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Review Article

Thromboembolic disease in palliative and end-of-life care: A narrative review

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ABSTRACT

Venous thromboembolism (VTE) is both common and a potential contributor to symptom burden in patients receiving palliative and end-of-life care. Many of the VTE treatment and prophylaxis recommendations are drawn from data of clinical trials assessing conventional VTE and cancer-associated thrombosis that excluded patients receiving specialist palliative or hospice care. In this group, the epidemiology of VTE and associated outcomes, as well as the risks and benefits of treatment in keeping with a palliative approach are of growing clinical and research interest. This narrative review summarizes current knowledge and challenges in the management of thromboembolic disease in palliative care, highlighting the complexity of decisions surrounding VTE treatment and prophylaxis.

1. Introduction

Venous thromboembolism (VTE) has well-recognized risk factors that include immobility, recent surgery, medical illness, and cancer [1,2]. In acutely hospitalized medical patients with or without cancer, routine prophylaxis is accepted standard of care [3–6]. In cancer patients, the risk of VTE is increased in those with more advanced disease [7], and this elevated risk appears to apply to patients receiving palliative or end-of-life care [8–10]. However, the true incidence and prevalence of VTE in specialist palliative care units (SPCU) and in hospice care have not been firmly established. While fatal pulmonary embolism (PE) is the ideal primary outcome measure of VTE-related studies, perhaps equally important in the palliative care population is the significant symptom burden caused by VTE and its impact on quality of life [11]. This not only includes pain and edema from acute occlusive deep vein thrombosis (DVT) and/or chest pain and severe breathlessness from acute PE, but also associated acute and long-term psychological distress [11,12].

Symptom management is paramount in palliative care, which focuses on prevention and relief of suffering and improving patients' quality of life [13]. Palliative care reaches beyond end-of-life care, often from the initial diagnosis of a life-threatening illness. A growing body of evidence now emphasizes the importance of palliative care early in the death trajectory [14]. Palliative care specialists are increasingly involved early in the course of illness and provide support and symptom management in conjunction with therapies intended to prolong life. In addition, the disease trajectory both for cancer and non-malignant diseases such as HIV has dramatically changed in recent decades with the introduction of novel therapies that have extended life expectancy and made many conditions with previously short prognoses into chronic diseases [15,16]. In the past twenty years, 5-year survival in newly diagnosed metastatic breast cancer has doubled from 18 to 36%, with a small but meaningful subgroup of long-term survivors [17]. A similar trend is seen in myeloma, in which the majority of patients can expect to live longer than 5 years [18]. The success in most cases is not due to single therapeutic breakthrough but through multiple available therapies used sequentially each with modest additional benefit. Management of cancer as chronic disease has led to new disease and treatment-related complications. Alongside the cancer population, > 20% of patients admitted to SPCU have no cancer diagnosis but have comorbidities that project similar life expectancy and pose equally difficult symptom management challenges [19]. Patients receiving palliative care therefore comprise an increasingly heterogenous group with respect to diagnoses and stage of disease, many of whom—including those with no confirmed cancer diagnosis—would be considered to be at high risk of VTE and its related symptoms. At the same time, many patients may prioritize symptom relief and quality of life over prolongation of life.

The study and clinical management of VTE in the palliative care setting remain challenging for several reasons [20]. Defining a

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"palliative care" population is problematic given this group's considerable heterogeneity, which limits any generalizable findings or recommendations. Patients in SPCU or hospice may be more representative of those at the very end of life, in contrast to the patient with advanced disease followed for symptom management as outpatient. Studies that include or focus on patients with "palliative indicators" such as presence of metastatic disease or based on short term mortality may provide additional information but have some important differences from the SPCU/hospice population. Trials that have informed clinical guidelines for management of VTE historically excluded patients with an estimated life expectancy of < 3–6 months or being treated with palliative intent. There are, therefore, limited data and no randomized trials directly pertaining to this group, nor do any evidence-based guidelines exist to inform treatment and prophylaxis for VTE in this group. Furthermore, investigations, treatment, and prevention measures for VTE in supportive and palliative care must balance their possible benefits with their burden and detraction from quality of life, especially near the end of life [21]. These goals are important to consider for any disease or intervention in palliative care but are particularly relevant to VTE, where the disease itself may cause distressing symptoms, investigations may be burdensome, and therapies carry inherent risks. Given the goals of palliative care, symptom relief and other health system outcomes may be more relevant than VTE prevention and mortality [11,22]. This narrative review summarizes the current knowledge and challenges in managing VTE in palliative care and at the end of life.

2. Epidemiology

Although patients admitted to SPCU or hospice care frequently have numerous risk factors for VTE [9,10], the true prevalence and incidence of VTE in this setting remains unclear. Few population-based studies in this patient group exist, and underestimation due to lack of confirmatory testing for VTE remains an important but understandable issue in a setting where medical interventions are often minimized. VTE has been reported to be present in up to 50% of cancer patients postmortem, although it is not known whether these contributed to symptoms or death, or were just part of the agonal process [23]. One study, using light reflection rheography to identify DVT in hospice patients, suggested a 50% prevalence of DVT, 9% of whom had classical symptoms of VTE [24]. However, despite being a highly sensitive test for venous flow reduction, light reflection rheography has a low specificity for VTE and does not differentiate between distal and proximal obstruction, nor does it indicate whether the cause of obstruction is intrinsic or extrinsic. While symptomatic VTE may complicate the course of up to 15% of advanced cancer patients, reports specific to palliative care unit and hospice settings are scarce [8]. Previous studies reporting prevalence of established VTE in patients admitted to SPCU or hospice ranged from 6 to 12%, and was higher in those studies with a greater proportion of cancer patients [10,25–28]. Amongst the few studies that recorded new symptomatic VTE in patients admitted to SPCU or hospice, incidence ranged from form 0.5 to 8% [25,26,28,29]. More recently, HIDDen [30] screened 343 cancer patients admitted to SPCU with bilateral femoral vein compression ultrasound; the estimated prevalence of femoral DVT was 28% and only 4 patients developed a new DVT during admission. Of those with confirmed DVT, 53% reported ipsilateral leg edema but only 23% reported pain.

3. Diagnosis

While the gold standard diagnostic studies for VTE, namely compression ultrasonography and computed tomography pulmonary angiography, are best placed to diagnose DVT or PE in patients receiving palliative care, there are multiple challenges that impact clinical decision making within this clinical setting [20]. First, recognizing VTE symptoms in patients with advanced disease and multiple comorbidities frequently poses a challenge as VTE symptoms may mimic other common conditions seen in this group [11,20]. Secondly, commonly used clinical prediction tools and non-invasive testing such as the D-dimer testing are only useful in healthy subjects with a low pretest probability of VTE [2], virtually excluding patients in the palliative care population. An important factor to consider in palliative and end-of-life care is that a decision to pursue confirmatory testing includes the impact of investigations which may involve burdensome tests requiring admission or transfer to another healthcare facility, and ultimately whether treatment would be expected to improve quality of life.

4. Treatment

Decisions surrounding initiation and duration of treatment for confirmed VTE are complex in palliative care because: i) the potential benefits are uncertain and risks may be increased, ii) goals and outcomes of interest may differ from other groups, and iii) there is a lack of randomized trials to inform clinical practice [11,20]. Generally, in patients with and without cancer who have established acute VTE, anticoagulation is the mainstay of therapy with a goal of reducing mortality and morbidity including recurrent events [5,6,31,32]. For over 60 years the anticoagulant of choice has been warfarin, which has been largely replaced by direct oral anticoagulants (DOACs). In the cancer setting, warfarin has been associated with a high rate of bleeding with hospice specific data suggesting rates as high as 88% [33]. Following publication of the landmark CLOT study and subsequent corroborative randomized control trials [34–37], low molecular weight heparin (LMWH) has been recommended first line in the treatment of cancer-associated thrombosis (CAT). Although these studies evaluated anticoagulation for only 3–6 months guidelines in CAT support the use of therapeutic dose of LMWH of indefinite duration in patients with advanced or metastatic cancers at high risk of recurrent events [5,6,32]. Driving these recommendations are the randomized trials have established that LWMH is more efficacious than warfarin in terms of recurrent with similar or lower risk of major bleeding episodes [34–37]. It is important to note that the trials evaluating warfarin versus LMWH in CAT excluded patients with a life expectancy of < 3 months, poor performance status, increased bleeding risk, renal impairment, weight < 40 kg, thrombocytopenia, and other comorbidities common in palliative patients. Within these randomized trials, the prevalence of metastatic disease, a possible palliative indicator, ranged from approximately 40 to 70% (Table 1) [34–38]. Amongst the clinical trials evaluating DOACs versus warfarin, in a subgroup analysis of CAT, the definition of active cancer varied and fewer than 25% of patients had metastatic disease [39]. Furthermore, a group similar to a SPCU or hospice population was not represented in any trials of the management of acute VTE in patients with or without cancer.

A meta-analysis focusing on studies which included advanced-stage cancer patients, although not exclusively receiving palliative care or in SPCU, reported that LMWH seems to be efficacious and safe for these patients [8]. In a case series of 62 patients with advanced malignancy receiving LMWH for VTE and undergoing specialist palliative care, 3

Table 1
Proportion of patients with metastatic disease recruited to studies of anticoagulation in the treatment of cancer associated thrombosis.

Study	Direct oral anticoagulant	Low molecular weight heparin	Warfarin
CLOT [34]		66%	69%
LITE [37]		47%	36%
CATCH [38]		55%	54%
ONCENOX [36]		54%	52%
HOKUSAI CANCER [51]	52%	53%	
SELECT-D [52]	58%	58%	

out of 7 patients who stopped anticoagulation after 6 months developed recurrent symptomatic VTE, and no major bleeds were seen in those who continued LMWH [40]. This suggested that the benefit to continuing LMWH for extended treatment duration may outweigh the risks of bleeding. However, in another study of 71 cancer patients with VTE admitted to a palliative care unit and treated with therapeutic dose LMWH, recurrence of VTE was 8.5% despite therapeutic anticoagulation and a total of 11.3% of the patients suffered a major bleeding complication [10]. More recently prospective observational study of 22 SPCUs in France identified an incidence of clinically relevant bleeding (CRB) plus clinically relevant non-major bleeding (CRNMB) of 9.8% at 3 months (95% CI 8.3–11.6) amongst their 1196 cancer patients [26]. Of these, 527 (44%) were receiving LMWH thromboprophylaxis and 69 (5.7%) therapeutic LMWH. Multivariate analysis suggested an association between bleeding complications and pharmacological thromboprophylaxis (HR 1.48, 95% CI 1.02–2.15, $p = 0.04$). Numbers were too small to show a statistical association with higher doses. Altogether, these reports suggest that the risk of both recurrent VTE and bleeding may be higher than anticipated in the palliative care population and highlight some of the specific challenges in managing CAT. Guidance on the management of some of these challenging scenarios in CAT including recurrent VTE despite anticoagulation, bleeding complications, and thrombocytopenia are provided by the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis and are summarized in Table 2 [41,42].

In a population with limited life expectancy, quality of life and symptom relief may be more important endpoints than survival and recurrent VTE. These outcome measures are subjective and not as frequently reported. Therefore, decisions to proceed or withhold anticoagulation for the management of VTE in this patient population have proven to be difficult and depend largely on an individual clinician's judgement [43,44]. All recurrent VTE events in the case series mentioned above were reportedly symptomatic [40]. In a prospective study of unselected patients ($n = 6$) admitted to a palliative care unit, all patients who were started on LMWH for a new diagnosis of symptomatic DVT were noted to have "symptomatic improvement", although no objective scales were used [25]. As many of the conclusions on symptom relief are drawn from literature in the non-palliative setting, study of symptomatic outcomes in this population that accounts for goals of care would be beneficial.

Palliative care clinicians must also be vigilant in addressing the acceptability of investigations and interventions as it pertains to a patient's quality of life. While subcutaneous LMWH may be perceived by certain clinicians as an uncomfortable intervention, qualitative studies of cancer patients suggest that LMWH was acceptable, offered a sense of optimism about treatment, and provided simplicity when contrasted to warfarin which required INR monitoring [45,46]. While it was associated with bruising at the injection sites, patients deemed this an acceptable trade-off for their strongly negative experiences of symptomatic VTE [46]. Even in the absence of acute VTE, patients saw LMWH as an acceptable intervention for prophylaxis [47]. The perceived harm or discomfort associated with subcutaneous LMWH administration may therefore be more exaggerated in the eyes of healthcare practitioners compared to patients.

Outside the supportive and palliative care setting, DOACs have become the preferred choice for treatment of VTE in many patients with VTE including those with CAT, as emerging evidence showed that DOACs might be a reasonable for some cancer patients [5,6,31,32]. However, while DOACs might seem appealing for ease of use and avoidance of injections and monitoring, there are multiple factors that limit their applicability and potential use in the palliative care population. Caution is recommended with the use of DOACs in the frail and elderly, with underlying hepatic dysfunction, and with impaired renal function (with avoidance of DOACs altogether in those with a creatinine clearance < 30 mL/min) [31,48]. While specific reversal agents and monitoring tests of anticoagulant effect exist, they are expensive and currently not widely available outside of acute care settings [49]. Another important consideration is the multiple drug-drug interactions that exist with these agents, leading to increased or reduced DOAC plasma levels. Amongst many medications with such interactions, drugs common in palliative care patients include chemotherapeutic and immunosuppressive agents, hormonal therapies, tyrosine kinase inhibitors, and dexamethasone (Table 3) [48,50]. Until recently, there were no adequately powered RCTs comparing DOACs with LMWH in the treatment of CAT. [39] The recently published Hokusai VTE Cancer trial showed that edoxaban was non-inferior to LMWH for the management of CAT, based on a composite end point of recurrent VTE and major bleeding [51]. Secondary analysis suggested that the rate of recurrent VTE was lower in the edoxaban arm but this was at the expense of a significant increase in major bleeding events from 3% to 6%. Similarly, the SELECT-D study reported a lower rate of recurrent VTE amongst patients on rivaroxaban compared with LMWH but rivaroxaban carried a significantly higher risk of CRNMB (13% vs. 4%) [52]. While more than half of the patients in both these studies had metastatic disease, few had significant functional impairment and those with a life expectancy of < 6 months were excluded (Table 1). In the palliative care population, where underlying coagulopathy, organ dysfunction, frailty, and polypharmacy are all common, it remains to be seen what role DOACS will play, especially when bleeding complications are a concern.

Finally, although guidelines indefinite anticoagulation for CAT and unprovoked VTE, there is limited data to guide tailoring length of anticoagulation near the end of life. In a recent case series of 214 patients with CAT who died over a 2-year period, 50% continued LMWH until death and 11% up to 7 days prior to death [53]. In those who discontinued anticoagulation earlier, there were no reported symptoms attributable to recurrent VTE. Furthermore, CRNMB occurred in 7% of the patients who continued LMWH to within 7 days of death. The symptomatic risks and benefits of discontinuing anticoagulation in the terminal phase merit further study.

Table 2
Management of challenging cases of cancer associated thrombosis: International Society Thrombosis and Hemostasis Scientific Sub Committee recommendations [41,42].

Recurrent VTE despite anticoagulation

1. If on warfarin, switch to therapeutic LMWH
2. If already on LMWH, increase dose by 25% or increase back up to therapeutic weight adjusted dose if they are receiving non-therapeutic dosing.
3. If no symptomatic improvement, use peak anti-Xa level to estimate next does escalation.

Management of CAT in thrombocytopenia

1. For platelet count $> 50 \times 10^9 L^{-1}$ give full therapeutic dose LMWH
2. For acute CAT and platelet count $< 50 \times 10^9 L^{-1}$
   a. Full anticoagulation with platelet transfusion to maintain platelet count $> 50 \times 10^9 L^{-1}$
   b. If platelet transfusion not possible, consider retrievable IVC filter
3. For subacute or chronic CAT and thrombocytopenia (platelet count $< 50 \times 10^9 L^{-1}$)
   a. Reduce therapeutic dose by 50% or use prophylactic dose for platelet count $25–50 \times 10^9 L^{-1}$
   b. Omit LMWH if platelet count $< 25 \times 10^9 L^{-1}$

Bleeding while anticoagulated

1. Assess each bleeding episode to identify bleeding source, severity, impact and reversibility
2. Provide supportive measures to stop bleeding including transfusion where indicated
3. For a major or life-threatening bleeding episode: withhold anticoagulation
   a. Consider IVC filter insertion in patients with acute or subacute CAT with a major or life-threatening bleeding episode.
   b. Do not consider IVC filter insertion in patients with chronic CAT.
   c. Once bleeding resolves: remove retrievable filter (if inserted) and resume/ initiate anticoagulation

Table 3
Common drug-drug interactions with direct oral anticoagulants, based on Lee and Peterson [50].

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Interaction effect	P-glycoprotein	P-glycoprotein CYP3A4	P-glycoprotein CYP3A4	P-glycoprotein
Increases DOAC plasma levels[a]	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib
Reduces DOAC plasma levels[b]	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

Abbreviations: DOAC, direct oral anticoagulant.
[a] Drugs that inhibit P-GP or CYP3A4 can increase DOAC levels.
[b] Drugs that induce P-GP or CYP3A4 can lower DOAC levels.

5. Thromboprophylaxis

Unless actively bleeding or at high risk of bleeding, primary thromboprophylaxis is recommended for acutely ill hospitalized medical patients, including those with underlying cancer [3–6]. For patients receiving palliative care, expert opinion-based guidelines suggest considering pharmacological VTE prophylaxis with LMWH taking into account conventional thrombotic and bleeding risk factors, as well as life expectancy and patient or caregiver preferences, with daily re-evaluation [4]. According to these guidelines, thromboprophylaxis should not be given in the last days of life—arguably any symptoms attributable to VTE can be managed with end-of-life medicines. Less than twenty years ago, in contrast to the acute care setting, few SPCUs had thromboprophylaxis protocols and prophylactic LMWH was rarely initiated or continued by palliative care specialists for their inpatients [54]. With increasing recognition of the risks of VTE in palliative care patients, SPCUs and hospices began implementing these protocols, and while the topic of pharmacologic thromboprophylaxis in this setting gained research attention, its use remains controversial [9,10,25,29,54–59]. These studies highlighted some of the pitfalls in assuming that thromboprophylaxis guidelines for acutely hospitalized patients applied to the palliative care population. Meaningful outcomes in the SPCU and hospice setting differ substantially from those in the general population—prophylactic LMWH can be considered a life-prolonging therapy with associated risks of harm, which includes an extended symptomatic dying experience [56]. This alone makes a sensible case against pharmacologic prophylaxis in palliative care.

The only randomized study investigating LMWH thromboprophylaxis in a palliative care setting recruited only 20 participants and was therefore underpowered to detect an important clinical difference and produce any reliable conclusions on the utility of this intervention [29]. A more recent multicenter observational study of 1199 patients (90% of whom had a cancer diagnosis) admitted to palliative care units that excluded those requiring therapeutic anticoagulation on admission demonstrated a low incidence of VTE but a high incidence of CRB (9.8%), which was associated with antithrombotic therapy (the majority of which was prophylactic dose LMWH) [26]. The results suggested that the bleeding risks of VTE prophylaxis might outweigh the benefits in this population. A small prospective study of patients admitted to a palliative care unit for whom primary thromboprophylaxis was discontinued or never initiated reported rate of new symptomatic VTE of 7.6% [25]. The authors concluded that thromboprophylaxis may be discontinued safely, deeming this may not to be a clinically important risk. Given that this incidence of VTE is higher or at least as high as in the general hospitalized population, where thromboprophylaxis is routinely recommended, this provides some insight into the relative value of therapy placed by some investigators in the palliative care population.

HIDDen challenged many of the previous views about the clinical relevance of VTE in the SPCU setting [30]. In this prospective longitudinal observational study conducted in 5 SPCUs in England, Wales and Northern Ireland, 343 cancer patients underwent bilateral femoral vein ultrasonography on admission and weekly until death or discharge (maximum 3 weeks). Data were collected on performance status, attributable symptoms and variables known to be associated with VTE. Mean Australian-modified Karnofsky Performance Score of 49 and survival of 44 days amongst participants indicated a highly dependent cohort with a poor. While the prevalence of DVT was high at 28%, receipt of pharmacologic thromboprophylaxis was not associated with the presence of DVT, and DVT conferred no survival difference nor symptoms besides leg edema. Interestingly of 1390 patients screened, 397 were ineligible as they were expected to die within 5 days, once again illustrating that a significant proportion of the hospice/SPCU population would be inappropriate for thromboprophylaxis even if there were evidence of efficacy. Many patients die with—but not necessarily from or with symptoms from—DVT, and thromboprophylaxis seemed to confer little benefit. This study may be the strongest evidence to date on thromboprophylaxis in palliative care, although the data should be considered in the context of the population studied. These results represent a completely new population which is excluded from all the previous CAT studies, but it would be unwise to extrapolate apply these data to all palliative care patients, particularly those with a better performance status.

Some experts have sought to balance the risks and benefits of thromboprophylaxis in the palliative care population by employing a risk assessment approach. Risk assessment for VTE is an important factor for decisions surrounding thromboprophylaxis, yet risk assessment tools have not been well studied in the hospice and palliative care unit population. Johnson et al. investigated Thromboembolic Risk Factors Consensus Group criteria and factors associated with temporary elevated risk of VTE in 1164 hospice patients, which demonstrated an expected significant risk for VTE but also showed that higher scores were predictive for symptoms attributable to VTE in 21% of patients [9]. However, VTE was not definitely confirmed, and they were unable to draw any conclusions surrounding the efficacy of thromboprophylaxis. Furthermore, only 45% of patients in the group at risk of VTE had no contraindications to anticoagulation or were not already anticoagulated.

Unlike the general medical population admitted to hospital, the accumulated evidence regarding thromboprophylaxis in palliative care show an increased risk of bleeding with limited evidence of benefit, suggesting that it should not be applied as routine care.

While LMWH remains the guideline-recommended pharmacologic agent for VTE prophylaxis in hospitalized patients with active malignancy, a recent randomized placebo-controlled trial indicated a potential role for DOACs in preventing VTE in ambulatory cancer patients:

Table 4
Research opportunities in the management of cancer associated thrombosis in palliative care.

Category	Research questions	Suggested methodology
Scope of the problem	How many patients admitted to hospices have contraindications to thromboprophylaxis? What is the cost burden of CAT to palliative care settings?	Co-ordinated multi-center single day observational study Health economic analyses in different countries with different payment tariffs for palliative care
Treatment of CAT	What is the role of DOACs in the initial treatment of CAT? What is the role of inferior vena cava filters in palliative care? How should we anticoagulate palliative CAT patients after 6 months of full anticoagulation? ● Which agent? ● Which dose?	Randomized controlled trial of DOAC vs LMWH (vs no anticoagulant) Observational study
Thromboprophylaxis	In advanced cancer patients acutely admitted to hospital, is the prevalence of DVT similar to that observed in HIDDen? Does the risk of VTE change with performance status/prognosis?	Observational study stratified according to functional status/ performance (e.g. Karnofsky Performance Status)
Biomarkers	How do we identify patients at greatest risk of recurrent symptomatic VTE? Can we predict which patients will form pulmonary emboli? Can markers of thrombotic activity predict prognosis?	Observational cohort study of established biomarkers and tools, e.g. Khorana, D-dimer, tissue factor microparticles Fractal analysis, clot contraction studies Longitudinal observational study
Clinical decision making	How can we decide the best choice of anticoagulant for patients with advanced cancer and thrombosis? How can we develop shared decision making with patients?	Development of a clinical decision making tool Ensure patient preferences and values are represented in the decision making tool. Discrete choice experiment methodology.

Abbreviations: CAT, cancer associated thrombosis; VTE, venous thromboembolism; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant.

Apixaban 2.5 mg twice daily significantly reduced the rate of VTE but conferred a higher risk of major bleeding [60]. Ambulatory cancer patients may well be followed by outpatient palliative care or home hospice programs, and therefore palliative care specialists may increasingly care for patients on DOACS for this purpose. As with the studies of DOACS for treatment for established CAT, these results must be interpreted with caution—they do not apply to a palliative care population with a poor functional status, where the risk of bleeding with continuation of these agents likely outweighs their benefit.

6. Future directions and research

Amongst patients with metastatic disease, trends of improved survival and increasing receipt of systemic anticancer therapies suggest that CAT will continue to be a frequently encountered problem by clinicians providing care for this group. Table 4 highlights the future challenges in the hospice population that warrant further research and possible approaches to studying them. Some research questions are best answered through established research techniques and methodologies, although they may also lend themselves to more novel biomarker work such as fractal dimension and clot contraction studies [61–63]. Most importantly such studies need to be undertaken in the SPCU/hospice populations in order to be representative of the clinical scenarios they aim to guide. The success of recruiting to the HIDDen study is testament demonstrates the feasibility of undertaking adequately powered CAT studies within the hospice and charitable sector. However, this requires collaborative working across palliative care services and between haematology, oncology, and palliative care specialists.

7. Conclusion

In summary, VTE commonly occurs in patients receiving palliative and end-of-life care. While it may cause distressing symptoms, it is often asymptomatic. The study and management of VTE continues to be a challenge in palliative care patients, who comprise a diverse group with multiple competing risks, and whose outcomes of interest and goals may differ significantly from those in the general population. Treatment recommendations for confirmed VTE in this population are largely guided by the randomized trials of anticoagulants in CAT, in which the patients studied did not closely resemble those in SPCU or hospice. While reducing the risk of recurrent symptomatic VTE would be desirable, one must consider the significant risk of bleeding and the paucity of evidence to demonstrate symptomatic benefit from treatment—especially closer to the terminal phase. Adding to this, recent studies suggest that the value of thromboprophylaxis in this patient population may be limited and risk of bleeding very high. These decisions are complex, involving clinical judgement and an individualized approach that balances patient and family goals to minimize suffering.

Our review highlights the complexity of this topic and the need for further studies on VTE treatment and prophylaxis specific to patients receiving palliative and end-of-life care using patient-important outcomes.

Conflict of interest statement

NCY and PT report no conflicts of interest. MC has received research funding from Leo Pharma, Pfizer and BMS, and honoraria from Pfizer, Bayer, BMS, Sanofi, Leo Pharma and Servier. SN has received honoraria from Pfizer, Bayer, BMS, Boheringer Ingelheimi and Leo Pharma.

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