with cancer, and to improve rates of TP prescription as well as treatment of confirmed VTE in this patient population. Similar to the ASCO guidelines, these recommend TP for hospitalised patients with cancer confined to bed with an acute medical complication; prior to and after elective major abdominal or pelvic surgery; but not for ambulatory patients receiving chemotherapy or hormonal therapy (although TP could be considered in high-risk patients as per their Khorana score), and not for patients with central venous catheters. LMWH or unfractionated heparin (for hospitalised patients) were the recommended treatments (Mandala et al. 2011).

**2.6.3 American College of Chest Physicians guidelines**

The ACCP guidelines recommend that each institution develop a formal, written policy around TP. It recommends strategies such as educational materials and meetings, in conjunction with computer decision supports, preprinted orders and periodic audits of compliance rates. Specifically for patients with cancer, routine TP in the form of LMWH is recommended for patients undergoing surgery, or who are bedridden due to an acute medical illness. The routine use of TP is not recommended for patients with central venous catheters, receiving chemotherapy or hormonal therapy, or to improve survival (Kearon et al. 2016).

**2.6.4 National Institute for Health and Care Excellence guidelines**

The NICE guidelines suggest that most mobile patients with cancer do not require TP unless they have additional risk factors for VTE beyond their cancer diagnosis. Special reference is made to patients with myeloma who are receiving treatment with thalidomide, pomalidomide or lenalidomide with steroids, and patients with pancreatic cancer receiving chemotherapy; both are considered higher-risk populations for whom TP should be considered.

The NICE guidelines are the only ones to include a specific section related to palliative care patients. It is suggested that TP should be considered for hospitalised palliative care patients, with the exception of patients in the last days of life. Additional considerations include
temporary increases in risk factors for VTE, risk of bleeding, estimated life expectancy, and the goals and preferences of the patient and/or their substitute decision maker (SDM). Use of TP should be regularly reviewed, including the views of not just the multidisciplinary clinical team, but also the patient and/or their SDM (NICE, 2018).

2.7 Strength of the evidence supporting current recommendations

For all of the above-mentioned guidelines, data relating to patients with advanced cancer were extrapolated from large, placebo-controlled trials of medically unwell hospitalised patients. A systematic review and pooled analysis looking specifically at the evidence supporting TP for patients with advanced cancer was published in 2014 (Carrier et al. 2014). This found that only three trials included VTE as a primary outcome and analysed their results based on a cancer diagnosis (Cohen 2006; Leizorovicz 2004; Samama et al. 1999). Of 5134 study subjects across all three trials, only 307 (6%) had cancer, and none of the studies described the cancer status of included subjects (active cancer versus history of cancer; early stage versus metastatic; under treatment or not). Subjects were not stratified based on cancer type, BMI, biomarkers, cancer treatments, or other VTE risk factors. The pooled relative risk of VTE was 0.91 (95% CI 0.21-4.0) for patients with cancer receiving TP compared with placebo (Carrier et al. 2014).

Four additional placebo-controlled trials reported symptomatic VTE as secondary events (Fraisse et al. 2000; Kakkar et al. 2011; Lederle et al. 2006; Mahé et al. 2005). Again, none reported results based on cancer status. None of these trials reported major bleeding rates based on cancer status. There was important heterogeneity between the included studies, and each of the three trials including VTE as a primary outcome used different anticoagulant drugs (fondaparinux, dalteparin, and enoxaparin), making it challenging to compare the results. The authors concluded that, although hospitalised patients with cancer are a population with increased risk of both VTE and bleeding, the strength of the evidence (in terms of risk-benefit ratio) remains unclear (Carrier et al. 2014).
2.8 Bleeding among anticoagulated patients with cancer

The decision to treat with TP is further complicated by the increased risk of bleeding among anticoagulated patients with cancer, with a two-fold higher risk of major bleeding cited in one study compared with anticoagulated patients without cancer (Prandoni et al. 2002), or 7% of patients on anticoagulation for VTE (Hull et al. 2006; Lee et al. 2003; Meyer et al. 2002). These data are all based on patients receiving therapeutic doses of anticoagulation; there are no corresponding data on the risk of bleeding on TP.

2.8.1 Classification of bleeding

Bleeding can manifest itself in several different ways, from minor bruising to catastrophic hemorrhage. The International Society on Thrombosis and Hemostasis (ISTH) classifies non-surgical bleeding as major or non-major. Major bleeding includes fatal events; a hemoglobin drop of 20g/l; bleeding that requires transfusion of two or more units of packed cells; and/or symptomatic bleeding into a major organ. Non-major bleeding is considered clinically relevant if it does not meet criteria for a major bleed but requires hospitalisation or another intervention (Schulman et al. 2005).

A meta-analysis of patients receiving warfarin for VTE reported a bleeding rate of 7.22 per 100 patient-years (95% CI 7.19-7.24) (Linkins et al. 2003). A lower rate of 2.57 per 100 patient-years was reported in a multicentre registry reporting the annual incidence of bleeding on anticoagulation (Ruíz-Giménez et al. 2008). Neither of these reported specific bleeding rates among patients with cancer receiving anticoagulants, however. In one study of 3358 hospitalised patients with cancer, major and clinically relevant bleeding was reported in 69 (2.1%), of whom 51 were considered major bleeds and 18 non-major but clinically relevant bleeds. Of the 69, 35 (51%) were receiving anticoagulants (Patell et al. 2017).

2.8.2 Risk factors for bleeding on anticoagulation

Risk factors for anticoagulant-associated bleeding include patient factors such as increased age, history of bleeding, and comorbidities such as diabetes, hypertension, previous stroke,
congestive cardiac failure, renal or liver disease, alcohol abuse, and cancer. The presence of genetic polymorphisms or specific biomarkers (such as elevated hemoglobin or hematocrit and growth differentiation factor-15), and medications (such as antiplatelet agents and non-steroidal anti-inflammatory drugs, NSAIDs) are additional risk factors (Parks & Fang 2017, see Table 4).

Table 4: Risk factors for bleeding on anticoagulation

<table>
<thead>
<tr>
<th>RISK FACTORS FOR BLEEDING ON ANTICOAGULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
</tr>
<tr>
<td>Prior bleeding</td>
</tr>
<tr>
<td>Medical comorbidities (diabetes, hypertension, prior stroke, congestive cardiac failure, renal disease, liver disease, alcohol abuse, cancer)</td>
</tr>
<tr>
<td>Medications (antiplatelet agents, NSAIDs)</td>
</tr>
<tr>
<td>Elevated hemoglobin or hematocrit</td>
</tr>
<tr>
<td>Presence of biomarkers (such as growth differentiation factor-15)</td>
</tr>
</tbody>
</table>

Modified from Parks & Fang, 2017

2.8.3 Bleeding risk assessment tools for anticoagulated patients

Several different tools have been developed to estimate the risk of bleeding when debating the risks and benefits of anticoagulation for individual patients. Most of these were developed and validated for patients with atrial fibrillation, rather than for VTE, however. One of the earliest tools was the Outpatient Bleeding Risk Index (OBRI), later modified to the m-OBRI, which was developed and validated in outpatients with a variety of indications for anticoagulation. Factors including age ≥65 years, prior stroke, prior GI bleed, and any of: recent myocardial infarction, diabetes, hematocrit <30%, and creatinine >90 µmol/l are incorporated into this tool. Factors are summed and patients are classified as low, intermediate or high risk of developing a major bleed in three or 12 months (Beyth et al. 1998), see Table 5.
Table 5: Outpatient Bleeding Risk Index

<table>
<thead>
<tr>
<th>Risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age ≥65 years</td>
<td>(1 point)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>(1 point)</td>
</tr>
<tr>
<td>Prior GI bleed</td>
<td>(1 point)</td>
</tr>
<tr>
<td>Recent myocardial infarction, Hematocrit &lt;30%, Creatinine &gt;90 µmol/l, diabetes mellitus</td>
<td>(1 point)</td>
</tr>
<tr>
<td><strong>Total score:</strong> (maximum 4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0: low risk, estimated bleeding risk 2% at 3 months, 3% at 12 months</td>
<td></td>
</tr>
<tr>
<td>Score 1-2: intermediate risk, estimated bleeding risk 5% at 3 months, 12% at 12 months</td>
<td></td>
</tr>
<tr>
<td>Score ≥3: high risk, estimated bleeding risk 23% at 3 months, 48% at 12 months</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Beyth et al, 1998

Others include HEMORRH2AGES, which was developed among patients with atrial fibrillation and incorporates factors such as age >75 years, renal or liver dysfunction, alcohol abuse, malignancy, thrombocytopenia, anemia, uncontrolled hypertension, genetic factors, excessive falls risk, stroke, and previous hemorrhage. Two points are assigned to a previous bleed, one to each of the other risk factors. The risk of bleeding per 100 patient-years has been shown to increase with each additional point, from 1.9 for a score of zero to 12.3 for scores ≥5 (Gage et al. 2006).

Another is the HAS-BLED, which includes seven clinical parameters: hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age >65 years, and drugs (including NSAIDs and antiplatelet agents) or alcohol. One point is assigned to each risk factor; there is an increased rate of bleeding per 100 patient-years, from 1.13 for a score of zero, to 12.5 for a score ≥5 (Pisters et al. 2010).
Table 6: HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>CLINICAL PARAMETER</th>
<th>ASSIGNED POINT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver or renal function</td>
<td>1 point each, maximum 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol</td>
<td>1 point each, maximum 2</td>
</tr>
</tbody>
</table>

RISK STRATIFICATION BASED ON SCORE BLEEDING RISK/100 PATIENT-YEARS

<table>
<thead>
<tr>
<th>RISK STRATIFICATION</th>
<th>BLEEDING RISK/100 PATIENT-YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Modified from Pisters et al, 2010

There are also several VTE-specific risk scores, including the RIETE registry score, derived from a multicentre, observational registry of patients with acute, symptomatic VTE. This identified the following clinical and biochemical variables as independently associated with fatal bleeding within the first three months of therapy: creatinine >90µmol/l, hemoglobin <130g/l for men and 120g/l for women, cancer, clinically overt PE, and age >75 years, see Table 7 (Nieto et al. 2008).
### Table 7: RIETE Score for Fatal Bleeding in patients receiving anticoagulation for acute venous thromboembolism

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic cancer</td>
<td>2</td>
</tr>
<tr>
<td>Recent major bleed (within 30 days of VTE)</td>
<td>1.5</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1</td>
</tr>
<tr>
<td>Immobile for ≥ days</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal prothrombin time</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine clearance &lt;30ml/min</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &lt;100</td>
<td>1</td>
</tr>
<tr>
<td>Anemia (Hemoglobin &lt;130g/L males; 120g/L females)</td>
<td>1</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>-1</td>
</tr>
</tbody>
</table>

#### RISK STRATIFICATION

<table>
<thead>
<tr>
<th>SCORE</th>
<th>BLEEDING RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>0.1%</td>
</tr>
<tr>
<td>1.5-4</td>
<td>0.72%</td>
</tr>
<tr>
<td>&gt;4</td>
<td>1.44%</td>
</tr>
</tbody>
</table>

Modified from Nieto et al, 2013.

The ACCP consensus guidelines also developed a scoring system for bleeding risk; this includes 18 variables based on a literature review rather than through the development of a formal model, however. Included factors are: age (>65 years and >75 years, respectively), previous bleed, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, anemia, on antiplatelet therapy, poor anticoagulant control, previous stroke, diabetes mellitus, comorbidities, recent surgery, frequent falls, alcohol abuse, and use of NSAIDs. Each is assigned a point, and patients risk of bleeding within the first three months of treatment and after three months of treatment are classified as low (zero risk factors), moderate (one risk factor) or high (≥2 risk factors) (Kearon et al. 2016; Parks & Fang 2017).
None of the existing risk assessment tools has been shown to be vastly superior to any other to date, irrespective of the baseline population included (atrial fibrillation versus VTE), and all are, at best, only modestly predictive of bleeding risk according to a review from 2013 (Lopes et al. 2013). The HAS-BLED is considered the most widely validated across different populations and has been incorporated into guidelines in both Europe and Canada (Skanes et al. 2012; Camm et al. 2012).

2.9 Thromboprophylaxis for patients with advanced cancer admitted to palliative care settings

Historically, patients admitted to palliative care units or residential hospices were close to the end-of-life (Sheard et al. 2012), and aggressive measures to sustain life, including anticoagulation, were considered unnecessary and inappropriate (NICE, 2018). The timing of palliative care involvement within cancer care has shifted dramatically over the last decade. Early palliative care, concurrent with active oncology care, is now recommended for patients with advanced incurable illness and/or high symptom burden (Ferrell et al. 2017). Increasingly, patients are admitted to palliative care units or residential hospices for brief periods of symptom assessment and management and are subsequently discharged home to continue active anticancer treatments. Discharge rates of up to 60% are reported across different settings internationally (Bryson et al. 2010; Hui et al. 2010; Gartner et al. 2012). As such, this subset of patients admitted to palliative care settings may more closely resemble patients admitted to acute care settings than the traditional palliative care demographic. Robust evidence and/or guidelines around the appropriateness of TP for these patients is lacking. Only the NICE guideline specifically makes reference to this patient population (NICE, 2018), the Pan-Birmingham Cancer Network Guidelines were developed to try to address this area of clinical care (Lock et al, 2011), but these have not been formally validated and are not widely used. Physician attitudes toward TP in palliative care settings suggest a pervasive underestimation of the significance of VTE and lack of departmental policies around TP, coupled in some cases with a nihilistic attitude towards TP (Johnson & Sherry 1997; Noble et al. 2008).
Chapter 3: Aims, Objectives & Hypothesis
Aim, Objectives & Hypothesis

3.1 Aim

The aim of this study is to assess and compare the practices of physicians working in palliative care and medical oncology around TP for patients with advanced cancer admitted to acute hospital settings, palliative care units or residential hospices.

3.2 Objectives

a) To examine the likelihood that medical oncologists and palliative care physicians will consider TP for inpatients with advanced cancer.

b) To explore physician-related factors that may influence likelihood to treat with TP (physician speciality, gender, years in practice, clinical work setting, academic work setting, and access to palliative care services).

c) To explore patient-related factors that may influence likelihood of treatment with TP (patient age, reason for admission, place of admission, performance status and bleeding risk).

3.3 Hypothesis

Medical oncologists will be more likely to prescribe TP for inpatients with advanced cancer than palliative care physicians. This was based on a small number of studies suggesting that palliative care physicians infrequently encounter VTE in their practice (Johnson & Sherry, 1997; Noble et al. 2008); lack of recommendations around the use of TP for patients in palliative care settings (NICE, 2018); and a lack of TP policies or guidelines in palliative care settings (Noble & Finlay, 2006). In addition, medical oncologists are increasingly likely to prescribe aggressive care measures (including chemotherapy and utilisation of intensive care unit beds) for patients with advanced cancer, even close to the end of life (Earle et al. 2004; Ho et al. 2011). From this, we extrapolated that medical oncologists, as a group, would be more likely to prescribe TP than palliative care physicians.
Chapter 4: Methods
Methods

4.1 Setting

The study was a Canadian national web-based survey of medical oncologists and palliative care physicians.

4.2 Participants

Participants were medical oncologists and palliative care physicians currently working in Canada in any clinical setting.

4.3 Study design

This cross-sectional survey study had two components: a demographics questionnaire and a factorial survey.

4.4 Design considerations

We considered several different options in terms of study design for this project, including a Bayesian approach and discrete choice experiments. Ultimately, we decided to use a fractional factorial survey approach.

4.4.1 Bayesian approach

Bayes theorem uses new data to update pre-existing evidence and is used to identify how probabilities change in light of new data. Pre-existing knowledge or data (which can include any range of information from randomised controlled trials, case reports, or expert consensus) are expressed as prior probabilities or ‘priors’; new observations are expressed in terms of their likelihood. As new observations are made, the original hypotheses are challenged, and their probability of truth is recalculated. This allows for the simultaneous use of old and new information to influence decision-making (Johnson et al. 2018).
This approach has not, to our knowledge, been used in any studies exploring thromboprophylaxis for patients with advanced cancer. Typically, this methodology is used in studies of rare or unusual conditions where high-quality research is lacking and other research methodologies are considered unsuitable, often due to sample size limiting power, or recruitment issues. It is increasingly used, for example, in rheumatological studies where there may be a small number of experts/potential respondents/patients in relation to a particular rare disease. Because our research question involved a commonly encountered patient population (patients with advanced cancer) and a large potential pool of respondents across both medical oncology and palliative care physicians, we felt it was not the best approach for the proposed study.

4.4.2 Discrete Choice Experiments

Discrete choice experiments (DCEs) are used to assess preferences of patients or other stakeholders regarding trade-offs, typically in terms of treatments and/or outcomes. Although most commonly used in health economics research, DCEs have also been used in healthcare outcomes research, as a means of identifying and evaluating the relative importance of aspects of decision-making related to healthcare services and health outcomes (Reed Johnson et al. 2013). DCEs are based on two assumptions. The first is that interventions, policies or services can be described by their characteristics; the second assumption is that the valuation of an individual is dependent upon the level of these characteristics (Ryan 2004). Through identifying key characteristics of alternative treatment options (such as adverse effects or impact on prognosis), assigning levels to each characteristic (such as absent, mild, moderate, or severe for adverse effects), and varying the levels between different options or scenarios, it is possible to estimate the relative importance of each attribute to an individual, and the trade-offs made between different attributes, as the levels are varied.

To our knowledge, DCEs have not been used to date in any published literature around TP in advanced cancer. This methodology has been used in other oncology studies, however, such as the willingness of patients with ovarian cancer to travel longer distances to receive treatment at a hospital with better survival outcomes (Shalowitz et al. 2018). DCEs have been
shown to have high internal validity, and limited studies assessing their external validity have been positive (Ryan 2004). Because DCEs are most commonly used in patient-based outcomes research or health economics research, we opted to not use this methodology for our project, where the population of interest was physicians.

4.4.3 Factorial surveys

Factorial surveys have been described as ‘short stories about hypothetical characters in specified circumstances, to whose situation the interviewee is invited to respond’ (Finch 1987); or a technique for applying experimental design to survey research (Rossi & Nock, 1982). Unlike attitudinal scales that ask direct questions about beliefs or values, vignettes are designed to obtain deeper insights by assessing individuals’ values or beliefs in a contextualised scenario or situation (Alexander & Becker, 1978; Finch 1987).

The core element of a factorial survey is a multidimensional experimental design; which allows for more subtle questioning of respondents and reduces the likelihood of responses based on social desirability (Auspurg & Hinz, 2015). In a factorial survey, respondents are presented with hypothetical scenarios (also known as vignettes). The scenarios are systematically constructed based on factors considered relevant to the judgement process. Scenarios are then varied across different pre-defined dimensions of interest (known as factors), and respondents are asked to rate the vignettes, typically across a Likert scale. The amount of clinical detail afforded within a vignette can provide valuable insight into respondents’ judgements. It is assumed that respondents base their judgements on a relatively small number of factors and follow consistent rules when making these judgements. As such, judgements will be influenced by both respondent characteristics and vignette variables (Hox et al. 1991).

Vignettes are widely used across healthcare and social sciences literature. They are believed to more closely mirror real-life scenarios by incorporating more complex considerations of trade-offs than can be offered by a traditional survey or questionnaire. It is also a reasonably cost-effective study design. Since respondents typically evaluate several vignettes, it is possible to increase the number of observations without the need to recruit
additional respondents (Auspurg & Hinz, 2015). Factorial surveys have high internal validity through the integration of experiments into surveys and avoiding the unidimensional limitations seen in experimental studies; the recruitment of large numbers of respondents from random population samples increases external validity (Mutz, 2011).

4.4.3.1 Fractional factorial surveys

A study is considered a full factorial design if respondents are given every possible vignette (Ulrich & Ratcliffe 2007). When respondents are asked to consider all vignettes within the universe, it is assumed that all of the factors and interactions between the factors are uncorrelated or orthogonal (Auspurg & Hinz, 2015). Depending on the number of factors and the number of possible vignettes, this has the potential to be overly burdensome for respondents, however. It has been suggested that no more than ten vignettes should be used per respondent to minimise the risk of respondent fatigue or the use of simplifying heuristics (Auspurg & Hinz, 2015). A fractional factorial design is often used instead, whereby each respondent is given a fraction of all the possible vignettes (Ulrich & Ratcliffe, 2007). Although a smaller number of vignettes may be advantageous in terms of completion rates, the disadvantage of a fractional factorial design is the loss of orthogonality, since all possible combinations of factors no longer exist for each respondent (Auspurg & Hinz, 2015).

4.4.3.2 Sample size calculation

We estimated a sample size of 62 physicians per group would be required to detect a medium effect size between the two physician groups using a binary outcome for likelihood to treat with TP, with 80% power (5% significance).

4.5 Survey design

The survey (Appendix 2) was designed by the study team, as there was limited similar research involving both groups of physicians and no validated instruments were available. It focused exclusively on physician perspectives.
The survey included questions on demographics, followed by a random selection of eight vignettes from a total vignette universe of 32 scenarios.

4.5.1 Demographics

Medical oncologists and palliative care physicians were asked basic questions relating to their demographic characteristics. These covered gender, medical specialty, years working in their chosen specialty, year of graduation, clinical work setting (working in a setting affiliated with a teaching program), academic work setting, access to palliative care services, and, if applicable, the type(s) of palliative care services available to them (such as inpatient consultation services, acute palliative care units, residential hospice or long-term palliative care units, outpatient palliative care clinics, and community-based services).

4.5.2 Vignettes/clinical case scenarios

In this section, we sought to examine an individual physician’s likelihood to consider treating patients with TP across a variety of patient factors. These factors were identified through a literature review as well as clinical consensus from a group comprising representatives from medical oncology, palliative care, and general internal medicine. Through these methods, we generated a list of potential patient factors which we then reduced based on group consensus. Item reduction was considered necessary to limit the included factors to a manageable number (Burns et al. 2008). The literature suggests that seven factors (+/- two) is the optimal number to use, with the greatest level of judgement consistency seen (Auspurg et al. 2014). It has also been consistently demonstrated that individuals can retain up to seven separate pieces of information in their short-term memory, making this the maximum optimal number of factors (Miller, 1994). We wanted to balance our desire to present as much information as possible while avoiding overly lengthy vignettes which have been shown to be associated with lower response rates.

The final patient factors were: age, reason for admission, place of admission, performance status and bleeding risk. We had also considered including factors related to the underlying cancer diagnosis and the expressed goals of care of the hypothetical patients. We
felt, however, that medical oncologists may have greater awareness of the individual risks posed by different cancer primaries compared with palliative care physicians who may not work exclusively with cancer patients, and that this information may not be interpreted in the same way by both groups of physicians. For goals of care, while we felt this was an important factor, we ultimately decided it should not influence the immediate consideration of TP by a physician faced with a clinical vignette (which was the focus of the current study), although it undoubtedly should influence the final decision to treat with TP. Factors were dichotomised into age: ≤65 years or >65 years; reason for admission: potentially reversible or likely irreversible; place of admission: acute setting versus palliative care setting; performance status: good (Eastern Cooperative Oncology Group, [ECOG] 0-2) or poor (3 or higher); and bleeding risk: low (HASBLED 0 or 1) versus high (HASBLED 2 or higher). The use of two levels per factor was chosen to allow for a more efficient universe (the size of the universe is determined by the number of levels). Using the same number of levels throughout has been recommended as optimal to avoid number-of-level effects (where dimensions with higher numbers of levels attract greater attention from respondents than those with lower numbers of levels) which can lead to a response bias (Auspurg & Hinz, 2015). These factors were combined into 32 brief clinical scenarios to cover all combinations of factors ($2^5=32$).

The vignette format was developed and modified by consensus from the Program Advisory Committee. Individual vignettes were designed to a standardised format, aimed at presenting the factors in a clinical scenario that was realistic and familiar. Attention was paid to the length of each vignette to minimise overly-wordy paragraphs (Burns et al. 2008). Where bloodwork was mentioned, we included normal ranges as reference points. For each presented ECOG and HAS-BLED score, we included a brief description within each vignette as a footnote for the convenience of the respondent. Each vignette was followed by the same question: based on this information, how likely would you be to start this person on thromboprophylaxis? (See Appendix 2). A five-point ordinal or Likert scale was used to determine responses (see Section 4.7.1).
4.6 Validated measures incorporated into the vignettes

We incorporated a measure of patient performance status and an estimate of the risk of bleeding into the vignettes, the ECOG performance status and HAS-BLED measures, respectively. These are discussed in greater detail below.

4.6.1 Eastern Cooperative Oncology Group performance status

Performance status was measured using the ECOG scale. This is a six-point measure ranging from 0 (fully active) to 5 (dead). It assesses a patient’s ability for self-care and ambulation, and is widely used across oncology and palliative care (see Table 8) (Oken et al. 1982).

Table 8: ECOG Performance Status

<table>
<thead>
<tr>
<th>ECOG DESCRIPTION</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry out all pre-morbid activities without limitation</td>
<td>0</td>
</tr>
<tr>
<td>Ambulatory and able to carry out light or sedentary work, e.g. office work, light</td>
<td>1</td>
</tr>
<tr>
<td>housework; restricted in physically strenuous activities</td>
<td></td>
</tr>
<tr>
<td>Up and about &gt;50% of waking hours; unable to carry out any work activities but</td>
<td>2</td>
</tr>
<tr>
<td>independent in ambulation and self-care</td>
<td></td>
</tr>
<tr>
<td>Confined to chair or bed &gt;50% waking hours; capable of limited self-care only</td>
<td>3</td>
</tr>
<tr>
<td>Totally disabled and confined to bed or chair</td>
<td>4</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
</tr>
</tbody>
</table>

Modified from Oken et al, 1982

4.6.2 HAS-BLED risk of bleeding on anticoagulation

Bleeding risk was assessed using the HAS-BLED scale (Pisters et al. 2010)(see Section 2.8.3). Despite its development for patients with atrial fibrillation rather than VTE, HAS-BLED remains the most widely cited and validated bleeding risk score, and thus was felt to be most likely to be familiar to participants (Parks & Fang 2017).
4.7 Outcomes measured

4.7.1 Primary outcome

Participants were asked to indicate their likelihood of prescribing TP on a five-point Likert scale of highly unlikely, unlikely, neutral, likely and highly likely. Participants could add free-text comments relating to their decision-making for each scenario.

4.7.2 Free-text comments

An open-ended question was included at the end of each vignette and at the end of the survey to allow participants to identify other issues related to their decision-making around TP for inpatients with advanced cancer, and/or to comment broadly on the survey (O’Cathain & Thomas 2004).

4.8 Ethics

Research Ethics Board (REB) approval was sought from the University Health Network (UHN) in August 2017 and granted on November 16th, 2017. Recruitment began on December 1st, 2017 and closed on January 31st, 2018.

The main ethical consideration in this study was respondent confidentiality. Data were collected electronically and entered into a computerized database. Email addresses were collected for medical oncologists for the purpose of inviting them to participate; they were not maintained as part of the database. Instead, all participants were identified by a unique study number.

There were no major risks for participants involved in this study. The potential benefits to participants included the opportunity to express their perspectives on the use of primary TP for inpatients with advanced cancer, to contribute to the literature in this area, to identify knowledge or educational gaps around the use of TP in patients with advanced cancer, as well as to aid in the development of potential future guidelines and policies.
4.9 Study procedures

Consent to participate in the study was implied. The study was described in an introductory email sent to all potential respondents along with contact information for the study team. By clicking on the accompanying link to the study via SurveyMonkey, consent was assumed. Participation was entirely voluntary. We did not use any incentives to encourage participation due to budgetary constraints.

4.10 Recruitment

Participants were invited to complete the survey via email. The email consisted of a cover letter stating the objectives of the study and why this physician was selected to participate, as well as voluntary and confidential nature of participation. It also included information about the estimated time to complete the study as well as contact information for the research team (see Appendix 2). Slightly different processes were utilised to recruit physicians from each of the two groups under investigation.

4.10.1 Medical Oncologist recruitment

The names of eligible medical oncologists were identified through their registration with their provincial/territorial colleges of physicians and surgeons. Their email addresses were compiled through an internet search that included the search engine Google, the websites of individual hospitals and universities where the physicians were known to work, and the research and publication portals ResearchGate and PubMed. Each medical oncologist received two individual emails from the research group; an initial invitation followed by a reminder email sent two weeks later.

4.10.2 Palliative Care physician recruitment

Palliative care physicians were invited through the Canadian Society of Palliative Care Physicians (CSPCP). The CSPCP maintains a database of physician members who are actively involved in the delivery of palliative care in any setting (community-based care, palliative care
units or residential hospices, and acute care settings), and who have agreed to receive research surveys.

4.11 Survey administration

4.11.1 Medical Oncologists

For the medical oncologists, collected email addresses were grouped by province/territory, and were copied and pasted directly into SurveyMonkey. An introductory email with a link to the survey was then sent to each individual medical oncologist. A follow-up email was sent after two weeks to the entire group. Medical oncologists were asked to complete the survey once only.

4.11.2 Palliative Care

For the palliative care physicians, the study team did not have direct access to their email addresses as per the mandate of the CSPCP. Instead, the CSPCP distributed the introductory email along with the link to the survey on our behalf. This group received only one email invitation; a reminder email was not possible due to administrative limitations within the CSPCP.

4.11.3 Assignment of vignettes

The total universe of 32 vignettes was randomly compiled into four decks (A-D) within SurveyMonkey, each containing eight vignettes (1-8). SurveyMonkey offers a design feature entitled A/B tests (random assignment). This allows multiple different versions of a question or free-standing text to be displayed to different respondents, and sets the percentage of respondents that will be shown each variable (help.surveymonkey.com/articles/en_US/kb/What-is-Random-Assignment). Using this, we were able to ensure that approximately 25% of respondents received, for example, options 1A, 1B, 1C and 1D, respectively, ensuring an even split of vignettes across all respondents.
4.12 Data management

All data were collected electronically via SurveyMonkey. Individual responses were transferred directly from SurveyMonkey to an excel spreadsheet; data were checked manually to ensure the transferred information was correct across all respondents.

A raw database was maintained with all data points. The only identifying information was study number and basic demographic information relating to gender, medical specialty and year of graduation. A coded database was devised and imported into SPSS version 23 (IBM Corp. 2015). These aggregate data were used for analyses.

Respondent characteristics were converted from text to numerical values; for example, medical specialty was converted from palliative care to 0 and medical oncology to 1; gender from female to 0, male to 1. Years working in specialty was converted from five options (<5 years, 6-10, 11-15, 16-20, >20) to two options, ≤10 years (coded as 0) or >10 years (coded as 1), based on the number and distribution of respondents across all five original options. Work setting was converted to two options, teaching centre (0) versus non-teaching centre (1); practice environment was similarly coded as academic centre (0) or non-academic centre (1).

Patient characteristics were similarly converted to numerical values. These were all dichotomous options, so were converted to 0 and 1 as follows: age ≤65 was coded as 0, >65 as 1; acute care setting 0, palliative care setting 1; reversible reason for admission 0, irreversible reason for admission 1; good ECOG 0, poor ECOG 1; and low HASBLED 0, high 1.

Likelihood of prescribing TP was initially converted from five options on a Likert scale (very unlikely, unlikely, neutral, likely and very likely) into two options, no treat (including very unlikely, unlikely and neutral options) that was coded as 0; and treat (likely and very likely) that was coded as 1. A sensitivity analysis was subsequently performed with neutral responses categorised in the ‘treat’ group.

The format for factorial survey analyses requires that each row in the dataset contain vignette variables (relating to a single vignette), outcomes and respondent variables. The raw
data were therefore rearranged to create this format, converting from wide format (where each row corresponds to a single respondent and vignettes occupy subsequent columns) to long format (where each row corresponds to a single vignette and contains all the vignette variables and outcome as well as respondent variables). As such, there was one row for each vignette response and up to eight rows for each respondent, corresponding to their eight randomly-assigned vignettes. This was done within SPSS using the merge and reshape commands.

4.13 Missing data

All respondents who indicated a response to at least one vignette were included in the final analyses.

4.14 Statistical analyses

Factorial surveys produce hierarchical, or multilevel, data. The aim of the analysis is to detect systematic correlation structures between the independent and dependent variables. Since sampling occurs at both the respondent and the vignette level in factorial surveys, this leads to independent variables at both of these levels. Analyses should therefore consider relationships both within and between variables at both the respondent and the vignette level. Several different types of analyses have been suggested in the literature, including single-level, separate-level, and models for hierarchical data (Hox et al. 1991; Auspurg & Hinz, 2015).

4.14.1 Single-level analyses

In this analysis, specific variables are aggregated or disaggregated, such as assuming that respondents are all completely interchangeable, and including only vignette characteristics in the initial regression equation, then repeating by including respondent characteristics in subsequent regression equations (Hox et al. 1991).
4.14.2 Separate-levels analyses

Alternatively, separate-levels analysis can be considered. In this method, the respondent and vignette levels are separated. A separate regression equation is calculated for each respondent, leading to as many regression equations as there are respondents. In a second step, factor or cluster analysis on the individual regression parameters can be used to group respondents; alternatively, each first step parameter can be taken as a single dependent variable in a separate univariate regression analysis (Hox et al. 1991).

Neither of these analyses is considered optimal for factorial surveys, since it is accepted that judgements of vignettes by the same respondent will be more alike than those between different respondents; and vignettes are hierarchically nested within respondents. Instead, hierarchical models have been suggested as an alternative, optimal approach (Hox et al. 1991; Ausburg & Hinz, 2015).

4.14.3 Hierarchical models

In this model, there are two regression equations, one modelling the vignette effects within respondents and one between respondents. In the start model, all vignette (patient) variables were included in the within-respondents model. The between-respondents model contains all the respondent variables (overall corresponding to the hypothesis that both patient and respondent factors can modify the decision to treat with TP). Hierarchical linear models have been described as a good choice for factorial survey data since they are based on realistic assumptions about the data structure, and both main effects of individual factors and interactions between factors can be tested for significance (Hox et al. 1991).

4.15 Univariable analyses

4.15.1 Patient factors

Binary logistic regression was used to calculate the odds ratios associated with each of the patient factors on the primary outcome (‘treatment with TP’). Each of the categorical patient factors was sequentially chosen as the independent variable; ‘treatment with TP’ was the
dependent variable throughout. Omnibus tests identified how well the model performed generally; the model summary estimated how much of the variance in ‘treatment with TP’ was accounted for by each factor. Variables in the equation tables indicated the change in the predicted odds of ‘treatment with TP’ for each unit change in the independent variables, with corresponding p-values and 95% confidence intervals.

**4.15.2 Physician factors**

The same analyses were used for physician factors as outlined for patient factors above.

**4.16 Multivariable analyses**

All variables were included in the multivariable analyses. Since the results were dichotomised into ‘treat’ versus ‘no treat’ from the original Likert scale, a multiple hierarchical logistic regression was utilised. In SPSS, this was achieved using the following steps: analyse: regression: binary logistic regression. “Treat” was the dependent variable. Patient factors were entered at Step 1; physician factors were added at Step 2. A sensitivity analysis was conducted with neutral responses categorised as ‘treat’.
Chapter 5: THROMBOPROPHYLAXIS FOR INPATIENTS WITH ADVANCED CANCER IN PALLIATIVE CARE SETTINGS: A SYSTEMATIC REVIEW.

This chapter is modified from the following: Cai R, Zimmermann C, Krzyzanowska M, Granton J, Hannon B. Thromboprophylaxis for inpatients with advanced cancer: a systematic review. Submitted April 2018.
5.1 Abstract

Background:
Patients with advanced cancer have an elevated risk of venous thromboembolism (VTE). Increasingly, patients are admitted to palliative care settings for brief admissions, with greater numbers of discharges (versus deaths) reported internationally. There is limited guidance around the use of TP or incidence of VTE for these patients.

Aim:
To review the use of TP as well as incidence of VTE and bleeding on palliative care units or residential hospices for patients with advanced cancer.

Design:
A systematic review using the PRISMA checklist.

Data sources:
Medline, Embase and the Cochrane library were searched up to August 3rd, 2017 along with a grey literature search; the reference lists of selected papers were hand-searched. Inclusion criteria were original papers assessing TP use on palliative care units or residential hospices for adult inpatients with cancer. Two reviewers independently selected and appraised papers using a tool designed for disparate data. Heterogeneity in study design made a meta-analysis not possible.

Results:
Eleven full-text papers (nine quantitative, two qualitative) and ten abstracts were included. TP use ranged between 4-53%; VTE rates between 0.5-20%; and bleeding incidence was 0.01-9.8%. Risk assessment tools were used infrequently and adherence to international TP guidelines ranged between 5-71%. Physician opinions differed around the use of TP; patients were largely accepting of TP if it was offered.

Conclusions:
There is limited evidence around the optimal use of TP for patients with advanced cancer admitted to palliative care settings. Although some patients may derive benefit, further research in this area is warranted.
5.2 Introduction

The association between cancer and venous thromboembolism (VTE) has been long recognised (Trousseau 1865; Ambrus et al. 1975; Bick 1978), as has the contribution of VTE to morbidity and mortality in this patient population. The two-year cumulative incidence of VTE in cancer patients has been reported variably as 0.8-8% (Chew et al. 2006; Donnellan & Khorana 2017). Patients with advanced cancer are six-times more likely to develop VTE compared with age- and sex-matched controls without cancer, and cancer is implicated in up to 20% of newly-diagnosed cases of VTE (Cunningham et al. 2006; Geerts et al. 2008). VTE is the second most common cause of death among cancer patients (Shen & Pollak 1980), and is itself an independent predictor of mortality (Chew et al. 2006; Levitan et al. 1999; Kuderer et al. 2016).

VTE is particularly associated with certain types of primary cancer including ovary, brain, upper gastrointestinal (pancreas and stomach), renal, and hematological malignancies (lymphoma and leukaemia)(Levitan et al. 1999), as well as metastatic cancer (Chew et al. 2006; Blom & Doggen 2014). The underlying pathophysiology by which cancer increases VTE risk is complex, and includes direct activation of pro-coagulant pathways by cancer cells, as well as indirect mechanisms through systemic effects of cancer on platelets, endothelial cells and leukocytes (Donnellan & Khorana 2017). Several discrete time-points throughout the cancer trajectory are associated with an increased risk of VTE: around the time of diagnosis (Chew et al. 2006; Blom & Doggen 2014); while receiving chemotherapy(Blom & Doggen 2014); and during periods of hospitalisation (Mandala et al. 2011).

Much attention has been focused on hospitalised cancer patients and their associated risk of VTE. Several international groups have recommended thromboprophylaxis (TP) for this patient population, including the American Society of Clinical Oncology (ASCO)(Lyman et al. 2015), the European Society for Medical Oncology (Mandala et al. 2011), the American College of Chest Physicians (Geerts et al. 2008), and the National Institute for Health and Clinical Excellence (NICE, 2018). Daily subcutaneous injection of low-molecular-weight heparin (LMWH) is the recommended TP treatment of choice, comparing favorably with Vitamin K antagonists in systematic reviews of secondary prevention of VTE including a Cochrane review and a meta-
analysis (Romera et al. 2009; Posch et al. 2015; Lee 2003; Akl et al. 2008). Decisions around the use of TP are complicated however by the increased risk of bleeding among anticoagulated patients with advanced cancer. A 2.2-fold increased risk of major bleeding is commonly cited (Prandoni et al. 2002; García Escobar et al. 2017; Noble & Pasi 2010), although the true magnitude of this increased risk among hospitalised cancer patients has not been investigated extensively (Carrier et al. 2014).

Until recently, patients with advanced cancer admitted to palliative care units (PCUs) or residential hospices were typically close to the end of life, and were largely excluded from the studies that guided recommendations about TP (Donnellan & Khorana 2017). Based on several large-scale randomised controlled trials demonstrating the benefits of early palliative care interventions (Temel et al. 2010; Zimmermann et al. 2014; Bakitas et al. 2009), greater numbers of patients are now admitted to PCUs and hospices for brief periods of symptom management, with discharge rates approaching 60% in some PCUs (Bryson et al. 2010; Hui et al. 2010; Gartner et al. 2012). Only one of the current guidelines makes specific reference to this subset of patients. The NICE clinical guideline suggests that TP should be considered for patients admitted to PCUs or hospices with acute, potentially reversible pathology, in keeping with the goals of care of the patient and their family (NICE, 2018).

5.2.1 Aims

The purpose of the current paper was to review the literature around the use of TP for patients with advanced cancer admitted to PCUs or residential hospices, as well as the incidence of VTE and/or bleeding.

5.3 Methods

5.3.1 Study design

We designed the methodology for this systematic review using the PRISMA checklist. We searched the electronic databases Medline, Embase, and the Cochrane Library, tailoring the search strategy to each database, using appropriate subject headings and keywords (Appendix
3. We hand-searched past issues of Palliative Medicine and the Journal of Pain and Symptom Management from January 2000-August 2017 for non-indexed articles and conference abstracts. We also performed a grey literature search in the CENTRAL registry, TRIPP, and National Guidelines Clearinghouse. We reviewed the reference lists of relevant articles for potentially relevant records. The last electronic search was performed on August 3, 2017.

5.3.2 Inclusion and exclusion criteria

We included articles if they reported original research on adult inpatients with advanced cancer on PCUs or residential hospices, and focused on primary TP, as well as incidence of VTE and/or bleeding. Articles were excluded if they were limited to paediatric populations, outpatient care settings, or if they focused on the diagnosis or management of confirmed VTE. We excluded editorials, letters to the editor, case reports, case series, and review articles.

5.3.3 Study selection

Study selection was completed by two reviewers (RC and BH) based on the predefined inclusion and exclusion criteria. We retrieved the full text of articles identified as potentially relevant during title and abstract screen and these were independently reviewed for inclusion by both reviewers. We documented reasons for exclusion and resolved any differences in studies selected by discussion and consensus between the two reviewers.

5.3.4 Data extraction

We extracted data using a predefined data collection form that captured study design, location, setting, sample size, population, aim, research questions, method and analysis, intervention, results, and conclusions. Data extraction was completed independently by two reviewers (RC and BH) and we subsequently collated the findings were through discussion and consensus.

5.3.5 Quality appraisal

We used a checklist devised by Hawker et al for reviewing disparate data systematically to assess the methodological quality of full text articles included in the review. This uses nine criteria (abstract and title; introduction and aims; method and data; sampling; data analysis;
ethics and bias; results; transferability or generalizability; and implications and usefulness) with a maximum score of three per item (total maximum score 27, very poor/poor 0-9; fair 10-18; good ≥19)(Hawker et al. 2002), [Appendix 4]. Quality assessment was completed independently by two reviewers (RC and BH). We resolved any disagreements by discussion and consensus.

As the articles included in the review encompassed a range of study designs, we were unable to perform a statistical synthesis of the data. Instead, we conducted a narrative synthesis of the data to compare and contrast the study designs and conclusions.

5.4 Results

Database searching identified 6364 records, with an additional 25 identified through other sources. After removal of duplicates, the titles of 5491 unique records were screened, of which 5365 were excluded (3460 not related to TP; 1725 not specific to palliative care units; 96 not cancer patients; and 86 paediatric studies). The abstracts of the remaining 126 records were reviewed and a further 43 were excluded (21 not related to TP; 21 not related to PCU; one paediatric study). Eighty-three full-texts were reviewed and a further 62 were excluded (22 not related to TP; 22 not specific to PCU; 16 review papers/ not original research; one paediatric study and one non-cancer study). Twenty-one papers were included in the final review, with 11 full-text papers and ten conference abstracts (Figure 1).

5.4.1 Full-text papers included in final review

Eleven full-text papers were included in the final analysis (Table 9), spanning the years 2006-2017. Five were from the United Kingdom (UK)(Gillon et al. 2011; Johnson et al. 2014; Noble & Finlay 2006; Noble et al. 2006; Noble et al. 2008), two each were from Austria (Gartner et al. 2012; Kierner et al. 2008) and Switzerland (Pautex et al. 2013; Weber et al. 2008), with one each from Canada (Legault et al. 2011) and France (Tardy et al. 2015). Six studies focused exclusively on patients with cancer (Noble & Finlay 2006; Noble et al. 2008; Noble et al. 2006; Kierner et al. 2008; Pautex et al. 2013; Weber et al. 2008); five included other diagnoses including heart failure, AIDS, neurological and respiratory conditions (Gillon et al. 2011; Johnson
et al. 2014; Gartner et al. 2012; Legault et al. 2011; Tardy et al. 2015). In all, cancer accounted for 77-92% of patients in these studies.

The studies included utilised a range of methodologies. These included one randomized controlled trial (Weber et al. 2008); one cross-sectional study (Gartner et al. 2012); two prospective studies (Legault et al. 2011; Tardy et al. 2015); two physician surveys (Noble & Finlay 2006; Kierner et al. 2008); two qualitative studies (one with patients; the other with healthcare professionals) (Noble et al. 2006; Noble et al. 2008); and three retrospective chart reviews (Gillon et al. 2011; Johnson et al. 2014; Pautex et al. 2012). These are discussed in further detail below and in Table 9.

5.4.2 Abstracts included in the final review

A further ten abstracts were identified where full texts were either not available (N=9) or not available in English (Garzon-Rodriguez et al. 2015) (Table 10). A full quality appraisal was not possible for these abstracts although some key findings are highlighted below and in the table. In terms of geographical distribution, the majority were from Europe, with five from the UK (McMullan et al. 2012; Johnson et al. 2012; Brabin et al. 2008; Thorley et al. 2016; Thomas et al. 2016), and one each from Canada (Chanthong et al. 2011), Germany (Alt-Epping et al. 2010), Italy (Bertola et al. 2014), Romania (Ciuhu et al. 2016) and Spain (Garzon-Rodriguez et al. 2015). The majority (seven) were retrospective chart reviews (McMullan et al. 2012; Chanthong et al. 2011; Bertola et al. 2014; Ciuhu et al. 2016; Brabin et al. 2008; Thorley et al. 2016; Thomas et al. 2016) with one survey (Alt-Epping et al. 2010), one qualitative study (Johnson et al. 2012) and one prospective study (Garzon-Rodriguez et al. 2015). Sample sizes ranged between 40-2642 patients (McMullan et al. 2012; Ciuhu et al. 2016).

5.4.3 Use of thromboprophylaxis on PCUs or residential hospices

One full-text paper and six abstracts assessed the use of TP on PCUs, with all demonstrating low rates of initiation or continuation of TP (Tardy et al. 2015; McMullan et al. 2012; Chanthong et al. 2011; Alt-Epping et al. 2010; Bertola et al. 2014; Ciuhu et al. 2016; Brabin et al 2008).

Overall, TP was initiated in 4-53% of admitted patients (Brabin et al 2008; Tardy et al. 2015).
The most recently published and largest study, from France, explored the bleeding risk of inpatients on PCUs in a multi-centre observational study of almost 1200 patients. Of these, 53% received TP (Tardy et al. 2015). Bertola et al found that 35% of patients (N=165) were receiving antithrombotic therapy on admission, either for existing VTE or as TP; treatment was discontinued in 85% of cases and continued in 11% up to the time of death (Bertola et al. 2014). Chanthong et al also reported low rates of TP use, with only 11% of 245 PCU patients receiving TP, four of whom later developed VTE (Chanthong et al. 2011). This trend continued in two retrospective chart reviews from the UK. McMullan et al reviewed 117 case notes, including 106 in their final analysis. Fifteen patients (14%) were admitted on TP, which was continued in 11 (10.4%); TP was initiated for 5% (McMullan et al. 2012). Brabin et al also found low rates of TP initiation (three of 75 patients) with documentation of decision-making recorded only in approximately one-third (Brabin et al. 2008). Alt-Epping et al’s survey of nine PCUs and one residential hospice (N=233) in Germany reported TP use in 68 patients (29%): four developed VTE and one bleeding (Alt-Epping et al. 2010). Ciuhu et al retrospectively reviewed the use of anticoagulants on a PCU over a 6-month period (n=2642); 13.6% of admissions were considered for antithrombotic therapy, which was TP in 81% (Ciuhu et al. 2016).

5.4.4 Incidence of venous thromboembolism and/or bleeding

Six full-text studies and four abstracts examined the incidence of VTE and/or bleeding among inpatients on PCUs or residential hospices, recruiting between 20-2642 patients (Gillon et al. 2011; Johnson et al. 2014; Pautex et al. 2013; Legault et al. 2011; Tardy et al. 2017; Garzon-Rodriguez et al. 2015; Chanthong et al. 2011; Alt-Epping et al. 2010; Ciuhu et al. 2016). Overall, the incidence of VTE ranged from 0.5-20% (Alt-Epping et al. 2010; Weber et al. 2008). Diagnosis of VTE varied, including clinical suspicion, radiological diagnosis with Doppler ultrasound and computed tomography (CT), and formal autopsy results.

Only one study was a randomised controlled trial, recruiting patients with advanced cancer admitted to a Swiss PCU with an estimated prognosis of less than six months. Patients were randomised to receive, or not receive, TP in the form of LMWH. Outcomes included incidence of VTE, episodes of bleeding, platelet counts and overall survival. Clinical suspicion of
VTE was followed by radiological confirmation. Of a proposed 778 patients (389 per arm) only 20 were successfully recruited; one in the LMWH arm developed a VTE, with one bleed in the LMWH arm versus two in the control. No patients in either arm developed thrombocytopenia as measured on days seven and 14. At three months, there was a tendency towards more deaths among controls, although this was not statistically significant (p=0.23). Of note, there was a statistically significant difference in performance status between the two arms at baseline (better in the LMWH arm, WHO performance status 2 versus 3, p=0.02) (Weber et al. 2008).

In a second Swiss study, Pautex et al utilised autopsy reports to assess whether the cause of death of cancer patients changed over a 20-year period, during which time the use of interventions such as broad-spectrum antibiotics and TP became more commonplace on PCUs. In a chart review of 240 patients who underwent autopsies between 2004 and 2010, 103 (43%) had been prescribed TP; of these, 19% had VTE at autopsy and bleeding was reported in two (0.01%). These findings were comparable with earlier studies, where VTE was reported as the cause of death in 8-20% (Pautex et al. 2013).

The only North American paper was a quality improvement study from a Canadian tertiary PCU. In contrast with the other papers, which focused on the initiation of TP, in this study TP was not offered routinely (and was stopped for patients admitted on TP). Instead, 127 patients were monitored for clinical signs and symptoms of VTE; this was confirmed radiologically by Doppler ultrasound when necessary (CT was not available). TP was stopped in almost 90% of patients (36/41 admissions), only one of whom subsequently developed a VTE. Bleeding was reported in three patients, all of whom were receiving secondary TP following confirmed VTE (Legault et al. 2011).

Tardy et al’s study exploring clinically relevant bleeding in patients admitted to a PCU reported a cumulative bleeding incidence of 9.8% at three months, versus a 0.5% incidence of symptomatic VTE confirmed by ultrasound. Bleeding occurred in 11% receiving TP and 8.4% of those not receiving TP. On multivariate analysis, TP increased the risk of clinically relevant bleeding by a factor of 1.5 (95% CI 1.02-2.15, p=0.04). Twenty-three patients died of bleeding-
related events with a case-fatality rate of 71.9% (Tardy et al. 2017). Bleeding risk was also assessed in four abstracts, all reporting low incidences of bleeding from 0.01-6% (Garzon-Rodriguez et al. 2015; Chanthong et al. 2011; Alt-Epping et al. 2010; Ciuhu et al. 2016). Garzon-Rodriguez et al prospectively assessed the risk of bleeding associated with TP, reporting minor bleeding in 6% of patients on antithrombotic therapy (primary TP or treatment for VTE) (Garzon-Rodriguez et al. 2015).

Two additional full-text studies recorded the development of symptoms related to VTE (chest pain, leg swelling and breathlessness) as secondary outcomes. Among a total of 778 patients across both studies, 13 developed chest pain (1.7%), 17 lower limb swelling (2.2%), 54 breathlessness (6.9%) and three both lower limb swelling and breathlessness (0.4%). Radiological confirmation of VTE was not performed, however (Gillon et al. 2011; Johnson et al. 2014).

5.4.5 Clinician decision-making around thromboprophylaxis

Three full-text studies and two abstracts explored factors influencing clinician decision-making around the use of TP for inpatients on PCUs (Noble & Finlay 2006; Noble et al. 2008; Kierner et al. 2008; Johnson et al. 2012; Alt-Epping et al. 2010). An Austrian study presented a single case with nine alternative scenarios (based on previous VTE; atrial fibrillation; TP with either LMWH or warfarin; and varying performance status) to a convenience sample of 20 academic physicians working in palliative care, oncology, thrombosis, and intensive care, respectively, to explore differences in TP prescribing practices. There was unanimous agreement to withdraw TP when the patient was recognised as actively dying based on their performance status. When a better performance status was presented, palliative care physicians were least likely to prescribe TP (80%) and oncologists most likely (100%), although robust statistical analysis was lacking with only descriptive statistics presented in the results (Kierner et al. 2008).

Noble & Finlay administered a survey with a single clinical scenario by telephone to physicians and senior nurses working on PCUs across the UK in 2000 (N=140) and again in 2005 (N=169). At the earlier time-point, 75% respondents indicated they would stop TP on admission for a patient with a high thrombotic risk and good prognosis; by 2005 this number had dropped
to 18%. Additionally, the number of PCUs with formal policies around TP increased from 2% in 2000 to 7% in 2005. Both changes were statistically significant (p<0.001) (Noble & Finlay 2006).

The same research group conducted a subsequent qualitative study exploring the views of palliative care physicians towards TP on PCUs in 2008. Using semi-structured interviews with 12 PCU directors (chosen purposively based on not having a TP policy in the earlier study), the authors collected information about the relative acuity of each PCU and services offered; interviewees’ experiences of VTE on their PCU and current TP practice; and their perceptions around the need for further research in this area. Although respondents acknowledged that practices on PCUs were changing to adopt more aggressive and invasive interventions, most felt that VTE was infrequently encountered, and that TP research, guidelines or policies were unnecessary. TP was considered by some to be a life-prolonging intervention that was contrary to the traditional ethos of PCUs; others felt that a rapid death from a VTE may be preferable to other cancer-related causes of death (Noble et al. 2008).

Two abstracts explored physicians' decision-making around TP (Johnson et al. 2012; Alt-Epping et al. 2010). In a study from the UK, Johnson et al conducted qualitative interviews with palliative care physicians, family physicians and oncologists (N=45). Differences in the use of TP were noted between acute hospital versus PCU settings. In the acute setting, there was concern about potential overuse of TP; in PCUs some respondents felt that TP was underutilised (Johnson et al. 2012). Alt-Epping found that policies or procedures for anticoagulation therapy (including TP) were available for only 48 of 233 patients (Alt-Epping et al. 2010).

5.4.6 Use of risk assessment criteria or adherence to international guidelines

Three full-text studies and three abstracts used risk assessment tools or international guidelines to quantify the number of patients on their PCUs meeting criteria for TP, or having contraindications to TP (Gillon et al. 2011; Johnson et al. 2014; Gartner et al. 2012; McMullan et al. 2012; Thorley et al. 2016; Thomas et al 2016). One cross-sectional study compared practices on 21 PCUs in Austria around the use of TP to the ASCO TP guidelines. Of 115 patients with cancer, 49% were receiving primary or secondary TP, while 24% had unspecified contraindications. In 18%, TP had been withdrawn upon admission to the PCU. Overall, 71% of
patients with cancer were prescribed TP in accordance with ASCO guidelines (Gartner et al. 2012).

Two UK studies evaluated the use of a VTE risk assessment tool, the Pan-Birmingham Cancer Network palliative-modified Thromboembolic Risk Factors Consensus Group (THRIFT) criteria. In addition to THRIFT, which classifies the risk of VTE as low, moderate or high, an assessment of temporary elevated risk (TER) of VTE was used. Despite the use of these tools, TP prescription rates remained low across both studies, ranging between 5-65% for moderate-to-high risk patients (Gillon et al. 2011; Johnson et al. 2014).

Gillon et al assessed TP practices across three hospices in the UK, comparing results before (N=300) and after (N=350) implementation of a VTE prevention policy. At both time-points, although almost all patients had a medium or high THRIFT score (96-100%), less than 10% had an elevated TER. Large numbers of patients had contraindications to TP (40%), including bleeding, thrombocytopenia and proximity to death. Prior to implementation of the policy, the use of TP was low among suitable patients, with only three of 11 patients with a temporary elevated risk and without contraindications receiving TP. After implementation, this increased to 13 of 20 (1% and 3.7% of the total samples, respectively), with improved documentation of TP risk (5% before implementation, 81% after) (Gillon et al. 2011).

In a second study from the same group, data were collected retrospectively from seven residential hospices (N=1164) using THRIFT and TER; information was also collected about the development of symptoms related to VTE. Ninety-five percent of the clinically relevant population (total sample minus patients for whom TP was contraindicated) had a moderate or high THRIFT score. TP was initiated for 30% of the high-risk group and 5% of those with moderate risk. There was a significant association between THRIFT and TER assessments and use of TP (p<0.0001 for both). However, for the outcome of development of VTE symptoms, there was a significant association for TER (21% developed symptoms vs 9% without TER, p<0.001) but not for THRIFT (p=0.4). TER had moderate sensitivity (41.9%) and specificity (79%), whereas THRIFT had a higher sensitivity (98.4%) but poor specificity (5.8%) (Johnson et al. 2014).
Thorley et al’s abstract reported high rates of risk assessment completion within 24 hours of admission (69%); 52% of patients with an elevated risk were started on TP (Thorley et al. 2016). Thomas et al used an audit tool based on the NICE guidelines, reporting high rates of risk assessment completion upon admission to PCU (84%). However, only 4% of patients were prescribed TP on admission and only 5% had subsequent daily review of their need for TP (Thomas et al. 2016). McMullan et al also compared decision-making around TP with the NICE guidelines, finding that although 88% of patients admitted had two or more risk factors for VTE and 39% had contra-indications, TP was only started in 5%. A further 35% developed potentially reversible risk factors over the course of their admission that met the NICE criteria, but none received TP. Clinical decision-making around TP was documented in only 12% (McMullan et al. 2012).

5.4.7 Patients’ attitudes towards thromboprophylaxis

Only two full-text studies and two abstracts considered patients’ opinions regarding the use of TP (Noble et al. 2006; Gartner et al. 2012; Garzon-Rodriguez et al. 2015; McMullan et al. 2012). Noble et al interviewed 28 inpatients already receiving TP on a PCU within a regional cancer centre in the UK. All had a poor performance status at the time of the interview (ECOG 4; totally confined to bed or chair). Most demonstrated good illness understanding as well as insight into the rationale behind the use of TP for the duration of their inpatient stay. All found the treatment to be acceptable, and saw TP as an intervention that may maintain their quality of life (Noble et al. 2006). Elsewhere, Gartner et al reported as a secondary outcome that documentation about patient involvement in decision-making around TP was available for 48 of 134 patients; 87% of those patients who were involved in the decision-making process (33/38) opted to receive TP (Gartner et al. 2012).

Garzon-Rodriguez assessed patient awareness and acceptance of TP as secondary outcomes for their study assessing the incidence of VTE on a PCU, as well as TP use and complications. Although only 30% of patients reported pre-admission awareness of the risk of VTE, there was overwhelming acceptance of TP (92%) (Garzon-Rodriguez et al. 2015). In their study of TP use in specialist palliative care units in Northern Ireland, McMullan et al reported
that there was no documentation around discussions about TP with patients, in the form of either verbal or written information (McMullan et al. 2012).

5.4.8 Quality assessment of included studies

Quality scores ranged from 19 (Kierner et al. 2008) to 25 (Noble et al. 2006; Noble et al. 2008) out of 27 (mean 23, median 23). The greatest limitations were clear definition of aims, methodology, sampling, and transferability. Five of the 11 papers had poorly defined aims and objectives (Johnson et al. 2014; Noble & Finlay 2006; Kierner et al. 2008; Weber et al. 2008; Legault et al. 2011). Three of the studies were retrospective, and relied upon accurate documentation within the case notes (Gillon et al. 2011; Johnson et al. 2014; Pautex et al. 2013). More than half of the included studies had limitations related to sampling (seven of 11 papers) (Gillon et al. 2011; Noble & Finlay 2006; Noble et al. 2008; Gartner et al. 2012; Weber et al. 2008; Legault et al. 2011; Tardy et al. 2015). The single randomized controlled trial included failed to recruit its target sample size, and there were important baseline differences between intervention and control arms in performance status and discharge disposition (Weber et al. 2008). Five studies included all patients admitted to a PCU over a defined time period and didn’t account for reasons for admission, presence of temporary or reversible risk factors, and, in some cases, prognosis (Gillon et al. 2011; Gartner et al. 2012; Weber et al. 2008; Legault et al. 2011; Tardy et al. 2015). One qualitative study purposively sampled patients who were already receiving TP; the attitudes of patients who had declined TP were not explored (Noble et al. 2006). A second qualitative study examined PCUs that lacked TP policies; the attitudes of clinicians working on PCUs with policies were not assessed (Noble et al. 2008). Only two studies used a risk assessment tool specifically designed for inpatients on PCUs (Gillon et al. 2011; Johnson et al. 2014). Assessment of transferability of the results was challenging due to the heterogeneity in study type and aims, as well as the geographical spread of studies (Figure 2).

5.5 Discussion

Our systematic review demonstrates limited high-quality research around the use of TP as well as incidence of VTE and/or bleeding on PCUs and residential hospices. Only 11 full-text papers
and ten abstracts were included in the final review, with wide heterogeneity in study design and outcomes. Use of TP varied widely across studies, from 4-53%. It remains challenging to draw any firm conclusions about the utility of TP for select populations of patients admitted to PCUs and residential hospices.

5.5.1 Limited evidence to support thromboprophylaxis use

Despite the endorsement of several international bodies (Geerts et al. 2008; Mandala et al. 2011; Lyman et al. 2015; NICE, 2018), the strength of the evidence underpinning existing TP guidelines for use among hospitalised patients with cancer is limited, especially in terms of its application to patients in diverse clinical settings and situations. A systematic review and pooled analysis of the efficacy of TP for hospitalised cancer patients identified only three placebo-controlled randomised trials measuring VTE as a primary outcome and analysed the results based on diagnostic subgroups. Patients with cancer accounted for only 6% of the total population studied, with a pooled relative risk of VTE of 0.91 among patients receiving TP versus placebo (Carrier et al. 2014). While patients with cancer encompassed between 5-16% of patients across these studies, no information was provided about the site(s) or stage of cancers; studies did not differentiate between patients with a previous cancer diagnosis versus those with active cancer; and one study excluded patients with brain metastases (Samama et al. 1999; Cohen 2006; Leizorovicz 2004). It is therefore impossible to draw conclusions from these results with regard to patients on PCUs or residential hospices.

5.5.2 Lack of clarity around the true frequency of venous thromboembolism in palliative care settings

The true frequency with which VTE occurs on PCUs and residential hospices remains unclear, ranging from 0.5-20% across the studies in our review. The retrospective nature of several of these studies is an important limitation, as they rely upon accurate documentation of symptoms or signs of VTE. The diagnostic tools utilised varied from clinical suspicion, to the use of Doppler ultrasound or CT, to formal autopsy reports. As signs and symptoms of VTE can easily be attributed to other causes in advanced cancer, clinical suspicion alone is not a reliable marker of the incidence of VTE (Donnellan & Khorana 2017; Noble & Pasi 2010).
5.5.3 Lack of clarity around the true frequency of bleeding in palliative care settings

Similarly, our review identified wide variations in the incidence of bleeding among anticoagulated patients, ranging between 0.01-9.8% (Alt-Epping et al. 2010; Tardy et al, 2015). Patients receiving cancer treatment have been shown consistently to have higher rates of bleeding, which are independent of anticoagulant dose (Prandoni et al. 2002; Gussoni et al. 2013). Concerns about bleeding have been cited as a barrier to the initiation of TP, and relative contraindications to anticoagulation (including thrombocytopenia, active or previous bleeding) were reported in nearly one third of patients in one study (Zwicker et al. 2014). The wide variability in results for both the incidence of VTE and bleeding on anticoagulation suggest that decisions should be made on a case-by-case basis, considering the unique clinical profile and goals of care of each admitted patient.

5.5.4 Geographical distribution of included studies

The majority of papers and abstracts were from Europe (95%) with most from the UK (47.6%) where there are specific guidelines and risk assessment tools that specifically address the use of TP for inpatients on palliative care units and residential hospices (NICE, 2018; Lock, 2011). National risk assessment targets exist for hospitalised patients in the National Health Service (NHS) in the UK since 2010; these set a target of 95% of hospitalised patients undergoing risk assessment for VTE upon admission, with mandatory quarterly reporting (NHS, 2017). Although PCUs and residential hospices are not subject to these targets, the practices may permeate through to these settings, and many patients are likely transferred from acute care settings to PCUs and residential hospices on TP. Such standards are not the norm in other countries and may explain some of the differences identified in our review, as well as the broader exploration of this topic among UK researchers.

5.5.5 Infrequent use of risk assessment tools or international guidelines

Only two of the full-text papers utilised risk assessment tools, with both using the Pan-Birmingham Cancer Network palliative-modified Thromboembolic Risk Factors (THRIFT) Consensus Group criteria (Gillon et al. 2011; Johnson et al. 2014). These consensus-based
guidelines have not been formally validated, although they are aimed specifically at aiding decision-making around TP for patients whose treatment is primarily palliative and in the inpatient setting (Lock, 2011). Several other tools have been developed and validated to help predict VTE risk in cancer patients using combinations of clinical and laboratory parameters as well as biomarkers; these were developed mainly for ambulatory patients before or after initiation of chemotherapy, or limited to specific cancer sites (Khorana et al. 2008; Ay et al. 2011; Gerotziafas et al. 2017). An additional paper and two abstracts compared practices to international recommendations from ASCO and NICE, respectively. Many of these recommendations provide limited nuanced guidance based on individual patient characteristics or subsets of patients. The NICE guidelines are the only ones, to our knowledge, that specifically address the area of patients admitted to PCUs or residential hospices (NICE, 2018).

5.5.6 Strengths and limitations of the review

Our review has a number of strengths and limitations. We used a broad search strategy and extended our search to include the grey literature as well as reviewing the reference lists of selected papers. Two independent reviewers selected studies for inclusion and conducted the quality appraisal. Despite this, we may have omitted papers that included PCUs and residential hospices and/or TP as a subset of a larger population. Our quality appraisal tool was chosen to permit inclusion of both qualitative and quantitative papers. We included non-English papers but were unable to appraise fully the single Spanish-language full-text paper that met our inclusion criteria (we did, however, include the abstract). Most of the included studies did not differentiate between different reasons for admission in their assessment of TP use or average time from admission to death or discharge, making the results challenging to interpret and generalise. Several studies reported high mortality rates at three months (>80%) (Legault et al. 2011; Tardy et al. 2015); their results may therefore not be applicable to a subset of patients with a longer prognosis, better performance status, and temporary or reversible risk factors for VTE admitted to PCUs and residential hospices. Heterogeneity in study design made a meta-analysis impossible.
5.6 Conclusions

Patients with advanced cancer admitted to PCUs and residential hospices are an increasingly heterogeneous population. Growing numbers are admitted to these settings for brief periods of symptom control; this subset may have temporary elevated risk factors for VTE similar to those experienced by patients admitted to acute care settings. It remains unclear whether TP should be offered routinely to this patient group. There is a need for additional research around the true incidence of VTE and bleeding among select patients, and for education of physicians and patients around VTE risk. Based on this, greater adoption of routine risk assessment upon and throughout admission to PCUs and residential hospices may be warranted needed. Multicentre studies may be necessary to conduct appropriately powered studies that address the issues identified with recruitment and retention of suitable patients. Additional outcome measures, including patient quality of life, transfusion requirements, and survival, may also be illuminating.
### Table 9: Full-text papers included in the final review

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Year</th>
<th>Population</th>
<th>Methods</th>
<th>Outcome</th>
<th>Quality score (max 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noble &amp; Finlay, 2006</td>
<td>Survey</td>
<td>2006</td>
<td>Interviews with physicians or senior nurses working in UK PCUs with &gt;7 beds. 140 responses in 2000; 169 in 2005.</td>
<td>Semi-structured telephone survey using a single clinical scenario; question regarding the presence or absence of a TP policy.</td>
<td>Reduced rates of discontinuing TP in 2005 compared with 2000 (18% versus 75%); more PCUs had TP policy in 2005 compared with 2000 (19% versus 2%).</td>
<td>25</td>
</tr>
<tr>
<td>Noble et al, 2006</td>
<td>Qualitative</td>
<td>2006</td>
<td>28 PCU inpatients with advanced cancer &amp; poor performance status receiving TP.</td>
<td>Semi-structured interviews addressing disease history, understanding of TP, and impact of TP on quality of life.</td>
<td>Patients had good insight into prognosis, good understanding of TP and found LMWH acceptable.</td>
<td>23</td>
</tr>
<tr>
<td>Noble et al, 2008</td>
<td>Qualitative</td>
<td>2008</td>
<td>12 medical directors of PCUs which lacked a TP policy.</td>
<td>Semi-structured interviews covering interventions provided by the PCU; perceived rates of VTE; current TP practice or policy; and perceptions of future research needed.</td>
<td>Major themes identified were changing practice in palliative care; perceived low rates of VTE leading to resistance to TP policies; potential openness to change if supporting evidence. TP considered potentially life-prolonging.</td>
<td>25</td>
</tr>
<tr>
<td>Gillon et al, 2011</td>
<td>Retrospective chart review</td>
<td>2011</td>
<td>300 consecutive admissions (86% cancer) to 3 hospices pre-implementation of VTE prevention policy; 350 consecutive admissions (77% cancer) after implementation.</td>
<td>Chart review collecting patient demographics; VTE risk using risk assessment tool (THRIFT); TP use; and documentation of TP decision-making.</td>
<td>Majority of patient shad medium or high THRIFT scores, 40% with contra-indication to TP. VTE prevention policy increased documentation of TP decisions (81% versus 5%) but did not increase use of TP overall.</td>
<td>24</td>
</tr>
<tr>
<td>Johnson et al, 2014</td>
<td>Retrospective chart review</td>
<td>2014</td>
<td>1164 consecutive admissions to 7 hospices</td>
<td>Chart review reviewing use of TP following implementation of risk assessment guidelines (THRIFT &amp; TER); also documented development of symptoms of potential VTE.</td>
<td>Stronger association between elevated TER and development of VTE symptoms compared with THRIFT (p&lt;0.001 versus p=0.4).</td>
<td>24</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Year</td>
<td>Setting/Population Details</td>
<td>Methods</td>
<td>Findings/Results</td>
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<tr>
<td>Kierner et al, 2008</td>
<td>Survey</td>
<td>2008</td>
<td>20 physicians from palliative medicine, oncology, ICU, thrombosis &amp; hemostasis.</td>
<td>Clinical scenarios were presented with variable medical history, TP contraindications, and performance status. Physicians were asked to comment on their use of TP or not in each scenario.</td>
<td>Performance status influenced use of TP more than actual thromboembolic risk. TP was universally discontinued in patients who were actively dying.</td>
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<tr>
<td>Gartner et al. 2012</td>
<td>Cross-sectional</td>
<td>2011</td>
<td>134 inpatients in 21 PCUs. 86% of population had cancer.</td>
<td>Diagnosis, demographics, TP use, performance status, mental status were collected via questionnaires to compare actual TP use with current international recommendations.</td>
<td>86% response rate, with 47% on LMWH for either primary or secondary TP. 71% of cancer patients appropriately received TP in accordance with guidelines.</td>
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<td>Canada</td>
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<tr>
<td>Legault et al, 2011</td>
<td>Prospective chart review</td>
<td>2011</td>
<td>127 consecutive patients admitted to a single tertiary PCU (92% cancer).</td>
<td>A protocol was developed which encouraged TP discontinuation on PCU admission. Chart review collecting demographics, performance status, anticoagulation use, clinical signs of VTE; and followed up for 2 months.</td>
<td>Very low incidence of VTE following TP discontinuation when admitted to PCU (1 of 36). Bleeding in 3 patients on anticoagulants for existing VTE.</td>
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<td>Switzerland</td>
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<tr>
<td>Weber et al, 2008</td>
<td>Randomised controlled trial</td>
<td>2008</td>
<td>20 cancer patients admitted to PCU with life expectancy &lt;6 months.</td>
<td>Patients randomized to receive either LMWH or control. Outcomes included VTE incidence, bleeding, platelet counts, and overall survival.</td>
<td>One VTE in intervention arm. Similar bleeding episodes in both arms. No difference in platelet counts. Non-significant tendency towards more deaths in control arm at 3 months (p=0.23). Better performance status in LMWH arm. Significantly underpowered.</td>
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<tr>
<td>Pautex et al, 2012</td>
<td>Retrospective chart review</td>
<td>2013</td>
<td>240 patients with advanced cancer hospitalized between 2004-2010 who had an autopsy.</td>
<td>Chart review collecting demographics; cancer history; comorbidities; and autopsy results.</td>
<td>VTE-related death in 20% of patients. Causes of death did not change from earlier studies despite increasing use of TP.</td>
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<tr>
<td>France</td>
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<tr>
<td>Tardy et al, 2017</td>
<td>Prospective</td>
<td>2017</td>
<td>1199 patients admitted to PCU</td>
<td>Chart review collecting demographics; cancer history; comorbidities; and autopsy results.</td>
<td>High incidence of bleeding in both.</td>
<td></td>
</tr>
</tbody>
</table>

56
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Setting (Cancer %)</th>
<th>Demographics: Admission; Performance Status; Treatment History; Medical History.</th>
<th>Patients receiving TP (11%) and those not receiving TP (8.4%). 53% prescribed TP, but low reported incidence of VTE (0.5%).</th>
</tr>
</thead>
</table>
Table 10: Abstracts included in the final review

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Year</th>
<th>Population</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorley et al,</td>
<td>Retrospective</td>
<td>2016</td>
<td>102 hospital and hospice palliative care inpatients without known thromboembolic disease.</td>
<td>Multi-centre regional case review audit using risk assessment pro formas completed by each participating unit.</td>
<td>69% had a VTE risk assessment within 24 hours of admission. 52% of patients with reversible pathology or presumed temporarily reduced mobility were given prophylactic LMWH. 56% of patients on LMWH later diagnosed as dying had their LMWH stopped.</td>
</tr>
<tr>
<td>Thomas et al,</td>
<td>Retrospective</td>
<td>2016</td>
<td>100 patients admitted consecutively to hospice.</td>
<td>An audit tool designed based on 2014 TP guidelines was used to assess consideration and documentation of decisions surrounding TP.</td>
<td>16% did not receive risk assessment on admission. 4 patients were prescribed TP on admission, and of those that developed a potentially reversible increase in VTE risk, only 1/20 patients were given TP. Subsequent review of decisions around TP were infrequent.</td>
</tr>
<tr>
<td>Johnson et al,</td>
<td>Qualitative</td>
<td>2012</td>
<td>45 physicians (range of palliative physicians, oncologists, and GPs).</td>
<td>Interviews were conducted to explore doctors' decisions about diagnosis and management of VTE.</td>
<td>Differences in TP practice in acute hospitals vs. PCUs suggest that TP decision-making may be potentially determined by place of admission and driven by national targets. There were divergent views among palliative care physicians about TP.</td>
</tr>
<tr>
<td>McMullan et al,</td>
<td>Retrospective</td>
<td>2012</td>
<td>40 consecutive cancer patients admitted to each of 3 PCUs (117 charts total).</td>
<td>Charts reviewed to assess VTE prophylaxis practice in Northern Ireland.</td>
<td>88% had 2 or more VTE risk factors and 61% had no TP contraindications. Documentation of risk was poor (5%). 11/15 patients on TP on admission had TP continued. TP commenced in 5% of admissions. Decisions regarding TP were documented in 12%.</td>
</tr>
<tr>
<td>Brabin et al,</td>
<td>Retrospective</td>
<td>2008</td>
<td>75 patients admitted to hospice for symptomatic control, respite, or rehabilitation.</td>
<td>Chart review to examine risk of VTE and appropriateness of TP in hospice patients.</td>
<td>Primary TP started in 3 patients. Reasons for avoiding TP were recorded for 32% of patients and included pre-existing TP use, bleeding</td>
</tr>
<tr>
<td>Country</td>
<td>Study Years</td>
<td>Study Design</td>
<td>Patients Admitted/Settings</td>
<td>Description</td>
<td>Results</td>
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<tr>
<td>Romania</td>
<td>Ciuhu et al, 2016</td>
<td>Retrospective chart</td>
<td>2016 2642 cancer patients admitted to palliative care unit in a 6-month period.</td>
<td>Chart review to evaluate the antithrombotic treatments received by PCU patients.</td>
<td>13.6% met criteria for antithrombotic therapy during hospitalization; treatment was initiated in 63.0%. In 81.4% of cases, this was TP. Bleeding occurred in 15 patients (3.9%).</td>
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<tr>
<td>Italy</td>
<td>Bertola et al, 2014</td>
<td>Retrospective chart</td>
<td>2014 165 cancer patients treated by a specialist palliative care team in hospice.</td>
<td>Chart review of a sample of patients to review clinical features, VTE risk factors, and prescriptions.</td>
<td>55% had cancer-related VTE risk factors and 36% were on TP on admission. TP was discontinued in 85% over the course of their admission; 11% were still on TP at death.</td>
</tr>
<tr>
<td>Germany</td>
<td>Alt-Epping et al, 2010</td>
<td>Survey</td>
<td>2010 233 inpatients admitted to 9 PCU’s, and 1 hospice.</td>
<td>Questionnaires completed to assess practice of TP treatment and decision-making.</td>
<td>Overall, 51.9% patients received anticoagulant therapy. The major indication was TP, in 68 patients. Bleeding was reported in 1 patient.</td>
</tr>
<tr>
<td>Canada</td>
<td>Chanthong et al, 2011</td>
<td>Retrospective chart</td>
<td>2011 245 patients admitted to a tertiary PCU.</td>
<td>Chart review to review use of TP, complications from TP use, and prevalence of VTE on a PCU.</td>
<td>11% of patients admitted received TP. 7% of patients developed symptoms of VTE. Of 18 patients who developed VTE, 4 had received TP. Bleeding was reported in 5%.</td>
</tr>
<tr>
<td>Spain</td>
<td>Garzon-Rodriguez et al, 2015</td>
<td>Prospective chart review</td>
<td>2012 140 patients consecutively admitted to an acute PCU.</td>
<td>Chart review of demographic data, VTE risk factors, VTE incidence during hospitalization and 15 days post-discharge, and complications of LMWH.</td>
<td>7.1% of patients had a VTE event on admission, during hospitalization, or 15 days post-discharge. Patients with VTE had a higher mean length of stay. PE was more common than DVT. Minor bleeding was reported in 6% receiving TP.</td>
</tr>
</tbody>
</table>
Figure 1: PRISMA flow diagram

Records identified through database searching (n = 6364)

Additional records identified through other sources (n = 25)

Records after duplicates removed (n = 5491)

Records excluded (n = 5365)

Abstracts excluded (n = 43)
Not TP (21)
Not PCU (21)
Paediatrics (1)

Full-text articles excluded (n = 62)
Not TP (22)
Not PCU (22)
Review (16)
Paediatrics (1)
Non-cancer (1)

Abstracts screened (n = 126)

Full-text articles assessed for eligibility (n = 83)

Studies included in qualitative synthesis (n = 21)
11 full-text studies
Figure 2: Quality assessment of included articles (n=11)
Chapter 6: Medical Oncologists' and Palliative Care Physicians' Attitudes towards Thromboprophylaxis for Hospitalised Patients with Advanced Cancer.
6.1 Abstract

Background:

Patients with advanced cancer are increasingly discharged from palliative care settings following focused symptom management admissions. Thromboprophylaxis (TP) is recommended for patients with cancer admitted to acute care settings; less is known about TP use in palliative care settings. This study aimed to explore the opinions of Canadian medical oncologists (MO) and palliative care (PC) physicians regarding the use of primary TP for inpatients with advanced cancer.

Methods:

An email survey was administered to all Canadian MO and PC physicians. A fractional factorial survey was designed to evaluate the impact of patient factors (age, clinical setting, reason for admission, pre-admission performance scale (ECOG), and risk of bleeding on anticoagulation (HASBLED)), and physician demographics on prescribing TP. Each respondent received eight vignettes randomly selected from a complete set of 32. A hierarchical regression model was used to evaluate the odds of prescribing TP, adjusted for patient factors.

Results:

606 MO & 491 PC were surveyed; response rates were 11.1 & 15%, respectively. MO were predominantly male (59.7%); PC female (60.3%); most worked in academic environments (90.3% MO; 73.9% PC). Multivariable hierarchical logistic regression confirmed all patient factors apart from age were statistically significant for prescribing TP (OR range: 1.34[95%CI 1.01-1.77] for good ECOG to 2.53[95%CI 1.9-3.37], for reversible reason for admission); as was medical specialty (OR for medical oncologists 2.09[95%CI 1.56-2.8]).

Conclusions:

MO have higher odds of prescribing TP for inpatients than PC. Further research exploring the drivers of these differing practices is warranted.
6.2 Introduction

The increased incidence of venous thromboembolism (VTE) among patients with cancer is well-recognised (Trousseau, 1865). Up to 20% of all episodes of VTE (including deep vein thrombosis and pulmonary embolus) occur in patients with cancer, and VTE is the second most common cause of death among patients with cancer (Shen & Pollak, 1980). Risk factors for VTE among patients with advanced cancer include cancer type, stage and certain treatment modalities (Khorana et al. 2007). There is a clear positive association between aggressive cancers (as defined by their average one-year mortality rates) and the potential for VTE (Timp et al. 2013). As patients live for longer due to advances in treatments, coupled with improved diagnostic modalities to identify VTE, the incidence of VTE in this patient population appears to be growing (Khorana et al. 2007; Frere et al. 2016), as is the acknowledgement of the independent contribution of VTE to morbidity and mortality in patients with advanced cancer (Chew et al. 2006; Levitan et al. 1999; Kuderer et al. 2016). Several influential medical organisations have published guidelines and recommendations around the prevention and management of VTE, with particular attention paid to hospitalised patients who, if bedbound, have an additional, temporary risk factor for VTE. In the absence of contra-indications, thromboprophylaxis (TP) is now recommended for medically unwell patients with advanced cancer admitted to acute care settings (Lyman et al. 2014; Mandala et al. 2011; Kearon et al. 2016; NICE, 2018).

Little attention has been paid to patients admitted to palliative care units or residential hospices in terms of their suitability for TP. Historically, patients admitted to these settings were close to the end-of-life and TP was considered inappropriate (Sheard et al. 2012). Palliative care practices have evolved significantly over the past decade, however, with a widespread adoption of early palliative care interventions following the publication of several randomised controlled trials demonstrating a variety of benefits from improved satisfaction with care and quality of life, to improved survival among patients who received early palliative care alongside standard oncology care (Bakitas et al. 2009; Temel et al. 2010; Zimmermann et al. 2014). Increasingly, patients are admitted to palliative care units for brief periods of symptom assessment, followed by discharge home to continue anticancer treatments (Bryson
et al. 2010; Hui et al. 2010; Gartner et al. 2012). Although these patients may closely resemble those admitted to acute care settings, there are limited guidelines around the use of TP in this setting (NICE, 2018), and limited clinical data describing the use of TP by palliative care physicians.

6.2.1 Study aims

The aim of the current study was to assess the attitudes of physicians working in medical oncology and palliative care around the use of TP for inpatients with advanced cancer. We hypothesised that medical oncologists would be more likely to prescribe TP than palliative care physicians.

6.3 Methods

6.3.1 Study description

To understand physician attitudes towards TP, we conducted a national, cross-sectional survey of physicians working in medical oncology and palliative care across Canada.

6.3.2 Physician recruitment

Medical oncologists were identified through their specialty designation on the provincial/territorial colleges of physicians and surgeons’ websites. These websites do not include physician email addresses, so these were identified through an extensive internet search including searching the websites of individual hospitals and universities, Google searches, as well as the research websites PubMed and ResearchGate. Palliative care physicians were identified through the Canadian Society for Palliative Care Physicians (CSPCP). This group collects data from members regarding their willingness to complete research surveys as part of their membership application and renewal process. The CSPCP distributes surveys to willing members following approval by their vetting committee. Medical oncologists received two emails, sent two weeks apart; palliative care physicians received only one email only, due to administrative limitations within the CSPCP.
6.3.3 Study design: demographic questionnaire

The surveys consisted of a demographic questionnaire followed by a series of clinical scenarios or vignettes (see Appendix 2). The demographic questionnaire captured information relating to medical specialty (medical oncology or palliative care), gender, years working in specialty, year of graduation, clinical work setting (teaching or non-teaching), academic setting (academic centre or non-academic centre), access to palliative care services, and if so, what type(s) of services (acute palliative care unit\(^1\); residential hospice or long-term palliative care unit\(^2\); inpatient consultation services; outpatient clinics, and/or community-based teams).

6.3.4 Study design: fractional factorial survey

A series of clinical scenarios were developed using the fractional factorial survey approach. Factorial surveys are widely used across the healthcare literature (Auspurg & Hinz, 2015). They are believed to more closely reflect real-life behaviours and scenarios by incorporating more complex considerations of potential trade-offs than can typically be captured in a questionnaire or traditional survey. The clinical scenarios consist of several predefined factors or dimensions, which are varied between scenarios to allow for subtle exploration of respondents’ judgements (Auspurg & Hinz 2015). For the current study, we identified five patient factors felt to influence decision-making around TP based on clinical consensus and a review of the literature: patient age, admission setting (acute versus palliative care); reason for admission (potentially reversible versus irreversible); pre-admission performance status (measured using the Eastern Cooperative Oncology Group, ECOG (Oken et al. 1982) and classified as good [ECOG 0-2] or poor [ECOG 3-4]); and risk of bleeding on anticoagulation (HAS-BLED) (Pisters et al. 2010), classified as low (HAS-BLED 0-2) or high (HAS-BLED ≥3). These five factors were dichotomised, leaving a total of 32 potential scenarios to explore (2\(^5\)). Vignettes were presented in a standardised format; an example is shown in Box 1.

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1. Acute palliative care unit indicates a short-term facility where patients are typically admitted for brief periods of symptom management and are subsequently discharged.
2. Long-term palliative care unit or residential hospice indicates a facility where patients are typically admitted for end-of-life care and where length of stay can be up to three months.
This number of vignettes was considered too onerous for all respondents to review, however, so a fractional factorial approach was utilised, whereby each respondent was asked to complete eight randomly selected vignettes. The entire universe of 32 vignettes was divided into eight blocks, each containing four vignettes. The software used to develop the survey assigned 25% of respondents to each of the four options within each block, thus ensuring an even distribution of vignettes across all respondents (SurveyMonkey). One block was set up to include vignettes where the only reasonable response would be to not treat with TP; this was done to ensure internal validity. Each vignette was followed by the question: ‘Based on the information provided, how likely would you be to consider TP for this patient?’ Responses were indicated along a five-point Likert scale ranging from ‘very unlikely’ to ‘very likely’. The Likert responses were subsequently dichotomised into ‘treat’ (defined as a response of ‘very likely’ or ‘likely’) and ‘no treat’ (responses of ‘neutral’, ‘unlikely’ or ‘very unlikely’). A sensitivity analysis was subsequently performed with neutral responses in the ‘treat’ category.

6.3.5 Pilot testing

Pilot testing was completed among a convenience sample of physicians from medical oncology, palliative care and general internal medicine. This was done to assess clarity of wording and instructions, ease of completion, completion time, and to identify any ambiguity within the vignettes (Ulrich & Ratcliffe, 2007). The average time to complete the survey was five minutes. Research Ethics Board approval was sought and granted on November 16th, 2017.

6.4 Statistical considerations

Descriptive statistics were used to summarize the demographics and characteristics of the two physician groups. Univariable regression models were used to predict the influence of individual patient and physician factors on decision-making around TP; multiple regression was used to identify interplay between the factors, and specifically whether medical oncologists were more likely to prescribe TP after accounting for patient factors.
6.4.1 Sample size calculation

We estimated a sample size of 63 physicians per group would be required to detect a medium effect size, with 80% power (5% significance).

6.4.2 Analysing factorial surveys

Factorial surveys produce multilevel data where both respondents and vignettes are sampled, and where there are variables at both the respondent and the vignette level. In order to consider the relationships both within and between levels, hierarchical linear models were used for the statistical analyses. This model poses two regression equations, one modelling vignette effects within respondents, and the other between respondents (Hox et al, 1991; Auspurg & Hinz, 2015). SPSS version 23 (IBM Corp. 2015) was used for all statistical analyses.

6.5 Results

6.5.1 Response rate

Surveys were sent to 606 Medical Oncologists and 491 palliative care physicians. Of the 606 emails sent to medical oncologists, 62 were completed (173 opened, 377 unopened and 46 bounced, with 10 opting out), giving a response rate of 11.1% of all received emails (62/560) or 36% of opened emails. Of the 491 palliative care emails sent, 73 surveys were completed (245 opened, 11 bounced and 1 unsubscribe), with a response rate of 15% of received emails (73/480) or 29.7% of opened emails.

6.5.2 Respondent demographics

Table 11 shows the demographic and practice characteristics of respondents. Of the 62 medical oncologists, 59.7% (n=37) were male, and 70.9% (n=44) had been working in the specialty for ≤10 years. 93.5% (n=58) worked in a teaching setting, and 90.3% (n=56) had an academic appointment. All had access to palliative care services across a variety of settings (inpatient consultation services 96.7%, acute palliative care units 67%, long-term palliative care units or residential hospices 62.9%, outpatient clinics 93.5%, and community-based teams 70.9%). The palliative care physicians were more likely to be female (60.3%, n=44), working in the specialty
for ≤10 years (57.5%, n=42), were affiliated with a teaching centre in 76.7% (n=56) and had an academic appointment in 73.9% (n=54). Approximately one third of palliative care physicians reported their practice consisted of cancer patients predominantly (≥90% cancer patients). The vast majority (94.5%) of palliative care physicians had access to an inpatient consultation team; 67% to an acute palliative care unit; 94.5% to a long-term palliative care unit or residential hospice; 73.9% palliative care clinics; and 93.1% a community-based team.

6.5.3 Overall responses and free-text comments

Overall, 32.3% of medical oncologists opted to treat ≥75% of the presented cases versus 13.7% of palliative care physicians; 62.9% of medical oncologists opted to treat ≥50% of the presented cases compared with 34.2% of palliative care physicians (Figure 3). We reviewed the free-text options within each vignette and conducted a content analysis of the comments by assigning codes to each unique theme. Codes were assigned to each comment; two themes were consistently identified, around goals of care and the need to temporarily withhold TP in certain circumstances. Palliative care physicians were more likely to comment on the importance of identifying the patient’s goals of care (16 [22%] of palliative care physicians mentioned this versus 6 [9.6%] of medical oncologists); medical oncologists were more likely to comment on the potential need for interventions (such as thoracenteses or nephrostomy tubes) that might necessitate delaying the initiation of or holding TP temporarily (22.5% of medical oncologists [n=14] mentioned this versus 6.8% of palliative care physicians [n=5]).

Table 12 and Figure 4 compare the number of medical oncologists versus palliative care physicians who chose to treat for each of the 32 individual vignettes. A higher percentage of medical oncologists chose to treat for each vignette in all but four cases, although in all four the numbers who chose to treat were small (less than seven per physician group). All four vignette options in Block seven were designed to elicit a ‘no treat’ response; 100% of medical oncologists and 95% of palliative care physicians agreed that they were ‘unlikely’ or ‘very unlikely’ to treat in these scenarios.

In order to explore the variance between patient and physician factors and how they might influence one another, we reviewed the ten vignettes where the majority of medical
oncologists and palliative care physicians, respectively, chose to treat with TP. For medical oncologists, the percentage of respondents who chose to treat for these ten vignettes ranged from 72.7-94.4%. In eight of the vignettes, the hypothetical patient was admitted to an acute care setting, and in seven they were young, suggesting these may be the factors considered most important by medical oncologists. Six of the ten scenarios described a patient admitted with a potentially reversible cause and a good ECOG, with an equal split between low and high HAS-BLED scores. For palliative care physicians, 42.9-75% chose to treat in the top ten scored vignettes. In seven cases the patient was young, followed by reversible cause for admission, good ECOG and low HAS-BLED (six cases each); setting was equally split between palliative care and acute care settings suggesting this was the least important factor for palliative care physicians.

We also reviewed the ten vignettes with the greatest percentage difference between medical oncologists and palliative care physicians’ likelihood of treating with TP. In eight of the ten scenarios, the hypothetical patient was admitted to an acute care setting, and in seven, the HAS-BLED was described as low, suggesting that setting and risk of bleeding may have influenced medical oncologists’ decision-making above other factors such as age (in eight scenarios the patient was older), ECOG (6 scenarios described a poor pre-admission ECOG), or reversibility (50% of the scenarios were potentially reversible), compared with palliative care physicians.

6.5.4 Univariable regression

Results of the univariable logistic regression used to identify patient and physician factors associated with the likelihood of treatment with TP are presented in Table 13. All five patient factors were statistically significant on univariable analyses; physicians had a higher odds of prescribing TP for younger patients compared with older, odds ratios (OR) 1.35, (95% CI 1.05-1.74, p=0.02); for patients admitted to acute care settings compared with palliative care settings, OR 2.09 (95% CI 1.62-2.71, p<0.001); for patients admitted with reversible causes compared with irreversible causes, OR 2.48 (95% CI 1.92-3.22, p<0.001); for patients with a better pre-admission ECOG compared with a poorer ECOG, OR 1.79 (95% CI 1.39-3.31,
p<0.001); and for patients with a lower risk of bleeding as per HASBLED compared with a higher HAS-BLED, OR 2.38 (95% CI 1.84-3.09, p<0.001). Of the physician factors, only medical specialty was significant, with medical oncologists at higher odds of prescribing TP compared with palliative care physicians, OR 1.95 (1.49-2.56), p<0.001.

6.5.5 Multivariable regression

A multivariable hierarchical logistic regression was then used to assess if factors remained statistically significant when accounting for each other. At step one, we entered patient factors, followed by physician factors at step two of the regression model. Table 14 shows that all patient factors, with the exception of age, remained statistically significant in the multivariable regression model. The ORs ranged from 1.34 higher odds of treating with TP for good ECOG compared with poor ECOG (95% CI 1.01-1.77, p=0.04), to 2.53 for reversible cause for admission compared with an irreversible cause for admission, (95% CI 1.90-3.37, p<0.001).

At step 2 of the multivariable regression model, we added the physician factors. Medical specialty was the only factor that was statistically significant, with medical oncologists remaining at higher odds of prescribing TP compared with palliative care physicians, OR 2.09 (95% CI 1.56-2.8, p<0.0001).

The full model significantly predicted treatment with TP (omnibus chi square=45.11, df=5, p<0.0001). The model accounted for between 15.2-20.5% of the variance in treatment with TP, with 77.9% of non-treatment successfully predicted and 53.5% of treatment predicted. Overall, 67.6% of predictions were accurate.

6.5.6 Data split by medical specialty

The data were then split by medical specialty to identify any factors unique to either medical oncologists or palliative care physicians in their decision-making around TP. On univariable logistic regression for medical oncologists, admission to an acute care setting (OR 2.86 [95% CI 1.97-4.15, p<0.0001], reversible cause for admission (OR 2.19 [95% CI 1.52-3.16], p<0.0001), good ECOG (OR 1.93 [95% CI 1.34-2.78], p<0.0001), and low HAS-BLED (OR 2.68 [95% CI 1.85-3.88], p<0.0001) were all associated with higher odds of treating with TP; age was not
significant however (OR 1.08 [95% CI 0.75-1.54], p=0.69). For palliative care physicians, younger patient age was significant (OR 1.69 [95% CI 1.18-2.42, p=0.004), as was reversible cause for admission (OR 2.82 [95% CI 1.94-4.07, p<0.0001), good ECOG (OR 1.66 [95% CI 1.16-2.37], p=0.006), and low HAS-BLED (OR 2.13 [95% CI 1.48-3.06], p<0.0001); setting was not significant for this physician group (acute setting OR 1.55 [95% CI 1.09-2.22], p=0.16). For physician factors, none were significant for either medical oncologists or palliative care physicians (Table 15).

On multivariable hierarchical logistic regression for medical oncologists, good ECOG was no longer significant (OR 1.40 [95% CI 0.93-2.11], p=0.11) but the other factors remained significant. Low HAS-BLED was associated with higher odds of treating with TP (OR 2.49 [95% CI 1.66-3.76], p<0.0001), as was admission to an acute care setting (OR 2.99 [95% CI 2.00-4.49], p<0.0001) and admission with a reversible cause (OR 2.56 [95% CI 1.68-3.87], p<0.0001). For palliative care physicians, there were similar findings for low HAS-BLED (OR 2.07 [95% CI 1.41-3.04], p<0.0001), admission to an acute care setting (OR 1.54 [95% CI 1.05-2.25], p=0.02), and admission with a reversible cause (OR 2.62 [95% CI 1.76-3.89], p<0.0001); age and ECOG were not significant. Physician factors were again not significant for either group (Table 16).

6.5.7 Sensitivity analysis with ‘neutral’ responses categorised as ‘treat’: univariable regression

We subsequently repeated the analyses with neutral responses re-categorised as ‘treat’; these results are presented in Tables 17 (univariate regression) and 18 (multivariate regression). In this model, on univariate analyses, all patient factors remained statistically significant as before. Reversible cause for admission was associated with the highest odds of treating with TP, OR 3.02 (95% CI 2.34-3.89, p<0.001); age < 65 years was associated with 1.35 times higher odds of treating with TP compared with age ≥65 years (95% CI 1.06-1.73, p=0.016).

For physician factors, medical oncologists remained at 1.94 higher odds of treating with TP compared with palliative care physicians (95% CI 1.51-2.48, p<0.001). Two additional physician factors were significant, however. Male physicians were at higher odds of treating with TP compared with females (OR 1.52, 95% CI 1.51-2.48, p<0.001); as was working in a teaching setting compared with a non-teaching setting (OR 1.53, 95% CI 1.08-2.16, p=0.02).
6.5.8 Sensitivity analysis with ‘neutral’ responses categorised as ‘treat’: multivariable regression

On multivariable hierarchical logistic regression, patient age was no longer significant as before, but the remaining patient factors were significant. These ranged from increased odds of 1.34 for good ECOG (95% CI 1.02-1.77, p=0.04) to 3.16 times higher odds for reversible reason for admission (95% CI 2.38-4.19, p<0.001). After controlling for patient factors, medical specialty remained statistically significant, with medical oncologists at 1.87 times higher odds for treating with TP compared with palliative care physicians (95% CI 1.40-2.51, p<0.001). Gender was also significant, with male physicians at 1.39 higher odds of prescribing TP compared with females (95% CI 1.04-1.85, p=0.02), see Table 18.

6.6 Discussion

Our results indicate that several patient factors appear to influence decision-making around TP, with admission to an acute care setting, potentially reversible reason for admission, better performance status, and low risk of bleeding on anticoagulation, all associated with higher odds of treatment with TP among both medical oncologists and palliative care physicians on multivariable regression. As we had hypothesised, medical oncologists had higher odds of treating with TP compared with palliative care physicians, even after controlling for these patient factors.

6.6.1 Consideration of the results alongside the existing literature

There is a very limited literature around individual patient and physician factors and how these may influence decision-making around TP for patients with advanced cancer. Palliative care physicians have been shown to under-recognise or undertreat VTE (Johnson & Sherry, 1997). In some cases, this has been driven by a somewhat nihilistic approach, suggesting that death from VTE may be more rapid and preferable to other causes of death related to advanced cancer (Noble et al. 2008). Only one other study, to our knowledge, has compared medical oncologists’ and palliative care physicians’ (along with hematologists' and intensive care specialists’) attitudes towards TP using clinical vignettes. This was a small, single-centre study of 20
physicians that found that the use of TP varied according to performance status, with all 20 physicians electing to withdraw TP when the hypothetical patient was actively dying. Palliative care physicians were least likely to prescribe TP compared with the other physician groups, irrespective of performance status (Kierner et al. 2008).

6.6.2 The changing face of palliative care

Studies have noted a change in attitudes of some palliative care physicians, with increasing numbers of palliative care units in the UK having formal TP policies between 2000 and 2005 (Noble & Finlay, 2006). Palliative care physicians are increasingly involved in the care of patients with advanced cancer while they continue to receive active anticancer treatment and are ambulatory (Bakitas et al. 2009; Temel et al. 2010; Zimmermann et al. 2014); increasing numbers of patients are admitted to palliative care units for brief stays with potentially reversible conditions (Bryson et al. 2010; Hui et al. 2010; Gartner et al. 2012). This subset of patients may benefit from TP just as they might if admitted to an acute setting. Our study suggests that the clinical practices of palliative care physicians around TP may not have kept pace with the changing demographics of many patients seen by this group of physicians, and that the historical culture of less aggressive care within palliative care settings may not have changed significantly.

6.6.3 Postgraduate training differences between medical oncologists and palliative care physicians

Our study focussed on physicians working as medical oncologists and palliative care physicians across Canada. Until 2017, the formal route to becoming a certified palliative care physician in Canada involved a single year of added competence jointly accredited by the Royal College of Physicians and Surgeons as well as the College of Family Physicians of Canada (Monette 2012); the majority of applicants came from family medicine backgrounds however. In 2017, palliative care became a medical subspecialty through the Royal College of Physicians and Surgeons of Canada; certification involves an additional two years of subspecialty training following three years of internal medicine training. It is likely that the vast majority of palliative care physicians who completed our survey completed the former training route, so their
exposure to hospitalised cancer patients and awareness of the TP guidelines for these patients may differ from medical oncologists, whose training in internal medicine before specialising in medical oncology is predominantly hospital-based. As such, our results may reflect an important knowledge gap among palliative care physicians based on limited exposure to acutely unwell patients with advanced cancer during their training. This has also been suggested as a reason for increasingly aggressive care on palliative care settings in the UK, following formalisation of the medical specialty training program in palliative medicine there (Noble et al. 2008).

6.6.4 Strengths and limitations of the study

Our study has a number of strengths and limitations. The overall response rates for both medical oncologists and palliative care physicians were low, although consistent with the literature around typical response rates for physician surveys which has consistently demonstrated declining survey response rates over the past decade (Cook et al. 2016; Cunningham et al. 2015). The survey was administered via email only; sending additional follow-up emails, adding mail-based questionnaires or offering incentives may have improved the response rates. The majority of respondents worked in teaching hospitals and were affiliated with academic centres; our results cannot be generalised to physicians working across other settings. Bearing these demographics in mind, it is possible that the non-responders (more experienced physicians working in non-academic centres), especially in the palliative care group, may have been even less likely to prescribe TP than responders, and that the difference between medical specialties found here may have been further magnified by the inclusion of non-responders. We were unable to obtain additional information about non-responders through the CSPCP or the Colleges of Physicians and Surgeons; a follow-up questionnaire aimed at non-responders to better understand their reasons for non-participation as well as to obtain some baseline demographics may have provided important data to inform the generalisability of our findings.

We chose to use a fractional factorial design, rather than a full factorial (where all respondents complete all possible vignettes). Although this is associated with a degree of loss
of orthogonality, we felt that 32 vignettes were excessive and likely to be associated with higher non-completion rates or simplifying heuristics (Auspurg & Hinz, 2015).

We utilised the HAS-BLED as a marker for risk of bleeding on anticoagulation. This was originally designed to measure the bleeding risk for patients anticoagulated for atrial fibrillation rather than VTE or prophylaxis specifically (Pisters et al. 2010); nonetheless, it is the most commonly cited and validated tool of its kind (Parks & Fang 2017) which we felt would be most recognisable to respondents.

Despite these limitations, our final sample size is one of the largest reported for physician-based studies of TP practices. It is also to our knowledge, the first national study of TP practices for inpatients with advanced cancer.

6.7 Conclusions

Patient factors including reason for admission, place of admission, pre-admission performance status, and risk of bleeding on anticoagulation, all appear to influence physician decision-making around the use of TP for inpatients with advanced cancer. Medical oncologists are at higher odds of prescribing TP for inpatients with advanced cancer than palliative care physicians, even after controlling for these patient factors. These differences may reflect deeply-rooted cultural attitudes towards perceived aggressive interventions within palliative care settings; they may also relate to different training programs to specialise in medical oncology and palliative care, respectively. A deeper exploration of the attitudes and training experiences of palliative care physicians and medical oncologists through qualitative interviewing may help to better understand these differences.
Table 11: Participant demographics

<table>
<thead>
<tr>
<th></th>
<th>Medical Oncology n=62 (%)</th>
<th>Palliative Care n=73 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (59.7)</td>
<td>29 (39.7)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (40.3)</td>
<td>44 (60.3)</td>
</tr>
<tr>
<td><strong>Years working in specialty:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>44 (70.9)</td>
<td>42 (57.5)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>18 (29.1)</td>
<td>35 (42.5)</td>
</tr>
<tr>
<td><strong>Work setting:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>58 (93.5)</td>
<td>56 (76.7)</td>
</tr>
<tr>
<td>Community hospital</td>
<td>04 (6.5)</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td><strong>Practice environment:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic teaching centre</td>
<td>56 (90.3)</td>
<td>54 (73.9)</td>
</tr>
<tr>
<td>Non-academic centre</td>
<td>06 (9.7)</td>
<td>19 (26.1)</td>
</tr>
<tr>
<td><strong>% patients with cancer:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90%</td>
<td>56 (90.3)</td>
<td>23 (31.5)</td>
</tr>
<tr>
<td>&lt;90%</td>
<td>06 (9.7)</td>
<td>50 (68.5)</td>
</tr>
<tr>
<td><strong>Access to palliative care services:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>What services?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute PCU</td>
<td>42 (67.7)</td>
<td>49 (67.1)</td>
</tr>
<tr>
<td>PCU or hospice</td>
<td>39 (62.9)</td>
<td>69 (94.5)</td>
</tr>
<tr>
<td>Inpatient consults</td>
<td>60 (96.7)</td>
<td>69 (94.5)</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>58 (93.5)</td>
<td>54 (73.9)</td>
</tr>
<tr>
<td>Community team</td>
<td>44 (70.9)</td>
<td>68 (93.1)</td>
</tr>
</tbody>
</table>
Table 12: number of ‘treat’ by physician specialty for each vignette

<table>
<thead>
<tr>
<th>Vignette*</th>
<th>Medical Oncology treat (%)</th>
<th>Palliative Care treat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A: Old/acute/irreversible/poor ECOG/low HASBLED*</td>
<td>14/20 (70)</td>
<td>6/19 (31.6)</td>
</tr>
<tr>
<td>1B: Young/PCU/irreversible/good ECOG/low HASBLED</td>
<td>7/12 (58.3)</td>
<td>7/19 (36.8)</td>
</tr>
<tr>
<td>1C: Young/acute/irreversible/good ECOG, high HASBLED</td>
<td>7/18 (38.9)</td>
<td>2/12 (16.7)</td>
</tr>
<tr>
<td>1D: Old/PCU/reversible/poor ECOG/low HASBLED</td>
<td>8/12 (66.6)</td>
<td>6/20 (30)</td>
</tr>
<tr>
<td>2A: Old/acute/irreversible/poor ECOG/high HASBLED</td>
<td>11/14 (78.6)</td>
<td>9/21 (42.9)</td>
</tr>
<tr>
<td>2B: Old/acute/reversible/poor ECOG/low HASBLED</td>
<td>5/14 (35.7)</td>
<td>3/15 (20)</td>
</tr>
<tr>
<td>2C: Old/PCU/reversible/poor ECOG/high HASBLED</td>
<td>3/24 (12.5)</td>
<td>3/19 (15.8)</td>
</tr>
<tr>
<td>2D: Old/acute/reversible/good ECOG/high HASBLED</td>
<td>1/8 (12.5)</td>
<td>4/14 (28.6)</td>
</tr>
<tr>
<td>3A: Young/acute/reversible/poor ECOG/low HASBLED</td>
<td>7/9 (77.8)</td>
<td>11/16 (68.8)</td>
</tr>
<tr>
<td>3B: Old/PCU/irreversible/poor ECOG/high HASBLED</td>
<td>3/14 (21.4)</td>
<td>1/18 (5.6)</td>
</tr>
<tr>
<td>3C: Young/acute/irreversible/good ECOG/low HASBLED</td>
<td>18/21 (85.7)</td>
<td>12/18 (66.7)</td>
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<tr>
<td>3D: Old/PCU/irreversible/good ECOG/low HASBLED</td>
<td>8/11 (72.7)</td>
<td>9/18 (50)</td>
</tr>
<tr>
<td>4A: Old/acute/reversible/good ECOG/low HASBLED</td>
<td>10/15 (66.7)</td>
<td>6/17 (35.3)</td>
</tr>
<tr>
<td>4B: Young/PCU/reversible/poor ECOG/high HASBLED</td>
<td>6/16 (37.5)</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>4C: Young/acute/reversible/poor ECOG/high HASBLED</td>
<td>13/16 (81.3)</td>
<td>5/17 (29.4)</td>
</tr>
<tr>
<td>Group</td>
<td>Description</td>
<td>Proportion</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>4D</td>
<td>Young/acute/reversible/poor ECOG/low HASBLED</td>
<td>8/11 (72.7)</td>
</tr>
<tr>
<td>5A</td>
<td>Young/PCU/reversible/poor ECOG/low HASBLED</td>
<td>10/17 (58.8)</td>
</tr>
<tr>
<td>5B</td>
<td>Old/PCU/irreversible/good ECOG/high HASBLED</td>
<td>0/8 (0)</td>
</tr>
<tr>
<td>5C</td>
<td>Old/PCU/reversible/good ECOG/low HASBLED</td>
<td>9/13 (69.2)</td>
</tr>
<tr>
<td>5D</td>
<td>Old/PCU/reversible/good ECOG/high HASBLED</td>
<td>11/21 (52.4)</td>
</tr>
<tr>
<td>6A</td>
<td>Old/acute/irreversible/poor ECOG/low HASBLED</td>
<td>11/16 (68.8)</td>
</tr>
<tr>
<td>6B</td>
<td>Old/acute/irreversible/good ECOG/low HASBLED</td>
<td>7/13 (53.8)</td>
</tr>
<tr>
<td>6C</td>
<td>Old/acute/irreversible/good ECOG/high HASBLED</td>
<td>14/18 (77.8)</td>
</tr>
<tr>
<td>6D</td>
<td>Old/PCU/irreversible/poor ECOG/low HASBLED</td>
<td>4/12 (33.3)</td>
</tr>
<tr>
<td>7A</td>
<td>Young/PCU/irreversible/poor ECOG/low HASBLED</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>7B</td>
<td>Young/PCU/irreversible/poor ECOG/high HASBLED</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>7C</td>
<td>Young/acute/irreversible/poor ECOG/high HASBLED</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>7D</td>
<td>Young/PCU/irreversible/good ECOG/high HASBLED</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>8A</td>
<td>Young/PCU/reversible/good ECOG/low HASBLED</td>
<td>15/18 (83.3)</td>
</tr>
<tr>
<td>8B</td>
<td>Young/PCU/reversible/good ECOG/high HASBLED</td>
<td>6/9 (66.7)</td>
</tr>
<tr>
<td>8C</td>
<td>Young/acute/reversible/good ECOG/low HASBLED</td>
<td>17/18 (94.4)</td>
</tr>
<tr>
<td>8D</td>
<td>Young/acute/reversible/good ECOG/high HASBLED</td>
<td>11/14 (78.6)</td>
</tr>
</tbody>
</table>
*Table legend*
Young: <65 years
Old: age ≥65 years
Acute: admitted to an acute care setting
PCU: palliative care unit
Reversible: reason for admission was considered potentially reversible
Irreversible: reason for admission was considered likely irreversible
Good ECOG: performance status 0-2
Poor ECOG: performance status ≥3
Low HAS-BLED: risk of bleeding on anticoagulation 0-2
High HAS-BLED: risk of bleeding on anticoagulation ≥3
Table 13: Univariate logistic regression with neutral responses categorized as ‘no treat’

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>1.35 (1.05-1.74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>2.09 (1.62-2.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Setting: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission: reversible cause</td>
<td>2.48 (1.92-3.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission: irreversible cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.79 (1.39-3.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HASBLED: low</td>
<td>2.38 (1.84-3.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HASBLED: high</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical specialty: medical oncology</td>
<td>1.95 (1.49-2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical specialty: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.25 (0.96-1.64)</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender: female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years in practice: ≤10</td>
<td>1.08 90.83-1.41)</td>
<td>0.58</td>
</tr>
<tr>
<td>Years in practice: &gt;10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work setting: teaching hospital</td>
<td>1.25 (0.85-1.83)</td>
<td>0.25</td>
</tr>
<tr>
<td>Work setting: non-teaching hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice environment: academic</td>
<td>1.11 (0.79-1.56)</td>
<td>0.55</td>
</tr>
<tr>
<td>Practice environment: non-academic centre</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 14: Multivariate hierarchical logistic regression with neutral responses categorized as ‘no treat’

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>1.07 (0.81-1.40)</td>
<td>0.65</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>2.12 (1.61-2.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Setting: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission: reversible cause</td>
<td>2.53 (1.90-3.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission: irreversible cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.34 (1.01-1.77)</td>
<td>0.04</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HASBLED: low</td>
<td>2.23 (1.69-2.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HASBLED: high</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical specialty: medical oncology</td>
<td>2.09 (1.56-2.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical specialty: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.31 (0.98-1.75)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender: female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years in practice &lt;10</td>
<td>1.003 (0.74-1.36)</td>
<td>0.98</td>
</tr>
<tr>
<td>Years in practice: &gt;10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work setting: teaching hospital</td>
<td>1.45 (0.88-2.39)</td>
<td>1.45</td>
</tr>
<tr>
<td>Work setting: non-teaching hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice setting: academic centre</td>
<td>0.94 (0.59-1.48)</td>
<td>0.78</td>
</tr>
<tr>
<td>Practice environment: non-academic centre</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15: Univariate logistic regression: data split by specialty

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical Oncology OR (95% CI)</th>
<th>p-value</th>
<th>Palliative Care OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&lt;65 years</td>
<td>1.08 (0.75-1.54)</td>
<td>0.69</td>
<td>1.69 (1.18-2.42)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age &gt;=65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>2.86 (1.97-4.15)</td>
<td>&lt;0.0001</td>
<td>1.55 (1.09-2.22)</td>
<td>0.16</td>
</tr>
<tr>
<td>Setting: PCU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversibility: reversible</td>
<td>2.19 (1.52-3.16)</td>
<td>&lt;0.0001</td>
<td>2.82 (1.94-4.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reversibility: irreversible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.93 (1.34-2.78)</td>
<td>&lt;0.0001</td>
<td>1.66 (1.16-2.37)</td>
<td>0.006</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED: low</td>
<td>2.68 (1.85-3.88)</td>
<td>&lt;0.0001</td>
<td>2.13 (1.48-3.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED: high</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Physician variables</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.26 (0.87-1.83)</td>
<td>0.22</td>
<td>1.23 (0.85-1.77)</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender: female</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Years in practice: &lt;10</td>
<td>1.22 (0.82-1.84)</td>
<td>0.32</td>
<td>1.03 (0.72-1.47)</td>
<td>0.89</td>
</tr>
<tr>
<td>Years in practice: &gt;=10</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work setting: teaching</td>
<td>1.42 (0.63-3.19)</td>
<td>0.40</td>
<td>1.03 (0.72-1.47)</td>
<td>0.89</td>
</tr>
<tr>
<td>Work setting: non-teaching</td>
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</tr>
<tr>
<td>Practice environment: academic</td>
<td>1.04 (0.55-1.98)</td>
<td>0.89</td>
<td>1.14 (0.75-1.73)</td>
<td>0.53</td>
</tr>
<tr>
<td>Practice environment: non-academic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 16: Multivariable hierarchical logistic regression: data split by specialty

<table>
<thead>
<tr>
<th>Factor</th>
<th>Medical Oncology OR (95% CI)</th>
<th>p value</th>
<th>Palliative Care OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>0.78 (0.52-1.16)</td>
<td>0.22</td>
<td>1.39 (0.95-2.05)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>2.99 (2.00-4.49)</td>
<td>&lt;0.0001</td>
<td>1.54 (1.05-2.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Setting: palliative care</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission: reversible cause</td>
<td>2.56 (1.68-3.87)</td>
<td>&lt;0.0001</td>
<td>2.62 (1.76-3.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission: irreversible cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.40 (0.93-2.11)</td>
<td>0.11</td>
<td>1.27 (0.86-1.87)</td>
<td>0.24</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HASBLED: low</td>
<td>2.49 (1.66-3.76)</td>
<td>&lt;0.0001</td>
<td>2.07 (1.41-3.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HASBLED: high</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.38 (0.89-2.11)</td>
<td>0.15</td>
<td>1.36 (0.89-2.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>Gender: female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years in practice &lt;10</td>
<td>0.94 (0.59-1.51)</td>
<td>0.81</td>
<td>0.97 (0.63-1.49)</td>
<td>0.88</td>
</tr>
<tr>
<td>Years in practice: &gt;10</td>
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</tr>
<tr>
<td>Work setting: teaching hospital</td>
<td>3.69 (0.81-16.98)</td>
<td>0.09</td>
<td>1.24 (0.71-2.17)</td>
<td>0.44</td>
</tr>
<tr>
<td>Work setting: non-teaching hospital</td>
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</tr>
<tr>
<td>Practice setting: academic centre</td>
<td>0.50 (0.16.62)</td>
<td>0.25</td>
<td>1.06 (0.62-1.81)</td>
<td>0.84</td>
</tr>
<tr>
<td>Practice environment: non-academic centre</td>
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</tbody>
</table>
Table 17: Univariate logistic regression with neutral responses categorized as ‘treat’

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>1.35 (1.06-1.73)</td>
<td>0.016</td>
</tr>
<tr>
<td>Age &gt;=65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>1.79 (1.39-2.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Setting: PCU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversibility: reversible</td>
<td>3.02 (2.34-3.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reversibility: irreversible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.82 (1.42-2.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED: low</td>
<td>2.46 (1.92-3.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED: high</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialty: medical oncology</td>
<td>1.94 (1.51-2.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Specialty: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.52 (1.18-1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender: female</td>
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<td></td>
</tr>
<tr>
<td>Years in practice: &lt;10</td>
<td>1.23 (0.95-1.58)</td>
<td>0.12</td>
</tr>
<tr>
<td>Years in practice: &gt;=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work setting: teaching</td>
<td>1.53 (1.08-2.16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Work setting: non-teaching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice environment: academic</td>
<td>1.21 (0.88-1.68)</td>
<td>0.24</td>
</tr>
<tr>
<td>Practice environment: non-academic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 18: Multivariate hierarchical logistic regression with neutral responses categorized as ‘treat’

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>1.01 (0.77-1.33)</td>
<td>0.92</td>
</tr>
<tr>
<td>Age &gt;= 65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: acute</td>
<td>1.82 (1.39-2.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Setting: PCU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversibility: reversible</td>
<td>3.16 (2.38-4.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reversibility: irreversible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG: good</td>
<td>1.34 (1.02-1.77)</td>
<td>0.04</td>
</tr>
<tr>
<td>ECOG: poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED: low</td>
<td>2.53 (1.91-3.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED: high</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialty: medical oncology</td>
<td>1.87 (1.40-2.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Specialty: palliative care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td>1.39 (1.04-1.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender: female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years in practice: &lt;10</td>
<td>0.95 (0.70-1.28)</td>
<td>0.74</td>
</tr>
<tr>
<td>Years in practice: &gt;=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work setting: teaching</td>
<td>1.57 (0.96-2.56)</td>
<td>0.07</td>
</tr>
<tr>
<td>Work setting: non-teaching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice environment: academic</td>
<td>1.27 (0.81-1.99)</td>
<td>0.29</td>
</tr>
<tr>
<td>Practice environment: non-academic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3: Percentage of medical oncologists and palliative care physicians who chose to treat ≥50% and ≥75% of assigned scenarios with TP.
Figure 4: Percentage of medical oncologists and palliative care physicians opting to treat for each individual vignette (n=32)
Box 2: Sample vignette

A 70-year old patient with bladder cancer with metastases to bone and lung is admitted under general Internal Medicine. He has a hypoactive delirium, and a Creatinine of 152 (normal range 64-110). His pre-admission ECOG was 3*. His HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely

*ECOG 3: Eastern cooperative Oncology group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the one-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (≥2/100 patient-years)
Chapter 7: General Discussion
General Discussion

The ‘multiple paper’ format of this thesis permits specific discussion sections for each chapter that contained new data (see Chapters 5 and 6). In the interest of minimising repetition and redundancy, this general discussion is limited to considering how our findings impact the overall theme running through this research, which was an interest in exploring TP for patients with advanced cancer, with a particular focus on patients with palliative care needs or involvement; considering how the results can be assimilated in a cohesive manner; and addressing the potential implications for patients, practice, and policy. Our results highlight some important heterogeneity in both the recognition and treatment of VTE in palliative care settings; as well as differences in practices and attitudes between medical oncologists and palliative care physicians, which will be discussed in further detail in this section.

7.1 Awareness of the significance of VTE among patients with advanced cancer

It is clear that there is a growing incidence and awareness of the significance of VTE among patients with advanced cancer (Khorana et al. 2007; Timp et al. 2013). The past 10-15 years have seen a rapid growth in the literature around TP for this patient group as well as the publication of a number of clinical practice guidelines endorsed by major international cancer and non-cancer bodies such as ASCO, ESMO, ACCP, and NICE (Lyman et al. 2014; Mandala et al. 2011; Kearon et al. 2016; NICE, 2018). In the UK, an increasing number of palliative care units and residential hospices now have formal policies regarding TP (increased from 2 to 7% between 2000 and 2005, with an estimated 19% expected to have policies by 2006) (Noble & Finlay 2006). Data from other countries is lacking at this time, however.

7.2 Ambiguity about the relevance and incidence of VTE for patients admitted to palliative care units or residential hospices

Despite this growing awareness of the association between VTE and cancer, extrapolating the data to palliative care settings appears to be more challenging. The data around the incidence of VTE on palliative care units and residential hospices demonstrates large disparities in reported rates. Our systematic review identified rates of VTE that ranged from 0.5-20% across 11 full-text papers and ten abstracts. There are several potential reasons for this wide variation, as outlined below.
7.2.1 Diagnostic challenges

There was significant heterogeneity in how VTE was diagnosed between studies in our systematic review. In several cases, clinical assessment alone was used to identify VTE; other facilities had access to diagnostic modalities including Doppler ultrasounds and/or CT scans to formally diagnose VTE. Several studies were retrospective and relied upon accurate documentation in the case-notes which may have been lacking (Gillon et al. 2011; Johnson et al. 2014; Pautex et al. 2012; McMullan et al. 2012; Chanthong et al. 2011; Bertola et al. 2014; Ciuhu et al. 2016; Brabin et al. 2008; Thorley et al. 2016; Thomas et al. 2016).

7.2.2. Failure to consider VTE as part of the differential diagnosis

Many of the symptoms of VTE can be easily attributed to other causes in patients with advanced cancer. Lower limb swelling, shortness of breath, and pain may all be caused by other factors related to advanced cancer; VTE may not have been considered in the differential diagnoses. Palliative care physicians have suggested in one study that they do not commonly encounter VTE in their practice (Noble et al. 2008), and to estimate the incidence of VTE at 1-5% among patients admitted to palliative care units in another (Johnson & Sherry 1997), which contrasts with other findings, including an autopsy study which identified VTE in 19% of patients with advanced cancer from one palliative care centre in Switzerland (Pautex et al. 2013). This may point towards a lack of awareness of the incidence of VTE among this patient population, and a knowledge gap among clinicians working on palliative care units or residential hospices.

7.2.3 Lack of differentiation between patient subgroups

The patient population served by individual palliative care units or residential hospices was not clearly defined in most of the studies included in our review. TP is generally considered inappropriate for patients who are actively dying as it does not confer a survival benefit in this instance (NICE, 2018). On the other hand, patients who are admitted to acute palliative care units for brief periods of symptom management may have a temporary elevated risk of VTE and may benefit from TP. Clear definitions of this subset of patients for whom TP may be appropriate, and studies focussing specifically on this subset of patients, may help to further estimate the magnitude of VTE in this population.
7.3 Use of thromboprophylaxis on palliative care units or residential hospices

Our review identified TP use on palliative care units or hospices ranging from 4-53% (Brabin et al. 2008; Tardy et al. 2015). With the exception of two studies where the use of TP was 29% and 53%, respectively (Alt-Epping et al. 2010; Tardy et al. 2015), in the remainder of included studies primary TP use ranged between 4-11.1% (Brabin et al. 2008; Ciuhu et al. 2016). This suggests that TP is considered in only approximately one in ten patients admitted to a palliative care unit or residential hospice. While the clinical characteristics of patients admitted to these units were not clearly defined, it seems likely that many patients who might benefit from TP are currently being overlooked. Internationally, rates of discharge from palliative care units are as high as 60% in some settings (Bryson et al. 2010; Hui et al. 2010; Gartner et al. 2012); many of these patients will have a temporary elevated risk of VTE over the course of their admission. While the risk of bleeding is commonly cited as a contra-indication to TP in patients with advanced cancer (and our review identified an incidence of bleeding that ranged from 0.01-9.8%) (Alt-Epping et al. 2010; Tardy et al. 2017), this does not completely account for the low rates of TP seen in our review. Furthermore, in several retrospective studies, there was no documentation regarding clinical decision-making around TP in the case-notes, or limited documentation about patient involvement in decision-making around TP, both of which suggest a lack of consideration of VTE as part of routine clinical practice on many palliative care units or residential hospices.

7.4 Differences between medical oncologists’ and palliative care physicians’ attitudes towards the use of thromboprophylaxis for inpatients with advanced cancer.

Our cross-sectional, national survey of Canadian medical oncologists and palliative care physicians, using a fractional factorial survey, identified important differences, at both the patient and the physician level, in terms of likelihood of prescribing TP.

7.4.1. The influence of patient factors on the use of thromboprophylaxis

We identified five patient factors that we hypothesised may influence decision-making around the use of TP; these factors were age, place of admission, reason for admission, pre-admission performance status; and risk of bleeding on anticoagulation. Across both physician groups, on
univariate logistic regression there were greater odds of treating with TP for younger patients (≤65 years) compared with older; patients admitted to acute care settings compared with those admitted to palliative care settings; patients admitted with potentially reversible causes compared with irreversible causes; patients with a good pre-admission performance status compared with a poor performance status; and patients with a low estimated risk of bleeding on anticoagulation compared with those with a higher bleeding risk. With the exception of patient age, all factors remained statistically significant on multivariable hierarchical logistic regression (see tables 13 and 14).

Patient factors have been infrequently explored in relation to use of TP in the literature. Only two other studies, to our knowledge, have used clinical scenarios to identify physician attitudes towards TP, one which looked at performance status, and another that looked at place of admission and reversibility. In the first, a virtual case was presented to 20 physicians working in medical oncology, hematology, palliative care, and intensive care. Three alternative scenarios were presented in relation to the virtual case with regards to presence or absence of previous thromboembolic events, along with three different performance status estimates using the Karnofsky Performance Scale Index (KI). All physicians withheld TP when the virtual patient was actively dying (KI of 10). This study was limited by its sample size, lack of description of how the scenarios were developed; and the use of descriptive statistics only in the analyses (Kierner et al. 2008).

In the second study, a single scenario was used as part of a telephone survey to explore TP practice changes over a five-year period in the UK (the study was conducted at two time-points, the first in 2000, the second in 2005). The scenario described a post-operative patient transferred to a palliative care unit for symptom management on TP and asked if the individual units would routinely continue the TP or stop it. There was a statistically significant difference between the two time-points, with 62% of palliative care units indicating they would stop TP in 2000, reduced to 18% by 2005, p<0.001. This study was limited by the use of a single scenario, and was administered to palliative care physicians only (Noble & Finlay 2006).

A third study (available only in abstract form) conducted qualitative interviews with physicians working in family medicine, palliative care and oncology. Here, the clinical setting within which patients were admitted was felt to be an important contributor to decisions around TP use, with a concern that TP was over-prescribed in some acute care settings, and under-prescribed in some palliative care settings (Johnson et al. 2012).
7.4.2 The influence of physician factors on the use of thromboprophylaxis

We also explored six physician factors which we felt might influence decision-making around TP; these were medical specialty (medical oncology or palliative care), gender, years working in specialty, clinical work setting (teaching versus non-teaching environment), academic work setting (academic versus non-academic centre), and for the medical oncologists, access to palliative care services. All medical oncologists indicated they had access to a variety of palliative care supports, so this factor was dropped from the subsequent analyses.

On univariate analyses, only medical specialty was significant, with medical oncologists at higher odds of prescribing TP compared with palliative care physicians (OR 1.94, [95% CI 1.49-2.56], p<0.001). On multivariate hierarchical logistic regression, even after accounting for patient factors, medical oncologists remained at higher odds of prescribing TP compared with palliative care physicians, as per our original hypothesis (OR 2.09, [95% CI 1.56-2.81], p<0.001).

Physician factors have also been poorly explored in the TP literature to date. In the Kierner et al study mentioned above, palliative care physicians were less likely to prescribe TP compared with medical oncologists, hematologists and intensive care physicians. For all physician groups, there was a direct relationship between patient performance status and likelihood of prescribing TP. For patients with a KI of 20, no palliative care physician prescribed TP compared with 40% of medical oncologists. When the KI was improved to 40%, 80% of palliative care physicians opted to prescribe TP versus 100% of medical oncologists. Only 20 physicians in total completed this study however, and no formal statistical analyses were presented in the paper (Kierner et al. 2008).

7.5 Exploring the differences between medical oncologists and palliative care physicians with regards to prescribing thromboprophylaxis

In terms of understanding the differences between medical oncologists and palliative care physicians identified in our results, it is important to consider both the historical focus of palliative care services and how this is evolving, as well as differences in postgraduate training between medical oncologists and palliative care physicians, and how this might influence decision-making around TP.
7.5.1 The evolution of palliative care

As outlined in section 2.9, historically palliative care was synonymous with end-of-life care and patients were typically referred only when all active treatment options had been exhausted (Sheard et al. 2012). This model was associated with a philosophy of ‘de-medicalising’ the dying process, limiting investigations or interventions at the end-of-life, and focussing almost exclusively on comfort care while optimising symptom management.

The past 10-15 years have seen a growing interest in the potential role for palliative care involvement earlier in the disease trajectory of patients with advanced, incurable cancer. As patients live for longer due to advances in diagnostic and therapeutic options, their symptom needs can be substantial, spanning several months or even years. Most medical oncologists acknowledge that they lack the time and expertise to adequately manage the complex physical and emotional issues experienced by many patients with advanced cancer (Jackson et al. 2008; Pfeil et al. 2015). Early palliative care intervention, alongside active anticancer treatment rather than sequential to it, has been shown in several RCTs to improve patient and caregiver satisfaction with care and quality of life, as well as symptom burden, and in some cases, prognosis (Bakitas et al. 2009; Temel et al. 2010; Zimmermann et al. 2014).

As the demographic profile of patients referred to palliative care services changes, this has important implications for clinical practice on inpatient palliative care units and residential hospices. Many of the patients admitted to palliative care units (especially acute units) are now interchangeable with those who might otherwise be admitted to acute care settings (with, for example, infections, spinal cord compressions, malignant hypercalcemia etc.). Our results suggest, however, that differences persist in the likelihood of receiving TP based on the place of admission irrespective of the risk of VTE, which has important implications for the quality of care offered in palliative care settings, and potentially for patient outcomes.

7.5.2 Differences in post-graduate training programs for medical oncologists and palliative care physicians

Another consideration is the degree of exposure to acutely unwell patients with advanced cancer during post-graduate training, and awareness of the existing guidelines or policies around the use of TP in this patient population, as outlined in Chapter 6. Medical oncologists typically train in internal
medicine before specialising in oncology; the vast majority of this training takes place in acute care settings and involves regular decision-making around risk factors for VTE and the use of TP when appropriate.

On the other hand, the typical post-graduate training path for many palliative care physicians in Canada often follows a more community-based focus. From 1999 to 2017, the typical route to becoming a palliative care physician in Canada was a one-year program of added competence jointly accredited by the Royal College of Physicians and Surgeons in Canada and the Canadian College of Family Physicians (Monette 2012). The vast majority of graduates from this program came from Family Medicine backgrounds, a training route which was much less likely to expose physicians to acutely unwell patients with advanced cancer in the acute care setting, and there may be an important knowledge gap among some palliative care physicians in this regard. Since 2017, palliative care has been recognised as a medical subspecialty through the Royal College of Physicians and Surgeons of Canada, whereby two years of palliative care training follow internal medicine training as for medical oncologists. It is possible that this cohort of palliative care physicians may demonstrate more aggressive care for their patients in the future, in keeping with their prior experiences and training.

This phenomenon has been described in one paper from the UK. In a qualitative study of 12 senior clinicians on palliative care units without TP policies, medical training pathways were identified as contributing to changing attitudes towards the aggressiveness of care on palliative care units or residential hospices. A growing workforce with internal medicine experiences following the formalisation of training pathways for palliative care through the Royal College of Physicians in the UK was identified by one clinician as more reflective of a ‘medical hospital team’ rather than a primary care team approach, and offered as a potential reason for the growing trend towards greater interventions within palliative care settings (Noble et al. 2008).

7.6 Implications for patients

The results of our systematic review suggest a lack of clarity around the incidence of VTE on palliative care units or residential hospices, as well as low rates of TP prescription in these settings. Although there is insufficient evidence to support the widespread prescription of TP for patients admitted to palliative care units or residential hospices at this time, greater consideration should be given to
evaluating the individual risk of VTE for each patient admitted to these settings, in tandem with the
goals of care and preferences of each individual patient. Our literature review demonstrated that
patients are infrequently involved in decision-making around TP in these settings (Noble et al. 2006;
Gartner et al. 2012; Garzon-Rodriguez et al. 2015; McMullan et al. 2012). When their opinions are
solicited, patients have demonstrated a good understanding of the risks of VTE, TP is considered both
a reasonable intervention, and is well-tolerated (Noble et al. 2006).

Our results also indicate that there are clinically and statistically significant differences in the
attitudes and practices of medical oncologists and palliative care physicians towards the use of TP for
inpatients with advanced cancer. The most appropriate approach has yet to be determined, and it
remains unclear whether the care provided in acute settings is potentially overly aggressive versus
that provided in palliative care units or residential hospices being insufficiently aggressive. The
differences uncovered by our study may have important implications at the individual patient level,
whereby patients admitted to an acute care setting may be more likely to be prescribed TP (or at
least consideration given to the prescription of TP and discussion around the risk/benefit ratio); the
same patient admitted to a palliative care setting may not be offered TP at all, and may be at higher
risk of poorer outcomes as a result. Decisions around the use of TP should involve the patient and/or
their SDM, with careful consideration of their goals of care, estimated risk of bleeding, presence of
temporary elevated risk of VTE, and treatment preferences.

7.7 Implications for practice

Our results indicate wholesale differences in the practices of medical oncologists and palliative care
physicians with respect to prescribing TP for inpatients with advanced cancer. We hypothesise that
some of these differences may represent knowledge or training gaps among palliative care physicians
regarding the significance of VTE among acutely unwell patients with advanced cancer, or to be
rooted in a historical philosophy of non-intervention on palliative care units which may no longer be
appropriate, at least for certain patient subgroups.

Education around the risk factors for VTE for patients who are acutely medically unwell with a
temporarily elevated risk of VTE, and who are expected to be discharged home, is needed for
palliative care practitioners. Although further research to clearly delineate the true incidence of VTE
in this patient population is needed, consideration of TP should form part of the care plan for
selected patients admitted to palliative care units or residential hospices. This will involve engagement not just with physicians but all members of the inter-disciplinary team who care for patients in these settings, including nurses, pharmacists and other allied health professionals such as physiotherapists and occupational therapists.

It is important to consider the potential cost implications of prescribing TP on palliative care units and residential hospices, many of whom have funding models which differ from the acute care setting. One report from Italy suggests the weekly and six-month costs associated with LMWH could be as much as US$154.59 and US$4019.29, respectively (2006 data) (Tassinari et al. 2008); another from the UK estimates that annual drug costs could increase by as much as 28% (US$12,245) if LMWH were offered to all inpatients on one particular palliative care unit, with a number needed to treat of 190 to prevent one symptomatic VTE (Chambers 2006). This number is difficult to interpret in light of the findings of our systematic review and the heterogeneity in reported VTE incidence and prevalence at this time and should be interpreted with a degree of caution. Looking at the acute palliative care unit at UHN, where 339 patients were admitted in 2017 with an approximate 50% discharge rate and an average length of stay of 13 days, the estimated additional cost incurred by prescribing prophylactic LMWH to 100 of these patients per year is $13,000 (based on cost per dose of 40mg enoxaparin within the hospital of approximately $10, data from personal communication with UHN pharmacy). This may represent an underestimation of costs however; on average 18% of patients were admitted for end-of-life care in 2017, suggesting that up to 72% (244 patients) were admitted with the expectation of discharge home and may have been initially considered appropriate for TP. Even if we estimate a high bleeding/contraindication rate of 33%, 161 patients may have been eligible for TP at some point during their admission, the costs could climb to $20,000 annually.

**7.8 Implications for policy**

Based on the results of our systematic review, there is insufficient evidence at this time to support the widespread use of TP for patients with advanced cancer admitted to palliative care units or residential hospices. Individual units should, however, aim to at least have a written policy around TP which is regularly reviewed and updated based on emerging evidence. This should include consideration of reason for admission and likelihood of discharge home, individual patient goals and preferences, and an objective assessment of the risks and benefits of treating (or not) with TP. This
should also be regularly reviewed over the course of the patient’s admission, taking into consideration changes in their clinical status and/or goals of care.

Existing guidelines such as the pan-Birmingham Cancer Network Guidelines should be used as a framework for assessing each patient’s suitability for TP (Lock, 2011). These have not been validated to date however and may need to be adapted based on the clinical setting and geographical location within which they are applied.

7.9 Strengths and weaknesses of this research

We recognise that our research has a number of strengths and weaknesses. Our systematic review was limited to studies published in English, unless a formal translated version was available (we included one Spanish abstract based on this). We focussed on patients admitted to palliative care units or residential hospices and did not include patients admitted to acute care settings where they may have been managed primarily by palliative care teams. The final number of included studies was small, and heterogeneity in study types made a meta-analysis impossible.

Strengths of the systematic review included a broad search strategy that included the grey literature, facilitated by an information specialist at UHN. Since this was a small but diverse literature landscape, we opted to include both qualitative and quantitative research, and utilised a quality appraisal tool that facilitated this. Two independent reviewers were involved in both the study selection phase and the quality appraisal phase.

Our survey was limited by a poor response rate (only 11.1% of medical oncologists and 15% of palliative care physicians responding to our emailed survey). This is not an atypical response rate to these types of studies however, and there is a well-documented trend in progressively lower response rates to physician surveys documented in the literature over the past ten to twenty years which raises important questions about the utility of this type of research moving forward (Sheehan et al. 2006; VanGeest et al. 2007; Cunningham et al. 2015). Access to additional information about non-responders was limited; for medical oncologists, we only had access to names and practice locations from the provincial and territorial colleges of physicians and surgeons; the CSPCP did not provide us with any demographic information about its broader membership that could have been used to inform important differences between responders and non-responders. A follow-up questionnaire targeting non-responders may have been useful in quantifying the magnitude of any
response bias. We were unable to employ any incentives to encourage an improved response rate due to budgetary constraints; even modest monetary incentives have been shown to increase physician response rates (OR 2.13) (VanGeest et al. 2007). We were also only able to send one email to the palliative care physicians, whereas the medical oncologists received two, due to administrative limitations within the CSPCP. Follow-up reminders have been shown to increase emailed survey response rates by up to 25% in one review (Sheehan et al. 2006). On a positive note, we did achieve our estimate sample size, and this study is the largest to date to simultaneously explore the opinions of both medical oncologists and palliative care physicians around the use of TP. Given that the majority of respondents were younger physicians working in teaching or academic centres, it is possible that any response bias seen in our sample tended towards more aggressive care and may have, in fact, underestimated the magnitude of the difference between medical oncologists and palliative care physicians. Older palliative care physicians or those working in non-acute, non-academic settings may be more likely to adopt a traditional, non-interventional approach towards TP use.

It is possible that our sampling techniques did not identify all eligible physicians, especially in the palliative care category. While all medical oncologists are registered by this designation with their respective colleges of physicians and surgeons, many palliative care physicians are registered as internists or family physicians, since palliative care has only been a medical subspecialty since 2017. Many physicians work in palliative care on a part-time basis or incorporate their palliative care practice into another area of medicine which is their primary designation. Not every practicing palliative care physician is a member of the CSPCP, however this was felt to represent the optimal way of identifying the largest number of physicians who self-identify as palliative care physicians nationally. Similarly, for the medical oncologists, our search strategy was more likely to identify physicians working in academic practices (whose email addresses were more readily available through universities or research papers) than those with a non-academic practice.

After consideration of several different study designs, we selected a factorial survey approach. Logistically we felt it was not feasible to administer all 32 vignettes to each respondent; instead we asked each to assess a subset of eight randomly-selected vignettes. This adds some limitations in terms of loss of orthogonality but is widely considered an acceptable approach for this type of research.
We utilised the ECOG and HAS-BLED measures of patient performance status and risk of bleeding on anticoagulation, respectively. Other measures of performance status, such as the Palliative Performance Scale (PPS) provide more clinically relevant information with regards to ambulation, activity, self-care, intake and consciousness level (Anderson et al. 1996), but may have been more familiar to the palliative care than the medical oncology group. We felt the ECOG would be familiar to both groups so ultimately elected to use this. The HAS-BLED, as mentioned in Section 2.8.3, was developed originally to assess the risk of bleeding among patients receiving therapeutic doses of anticoagulation for atrial fibrillation, not VTE, and has not been validated specifically among cancer patients. Although other risk assessment tools have been developed for VTE (see Section 2.8.3), none of the existing tools has been shown to be more predictive of bleeding risk than another; and the HAS-BLED has been shown in a recent study to be the most widely cited and utilised tool internationally (Parks & Fang, 2017). We recognise that the HAS-BLED may have over-estimated the bleeding risk among our patient population who were being prescribed prophylactic rather than therapeutic doses of anticoagulation, however there are no tools that estimate the risk of bleeding on TP and we felt it was important to utilise some measure of bleeding risk within the vignettes.

Our vignettes lacked information about patients’ goals of care or preferences around the use of TP. We recognise that this is an important consideration when prescribing TP but felt it was beyond the scope of the current study to include this. Our primary area of interest was whether physicians would consider TP for each assigned vignette; the final decision to treat would, of course, depend on the outcome of discussions with patients and/or their substitute decision makers around the risks and benefits of any proposed treatments. Place of admission may have been interpreted by some respondents as a proxy for goals of care, with perhaps an assumption around less aggressive care in a palliative care setting, which may have in turn influenced respondents’ decision-making.

In terms of physician factors, information about the scope of palliative care physicians’ practice, with an emphasis on identifying those who primarily cared for patients at the end-of-life predominantly versus those working in a model where greater numbers of patients were discharged might have been helpful. The presence of specific institutional guidelines around TP or an awareness of current TP recommendations may have influenced decision-making; we did not explore these in the current study.
Chapter 8: Conclusions
Conclusions

This work adds to the limited but important literature around the use of TP for patients with advanced cancer admitted to palliative care units or residential hospices. Through this research, we have conducted an in-depth systematic review of the literature exploring the incidence of VTE in palliative care settings, as well as rates of TP prescription and bleeding in this population. We then investigated potential differences in TP prescribing based on pre-determined patient factors of age, reason for admission, place of admission, pre-admission performance status, and risk of bleeding on anticoagulation. In particular we were interested in examining any differences in TP prescribing between medical oncologists and palliative care physicians, both as independent factors and after accounting for the patient factors listed above.

Our research indicates important heterogeneity in the recognition of the risk of VTE among patients with advanced cancer admitted to palliative care units or residential hospices, as well as low overall rates of TP prescription, and variable reporting in bleeding rates among patients receiving TP. Issues with study type (retrospective chart reviews made up 47% of all included studies [full-text and abstracts] in our systematic review), recruitment of patients for the single included RCT, and lack of differentiation between patients based on reason for admission and likelihood of discharge, made the results of our systematic review difficult to interpret or to generalise. Although there is insufficient evidence currently to support the widespread use of TP among patients with advanced cancer admitted to palliative care settings, it is clear that further research in this area is required as a matter of urgency to further clarify which patients may benefit from TP (based on available estimates of risk, benefits and patient preferences), in what settings, and the clinical and economic implications associated with these practice changes.

In addition, our research suggests that patient factors, including the setting to which they are admitted (acute versus palliative care), reason for admission (reversible versus irreversible), pre-admission performance status, and risk of bleeding on anticoagulation, all influence physician decision-making around the use of TP for patients with advanced cancer. Even accounting for these factors, there are statistically significant differences between medical oncologists and palliative care physicians in terms of their odds of treating with TP, with medical oncologists at 2.09 higher odds of
prescribing TP compared with palliative care physicians (95% CI 1.56-2.81, p<0.001). Potential reasons for these differences should be further explored in future research but may be associated with historical differences in the aggressiveness of care within acute care settings versus palliative care settings, as well as by differences in post-graduate training or education for medical oncologists (typically hospital-based) versus palliative care physicians (frequently community-based).
Future Directions

There are many potential avenues for future research based on our work to date, which potentially include individual physicians, patients, and larger organisations.

Physician-based research

To date, physician-based research around TP for patients with advanced cancer in palliative care settings has been limited to a small number of studies (our systematic review identified three full-text papers and two abstracts exploring clinician decision-making). Two of these utilised clinical scenarios or vignettes; a further two were qualitative interviews with physicians. In the first qualitative study, physicians who worked on palliative care units where there were no policies around VTE were interviewed; in the second (which was an abstract), palliative care physicians, family physicians and oncologists were interviewed. Similar to our survey findings, differences in the use of TP were described between acute and palliative care settings, with respondents commenting on a potential over-use of TP in acute settings versus under-use in palliative care settings. As a follow-up to our study, qualitative interviews with physicians from both acute and palliative care settings (to include both short-stay, acute palliative care units and more traditional long-term units) and medical oncologists may help to further explore some of the reasons for the differences seen in our study; to identify previously unconsidered factors contributing to the prescription (or not) of TP; as well as to define some of the potential barriers to changing practices; and identifying potential knowledge gaps among palliative care physicians in particular. Qualitative methodology is particularly useful for this type of research as it allows for richer exploration of the experiences of participants beyond the confines of a pre-determined set of criteria or formal questionnaire.

Patient-based research

The opinions and wishes of patients around the use of TP during inpatient hospitalisations have been explored in depth in only one published study to date, to our knowledge. In that paper, patients who were already receiving TP were asked about the acceptability of the treatment and their understanding of the risks of VTE. Contrary to previously-elicited physician comments that LMWH injections may be overly burdensome for patients, in this study, patients demonstrated a good
understanding of the risks of VTE and the benefits of TP, found LMWH acceptable, and felt TP had a positive impact on their quality of life (Noble et al. 2006). No studies have engaged patients in the initial decision-making process around the use of TP or explored how patients make decisions about the potential trade-offs of treatments versus associated risks. Qualitative interviews with patients admitted to a palliative care unit, or a study using a discrete choice experimental design, may be a potential avenue to explore in this regard. Alternatively, patient-related outcomes such as quality of life or satisfaction with care (specifically in relation to communication around the pros and cons of TP), could be explored quantitatively.

**Organisational-based research**

Throughout this research, it has become clear that decisions around the use of TP on palliative care units or residential hospices are, at best ad-hoc, and at worst, completely overlooked. In 2005, only 7% of palliative care units in the UK had formal VTE policies, and although the authors postulated that this would increase to 19% by the following year (Noble & Finlay 2006), there have been no follow-up studies to confirm this. Details regarding VTE policies on palliative care units beyond the UK are lacking and could form a future area for research.

Beyond having a formal policy, the use of clinical decision-making tools to identify patients with a temporary elevated risk of VTE upon and throughout admission is a further area worthy of exploration. The pan-Birmingham Cancer Network guidelines offer an algorithm to aid clinical decision-making and were designed for patients on palliative care units but have not been widely adopted and have not been clinically validated. Potential future studies could explore validating this tool, or the development of alternative decision-making supports for inpatients on palliative care units.

In order to conduct meaningful research to identify suitable patients for TP on palliative care units and to follow them longitudinally to record outcomes such as development of VTE, bleeding, and survival, it is likely that a multi-centred approach will be required to recruit a sufficiently large sample. This will involve developing partnerships with other centres, identifying realistic goals and outcomes, as well as applying for funding to support the research. In the absence of strong evidence to inform decision-making about TP in this patient population, a Delphi consensus process may be an alternative means of helping guide the development of national recommendations.
References


Alt-Epping, B. et al., 2010. Indicating anticoagulant therapy in palliative care - A multicenter survey. *Palliative Medicine, 1*, p.S137.


JAMA, 293(6), p.715.


Burns, K.E.A. et al., 2008. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ • JULY, 29(3).


Cook, D.A. et al., 2016. Incentive and Reminder Strategies to Improve Response Rate for Internet-Based Physician Surveys: A Randomized Experiment. *Journal of medical Internet research*, 18(9), p.e244.


Girolami, A. et al., Drug-Induced Thrombophilic or Prothrombotic States: An Underestimated Clinical Problem That Involves Both Legal and Illegal Compounds.


Knight, R., DeLap, R.J. & Zeldis, J.B., 2006. Lenalidomide and Venous Thrombosis in Multiple


NICE guideline 89. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism https://www.nice.org.uk/guidance/ng89


Noble, S.I.R. et al., 2006a. Acceptability of low molecular weight heparin thromboprophylaxis for


O’Cathain, A. & Thomas, K.J., 2004. &quot;Any other comments?&quot; Open questions on questionnaires - a bane or a bonus to research? *BMC medical research methodology,* 4, p.25.


Romera, A. et al., 2009. A Randomised Open-Label Trial Comparing Long-term Sub-Cutaneous Low-


Sheard, L. et al., 2012. The ethical decisions UK doctors make regarding advanced cancer patients at the end of life--the perceived (in) appropriateness of anticoagulation for venous


Appendix 1: pan-Birmingham Cancer Network Guideline for the primary prophylaxis for Venous Thromboembolism in palliative patients with malignancy whose treatment is primarily palliative

Step 1: General assessment
- Contra-indications to receiving TP?
- Actively dying patient?
- Actively bleeding patient?
- Patient already on anticoagulation?
- Previous issues/adverse events related to anticoagulation?
- Platelets <50
- **IF YES TO ANY OF THESE: UNSUITABLE FOR TP**

Step 2: assessment of benefit
- Evidence-based potential benefit from TP (e.g. recent major surgery; current acute medical illness)?
- Potential benefit without strong evidence base (e.g. bedbound due to acute medical illness; new spinal cord compression with expectation of functional recovery; pathological fracture with expectation of functional recovery)?
- **IF NO TO EITHER: NO INDICATION FOR TP**

Step 3: team-based decision
- Consider risks and benefits of treatment along with the patient
- Make a plan regarding duration of treatment and monitoring (max 14 days unless recent surgery)
- Start LMWH
- Assess q48H to review appropriateness of treatment

Modified from Lock et al., 2011
Dear colleague,

You are being asked to take part in a research study as a physician who cares for patients with advanced cancer. The purpose of this study is to identify physicians’ attitudes and opinions about the use of primary thromboprophylaxis for patients with advanced cancer admitted to both acute care settings and to hospices or palliative care units. It will take approximately 10 minutes to complete the survey.

Your participation in this study is completely voluntary. There are no foreseeable risks associated with this project. However, if you feel uncomfortable answering any questions, you can withdraw from the survey at any point without any consequences. If you decide to participate, please complete all questions to the best of your ability. It is very important for us to learn your opinions.

All information obtained during the study will be held in strict confidence. Representatives of the University Health Network (UHN) Research Ethics Board may look at the study records to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines. You will not be named in any reports, publication or presentations that may come from this study. Responses will be stored in a locked cabinet in the Department of Supportive Care at UHN and no identifying information will be on the survey.

The survey should be completed and returned online.

Questions about the study

If you have any questions, concerns or would like to speak to the study team for any reason, please write to Dr. Breffni Hannon at Breffni.Hannon@uhn.ca or to Dr. Monika Krzyzanowska at Monika.Krzyzanowska@uhn.ca. If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

By completing the survey, you are providing consent to participate in this study. We thank you for your time and participation.

Breffni Hannon, MB BCh BAO, MSc (candidate)

Monika Krzyzanowska, MD

Camilla Zimmermann, MD, PhD

John Granton, MD
1. Medical specialty

- Palliative Care
- Medical Oncology
- General Internal Medicine
- Other (please specify)

Subspecialty, if applicable

2. Sex

- Male
- Female
- Prefer not to say

3. Years working in specialty

- <=5
- 6-10
- 11-15
- 16-20
- >20

4. Year of graduation from Medical School
5. Work setting (check all that apply)
   - Acute Palliative Care Unit
   - Palliative Care Unit or hospice
   - Teaching hospital
   - Community hospital
   - Other (please specify)
   - Other (please specify)

6. Practice environment
   - Academic teaching centre
   - Non-academic teaching centre
   - Non-teaching centre

7. Out of all the patients that you saw last year, approximately what proportion had cancer?
   - <50%
   - 51-89%
   - >90%

8. Do you have access to palliative care services?
   - Yes
   - No

9. If yes, which of the following (please check all that apply)
   - outpatient palliative care clinic
   - inpatient consult service
   - acute palliative care unit
   - palliative care unit or hospice
   - community palliative care team
A 75-year old patient with gallbladder cancer is admitted under General Internal Medicine. Imaging reveals widespread metastatic spread including liver, peritoneum, and omentum with large-volume ascites. Her liver function tests are all elevated with a Bilirubin of 35, ALP 180, ALT 78, AST 90, and her Creatinine is also elevated at 147 (normal range 50-98). Her pre-admission ECOG was 3*. Her HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).

A 45-year old patient with multiple myeloma is transferred from the acute hospital setting to hospice following an admission with recurrent hypercalcemia (corrected Calcium 4.2) which has not responded to hydration and bisphosphonates. She has a HAS-BLED score of 0#. Her pre-admission ECOG was 1*. She was started on thromboprophylaxis while under General Internal Medicine.

Based on this information, how likely would you be to continue this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 0: Patient has a relatively low risk for major bleeding (~1/100 patient-years).
A 51-year old patient with head and neck cancer is admitted under General Internal Medicine with recurrent hypercalcemia (corrected Calcium 4.2). His history is significant for alcohol abuse and peptic ulcer disease with an upper GI bleed 2 years ago. He has a HAS-BLED score of 3#. His pre-admission ECOG was 2*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 0: fully active, able to carry out all pre-disease performance without restriction.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

A 75-year old patient with head and neck cancer is transferred from the acute hospital setting to a Palliative Care Unit following an admission with recurrent hypercalcemia (corrected Calcium on admission, 4.2). Her hypercalcemia has not responded to intravenous hydration and bisphosphonates. She has a HAS-BLED score of 0#. Her pre-admission ECOG was 3*. She was started on thromboprophylaxis when she was admitted under the General Internal Medicine service.

Based on this information, how likely would you be to continue her thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 0: relatively low risk for major bleed, approx. 1/100 patient years.
A 70-year old patient with bladder cancer with metastases to bone and lung is admitted under General Internal Medicine. He has a hypoactive delirium, and a Creatinine of 152 (normal range 64-110). His pre-admission ECOG was 3*. His HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).

A 66-year old patient with bladder cancer with liver and bone metastases is admitted under the General Internal Medicine service with an acute kidney injury and a Creatinine of 270 (previously 72, 1 week prior). He is found to have right-sided hydronephrosis on imaging. His HAS-BLED is 3#. His pre-admission ECOG was 3*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.
A 66-year old patient with endometrial cancer with lymph node and liver metastases is admitted to a Palliative Care Unit with a Creatinine of 324 (previously 72, 1 week prior). She is found to have right-sided hydronephrosis on imaging. Her HAS-BLED is 3#. Her pre-admission ECOG was 3*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

A 66-year old patient with prostate cancer and bone metastases is admitted under General Internal Medicine with an acute kidney injury. His Creatinine on admission is 324 (72 one week prior). He is found to have right-sided hydronephrosis on imaging. His HAS-BLED score is 3#. His pre-admission ECOG was 0*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 0: fully active, able to carry out all pre-disease performance without restriction.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely

Comments
12. **A** (25.0%) A 57-year old patient with prostate cancer and metastases to bone is admitted under General Internal Medicine for investigation of lower limb weakness, urinary retention and constipation. His pre-admission ECOG was 3*. His neurological examination reveals 1/5 power in his lower limbs bilaterally; an MRI spine shows multi-level spinal cord compression in his thoraco- and lumbar spine. His symptoms do not resolve with steroids and radiotherapy. His HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

**B** (25.0%) A 90-year old patient with gastric cancer with lymph node metastases is admitted from home to a Palliative Care Unit. His pre-admission ECOG was 3*. Imaging and bloodwork show widespread disease progression with multiple new liver and brain metastases. His HAS-BLED score is 3#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: high risk for major bleed.
C 25.0% A 57-year old patient with lung cancer and metastases to bone, lung and brain is admitted under General Internal Medicine for investigation of lower limb weakness, urinary retention and constipation. His pre-admission ECOG was 1*. His neurological examination reveals 1/5 power in his lower limbs bilaterally; an MRI spine shows multi-level spinal cord compression in his thoraco- and lumbar spine. His symptoms do not resolve with steroids and radiotherapy. His HAS-BLED score is 1#. 

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

D 25.0% A 71-year old patient with prostate cancer with liver and bone metastases is admitted to the Palliative Care Unit with new onset back pain, urinary retention and lower limb weakness. He is unable to tolerate an MRI due to severe pain. His HAS-BLED score is 1#. His pre-admission ECOG was 3*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding, approx. 1/100 patient-years.
13. A 25.0%
An 80-year old patient with metastatic ovarian cancer is admitted acutely to the General Internal Medicine service with new-onset ascites and a large left pleural effusion. Her pre-admission ECOG was 2*. Her HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding, approx. 1/100 patient-years.

B 25.0%
A 44-year old patient with thyroid cancer and extensive bone, liver, brain and lung metastases is admitted to an acute Palliative Care Unit with new-onset shortness of breath and fatigue. She is found to have a large left-sided pleural effusion. Her pre-admission ECOG was 3*. Her HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).
A 39-year old patient with breast cancer and extensive bone, liver, brain and lung metastases is admitted under General Internal Medicine with new-onset shortness of breath, abdominal distention and fatigue. She is found to have large-volume ascites. Her pre-admission ECOG was 3*. Her HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).

A 47-year old patient with lung cancer and extensive bone, liver and brain metastases is admitted under General Internal Medicine with new-onset shortness of breath. She is found to have a large left-sided pleural effusion. Her pre-admission ECOG was 3*. Her HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: Patient has a relatively low risk for major bleeding (~1/100 patient-years).
14. A 25.0%

A 45-year old patient with a primary brain tumour (Glioblastoma Multiforme) is admitted to hospice with a likely urinary tract infection causing fevers and delirium. His pre-admission ECOG was 3*. His HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

B 25.0%

A 72-year old patient with colon cancer is admitted from home to a Palliative Care Unit following a rapid functional decline at home over 5 days; prior to this his ECOG was 1*. Imaging and bloodwork show widespread disease progression with multiple new liver and brain metastases. His HAS-BLED score is 3#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

C 25.0%

A 78-year old patient is admitted to a Palliative Care Unit for investigation and management of a suspected small bowel obstruction; she has advanced ovarian cancer. Her pre-admission ECOG was 2*. Her HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).
A 78-year old patient is admitted to an acute Palliative Care Unit for investigation of a suspected small bowel obstruction; she has locally advanced ovarian cancer. Her pre-admission ECOG was 2*. Her HAS-BLED score is 3#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely

Comments
A 70-year old patient is admitted under General Internal Medicine with new-onset jaundice and raised liver function tests (Bilirubin 100, ALP 100, AST 22, ALT 39\(^*\)). She has a history of pancreas cancer with liver metastases and has progressed through two different lines of chemotherapy. Her ECOG was 3\(^*\) prior to admission. Her HAS-BLED score is 1\(^#\).

*Normal ranges: Bilirubin ≤22; ALP 40-150; AST 7-40; ALT 7-40*

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.*

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

An 83-year old patient with gastric cancer is admitted under General Internal Medicine following a rapid functional decline at home over 5 days; prior to this his ECOG was 1\(^*\). Imaging and bloodwork show widespread disease progression with multiple new liver and brain metastases. His HAS-BLED score is 1\(^#\).

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.*

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: Patient has a relatively low risk for major bleeding (~1/100 patient-years).
A 68-year old patient with pancreas cancer is admitted under General Internal Medicine. Imaging reveals widespread metastatic spread including liver, peritoneum, and omentum with large-volume ascites. Her liver function tests are all elevated with a Bilirubin of 35, ALP 180, ALT 78, AST 90, and her Creatinine is also elevated at 147*. Her pre-admission ECOG was 2*. Her HAS-BLED score is 2#.

*Normal ranges: Bilirubin ≤22; ALP 40-150; AST 7-40; ALT 7-40; Creatinine 50-98.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).

A 74-year old patient with gastric cancer is admitted to a Palliative Care Unit. His pre-admission ECOG was 3*. Imaging and bloodwork show widespread disease progression with multiple new liver and brain metastases. His HAS-BLED score is 1#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely
A 61-year old patient is admitted to a Palliative Care Unit. She has lymphoma, which has progressed through multiple lines of treatment including a stem cell transplant. She is profoundly pancytopenic (Hb 54, WBC 1.2 Platelets 14), with an INR of 1.45. Her HAS-BLED score is 1#; her pre-admission ECOG was 4*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 4: completely disabled, cannot carry out any self-care, totally confined to bed or chair.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 1: relatively low risk for major bleeding (~1/100 patient-years).

A 43-year old patient is admitted to a Palliative Care Unit. He has advanced leukemia, which has progressed through multiple lines of treatment. He is profoundly pancytopenic (Hb 60, WBC 1.2 Platelets 14), with an INR of 1.45. His HAS-BLED score is 2#; his pre-admission ECOG was 4*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 4: completely disabled, cannot carry out any self-care, totally confined to bed or chair.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).
C 25.0% A 45-year old patient is admitted to the Hematology floor of a cancer centre. He has advanced leukemia, which has progressed through multiple lines of treatment including a stem cell transplant. He is profoundly pancytopenic (Hemoglobin 60, WBC 1.2, Platelets 14) with an INR of 1.45. His HAS-BLED score is 2#. His pre-admission ECOG was 4*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 4: completely disabled, cannot carry out any self-care, totally confined to bed or chair.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: HAS-BLED 2: moderate risk for major bleed, approx. 2/100 patient years.

D 25.0% A 59-year old patient is admitted to a Palliative Care Unit. He has leukemia, which has progressed through multiple lines of treatment including a stem cell transplant. He is profoundly pancytopenic (Hb 60, WBC 1.2 Platelets 14), with an INR of 1.45. His HAS-BLED score is 3#; his pre-admission ECOG was 2*.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 3: Patient is at high risk of bleeding.

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely

Comments
A 50-year old patient is admitted to a Palliative Care Unit with pneumonia. She has breast cancer with metastases to bone and liver. She has been receiving second-line chemotherapy until her admission; this is currently on hold. Prior to her diagnosis of pneumonia, her ECOG was 1*. Her HAS-BLED score is 0#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physical activity but ambulatory and able to carry out work of a light or sedentary nature.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 0: low risk for major bleed, approx. 1/100 patient years.

A 28-year old patient with metastatic melanoma is admitted to an acute Palliative Care Unit with new-onset delirium; she is found to have an elevated WBC count and her chest x-ray shows a right lower lobe pneumonia. Her pre-admission ECOG was 1*. Her HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physical activity but ambulatory and able to carry out work of a light or sedentary nature.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleed, approx. 2/100 patient years.
A 50-year old patient is admitted under General Internal Medicine with pneumonia. She has metastatic colon cancer and has been receiving second-line chemotherapy. Prior to her pneumonia, her ECOG performance status was 1*. Her HAS-BLED score is 0#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 0: relatively low risk for major bleeding (~1/100 patient-years).

A 28-year old patient with metastatic melanoma is admitted under General Internal Medicine with new-onset delirium; she is found to have an elevated WBC count and her chest x-ray shows a right lower lobe pneumonia. Her pre-admission ECOG was 1*. Her HAS-BLED score is 2#.

Based on this information, how likely would you be to start this patient on thromboprophylaxis?

*ECOG: Eastern Cooperative Oncology Group performance status. ECOG 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

#HAS-BLED: predicts the 1-year risk of bleeding. HAS-BLED 2: moderate risk for major bleeding (~2/100 patient-years).
18. Thank you for completing our survey!
Appendix 3: Medline search strategy: systematic review

Ovid MEDLINE(R) 1946 to July Week 4 2017

# Searches Results Type

1  exp Neoplasms/ 3038666 Advanced
2  exp Medical Oncology/ 18918 Advanced
3  neoplas*.mp,kw. 2609180 Advanced
4  paraneoplas*.mp,kw. 11778 Advanced
5  cancer*.mp,kw. 1323321 Advanced
6  tumo?r*.mp,kw. 1707172 Advanced
7  onco*.mp,kw. 419267 Advanced
8  metast*.mp,kw. 438351 Advanced
9  malignan*.mp,kw. 458423 Advanced
10 carcin*.mp,kw. 863921 Advanced
11 adenocarc*.mp,kw. 203702 Advanced
12 lymphoma*.mp,kw. 208759 Advanced
13 leuk?emia*.mp,kw. 284825 Advanced
14 sarcoma*.mp,kw. 107139 Advanced
15 blastoma*.mp,kw. 1139 Advanced
16 melanoma*.mp,kw. 108991 Advanced
17 melanotic*.mp,kw. 2808 Advanced
18 neurilemmoma*.mp,kw. 13266 Advanced
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or/1-71 3926758 Advanced
exp Advance Care Planning/ 8242 Advanced
Palliative Care/ 49578 Advanced
Palliative Medicine/ 207 Advanced
Hospice Care/ 6210 Advanced
"Hospice and Palliative Care Nursing"/ 390 Advanced
Terminal Care/ 25875 Advanced
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or/92-106  612439 Advanced
72 and 91 and 107  983  Advanced
exp animals/ not (exp animals/ and exp humans/)  4445218  Advanced
108 not 109  966  Advanced
remove duplicates from 110  911  Advanced
Appendix 4: Hawker et al., checklist for reviewing disparate data systematically

This checklist is from Hawker, S., S. Payne, et al. (2002). "Appraising the Evidence: Reviewing Disparate Data Systematically." Qualitative Health Research 12(9): 1284-1290.

Please assess each paper on the following criteria. For scoring please refer to notes below.

- **Good**=4
- **Fair**=3
- **Poor**=2
- **Very poor**=1

Lower scores =poor quality

Notes for appraising the quality of each paper:

1. **Abstract and title:**
   - Did they provide a clear description of the study?
   - Good: Structured abstract with full information and clear title.
   - Fair: Abstract with most of the information.
   - Poor: Inadequate abstract.
   - Very Poor: No abstract.

2. **Introduction and aims:**
   - Was there a good background and clear statement of the aims of the research?
   - Good: Full but concise background to discussion/study containing up-to-date literature review and highlighting gaps in knowledge. Clear statement of aim AND objectives including research questions.
   - Fair: Some background and literature review. Research questions outlined.
   - Poor: Some background but no aim/objectives/questions. OR Aims/objectives but inadequate background.
   - Very Poor: No mention of aims/objectives. No background or literature review.

3. **Method and data:**
   - Is the method appropriate and clearly explained?
   - Good: Method is appropriate and described clearly (e.g., questionnaires included). Clear details of the data collection and recording.
   - Fair: Method appropriate, description could be better. Data described.
   - Poor: Questionable whether method is appropriate. Method described inadequately. Little description of data.
   - Very Poor: No mention of method, AND/OR Method inappropriate. AND/OR No details of data.

4. **Sampling:**
   - Was the sampling strategy appropriate to address the aims?
   - Good: Details (age/gender/race/context) of who was studied and how they were recruited. Why this group was targeted. The sample size was justified for the study. Response rates shown and explained.
   - Fair: Sample size justified. Most information given, but some missing.
   - Poor: Sampling mentioned but few descriptive details.
   - Very Poor: No details of sample.

5. **Data analysis:**
   - Was the description of the data analysis sufficiently rigorous?
   - Good: Clear description of how analysis was done. Qualitative studies: Description of how themes derived/respondent validation or triangulation. Quantitative studies: Reasons for tests selected hypothesis driven/ numbers and upstatistical significance discussed.
   - Fair: Qualitative: Descriptive discussion of analysis. Quantitative.
   - Poor: Minimal details about analysis.
   - Very Poor: No discussion of analysis.

6. **Ethics and bias:**
   - Have ethical issues been addressed, and what has necessary ethical approval gained? Has the relationship between researchers and participants been adequately considered?
Appendix 5: Contributions

The completion of this Master of Science thesis was made possible by several contributors.

I designed the study, along with my Program Advisory Committee, consisting of Dr. Monika Krzyzanowska, Dr. John Granton, Dr. Nathan Taback, and Dr. Camilla Zimmermann. For the systematic review component of the thesis, Ms. Rouhi Fazeldad, Information Specialist at the University Health Network Library and Information Services, Princess Margaret Cancer Centre, assisted with the literature review. Ms. Ting Cai assisted with study selection and appraising the quality of included studies for the review. She also assisted with identifying the names and emails of the medical oncologists for the survey component of the thesis.

I developed the survey instrument used in this study along with advice from my committee. I wrote and maintain the Research Ethics Board documentation submitted to the University Health Network. Design of the database and statistical analyses were conducted with support from Dr. Nathan Taback, a member of my Program Advisory Committee.