NICE guidelines on reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients undergoing surgery

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Summary
Venous thromboembolism (VTE) is most preventable and unacceptably over 25,000 people die of VTE annually in England. The scale of VTE mortality prompted the UK Department of Health to charge the National Institute for Health and Clinical Excellence (NICE) with the task of developing a national guideline for “reducing the risk of VTE in high risk surgical patients”. The VTE guideline development group was tasked to review the effectiveness of methods of prophylaxis in patients undergoing high risk surgical procedures and make recommendations on the most clinically and cost effective measure to reduce VTE in such populations. Systematic reviews and meta-analyses of published randomized trials of mechanical and pharmacological prophylaxis for VTE, as determined by objective methods of screening were primarily considered. Other inclusion criteria comprised of randomised clinical trials of specific types of major surgery deemed to be associated with high incidence of VTE. The studies compared a single method of prophylaxis with nil or another strategy. Clinical trials of mechanical devices used as an adjunct to pharmacological methods were also scrutinised.

All prophylactic strategies reduce the risk of developing post operative DVT compared to no prophylaxis. However, all pharmacological interventions are associated with an increased risk of bleeding. As mechanical methods demonstrate similar efficacy and risk reduction to pharmacological methods and without bleeding complications, they are recommended as first choice of venous thromboprophylaxis. It is also acknowledged that adding a mechanical device to low molecular weight heparin or

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unfractionated heparin in some high risk patients reduces the risk of postoperative DVT more significantly.
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Editor’s comments
It is not often as editor that the Journal of Orthopaedic Nursing presents work in which I have an interest and involvement. This nationally and globally important guideline publication will be of relevance to all orthopaedic nurses.

Introduction
Venous thromboembolism can seriously damage the health of hospitalised patients. It comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) a potentially fatal complication. Post thrombotic syndrome (PTS) is a long term complication of DVT and accounts for 25% of all leg ulcers (Nelzen et al., 1991). VTE accounts for 10% of mortality in the general hospital populations (Sandler and Martin, 1989) and unacceptably, every year over 25,000 people die of VTE in England which is more than 25 times the number who die from Methicillin Resistant Staphylococcus Aureus (MRSA) (House of Commons Health Committee, 2004–2005). However, VTE is most preventable (Autar, 2003). VTE risk assessment and stratification followed by the administration of the appropriate venous thromboprophylaxis, is ranked as the number one best intervention for creating safer health care practices (Shojania et al., 2001).

In response to the House of Commons Health report (2004–2005), the Department of Health commissioned NICE to produce a set of guidelines for the reduction of venous thromboembolism in patients undergoing orthopaedic surgery and other high risk surgical procedures.

Funded by NICE, the guidelines were developed by the National Collaborating Centre for Acute Care (NCC-AC). A multidisciplinary Guideline Development Group (GDG) was set up by the NCC-AC, composed of professional clinicians such as surgeons, anaesthetist, nurses and pharmacist, but all with recognised and specialised experience and patients’ representation and NCC-AC staff. The staff from the NCC-AC provided methodological support, in undertaking systematic searches, retrieval and appraisal of evidence and drafting the guideline. Within the remit of the guidelines, only adult inpatients undergoing VTE high risk surgical procedures listed in Table 1 were covered.

Within the remit of the guidelines, adult inpatients with the following VTE high risk factors were not covered unless they were also undergoing one of the VTE high risk surgical procedures identified in Table 1:

- Patients with acute myocardial infarction.
- Patients with an acute stroke.
- Patients with active cancer, including those treated with chemotherapy.
- Pregnancy and puerperium.
- Oral contraceptives and hormone replacement therapy (HRT).
- Long-distance travel.

Methodology
Systematic reviews and meta-analysis of published randomised clinical trials of mechanical and pharmacological prophylaxis were searched to facilitate the guideline development. Searches of clinical databases were performed using the generic and specific filters, free text terms and the relevant medical subject headings (MESH).

Data sources comprised Medline, Embase, The Cochrane Library (issue 2) and CINHAL searched up to August 2006. Papers identified after this cut off date were not considered. Bibliographies of identified reports and guidelines were screened and VTE experts contacted to identify the relevant literature and reports. The following web sites were accessed to identify additional guidelines and reports:

- Members of the Guidelines International Network’s web sites (http://www.g-i-n.net/).
- National electronic Library for Health (NeLH) (http://www.nelh.nhs.uk/).

Table 1  VTE high risk surgical procedures

<table>
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<th>Procedure</th>
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<tr>
<td>Major orthopaedic surgery</td>
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<tr>
<td>(total hip and knee replacement and hip fracture repair)</td>
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<tr>
<td>Major general surgery</td>
</tr>
<tr>
<td>Major gynaecological surgery</td>
</tr>
<tr>
<td>Major urological surgery, inclusive of open urological procedures</td>
</tr>
<tr>
<td>Neurosurgery</td>
</tr>
<tr>
<td>Cardiothoracic surgery</td>
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<tr>
<td>Major peripheral vascular surgery</td>
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</table>
Clinical recommendations on venous thromboprophylaxis modalities were based on the highest levels of evidence derived from high quality systematic reviews, meta-analyses and robust randomised clinical trials (RCTs). The hierarchy of evidence framework developed by the Scottish Intercollegiate Guidelines Network (SIGN) (2002) was used to steer the NICE guideline development (Table 2).

RCTs of mechanical and pharmacological prophylaxis for DVT confirmed by objective screening methods in patients undergoing one of the high risk surgery listed in Table 1 were the main inclusion criteria. All identified trials were also quality assessed before inclusion.

**Methods of venous thromboprophylaxis**

Methods of venous thromboprophylaxis were evaluated for their efficacy over no prophylaxis, as an adjunct, compared to other prophylaxis or when a combined regimen is used.

**Mechanical methods**

Mechanical methods of prophylaxis include graduated compression stockings, intermittent pneumatic compression devices, foot impulse devices and electrical stimulation. Biophysically, all the mechanical methods of prophylaxis promote venous return and combat venous stasis, which is one of Virchow’s triad in the causation of VTE (Cotton and Roberts, 1977).

**Graduated compression stockings**

Graduated compression stockings (GCSs) exert graded pressure from distal to proximal regions of the leg, increasing blood velocity and promoting venous return. A graduated compression profile of 18 mmHg at the ankle, 14 mmHg at the mid calf, 8 mmHg at the popliteal region, 10 mmHg at the lower thigh and 8 mmHg at the upper thigh, increases deep venous flow velocity by 75% (Sigel et al., 1973).

Two systematic reviews (Amaragiri and Lees, 2000; Roderick et al., 2005) comprising nine RCTs and 1344 participants, conclude that GCSs versus no prophylaxis reduce incidence of DVT by 53%. Wells et al. (1994) reported an overall DVT risk reduction of 68% by GCSs.

A meta-analysis of pooled data from nine RCTs demonstrated that adding GCSs to pharmacological prophylaxis produced a 55% risk reduction of proximal DVT (Kalodiki et al., 1996).

When GCSs are added to intermittent pneumatic devices (IPCDs), Scurr et al. (1987) claim that the combined and simultaneous use of the mechanical devices are more effective in the prevention of postoperative VTE. Incidence of DVT was 9% (7/78) in the non-stockinged legs compared to 1% (1/78) in the stockinged legs combined with IPCD.

Roderick et al. (2005) identified two RCTs (William and Palfrey, 1988; Porteous et al., 1989) comparing the efficacy of thigh over knee length. Meta-analysis of the two studies was inconclusive due to a limited number of reported events. On the other hand, when thigh length stockings were compared with knee length as an adjuvant to LMWH, thigh length reduced the risk of DVT by

<table>
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<th>Table 2</th>
<th>Levels of evidence (Scottish Intercollegiate Guidelines Network (SIGN), 2002)</th>
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<tr>
<td>Level of evidence</td>
<td>Type of evidence</td>
</tr>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a low risk of confounding, bias, or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2−</td>
<td>Case control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Nonanalytic studies (for example case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
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</tbody>
</table>
63% compared to knee length stockings (Howard et al., 2004). However, if thigh length stockings are not appropriate, for reason of fit or compliance, knee length stockings can be used instead (NICE, 2007).

Intermittent pneumatic compression devices

Intermittent pneumatic devices (IPCDs) use garments worn around the legs, which are inflated by a pneumatic pump. The pump produces intermittent cycles of compressed air, which alternately inflate and deflate the chamber garments, enhancing venous return. This mechanical action combats VTE through the dual haemodynamic effects of preventing venous stasis and stimulating fibrinolytic activity. This fibrinolytic mechanism is concerned with the dissolution of clots and prevention of thrombus formation.

A meta-analysis of 18 RCTs with 1990 participants reported that IPCDs reduce the risk of DVT by 56%, but no significant difference between groups for PE (Roderick et al., 2005). As an adjuvant to pharmacological prophylaxis, IPCDs reduce the risk of PE by 57% (Ramos et al., 1996).

The NICE guideline development group identified three RCTs (Hansberry et al., 1991; Ryan et al., 2002; Silbersack et al., 2004), evaluating the efficacy of IPCDs over GCSs. A meta-analysis of the three studies concluded that there is no significant difference between the two groups in the prevention of VTE.

Foot impulse devices

Foot impulse devices (FIDs) promote venous return and prevent stasis. Gardner and Fox (1983) first demonstrated the haemodynamic effect of the pumping mechanism in the sole of the foot activated by weight bearing. On weight bearing, the venous plexus in the sole is rapidly emptied into the deep veins of the legs. It is within this physiological mechanism that the foot impulse technology is designed to pulsate the venous pump artificially by venous plexus compression and simulating normal walking in immobilised patients.

A systematic review undertaken by Roderick et al. (2005) of 2 RCTs, comprising 126 participants concluded that FIDs reduce the risk of DVT by 65%. FIDs are as effective as LMWH for DVT prophylaxis, but without the bleeding complications (Warwick et al., 1998; Warwick et al., 2002). When FIDs are combined with LMWH, incidence of DVT is reduced significantly (Giannoni et al., 2006).

Used as an adjuvant to GCSs, FIDS reduce risk of DVT by 74%, compared with stockings alone (Stannard et al., 1996).

Electrical stimulation

Electrical stimulation (ES) devices are designed to activate the skeletal muscular venous pump and promote venous return, which then prevents stasis (Faghri et al., 1997). Browse and Negus (1970) reported that electrical stimulation reduces the risk of DVT by 59%, in patients’ own experimental and control legs. There is no evidence that ES reduces incidence of PE (Lindstrom et al., 1982). Nicolaides et al. (1983) claim that ES is less effective in reducing of DVT, compared with GCSs and IPCDs.

Pharmacological prophylaxis

Pharmacological prophylaxis includes heparins, warfarin, pentasaccharides and antiplatelets.

Heparins

Heparins are mixture of mucopolysaccharides of different lengths and hence different molecular sizes. Standard heparin is quick acting and is referred to as unfractionated heparin (UFH) to distinguish it from low molecular weight heparin (LMWH). UFH consists of a chain of molecular weight from 5000 to 40,000 Daltons (Da), average being 20,000 Da. Fractionating or depolymerisation of such heparin produces LMWH (average 3000 Da molecular weight) LMWH consists of a short chain of polysaccharides and is long acting, necessitating a daily dose only.

A systematic review by Collins et al. (1988) and 5 RCTs (Ballard et al., 1973; Belshaw et al., 1988; Christensen et al., 1989; Clarke-Pearson et al., 1989; Clarke-Pearson et al., 1990; Killichew et al., 2002) concluded that UFH reduces DVT by 56% and PE by 30%, but also increases the risk of major bleeding by 46%. Although UFH is an effective prophylaxis, it has now been largely superseded by LMWH, due to the ease of administration and the minimal monitoring required by the latter.

Three systematic reviews (Iorio and Agnelli, 2000; Mismetti et al., 2001; Zufferey et al., 2003) and three RCTs (Bergqvist et al., 1996; Wirth et al., 2001; Michot et al., 2002) pooled in 28 studies with 8935 patients considered the efficacy of LMWH over no prophylaxis. It concluded that LMWH reduces the risk of DVT by 51% and PE by 64%. However, LMWH increases the risk of major bleeding by 77% over no prophylaxis.
Pentasaccharides

Fondaparinux sodium is a synthetic pentasaccharide that binds and inhibits coagulation factor Xa. Five RCTs (Bauer et al., 2001; Eriksson et al., 2001; Turpie et al., 2002; Eriksson and Lassen, 2003; Agnelli et al., 2005) comparing efficacy of Fondaparinux over LMWH concluded that Fondaparinux reduces the risk of DVT by 48% compared to LMWH, but detected no significant difference on PE and major bleeding.

Oral anticoagulants

Oral anticoagulants (OACs) are vitamin K antagonists. Antagonism of vitamin K reduces the amount of clotting factors synthesis and therefore produces a state of anticoagulation. Two systematic reviews (Mismetti et al., 2004; Roderick et al., 2005) comprising 1320 participants concluded that OACs reduce the risk of DVT by 51% and PE by 82%, while at the same time increases bleeding risk by 58%.

Aspirin

A systematic review undertaken by the Antiplatelet Trialists’ Collaboration (ATC) (1994), concluded that aspirin as a prophylaxis alone reduces the risk of DVT by 31%. Collins et al. (1994) also concur that aspirin “alone” or “for greater effect” with other proven prophylaxis should be considered in high risk patients. However, the ATC meta-analysis methodology has several limitations. The meta-analysis pooled studies that were small in sample size, old and had significant heterogeneity in combining patients with trauma and the elective orthopaedic surgery group. The unblinded studies scrutinised using unmarketed drugs and drug company internal reports were heavily biased. Only one third of the studies included a group that received aspirin alone and a number of trials found aspirin to be inferior to other forms of prophylaxis. Aspirin is less effective than LMWH: relative risk reduction for LMWH over aspirin is 63% (Graor et al., 1992). In patients randomized to receive either aspirin or danaparoid, VTE was detected in 44% and 27%, respectively (Gent et al., 1996). Due to its overall inferior efficacy as a thromboprophylaxis, aspirin alone is not recommended by both ACCP (2004) and NICE (2007).

The efficacy of pharmacological prophylaxis in terms of VTE relative risk reduction (RRR) and associated bleeding risk are illustrated in Table 3.

Table 3  Efficacy and associated bleeding risk (NICE, 2007)

<table>
<thead>
<tr>
<th>Pharmacological prophylaxis</th>
<th>DVT (RRR %)</th>
<th>PE (RRR %)</th>
<th>Bleeding risk (%)</th>
</tr>
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<tbody>
<tr>
<td>UFH</td>
<td>56</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>LMWH</td>
<td>51</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>Warfarin (OAC)</td>
<td>51</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Aspirin</td>
<td>31</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>Aspirin as adjuvant to UFH</td>
<td>17</td>
<td>–</td>
<td>47</td>
</tr>
<tr>
<td>Fondaparinux v LMWH</td>
<td>48</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Early mobilisation and leg exercises, leg elevation and hydration

Immobility and lack of exercise have long been recognised as risk factors for developing VTE (Gibbs, 1957). It is also generally accepted that early mobilisation and leg exercises prevent venous stasis and subsequently reduce the risk of thrombus formation (Kierkegaard et al., 1987; Lassen and Borris, 1991). Although there are no RCTs identified attesting to the value of mobilisation and leg exercise in reducing VTE risk, on the balance of physiological evidence, NICE (2007) recommends that patients are encouraged to mobilise after surgery and leg exercises undertaken in immobilised patients.

Leg elevation reduces swelling and promotes venous return by its gravitational effect. Only one RCT identified (Rosengarten and Laird, 1971) concludes that there is no significant difference in VTE prevention between leg elevation and no leg elevation.

It is believed that dehydration predisposes to venous thromboembolism. Kelly et al. (2004) found a strong association between dehydration and VTE occurrence in patients with acute ischaemic stroke. It is therefore recommended that patients having surgery should not be allowed to become dehydrated (NICE, 2007).

Summary and discussion

- All patients should be assessed for VTE risk. Evidence based VTE risk factors derived from systematic reviews and meta-analyses (Edmonds et al., 2004) are highlighted in the NICE guidelines to facilitate a clinical decision support system for the uptake of the most appropriate prophylaxis. In fact, the VTE risk factors
significantly mirror the venous thrombogenic risk factors comprising the Autar DVT risk assessment scale (Autar, 2002; Autar, 2003). Acknowledging that the Autar DVT scale is one of the risk assessment models (RAMs) that have undergone the most rigorous testing and produced some promising results, NICE do not recommend any specific RAMs, on the basis that its broad remit covers all high risk surgery, whereas the Autar DVT scale is limited to its application and evaluation in orthopaedics, general surgery and medicine only.

- All patients should be given both written and verbal information about the risk of VTE and the effectiveness of prophylaxis.
- Mechanical prophylaxis is recommended as the first course of action. However, in patients with one or more risk factors, additional to the type of surgery, a combined regimen of mechanical and pharmacological and extended prophylaxis for 4 weeks is strongly advised (Table 4).
- Patients at risk should be offered thigh length compression stockings from admission until they return to their normal level of activity, unless contraindicated. Knee length stockings are acceptable alternative, if thigh length stockings are not appropriate for reasons of fit or compliance.
- IPCDs and FIDs can be considered as alternatives, or in addition to graduated compression stockings.
- Regional anaesthesia reduces the risk of VTE compared with general anaesthesia and its suitability should seriously be considered in some individual patients.
- Four weeks extended prophylaxis with LMWH or Fondaparinux, where licensed, must be considered in patients undergoing hip fracture repair or major elective orthopaedic surgery with one or more related risk factors (Table 4).

Ricky Autar was a working member of the guideline development group and a major contributor to the NICE VTE guidelines.

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