
Russell D. Hull1; Grace Townshend2

1University of Calgary, Calgary, Alberta, Canada; 2Watermeadow Medical, Witney, UK

Summary

This article reviews updated evidence-based knowledge on long-term treatment of deep-vein thrombosis (DVT) with low-molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs). Eleven trials were identified comparing the two treatments in a broad spectrum of patients with DVT and with >100 study participants. Four comparative trials were identified in patients with cancer and DVT (in whom anticoagulation treatment is more complex and bleeding complications more frequent). In the 11 trials in broad patient populations, LMWHs were as effective as VKAs in preventing recurrent venous thromboembolism (VTE), and there were no consistent differences in the incidence of bleeding complications during long-term treatment. In patients with cancer, VTE recurrence was significantly reduced with LMWH versus VKA in two studies, while major bleeding complications did not differ between groups in any of the four trials. Current evidence-based European and American guidelines recommend LMWH over VKA for the long-term treatment of DVT in patients with cancer. LMWH and VKA are recommended over the new oral anticoagulant drugs, for which there are limited data on use in long-term treatment. Post-thrombotic syndrome (PTS), a common complication of DVT, causes considerable morbidity. Long-term use of tinzaparin reduced the risk of PTS compared with VKA in one trial, and a meta-analysis of nine studies in total demonstrated a consistently favourable effect of LMWHs versus VKA on PTS-related outcomes. Given the limited treatment options available for PTS, this suggests that LMWH provides a useful therapeutic option in any patient particularly at risk of developing PTS.

Keywords

Deep-vein thrombosis, low-molecular-weight heparin, tinzaparin, post-thrombotic syndrome

Background

It is well established that patients who have experienced a deep-vein thrombosis (DVT) should receive anticoagulation therapy for at least three months in order to prevent recurrence (1). Traditionally, the choice for long-term treatment of DVT has been initial acute therapy with unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) followed by treatment with vitamin K antagonists (VKAs) for at least three months. With long-term VKA therapy, however, there is a requirement for frequent international normalised ratio (INR) monitoring and the risk of haemorrhagic complications. Other options for the long-term management of patients with DVT are therefore needed in order to prevent recurrence of venous thromboembolism (VTE), particularly in patients at high risk of bleeding.

Although subcutaneous LMWH is now widely accepted as the preferred treatment for acute DVT (1), there is still debate over whether these products are preferable to VKAs for longer-term treatment. A Cochrane Database Review of the available data in 2002 reported that long-term use of LMWH reduced the risk of bleeding compared with VKAs, and that LMWHs were possibly as effective as VKAs in preventing DVT recurrence (2). An update of this Cochrane review, published while the current manuscript was being finalised, came to similar conclusions (3). In addition, as more data are published regarding long-term use of the new oral anticoagulants (dabigatran, rivaroxaban), the possible benefits and challenges of these therapies will need to be compared with those previously available.

The aim of this article is to review updated evidence-based knowledge on long-term treatment of DVT with LMWH or VKA, in all patients and also separately in those with cancer. In addition to the traditional outcomes of recurrent VTE and bleeding, we will also consider post-thrombotic syndrome (PTS) and patient treatment satisfaction.

Long-term treatment with LMWH or VKA in a broad spectrum of patients with DVT

The most widely consulted guidelines on the prevention and treatment of DVT are those of the American College of Chest Physicians (ACCP), which were updated in 2012 (1). European guidelines...
lines were issued in the form of an International Consensus Statement in 2006 (4). The ACCP defines long-term treatment of DVT as treatment lasting between seven days and three months, while treatment for a period longer than three months is referred to as extended treatment (1). For clarity in this article, however, we have referred to all trials of three months or longer as ‘long-term’. The primary goal of long-term treatment is to ensure complete resolution of the initial DVT and to prevent new episodes of DVT from occurring.

A number of trials have been conducted comparing LMWH and VKA in the long-term (up to six months) treatment of VTE. The current article is a narrative review in which we sought to identify all trials comparing prospective, randomised treatment of DVT using long-term (≥ 3 months) treatment with LMWH versus VKA, in broad populations or limited to cancer patients, as follows: all trials identified in an earlier systematic review search (5) formed the basis of our selection (including trials that did not report outcomes relevant to PTS). We searched for any more recent trials using PubMed in English and by checking against the reference list of Kearon et al. 2012 (1).

We identified 11 trials published to date (as of April 2012), which included a broad spectrum of patients with DVT (i.e. not li-

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**Table 1: Trials of LMWH versus VKA for the long-term treatment of VTE in a broad spectrum of patients (6–16).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration of therapy (months)</th>
<th>Recurrent VTE (%)</th>
<th>p-value</th>
<th>Bleeding complications (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pini et al. 1994 (6)</td>
<td>Enoxaparin 4000 U od (n=93)</td>
<td>Warfarin (n=94)</td>
<td>3</td>
<td>LMWH 6.5</td>
<td>NS</td>
<td>LMWH 4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Das et al. 1996 (7)</td>
<td>Dalteparin 5000 U od (n=50)</td>
<td>Warfarin (n=55)</td>
<td>3</td>
<td>LMWH 10.0</td>
<td>NS</td>
<td>LMWH 0.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Lopaciuk et al. 1999 (8)</td>
<td>Nadroparin 85 IU/kg bd for 10 days, then od (n=101)</td>
<td>Acenocoumarol (n=101)</td>
<td>≥3</td>
<td>LMWH 2.0</td>
<td>NS</td>
<td>LMWH 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Gónzalez-Fajardo et al. 1999 (9)</td>
<td>Enoxaparin 4000 U bd for 7 days, then od (n=85)</td>
<td>Warfarin (n=80)</td>
<td>3</td>
<td>LMWH 9.5</td>
<td>&lt;0.05</td>
<td>LMWH 1.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Veiga et al. 2000 (10)</td>
<td>Enoxaparin 4000 U od (n=50)</td>
<td>Acenocoumarol (n=50)</td>
<td>3–6</td>
<td>LMWH 4.0</td>
<td>NS</td>
<td>LMWH 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>López-Beret et al. 2001 (11)</td>
<td>Nadroparin 0.1 ml/10 kg bd (n=81)</td>
<td>Acenocoumarol (n=77)</td>
<td>3–6</td>
<td>LMWH 2.5</td>
<td>NS</td>
<td>LMWH 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Kakkar et al. 2003 (12)</td>
<td>Bemiparin 115 IU/kg od for 10 days then 3500 IU od (n=94; Group C)</td>
<td>Acute-phase UFH then VKA (n=98; Group A) or acute-phase bemi-parin then VKA (n=105; Group B)</td>
<td>3</td>
<td>LMWH 2.9</td>
<td>NS</td>
<td>LMWH 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Daskalopoulos et al. 2005 (13)</td>
<td>Tinzaparin 175 IU/kg od (n=50)</td>
<td>Acenocoumarol (n=52)</td>
<td>6</td>
<td>LMWH 4.0</td>
<td>NS</td>
<td>LMWH 10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hull et al. 2007 (14)</td>
<td>Tinzaparin 175 IU/kg od (n=369)</td>
<td>Warfarin (n=368)</td>
<td>3</td>
<td>LMWH 8.9%</td>
<td>NS</td>
<td>LMWH 13.0</td>
<td>0.011</td>
</tr>
<tr>
<td>Hull et al. 2009 (15)</td>
<td>Tinzaparin 175 IU/kg od (n=240)</td>
<td>Warfarin (n=240)</td>
<td>3</td>
<td>LMWH 3.3</td>
<td>NS</td>
<td>LMWH 9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Romera et al. 2009 (16)</td>
<td>Tinzaparin 175 IU/kg od (n=119)</td>
<td>Acenocoumarol (n=122)</td>
<td>6</td>
<td>LMWH 4.2</td>
<td>NS</td>
<td>LMWH 0.8%</td>
<td>NS</td>
</tr>
</tbody>
</table>

All trials enrolled patients with DVT. Some trials included patients with pulmonary embolism in addition to DVT. Values show incidence at end of treatment period unless stated otherwise. Values were taken from or calculated from data in the published reports (based on ITT populations). Definitions of bleeding complications differed between studies but values shown here include major and minor bleeds unless stated otherwise. a LMWH doses during the long-term phase were as follows: <50% of therapeutic dose: Pini et al. (6), Das et al. (7), Gónzalez-Fajardo et al. (9), Veiga et al. (10), Kakkar et al. (12); >50% of therapeutic dose: Lopaciuk et al. (8), López-Beret et al. (11); Therapeutic dose: Daskalopoulos et al. (13), Hull et al. 2007 (14), Hull et al. 2009 (15), Romera et al. (16).

In each case, UFH or LMWH was used for initial therapy in the comparator arm, with oral anticoagulation starting on day 1 or later. b Initial therapy was with UFH for 10 days. c Patients were aged ≥75 years. d Dosage reported as 10.25 anti-Xa IU/mL in syringe, given at 0.1 mL/10 kg od if therapy continued after 3 months. e Major bleeds only; minor bleeding occurred in 4.9% of the LMWH group and 0% of the VKA group. f Values at 12-month follow-up. g At 3 months, rates were 4.9% (LMWH) and 5.7% (VKA) (NS). h Major bleeds only, bd, twice daily; DVT, deep-vein thrombosis; ITT, intention to treat; LMWH, low-molecular-weight heparin; NS, non-significant; od, once daily; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
An updated meta-analysis of the published evidence, included in

evidence have been conducted to compare the data across trials.

rare to use prophylactic doses of LMWH as an alternative to VKA

and prophylactic doses, and that, in patients with cancer, prophy-

cacy’ (2). Furthermore, a meta-analysis of studies using different

doses of LMWH. Since the earlier studies using prophylactic doses

With the exception of one study of enoxaparin (9), in which

LMWH showed significantly greater efficacy than VKA, no sig-
nificant difference was seen between LMWH and VKA in the pre-

vention of recurrent VTE during long-term treatment. Overall,

there was a low incidence of major bleeding events in all treatment

groups. A few studies demonstrated a significant benefit (p<0.05)

with LMWH over VKA with respect to incidence of bleeding com-

plications (6, 9, 14), while the remainder showed no significant
difference between the two treatments.

Table 1 includes studies that used prophylactic or therapeutic
doses of LMWH. Since the earlier studies using prophylactic doses
were performed, a Cochrane review concluded that low doses may
improve the safety of treatment, but ‘have an inverse effect on effi-
cacy’ (2). Furthermore, a meta-analysis of studies using different
doses of LMWH in the long-term treatment of VTE concluded that
full-dose LMWH for 3–6 months is as safe as intermediate and
prophylactic doses, and that, in patients with cancer, prophyl-
lactic doses rather than full treatment doses may incur additional
recurrences after treatment is stopped (17). In current practice it is
rare to use prophylactic doses of LMWH as an alternative to VKA
in patients with VTE (1).

Over the past few years, several meta-analyses of the available
evidence have been conducted to compare the data across trials.
An updated meta-analysis of the published evidence, included in
the recently updated ACCP guidelines, included only studies in
which LMWH was administered at ≥ 50% of the full therapeutic
dose (1). The overall relative effects and anticipated absolute ef-
fects are shown in Table 2 (1). This analysis reported the following
risk ratios and confidence intervals (CI) with LMWH com-
pared with VKA: recurrent VTE (0.62 [95% CI 0.46–0.84]), major
bleeding (0.81 [0.55–1.2]) and death (0.96 [0.81–1.13]).

Although this updated meta-analysis showed a significant re-
duction in risk of VTE with LMWH, the ACCP guidelines cur-
rently recommend VKA therapy over LMWH for long-term treat-
ment in patients with DVT of the leg and no cancer (1). In form-
ing these recommendations, the ACCP Guidelines Committee
took a number of factors into account including quality of the evi-
dence, patient preference and the size of the difference in efficacy.
Reasons given for the decision not to recommend LMWH over
VKA were as follows: evidence was not of a high enough quality
(the authors particularly noted the lack of blinded studies and a
potential for bias in the reporting of recurrent VTE), a small abso-
olute reduction in recurrent VTE events for patients with no cancer,
the higher cost of LMWH compared with VKA, and their assess-
ment that LMWH is a greater burden to patients than VKA ther-
apy due to the need for subcutaneous injections rather than oral
administration (1) (this last point is discussed further below).
These recommendations are in line with a greater consideration
of patient preference in the development of this version of the guide-
lines.

Similarly, the European guidelines recommend initial therapy
of DVT with LMWH, followed by warfarin for three months or
longer (4). It should, however, be noted that these guidelines have
not been updated since 2006, although an update is expected in
2013.

Two new meta-analyses were published while the current ar-
ticle was being finalised. The first was a Cochrane Database Re-
view update of the 2002 Cochrane review (2, 3). This update in-
cluded some small studies that were not analysed by the ACCP,
and excluded studies limited to cancer patients. The findings dif-

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Participants, n (studies)</th>
<th>Quality of the evidence</th>
<th>Relative effect: risk ratio (95% CI)</th>
<th>Subpopulation</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk with VKA per 1,000 population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk difference with LMWH per 1,000 population (95% CI)</td>
</tr>
<tr>
<td>Death</td>
<td>2496 (7 studies)</td>
<td>Moderate due to imprecision</td>
<td>0.96 (0.81–1.13)</td>
<td>–</td>
<td>164</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2727 (8 studies)</td>
<td>Moderate due to risk of bias</td>
<td>0.62 (0.46–0.84)</td>
<td>No cancer</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-metastatic cancer</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metastatic cancer</td>
<td>200</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2737 (8 studies)</td>
<td>Moderate due to imprecision</td>
<td>0.81 (0.55–1.2)</td>
<td>No cancer or non-metastatic cancer</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metastatic cancer</td>
<td>80</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; CI, confidence interval; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
ffered from those of the ACCP; in that bleeding was significantly lower with LMWH compared with VKA, with an odds ratio of 0.50 (95% CI: 0.31, 0.79). Other outcomes did not differ significantly: the odds ratios for recurrent VTE were 0.82 (95% CI: 0.59, 1.13), and for death, 1.06 (95% CI: 0.74, 1.54). The authors suggest that LMWH is possibly a safe alternative in some patients, but point out that it costs more than VKA.

A new meta-analysis of five trials comparing tinzaparin with VKA in the long-term treatment of VTE was also published recently (18). These included the four trials with tinzaparin that are shown in Table 1, plus an additional trial in patients with pulmonary embolism (19). In the overall population, VTE recurrence was similar in the two treatment groups, but in patients with cancer, recurrent VTE was lower with tinzaparin compared with VKA. These results for tinzaparin are in line with the results for LMWHs overall.

Long-term treatment with LMWH or VKA in patients with DVT and cancer

Patients with cancer who experience a DVT have an increased risk of recurrence, death and bleeding complications compared with patients without cancer (20, 21). Drug interactions, nausea and vomiting, and a number of other consequences of anti-cancer treatments, also make the response to VKA therapy unpredictable in these patients (1). This means that LMWH may provide a viable alternative to VKA in cancer patients who require long-term treatment of DVT.

To date, four trials have been published comparing the use of LMWH or VKA for long-term treatment of VTE specifically in patients with cancer, comprising a total of 571 patients in the combined LMWH treatment groups and 541 receiving VKA (Table 3) (22–25). As with the studies in broad populations, these studies also included acute-phase treatment with LMWH (LMWH arm) or UFH/LMWH, followed by oral anticoagulation from day 1 or later (comparator arm). The larger two of these trials, the benchmark CLOT trial with dalteparin (22) and the Main-LITE cancer trial with tinzaparin (prespecified subgroup analysis of the Main-LITE trial) (24), both found a significant reduction in VTE recurrence with LMWH over VKA (p=0.002 and p=0.044, respectively). The remaining two studies found no significant difference in the incidence of recurrent DVT between the two treatments. There was no significant difference between LMWH and VKA in the incidence of major bleeding complications in any of the trials.

One further large trial comparing the use of LMWH (tinzaparin) or VKA in patients with DVT and cancer (CATCH trial, www.clinicaltrials.gov/ct2/show/NCT01130025) is currently in progress. Results from this study will add to the currently available evidence in this patient population.

A recent Cochrane review reported results for pooled analyses of the four trials listed in Table 3 (26). The authors concluded that long-term LMWH significantly reduced recurrent VTE compared with VKA in patients with cancer (hazard ratio 0.47; 95% CI

Table 3: Trials of LMWH versus VKA for the long-term treatment of VTE in cancer patients (22–25).

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventiona</th>
<th>Comparatorb</th>
<th>Duration of therapy (months)</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 2003 – CLOT trial (22)</td>
<td>Dalteparin 200 IU od for 1 month, then approx 150 IU/kg (n=336)</td>
<td>Warfarin or acenocoumarol (n=336)</td>
<td>6</td>
<td>LMWH 8.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Meyer et al. 2002 – CANTHANOX trial (23)</td>
<td>Enoxaparin 1.5 mg/kg od (n=67)</td>
<td>Warfarin (n=71)</td>
<td>3</td>
<td>LMWH 10.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Hull et al. 2006 – Main-LITE – Cancer trial (24)</td>
<td>Tinzaparin 175 IU/kg od (n=100)</td>
<td>Warfarin (n=100)</td>
<td>3</td>
<td>LMWH 7.0</td>
<td>0.044</td>
</tr>
<tr>
<td>Deitcher et al. 2006 – ONCENOX trial (25)</td>
<td>Enoxaparin 1 mg/kg bd for 5 days then 1 mg/kg od (n=32, group 1a) Enoxaparin 1 mg/kg bd for 5 days then 1.5 mg/kg od (n=36, group 1b)</td>
<td>Warfarin (n=34)</td>
<td>6</td>
<td>LMWH (1a) 3.4 LMWH (1b) 3.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

For the study by Hull, DVT was an inclusion criterion; patients with pulmonary embolism in addition to DVT were also included. In the other studies, patients with either a DVT or pulmonary embolism were enrolled. Values show incidence at end of treatment period unless stated otherwise. LMWH doses were as follows: Therapeutic for 1 month, then 75% of therapeutic: Lee et al. (22); Therapeutic throughout study: Meyer et al. (23), Hull et al. (24), Group 1b in Deitcher et al. (25); Therapeutic for 5 days, then modified reduced dose: Group 1a in Deitcher et al. (25). In each case, UFH or LMWH was used for initial therapy in the comparator arm, with oral anticoagulation starting on day 1 or later. Values are for a combined endpoint of recurrent VTE or major bleeding. Values at 12-month follow-up. At 3 months, rates were 6.0% (LMWH) and 10.0% (VKA) (NS). bd, twice daily; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; NS, non-significant; od, once daily; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism. |
0.32 to 0.71). For bleeding, the results did not exclude a beneficial or harmful effect.

In line with the evidence outlined above, both the ACCP guidelines (1) and ‘hot-off-the-press’ guidelines from a European International Consensus Working Group (27) recommend LMWH over VKA for long-term therapy of patients with DVT of the leg and cancer. The ACCP recommendation is based on the large absolute reduction in recurrent VTE with LMWH compared with VKA (Table 2) and the fact that LMWH is better suited than VKA to the care of patients with cancer. The International Consensus Working Group concludes that, on the basis of several meta-analyses of trials in cancer patients, the use of LMWH in what they term ‘early maintenance treatment’ (10 days to 3 months) and long-term treatment (beyond 3 months) significantly reduces the risk of VTE recurrence compared with short-term UFH/LMWH followed by VKA (27). These guidelines are concordant with others from national and international cancer associations (e.g. ASCO, ESMO), which also recommend the use of LMWH rather than VKA for long-term treatment of patients with cancer and DVT (28, 29).

Despite such a strong consensus that long-term LMWH should be used in patients with cancer and DVT, guidelines are not always followed in clinical practice. One study of the implementation of treatment guidelines found that, of a population of cancer patients receiving long-term treatment for VTE, 64% were being treated with VKA rather than the guideline-recommended LMWH for long-term therapy (30). Oncologists may refrain from prescribing LMWH due to concerns over the risks of adverse events and a belief that patients with cancer will have low acceptance and tolerance of injecting LMWH (31). However, patients’ acceptance of injections may be greater than their physicians estimate it to be (see ‘Treatment satisfaction’ below).

Use of the new oral anticoagulants for long-term treatment of DVT

In the past few years, several new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have come onto the market. To date, very limited data are available regarding the long-term treatment of DVT with these drugs. At present, only one study of dabigatran (32) and one of rivaroxaban (33) in the long-term treatment of DVT have been published, and one study of rivaroxaban in the long-term treatment of PE (34).

In a six-month randomised trial, dabigatran demonstrated non-inferiority versus warfarin in preventing recurrence of VTE (dabigatran 2.4% vs VKA 2.1%, p<0.001 for the pre-specified non-inferiority margin), and a similar occurrence rate of major bleeding episodes (dabigatran 1.6% vs warfarin 1.9%) (32). In the DVT study for rivaroxaban, non-inferiority to VKA was demonstrated with regard to the incidence of recurrent VTE (rivaroxaban 2.1% vs VKA 3.0%, p<0.001) (33). A parallel randomised superiority study compared rivaroxaban with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for VTE. No difference in bleeding was seen between the two groups (33).

Although these results bode positively for further investigations of the new oral anticoagulants, due to the relative lack of data compared with those for UFH and LMWH, at present the ACCP guidelines recommend LMWH over dabigatran or rivaroxaban in patients with DVT and no cancer who are not treated with VKA therapy (1). Data on the new oral drugs were not available when the previous European guidelines were issued (4), but it is expected that these drugs will be covered in the updated guidelines, due to be published in 2013.

The data on the use of these drugs in cancer patients with DVT are even more limited. The studies of dabigatran and rivaroxaban in DVT included 4.8% and 7% of randomised patients with cancer, respectively (32, 33), but results were not reported separately for these patients. In their recently published statement, the International Consensus Working Group acknowledged the potential benefit of these new drugs, but considered it premature to issue guidance on their long-term use in patients with VTE and cancer (27). If cancer patients cannot be treated with long-term LMWH, the ACCP guidelines currently recommend VKA over dabigatran or rivaroxaban (1).

Long-term VTE therapy and PTS

PTS is the most common complication of DVT, occurring in 20–50% of patients within two years following a DVT (1, 35, 36). Predictors of a poor outcome in respect of PTS scores over 24 months include signs of PTS at one month post-DVT, DVT of the common femoral or iliac vein, higher body mass index, previous ipsilateral venous thrombosis, older age, and female gender (36). There is no objective test for the detection of PTS; rather, the syndrome is diagnosed on the basis of typical symptoms or clinical signs (37). The most common symptoms of PTS are persistent or intermittent pain, heaviness, swelling, itching, and tingling or cramping in the limb; these are typically aggravated by standing or walking. Typical clinical signs of PTS include oedema, venous ecstasias, hyperpigmentation, eczema and, in severe cases, lipodermatosclerosis and the presence of a venous ulcer. A venous ulcer is the most severe complication of PTS (35, 36). These symptoms can be chronic and lifestyle limiting, and can be very costly to manage; as such, they can have a severe negative impact on the health and quality of life of patients with VTE.

In spite of the prevalence and negative impact of PTS, the condition has not received as much research attention as other complications related to DVT (35). This may be partly because it is not straightforward to diagnose due to the lack of standardised definitions and wide range of symptoms, partly because PTS may not have been reported by end of follow-up, and partly because limited treatment options are available. It is important to reduce the risk of developing PTS by treating the initial DVT in a way that adequately removes thrombus; possibilities include anticoagulation alone (recommended by the ACCP), catheter-directed thrombolysis or systemic thrombolysis (1, 38). It is important that anticoagu-
ulation should be adequate, as shown in a recent study which reported that subtherapeutic anticoagulation with warfarin after a first, unprovoked DVT was significantly associated with the development of PTS (39).

Some of the more recent studies of long-term VTE therapy have investigated the incidence and severity of PTS. These include three studies comparing long-term LMWH versus VKA, which reported the occurrence of clinical signs of PTS as a specific outcome (13, 15, 40–42). Other trials of long-term VTE treatment have also reported PTS-related phenomena (7, 9, 11, 12, 16).

The Home-LITE trial evaluated efficacy and safety outcomes at 12 weeks and one year after treatment of DVT for 12 weeks with once-daily LMWH versus ‘usual care’ (initial LMWH followed by VKA) at home; in addition, the occurrence of PTS and venous leg ulcers and patients’ satisfaction with the given treatment were also assessed (15). After 12 weeks of treatment with either LMWH or VKA, the presence and severity of PTS was assessed using eight different dichotomous (Yes/No) questions regarding the presence or absence of the most common signs and symptoms of PTS. There was a trend favouring tinzaparin over the usual care group for all eight assessments. The overall odds ratio (OR) for the presence of signs/symptoms of PTS was 0.77 (95% CI, 0.67–0.90; p=0.001), with individual ORs ranging from 0.66 for ‘difficulty walking’ to 0.91 for ‘swelling worse at end of day’, all in favour of tinzaparin.

Figure 1: Risk ratios for the presence of venous ulcers (A) and absence of complete recanalisation of thrombosed veins, or complete lysis of thrombus (B), after treatment with long-term LMWH or oral anticoagulation (5). Recanalisation/lysis indicates the degree to which the initial DVT has resolved; a ratio of <1 favours tinzaparin. Both calculated using fixed-effect model. CI, confidence interval; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; OA, oral anticoagulant; Wt, weight. (Reprinted from Hull et al. Am J Med 2011; 124: 756–765, with permission from Elsevier.)
tinzaparin (15). Leg ulcers occurred in 0.5% of patients treated with tinzaparin (1/198) and in 4.1% of patients treated with ‘usual care’ (8/197), returning an OR of 0.12 (95% CI, 0.01–0.97; \( p = 0.02 \)) in favour of tinzaparin. These patient-reported results can be considered reliable because the signs/symptoms are based on items that are now recommended for defining the PTS (37), and because the questionnaire had face validity (15, 43). Furthermore, numerous studies have suggested that self-administered questionnaires on health-related outcomes may be more valid than interviewer-administered ones (44); and that, in some diseases, patient reporting of symptoms is at least as accurate as, or more accurate than, that of clinicians (45–48).

A systematic review of long-term LMWH and PTS found nine published studies that reported PTS-related outcomes for treatment of DVT with LMWH or a comparator drug (5). Due to the different definitions and assessments of PTS signs and symptoms, it was difficult to compare the incidence and severity of PTS across studies. However, results from this analysis showed a clear pattern of benefit with LMWH versus VKA for PTS-related outcomes such as signs and symptoms of the PTS, presence of recanalisation (an indicator of the degree to which the initial DVT has resolved; greater recanalisation may be associated with a lower risk of developing PTS) and degree of reflux (an indicator of valvular damage that may contribute to the PTS) (5). A second study in addition to Home-LITE also assessed the presence of venous ulcers in patients (13); combining these results from the two trials yielded an overall risk ratio for the occurrence of ulcers of 0.13 favouring tinzaparin (95% CI, 0.20–0.71; \( p = 0.019 \)) (5). The meta-analysis results for ulcers and recanalisation are shown in Figure 1.

### Treatment satisfaction

Treatment satisfaction and patient preference are increasingly important factors in both the formulation of treatment guidelines and in physician-prescribing decisions for the treatment of DVT.

Acceptance of LMWH treatment in patients with cancer was investigated in a study in palliative care (49). Effective VKA therapy requires regular monitoring to ensure that a target INR range of 2–3 is maintained (1). The more predictable pharmacokinetics of LMWH mean that these drugs require less monitoring, freeing patients from the requirement of regular laboratory visits. Participants reported optimism regarding therapy with LMWH and a sense of freedom resulting in particular from the lack of requirement for blood testing. Overall, patients found LMWH to be a preferable treatment to VKA (49). Furthermore, Lee et al. reported

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**Figure 2: Patient-reported satisfaction following 12 weeks of therapy with LMWH or VKA in the Home-LITE study (15).** Patients responded to questions on a 5-point Likert scale. These were condensed into three categories (Disagree, Neutral, Agree), assigned values of −1, 0 and +1 respectively (after reversing items where necessary, so that odds values <1 favour tinzaparin and ratios >1 favour usual care). Scores were summed for each subject to obtain an overall satisfaction score per individual, and these were compared between groups. CI, confidence interval; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist. (Reprinted from Hull et al. Am J Med 2009; 122: 762–769 with permission from Elsevier.)
that long-term self-injection of dalteparin was acceptable to patients in the CLOT study (22).

The Home-LITE trial included a questionnaire about items likely to affect treatment satisfaction, administered to all patients at 12 weeks (15). Questions were designed to assess patients’ attitudes towards various aspects of their treatment, such as discomfort associated with treatment and interference with daily life, and were scored on a 5-point Likert scale. The questionnaires for the two groups differed slightly but contained 11 questions in common, which could be compared between the groups. Three questions relating to injections were included only for the tinzaparin group, and four questions relating to changes in drug dosage were included only for the usual-care group. These questions could not be compared across the groups (15).

Patients in the tinzaparin group expressed significantly greater treatment satisfaction than those in the VKA group (p=0.0024), particularly regarding freedom from the inconvenience of blood monitoring (►Figure 2) (15). The method used to compare the groups meant that it was not possible to evaluate the relative ‘burden’ of injections. However, the high treatment satisfaction expressed by patients in the LMWH group suggests that patients value aspects of LMWH therapy and that a preference for oral therapy with VKA should not be assumed as a generalised phenomenon.

Discussion

Results from two published studies and a meta-analysis demonstrate that LMWHs offer clear benefits over VKA for long-term treatment of DVT in patients with cancer by significantly reducing recurrent VTE (1, 22, 24, 26). In these patients, LMWH should be the first choice of DVT therapy. This conclusion is supported by the current European and ACCP guidelines, which both recommend LMWH over VKA for the long-term treatment of DVT in patients with cancer (1, 27).

For patients without cancer who are receiving long-term treatment for DVT, individual studies did not generally show a significant difference between LMWH and VKA in reducing recurrent VTE. However, an updated meta-analysis, which included only studies in which LMWH was administered at ≥50% of the full therapeutic dose, suggested that LMWH reduces the risk of recurrent VTE without increasing the risk of bleeding (1). While LMWH is not the recommended standard option in ACCP guidelines, it offers a useful treatment choice. The ACCP recommendation is based in part on consideration of patient preferences, cost of therapy, and a perceived lack of tolerance for LMWH in patients with VTE (1). There is, however, evidence available showing that patient acceptance of LMWH is high (15, 22, 49), and oral therapy with VKA should therefore not be assumed to be the preferred option. While current guidelines do not recommend the new oral agents, if further evidence confirms their value in long-term treatment, they could play a major role in VTE patients without cancer.

In addition to efficacy in the prevention of recurrent DVT, other factors also have a significant impact on patient health and quality of life during long-term DVT treatment. In particular, attention should be paid to the risk of PTS. The Home-LITE trial showed that long-term use of tinzaparin reduced the risk of PTS compared with usual care and a meta-analysis demonstrated a favourable effect of LMWHs versus VKA on PTS-related outcomes. Given the high morbidity and economic burden of PTS, and the limited options for treating it, this finding would, if confirmed, be an important reason to use LMWH rather than oral anticoagulation.

In light of this evidence, LMWHs are the therapy of choice for long-term treatment in cancer patients, and offer an alternative for any patient whom the clinician feels may be particularly at risk of developing PTS.

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Conflicts of interest

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