Primary thromboprophylaxis in the palliative care setting: a qualitative systematic review

Sarah McLean  Department of Palliative Medicine, Mater Misericordiae University Hospital, Dublin, Ireland
Karen Ryan  Department of Palliative Medicine, Mater Misericordiae University Hospital, Dublin, Ireland
James S O’Donnell  Haemostasis Research Group, Institute of Molecular Medicine, Trinity College Dublin, Ireland; National Centre for Hereditary Coagulation Disorders, St James’s Hospital, Dublin, Ireland

Abstract
Symptomatic venous thromboembolism (VTE) occurs in 15% of patients with advanced malignancy. Primary thromboprophylaxis using low-molecular-weight heparin (LMWH) is supported by Level 1A evidence but is under-utilized in the palliative setting. A systematic search was performed of Medline, Cochrane Library, EMBASE, AMED, and Web of Science for papers published between 1960 and January 2010 using search terms: ‘palliative’, ‘thromboprophylaxis’, ‘thromboembolism’, ‘heparin’, and ‘advanced cancer’. Forty-two citations were obtained, of which 34 were excluded as they dealt with treatment of VTE, novel anticoagulants, or LMWH as a cancer treatment. Eight original articles were reviewed independently by two authors. Data was extracted according to a predetermined questionnaire. Studies examined practice in specialist palliative care (SPC) units, and attitudes held by a total of 32 physicians and 198 patients. Patients find LMWH acceptable, particularly patients who experienced a sudden decline in performance status. Reluctance to prescribe LMWH is based on physicians’ concerns regarding negative impact on quality of life, and lack of evidence specific to the palliative care setting. In conclusion, LMWH prophylaxis should be implemented in patients with a previously good performance status who have a transiently increased risk of VTE and no contraindications. Further research is required using outcome measures specific to palliative care.

Keywords
Advanced cancer, palliative, primary thromboprophylaxis, thromboembolism

Introduction
For many years, it has been recognized that venous thromboembolism (VTE) represents a common complication of malignancy.\(^1\) Meta-analyses have demonstrated that the relative risk of venous thromboembolism (VTE) is increased approximately six-fold in patients with cancer compared to age- and sex-matched controls without cancer.\(^2\) Symptomatic deep vein thrombosis (DVT) has been reported in up to 15% of patients with cancer, and post-mortem studies have demonstrated pulmonary embolism (PE) in as many as 50%.\(^3\) A variety of different mechanisms have been shown to mediate the increased risk of VTE associated with cancer. These include direct haemostatic abnormalities precipitated by tumour elaboration of tissue factor and inflammatory cytokines, elevated platelet numbers and activity, and vessel stasis.\(^4\) In addition to causing direct activation of the plasma coagulation cascade, cancer cells also increase thrombotic risk through interactions with platelets, and by influencing endothelial cell function. Furthermore, it is well established that specific therapeutic interventions such as chemotherapy and central venous catheters can further increase the absolute risk of VTE in cancer patients.\(^2\) In addition, the risk of VTE in cancer patients increases with age, metastases and prolonged immobilization.\(^5\)
There has been recent significant interest in the primary thromboprophylaxis of VTE in hospitalized patients, in particular in the setting of malignancy. An exciting development has been the identification of patient specific biomarkers, such as soluble P-selectin, which may help to differentiate patients with cancer who are at high or low risk of VTE. The Journal of Clinical Oncology, the official journal of the American Society of Clinical Oncology, devoted an issue in October 2009 to the topic of VTE in the cancer setting, and the National Institute for Health and Clinical Excellence (NICE) will release widely anticipated guidelines in early 2010, containing specific recommendations on prophylaxis for patients with advanced cancer and patients in the palliative care setting.

There is currently limited data regarding the incidence of VTE in patients with malignancy in palliative care. Physicians working in palliative medicine have been found to significantly under estimate the likely prevalence of VTE in hospice inpatients, and in one study estimated the prevalence to be only 1–5%. Nonetheless, Johnson et al. screened 287 patients on admission to a specialist palliative care (SPC) unit using light reflection rheography, demonstrating evidence of likely DVT in 52% of patients. Moreover, in 17% of these cases, bilateral DVTs were observed.

Development of VTE in cancer patients is of direct clinical significance, as it is associated with a significant reduction in overall survival. Furthermore, both DVT and PE are often associated with important symptomatology in cancer patients in the palliative care setting. In the study of Johnson et al., only 9% of likely venous thromboses were symptomatic at time of original diagnosis, but another 32% of patients with likely DVT subsequently developed symptoms that included significant lower limb pain and swelling. In addition, despite the fact that PE is typically considered a rapidly terminal event, previous studies have shown that fatal PE results in abrupt death in only a minority of cases (<10%). Rather, most patients took longer than 10 minutes to die, and experienced distressing symptoms including significant dyspnoea. Repeated sublethal pulmonary emboli may also cause significant dyspnoea and reduced exercise tolerance, particularly if there is an underlying cardio-respiratory condition. Cumulatively, these data demonstrate that symptomatic VTE (in the form of DVT and/or PE) has significant potential to adversely affect quality of life and increase symptom burden in patients receiving palliative care. In addition, symptomatic VTE may also constitute a barrier to discharge of patients from SPC units, from which up to 50% of patients may be discharged home following a period of respite or symptom management.

For patients in the palliative setting, primary prophylaxis options include mechanical methods such as compression stockings, unfractionated heparin (UFH), and low-molecular weight heparin (LMWH). Although compression stockings reduce the risk of DVT, there are no supportive studies outside of the surgical setting, they do not reduce the occurrence of PE, and they are not well tolerated. UFH is expensive, requires frequent monitoring, and is nursing-time intensive. Moreover, accumulating research suggests that LMWH may also have an independent beneficial effect overall survival in advanced malignancy. In the setting of advanced cancer, LMWH has been shown to be preferable to warfarin for the treatment of VTE, due to its superior efficacy, cost effectiveness and reduced bleeding risk.

The limitations of the vitamin K antagonists have prompted the quest for novel oral anticoagulants, and several oral agents are in the advanced stages of clinical development. An ideal agent should have predictable pharmacodynamic and pharmacokinetic properties, a fixed dosing schedule, a wide therapeutic window and should not require regular monitoring. Following successful phase II trials, two significant new treatments are currently undergoing phase III testing: rivaroxaban, an oral direct factor Xa inhibitor, and dabigatran, an oral direct thrombin inhibitor. Trials have, to date, evaluated efficacy and safety in the setting of VTE prophylaxis post-orthopaedic surgery, treatment of acute coronary syndrome, prevention of secondary VTE, and stroke prevention in atrial fibrillation. There has been one small phase II randomized trial of apixaban, a factor Xa inhibitor, for the prevention of VTE in patients with metastatic cancer on chemotherapy. A phase III trial of rivaroxaban for the prevention of acute VTE is ongoing, which will include a large number of patients with cancer in whom subgroup analysis will be possible. Trials to date have excluded patients with impaired renal or hepatic function, and the use of oral agents may be limited in patients in the palliative setting with limited oral intake. In addition none of the standard coagulation tests provides a good indication of drug levels, making monitoring difficult, and there are no specific antidotes available. Nonetheless, they have significant therapeutic potential in the future in the prevention of VTE in patients with advanced cancer and in the palliative setting, and further prospective trials are required to evaluate this further.

Previous randomized controlled trials have demonstrated that primary thromboprophylaxis can significantly reduce the incidence of VTE in immobile cancer patients. Consequently, international consensus guidelines now recommend the use of routine thromboprophylaxis with LMWH for immobile cancer patients (Level 1A). This has direct relevance for practice in...
relation to cancer patients in receipt of palliative care, in whom immobilization is approximately twice as common in as in general cancer patients. However, the appropriate role of primary thromboprophylaxis in this context represents a controversial area. In order to establish current practice and attitudes towards primary thromboprophylaxis within palliative medicine, we have performed a systematic review of the published literature relating to the use of primary thromboprophylaxis for patients with advanced cancer in the palliative care setting.

**Methods**

**Criteria for considering studies for this review**

**Studies.** All trials identified by the search criteria were considered eligible for inclusion, including published abstracts. Studies published in languages other than English were excluded.

**Participants.** The population addressed by the review was adult patients (over 18 years of age) who were described as having advanced or disseminated malignancy, being ‘palliative’ or in receipt of palliative care. Patients with non-malignant pathology in receipt of palliative care were also included in the search criteria. Patients who had previously had a thromboembolic event, or who were currently being treated for a thromboembolic event, were not included, as this review studied primary thromboprophylaxis only. Studies of patients in the acute hospital setting, outpatient setting and inpatient SPC units were included.

**Intervention.** The intervention considered by this review was primary prophylaxis of thromboembolism.

**Search strategy**

We performed a systematic search of Medline, the Cochrane Library, EMBASE, AMED and Web of Science for papers published between 1960 and April 2009. Search terms used were: ‘palliative’, ‘thromboprophylaxis’, ‘thromboembolism’, ‘heparin’, ‘novel anticoagulants’ and ‘advanced cancer’ using the Boolean operators ‘OR’ and ‘AND’. In addition, an Internet-based search was performed of the following journals: *Journal of Hospice and Palliative Nursing*, *Palliative Medicine*, *American Journal of Hospice and Palliative Medicine*, *The Journal of Pain and Symptom Management*, and the journals *Thrombosis Journal* and *Thrombosis and Haemostasis*, for relevant papers published since January 1990. Bibliographies were then used to obtain further relevant studies. The last electronic search was performed in January 2010.

Data extraction and synthesis. The titles and abstracts of all identified studies were examined. Potentially relevant studies were reviewed regarding their suitability for inclusion in the review. Each report that appeared to meet the criteria was independently reviewed by two authors. Data was extracted according to a predetermined checklist and questionnaire. Data collected were:

1. publication details;
2. study design, methods and context; limitations of research;
3. findings of research;
4. quality and validity of study.

Disagreements were resolved by consensus among the authors. In view of the heterogeneous nature of the data retrieved, quantifiable analysis (meta-analysis) was not performed as part of this review.

**Results**

The initial search identified: Pubmed, 466 results; EMBASE 2073 results; AMED, 49 results; and Web of Science, 604 results. Twenty-seven additional studies were identified through searches of relevant journals and bibliographies. On review of titles and abstracts of these results, a total of 42 relevant articles were identified. Five relevant articles were excluded, as they were in languages other English. Twenty-nine articles were excluded as they did not specifically look at primary thromboprophylaxis, patients in receipt of palliative care, or patients with advanced malignancy; or were investigating the effects of anticoagulation as a treatment in cancer. No studies investigating the use of novel anticoagulants in the setting of advanced cancer, or in the palliative setting, were identified. Eight pieces of relevant work were finally analysed for the purpose of the review (Figure 1).

**Overview of studies**

Articles reviewed consisted of eight original articles. One prospective randomized study (Weber et al.20), investigated outcomes in a cohort of 20 patients randomized to prophylactic LMWH or best supportive care. Two retrospective case series examined outcomes in a total of 75 patients (Kirkova and Fasinger,21 4 patients; Soto Cardenas et al.,22 71 patients).

Two studies examined practice regarding primary thromboprophylaxis in SPC units (Noble and Finlay,23 Brabin et al.24). Noble and Finlay23 compared primary thromboprophylaxis practice in a total of 140 SPC units in 2000 with practice in 169 SPC units in 2005. Brabin et al.24 performed a retrospective review
of practice in a single hospice in Scotland, with a patient population of 75.

A qualitative study performed by Noble et al. examined the acceptability of LMWH for primary thromboprophylaxis to 28 SPC unit inpatients. The attitudes of a total of 32 palliative care and other physicians towards the use of thromboprophylaxis in this patient population were studied in two qualitative studies (Kierner et al., Noble et al.).

**Settings.** Studies were undertaken in Switzerland, Spain, Austria, Scotland and Wales. All studies were based in SPC units.

**Patient populations.** A total of 198 patients were included in these studies. All were adult patients with an age range of 53–88 where specified, and all patients were under the care of palliative care physicians in SPC units. Noble et al. examined the views and opinions of a total of 28 patients regarding primary thromboprophylaxis. Practice regarding primary prophylaxis in a SPC unit population of 75 was studied. LMWH was compared with supportive care in 95 patients, prospectively in one study and retrospectively in two studies. In 68 of these patients prophylaxis was specified as primary. No studies looking specifically at patients with non-malignant pathology were identified, but in one study examining hospice inpatients, 71 of 75 patients had a diagnosis of a malignancy. Sites of malignancy were specified in 116 patients: head and neck, four patients; haematological malignancy, three patients; breast, 15 patients; lower GI, 15 patients; lung, 17 patients; upper GI, 20 patients; gynaecological, 10 patients; urological, 17 patients; primary brain, seven patients; unknown primary, eight patients.

An appraisal of studies is given in Table 1.

**The perception of VTE in modern palliative care practice**

The actual symptom burden associated with VTE in palliative care, and its cumulative effect on quality of life, has not been well defined. However, as discussed, the frequency of VTE may be as high as 50%. As already described, physicians working in palliative medicine have been found to significantly underestimate the likely prevalence of VTE in hospice inpatients. This lack of awareness may reflect limited access to diagnostic scans in SPC units, or that signs and symptoms, such as lower limb oedema and dyspnoea, are attributed to other pathology, for example, infection, hypoalbuminaemia and cardiac failure. Nevertheless, high response rates to surveys and questionnaires on the topic, as well as views expressed by physicians working in the field, indicate that the issue is a topical one on which more research is desired.
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<th>Study</th>
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| Weber et al.\textsuperscript{20}  
Prophylactic anti-coagulation in cancer palliative care: a prospective randomized study | Prospective randomized study. Patients assigned to LMWH or no treatment. Outcomes were occurrence of VTE, bleeding episodes, and survival from study entry. | 20 patients aged 55–80 all with advanced cancer and no history of VTE. | One VTE in LMWH group, none in control group. Non-significant tendency towards better survival in the LMWH group. | Not blinded, underpowered. Low accrual due to contraindications to LMWH and patients being unable to consent. Performance status was significantly worse in the control group. Causes of deaths not verified? Undetected VTE. |
| Soto Cardenas et al.\textsuperscript{22}  
Venous thromboembolism in patients with advanced cancer under palliative care: additional risk factors, primary/secondary prophylaxis and complications observed under normal clinical practice | Retrospective case series 71 patients who had advanced/disseminated malignancy and were admitted to a SPCU with objectively confirmed VTE over a 3-year period. Risk factors for VTE and use of thromboprophylaxis were analysed. | 60% had one or more risk factors for VTE in addition to cancer. 23% had received VTE prophylaxis. VTE related death occurred in 11 patients (15.5%). Pain and swelling was present in 94% and 51% of patients with DVT; dyspnoea was present in 80% with PE. | 68% of patients had no history of VTE – secondary prophylaxis in 32% of patients. 88% of patients were admitted from home. |
| Brabin et al.\textsuperscript{24}  
The role of primary thromboprophylaxis in hospice patients: a retrospective review of current practice | Retrospective review of thromboprophylaxis practice in a hospice. 75 hospice inpatients. 71/75 had advanced cancer | All patients had at least one VTE risk factor; 81% had three. 2 patients received TEDS, one received LMWH. Contraindications to LMWH documented in one third. Two patients who had not received prophylaxis developed VTE. | |
| Kirkova and Fasinger\textsuperscript{21}  
Thrombosis and anticoagulation in palliative care: an evolving clinical challenge | Retrospective case series 4 patients with advanced cancer and problems relating to VTE. | One patient with a good performance status who did not receive primary thromboprophylaxis passed away suddenly from a PE as a terminal event. | Small sample size, anecdotal in nature. |
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<tr>
<td>Noble et al.²⁶</td>
<td>Semi-structured audio-taped interviews held with 12 SPCU medical directors</td>
<td>12 palliative physicians</td>
<td>VTE not felt to be an important problem in palliative care; lack of evidence specific to palliative care cited as reason for lack of guidelines. All participants were receptive to change and a desire for further research was expressed.</td>
<td>Only directors of units known not to have thromboprophylaxis guidelines surveyed.</td>
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<td>Kierner et al.²⁵</td>
<td>Survey of physicians on whether they would use primary thromboprophylaxis on a virtual patient in various clinical scenarios.</td>
<td>5 specialists in each of: palliative medicine, oncology, intensive care, and coagulation. ( n = 20 )</td>
<td>All physicians opted to withdraw primary and secondary prophylaxis in patients with a Karnofsky index less than 10 or who were in the terminal phase. Decisions were based on the clinical status of the patient rather than the thromboembolic risk.</td>
<td>All physicians working and teaching in the same institution in Vienna, Austria.</td>
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<td>Noble and Finlay²³</td>
<td>Semi-structured telephone survey conducted in 2000 and 2005.</td>
<td>Senior doctors in hospice inpatient units. 140 units with 2447 beds in 2000; 169 units with 2802 beds in 2005 participated.</td>
<td>2% of units in 2000 and 7% in 2005 had thromboprophylaxis guidelines in place. Change in practice over time noted – in 2000 62% and 2005 18% of physicians would stop thromboprophylaxis in patients with a high thrombotic risk who were intended for discharge home.</td>
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<td>Noble et al.¹²</td>
<td>Semi-structured audiotaped interviews.</td>
<td>28 inpatients with advanced cancer receiving palliative care and LMWH. Half of patients had had spinal cord compression and half had been admitted for symptom control in context of steadily declining performance status</td>
<td>Overall thromboprophylaxis had a positive impact on quality of life due to reassurance. LMWH was more acceptable than thromboembolic deterrent stockings.</td>
<td>Prophylaxis was primary in 21 patients. It was not specified in 7 patients who had received LMWH previously whether this was for prophylaxis or treatment.</td>
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Infrequent use of guidelines on thromboprophylaxis in SPC units

The lack of an evidence base regarding the prevalence and symptomatic importance of VTE in the palliative setting has been cited as a reason for the lack of formal guidelines regarding primary thromboprophylaxis. In 2005, Noble and Finlay found that fewer than 10% of inpatient SPC care units across the United Kingdom had a policy in place regarding either primary or secondary thromboprophylaxis. However, this number had increased significantly compared with an earlier survey completed in 2000, when only 2% of units had developed such guidelines. Interestingly, guidelines, where present, were focused upon identifying patients with a favourable prognosis but at high risk of VTE, particularly patients with spinal cord compression.

Use of thromboprophylaxis in SPC units

While primary thromboprophylaxis using LMWH is routinely used in advanced malignancy in oncology wards, evidence suggests it is relatively rarely used in the SPC setting. In a retrospective review of 75 patients admitted to a hospice in Scotland for symptom control, respite or rehabilitation, all patients had at least one risk factor for VTE, and 81% had three risk factors. Nevertheless, only two patients received TED stockings, and one was prescribed prophylactic LMWH. Reasons for avoidance of prophylaxis were documented in one-third of cases and included bleeding (13 patients), anaemia (4 patients) and a dying patient (1 patient). Outcomes measured were: death during hospice admission (53%) and discharge home (47%). Two patients were diagnosed with VTE during or just after hospice admission, neither of who had received prophylaxis. A second retrospective analysis of 71 patients admitted to a SPCU specifically with a diagnosis of VTE revealed that only 10 patients (23.2%) had received thromboprophylaxis prior to admission. All patients had at least one risk factor in addition to cancer, including surgery and immobilization. VTE related death occurred in 11 patients (15.5%).

Despite these data regarding the limited use of thromboprophylaxis in palliative care practice, it is interesting that, where patients are admitted to the SPCU while receiving thromboprophylaxis, there has been a shift away from discontinuing LMWH towards a rational, individualized approach, which takes the patients' own preferences into account. Noble and Finlay questioned senior physicians in palliative medicine regarding whether they would routinely discontinue LMWH in a highly prothrombotic patient, even if that patient was intended for discharge home. In 2000, 62% of physicians stated they would routinely stop thromboprophylaxis. This is compared with 18% when a similar cohort were interviewed in 2005. Furthermore, in the 2005 group, 62% of physicians said they would continue the LMWH, and 20% would consider patient preferences when making the decision ($p < 0.001$). Consequently, while use of primary thromboprophylaxis in the palliative setting remains limited, it seems that the specialty is increasingly receptive to the intervention where there is a clinical rationale for it.

There appears to be a consensus within not only palliative care but also other specialties such as oncology and intensive care that primary thromboprophylaxis should be withdrawn in the terminal phase or when the Karnofsky score is less than 10, regardless of the thromboembolic risk. Kierner et al. aimed to compare the attitudes of physicians from different specialties by presenting a virtual case with various scenarios and stages of disease to physicians working in four different specialties. In a virtual patient with no prior history of VTE and a Karnofsky score of 40, they found that 100% of oncologists, 93% of haemostasis/thrombosis specialists, 93% of intensive care specialists and 80% of palliative care physicians would use primary thromboprophylaxis. In a patient with a Karnofsky score of 20, 40% of oncologists and no palliative care physicians would administer LMWH. All physicians agreed that they would withdraw thromboprophylaxis in the terminal phase or when the Karnofsky score was less than 10. The thromboembolic risk was less important in the decision-making process than the clinical condition and prognosis of the patient for physicians from all specialties, however palliative physicians were in general more reluctant to prescribe LMWH even in a patient with a moderate performance index.

Factors determining physician reluctance to use thromboprophylaxis in SPC units

As discussed previously, the reluctance of palliative physicians to prescribe LMWH is largely based on the concept that symptomatic VTE is not prevalent in their patients, coupled with the fact that there is a lack of evidence specific to palliative care regarding the burden of associated symptoms. In addition, Noble et al. found that many hospice directors regarded thromboprophylaxis as an intervention aimed to prevent sudden death from PE and, thus, a life-prolonging therapy. Consequently, such therapy was considered by some physicians to be at odds with the palliative care philosophy, or inappropriate on the grounds of futility. Furthermore, some physicians expressed the view that death from PE was a less distressing mode of death than from other causes.
Noble and Finlay also found that physicians were concerned that the once daily injections were invasive, could result in pain and bruising, and thus could compromise quality of life. Caution regarding adverse effects such as bleeding did not appear to be a major factor in the decision-making process around thromboprophylaxis. This attitude is supported by current evidence that LMWH thromboprophylaxis is a safe intervention.

Reliable cost–benefit analysis regarding the use of primary thromboprophylaxis for patients in the palliative setting is difficult given the limited amount of available evidence. Chambers calculated that the drug costs of one particular hospice would increase by 28% if LMWH were administered to all immobile cancer patients.

**Patients’ attitudes to thromboprophylaxis**

Since outcome measures for studies in palliative care focus on quality of life, the viewpoints of patients and their carers are crucial in assessing the effectiveness of interventions. In this context, hospice inpatients have been shown to consider LMWH an acceptable intervention for primary thromboprophylaxis.

A detailed semi-structured interview performed by Noble et al., with 28 SPCU inpatients who had all received LMWH for at least five consecutive days reported overall acceptability of the intervention. This group consisted of both patients with a previously good performance status who had a sudden deterioration due to acute spinal cord compression, and patients admitted for symptom control in the context of a more progressive decline in performance status. All patients had an ECOG score of 4 at the time of interview, and had good insight into their prognosis. Sites of primary disease were: breast (seven patients), prostate (three patients), lung (three patients), ovarian (three patients), colorectal (four patients), brain (one patient) and uterine (one patient); and all patients had experienced a combination of surgery, radiotherapy and chemotherapy. Twenty-one patients had not previously received LMWH thromboprophylaxis prior to this admission (three had previously received LMWH, four had received LMWH and anti-embolic stockings and four had worn anti-embolic stockings). Bruising was considered a negative side effect, however all found LMWH an acceptable intervention. LMWH was also considered to be a more acceptable intervention than anti-embolic stockings, which were found to be uncomfortable by those who had worn them.

Patients expressed fear regarding further complications and associated symptoms, and were unsurprisingly open to any proactive measures, which could optimize quality of life. In addition several expressed the desire to stay alive long enough to achieve certain goals or witness important events, such as the marriage of a daughter. This was especially relevant for the patients who had suffered a sudden deterioration as a result of acute spinal cord compression. Furthermore, patients recognized thromboprophylaxis as part of normal practice, and felt reassured that medical staff had not ‘given up on them’. Several patients expressed their need to be involved in decision making around interventions or treatment, and some expressed distress that major decisions regarding their medical care had been made in the past without their involvement.

While all patients understood their risk of VTE, and cited immobility and surgery as risk factors, their understanding of the consequences of clinical thrombosis was limited. Most patients focused on the potential for death, and as a result viewed LMWH positively as they thought it would prolong survival. No patients were aware of other symptoms of VTE. In addition, the patients included in this study had already implicitly given consent to LMWH, and were therefore a somewhat self-selected group.

This data supports previously published work in which patients have been shown to consider LMWH an acceptable intervention even for extended durations of time for the treatment of VTE. A short interview with 40 inpatients in the palliative setting who had received LMWH within the previous 4 weeks demonstrated that 97.5% considered therapeutic LMWH an acceptable intervention. Bruising was reported by 22.7% and 20% reported discomfort during injections, leading to discontinuation of the LMWH in one patient. However, no patient described experiencing dread or anxiety related to the injections.

**Changing attitudes**

As discussed above, there is accumulating evidence that palliative physicians are becoming more receptive to the potential use of thromboprophylaxis in SPC units. Of 12 hospice directors surveyed in 2008, all were amenable to a change in practice if evidence suggested it would improve patient care using relevant outcome measures. Another important finding from recent studies analysing the changing attitudes of palliative physicians was the marked increase (to 20%) in physicians who would take the patients’ preferences into account when making a decision whether or not to discontinue LMWH.

Since 1989, palliative care has been formally recognized as a medical specialty, and training is now structured through the Royal College of Physicians in the UK. A growing awareness of VTE within the specialty may be attributable in part to more physicians entering the specialty from an acute medical background.
Moreover, practice within the specialty has altered significantly over the last decade, with interventions such as intravenous fluids and antibiotics becoming increasingly commonplace. In addition the profile of hospice inpatients has changed, with an increasing number of short admissions for respite or rehabilitation with a plan in place for discharge home, rather than admissions specifically for end-of-life care. As the specialty becomes more integrated within acute medicine, and especially oncology, so it may be more influenced by practice in the acute setting.

Discussion

On the basis of the above literature, there is a clear need for further research into the prevalence of VTE in the palliative population of patients, and the associated symptom burden and effect on quality of life. In view of this lack of evidence, it is perhaps not surprising that clinical practice is variable across SPC units, and that many units do not have guidelines in place. Reasons for this are multifactorial, and include the perception by physicians working in palliative care that VTE is not prevalent; does not impose a significant symptom burden; and does not adversely affect quality of life. Concerns regarding implementation of primary thromboprophylaxis are focused on the concern that daily injections would impose a burden, which would outweigh any potential benefit. In addition some physicians consider prophylaxis in the palliative setting to be inappropriate on the grounds of futility. However, the qualitative research performed in particular by Noble et al. provides important insights into the attitudes of both physicians and patients around this topic.

Noble et al. found that patients find LMWH for primary thromboprophylaxis an acceptable intervention, although their understanding of the consequences of VTE was in some cases incomplete. In particular, patients who had experienced a sudden decline in performance status or mobility, due to spinal cord compression or fracture, expressed a desire that further complications be prevented as far as possible, and a wish to be involved in decision making relating to their care. The advent of novel oral anticoagulants may enable effective primary prevention of VTE without daily injections, however further research is required on the safety and efficacy of these agents in patients with cancer.

In patients with advanced cancer the pro-coagulable state will continue to the end of life. However, additional transient risk factors such as immobility or infection may vary on an intermittent basis. Prolonged primary thromboprophylaxis for up to 4 weeks may be considered following surgery in patients with high risk features such as residual cancer or previous VTE. Additional studies are required to determine the optimal duration of LMWH thromboprophylaxis in the palliative setting, and to further evaluate the risks associated with prolonged anticoagulation, particularly in elderly patients and those with central nervous system (CNS) malignancies. It is accepted that thromboprophylaxis should be withdrawn in the terminal phase, or when the Karnofsky score is less than 10, regardless of the thromboembolic risk.

On the basis of the evidence outlined above, we can conclude that a policy supporting the blanket use of primary thromboprophylaxis would clearly be inappropriate. However, it may be equally inappropriate not to consider appropriate thromboprophylaxis in patients who may be expected to make a partial recovery from an acute event. Thus, careful consideration of the risks of VTE and potential benefits of thromboprophylaxis need to be balanced against possible negative effects on quality of life. More research is needed to determine the actual burden of symptoms imposed by VTE on patients in receipt of palliative care. In particular, there is a paucity of research on the topic using specific outcome measures relevant to the palliative population. The studies covered in this review vary in their quality and robustness. Weber et al., Soto Cardenas et al., Kirkova and Fainsinger, compared primary thromboprophylaxis to best supportive care, were small in size and underpowered, highlighting the difficulty of performing research, and the underlying reasons for the relative lack of evidence, in this area. However, the qualitative research performed in particular by Noble et al. and by Kierner et al. provides important insights into the attitudes of both physicians and patients around this topic.

In this context, guidelines should be drawn up in SPC units where possible. Where guidelines are formulated, they should focus on enabling individualized decisions with consideration of relative risk and burden of treatment. In particular, guidelines should advocate a tailored approach, focusing on identifying patients with a previously good performance status, who have experienced an acute event such as spinal cord compression or a pathological fracture, and in whom a return to mobility may be expected. In this group of patients, who have a transiently increased risk of VTE, it would be appropriate to implement primary thromboprophylaxis, taking into account any possible contraindications, in the current absence of an evidence base to suggest otherwise. Duration of anticoagulation should be decided upon implementation. Anticoagulation should not be continued indefinitely, and should certainly be discontinued in the terminal phase. Clearly, education of both specialist palliative care physicians and physicians working in other fields dealing with patients with palliative care...
needs should be ongoing. Use of primary thromboprophylaxis should be audited regularly and practice should be reviewed as further evidence specific to the palliative care setting becomes available.

References


