Abstract
Deep vein thrombosis (DVT) is a significant, potentially fatal complication following surgery. Certain orthopaedic procedures, such as hip or knee arthroplasty, present a greater risk of venous thromboembolism (VTE) than others. These surgical risks are further compounded by individual patient risk factors. In the event of a DVT, treatment with low-molecular-weight heparin (LMWH) should be initiated on diagnosis, followed by initiation of oral anticoagulant therapy. Once the LMWH is discontinued, anticoagulation with warfarin should be continued for a period of time, to be determined by assessing the individual’s risk of VTE recurrence.

Introduction
Despite the introduction of pharmacological thromboprophylaxis for deep vein thrombosis (DVT) and pulmonary embolism, venous thromboembolism (VTE) remains a significant complication after surgery.

A DVT is a thrombus (clot) consisting of red blood cells, white blood cells and platelets bound together with fibrin strands, which forms in the venous portion of the vasculature. Although it can involve any vein in the body, it occurs most frequently in the lower limbs, affecting the superficial large veins, deep veins of the calf and likewise those above the knee. A DVT that occurs in deep knee or thigh veins is known as a proximal DVT.

A potentially fatal complication of VTE is pulmonary embolism (PE).

Pathogenesis
Thrombus formation may result when clotting homeostasis is altered by endothelial injury, abnormal blood flow or hypercoagulability.

Statistics
- DVT is common, with an annual incidence of 67/100 000.
- Untreated proximal DVT is associated with a 30-50% risk of PE, as well as a 12% mortality.
- Death occurs within one month of diagnosis in about six per cent of DVT cases.

Risk factors for the development of thromboembolism include:
- Immobility;
- Oestrogen use;
- Surgery/injury;
- Heart disease;
- Age (risk increases with age);
- Malignancy;
- Smoking;
- Inherited disorders, such as Antithrombin III deficiency and protein C deficiency;
- Obesity;
- The peripartum period;
- History of varicose veins;
- Inflammatory bowel disease;
- Splenectomy;
- Chronic lung disease;
- History of DVT or PE;
- Renal transplantation.

In addition, human immunodeficiency virus (HIV) infection is recognised to be a potentially hypercoagulable condition. The rate of VTE in HIV-infected individuals is estimated to be as high as 18%. Currently, most patients treated for VTE in South Africa are HIV positive.

Surgical patients are classified into four VTE risk levels, based on age, type of surgery, duration of surgery, duration of immobilisation and other risk factors. Surgical patients are classified into four VTE risk levels, based on age, type of surgery, duration of surgery, duration of immobilisation and other risk factors. See Table I.

Symptoms
Approximately half of patients with DVT have no symptoms at all. However, those who do have symptoms commonly report swelling, pain, tenderness and redness of the skin at the affected part of the body.

Diagnosis of DVT
Clinical signs and symptoms such as pain, swelling and calf tenderness should not be used to diagnose DVT, but should alert the practitioner to investigate further. The Wells Clinical Prediction Rule for diagnosing DVT is based on a scoring system using signs, symptoms and risk factors. It is frequently used to estimate the probability of DVT before performing more definitive testing. See Table II.
Table I: Classification of surgical risk for venous thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Surgery risk</th>
<th>Risk factors</th>
<th>Approximate deep vein thrombosis risk without prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Surgery duration &lt; 30 minutes Age &lt; 40 years Repair of small fractures</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Age 40-60 years Arthroscopy or repair of lower leg fractures Postoperative plaster cast</td>
<td>10-40%</td>
</tr>
<tr>
<td>High risk</td>
<td>Age &gt; 60 years OR Age 40-60 years, with additional VTE risk factors OR Immobilisation for &gt; four days</td>
<td>40-80%</td>
</tr>
<tr>
<td>Highest risk</td>
<td>Hip or knee arthroplasty Hip fracture repair Repair of open lower leg fractures Major trauma or spinal cord injury Multiple risk factors for VTE (age &gt; 40 years, prior VTE, cancer or hypercoagulable state).</td>
<td>40-80%</td>
</tr>
</tbody>
</table>

Table II: The Wells Clinical Prediction Rule

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within previous six months, or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilisation of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden &gt; 3 days, or major surgery within 12 weeks requiring general or regional anaesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localised tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
<tr>
<td>Probability of DVT: Low ≤ 0, intermediate 1-2, and high ≥ 3</td>
<td></td>
</tr>
</tbody>
</table>

* Tibial tuberosity: a large oblong elevation on the proximal, anterior aspect of the tibia.
* Collateral veins are produced by the body in response to insufficient circulation.

In patients with symptoms in both legs, the more symptomatic leg is used. (Adapted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep vein thrombosis in clinical management. Lancet. 1997;350:1795-1798).4

Further investigation may include:

- Computed tomography venography (CTV);
- Magnetic resonance imaging.

Treatment of DVT

Non-pharmacological measures

- Limb elevation and local application of heat.10
- Minimise activity for several days (limited to walking to the kitchen and bathroom).10
- Graded elastic compression stockings have been associated with a 50% reduced risk of post-thrombotic syndrome. Stockings with a pressure of 30-40 mmHg at the ankle are recommended for use during initial ambulation and for the first two years following an episode of VTE.10,11

Pharmacological measures

The primary objectives of therapy are to prevent clot extension and PE, and to reduce the risk of recurrent VTE.6

Treatment needs to be initiated as soon as possible after diagnosis. Currently available therapeutic options for initial treatment include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin.3 UFH has largely been replaced by LMWH thanks to its improved efficacy, longer biologic half-life, lower incidence of major bleeding, convenient dosing, shorter hospital stay and reduced risk of heparin-induced thrombocytopenia. In addition, LMWH does not require laboratory monitoring.3,10 Refer to Table III for dosing of LMWHs.

Once acute anticoagulation has been achieved, warfarin should be initiated. As a standard, 5 mg warfarin is given on day two of anticoagulation and titrated according to international normalised ratio (INR). INR should be closely monitored, especially in high-risk patients such as those who are malnourished, have a bleeding tendency, heart failure, liver disease, or are elderly.3 The INR should be measured two to
three days after starting warfarin therapy and then daily until stable.\textsuperscript{15} Warfarin should be administered at the lowest effective dose to achieve a therapeutic range of 2-3.\textsuperscript{10,16}

### Table III: Dosing of low-molecular-weight heparins

<table>
<thead>
<tr>
<th>Heparin Name</th>
<th>Dosing Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin sodium</td>
<td>1mg/kg subcutaneously, 12 hourly\textsuperscript{12}</td>
</tr>
<tr>
<td>Dalteparin sodium</td>
<td>200 IU/kg subcutaneously, once daily. (Daily dose should not exceed 18 000 IU)</td>
</tr>
<tr>
<td>Nadroparin calcium</td>
<td>Volume nadroparin subcutaneously twice daily according to weight:\textsuperscript{14}</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 kg 0.4 ml</td>
</tr>
<tr>
<td></td>
<td>50-59 kg 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>60-69 kg 0.6 ml</td>
</tr>
<tr>
<td></td>
<td>70-79 kg 0.7 ml</td>
</tr>
<tr>
<td></td>
<td>80-89 kg 0.8 ml</td>
</tr>
<tr>
<td></td>
<td>90 kg 0.9 ml</td>
</tr>
</tbody>
</table>

Seventy-two hours after initiating LMWH, a platelet count should be completed to assess possible heparin-induced thrombocytopenia. Heparin should be discontinued if the count drops below 100 000 cells/µl or below 50% of the initial count. Heparin should then be substituted with a hirudin derivative such as lepirudin (Refludin®).\textsuperscript{3}

LMWH should be given for at least five to seven days and can be stopped once the INR remains in the therapeutic range for at least two consecutive days.\textsuperscript{15}

Once the LMWH is discontinued, warfarin is continued as the drug of choice for long-term therapy to prevent clot recurrence. However, warfarin therapy is not suitable for all patients:10,17

- Warfarin is contraindicated in pregnancy.
- Patients with cancer may have a lower risk of recurrent thrombosis, if they receive long-term prophylaxis with LMWH, instead of warfarin.
- LMWH should be used long-term in patients who cannot use warfarin.

LMWH is initiated at the recommended dose for the first month, and then reduced to approximately 75% of the initial dose thereafter.\textsuperscript{17}

Once a patient has been stabilised on warfarin, the INR should be assessed every one to four weeks. More frequent monitoring is indicated in patients with an unstable dose response, when medications are changed, or when the patient is ill.\textsuperscript{16}

Deviations in INR outside of the target range should be investigated and the following possibilities considered:16

- Patient compliance and patient error;
- Drug interactions;
- Dietary interactions;
- Renal or liver dysfunction;
- Laboratory error.

**Duration of warfarin therapy in DVT**

The appropriate duration of anticoagulant therapy is determined using a number of factors such as the location of thrombi, whether the thromboembolism was a first-time or repeat occurrence, and the presence or absence of precipitating factors.\textsuperscript{18} See Table IV for guidelines on the duration of warfarin therapy, and Table V for dosage adjustments for patients on maintenance warfarin therapy.

### Table IV: Duration of warfarin therapy\textsuperscript{15}

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with VTE and a reversible risk factor (e.g. surgery or trauma)</td>
<td>At least three months</td>
</tr>
<tr>
<td>Patients with idiopathic DVT</td>
<td>At least six months</td>
</tr>
<tr>
<td>Patients with recurrent DVT or persistent risk factors</td>
<td>&gt; 6 months (however anticoagulant therapy lasting more than two years is associated with an increased risk of bleeding).</td>
</tr>
</tbody>
</table>

Once a patient has suffered an episode of VTE, it should be considered as a chronic disorder due to the risk of recurrence. Patients who have had an episode of DVT or PE have a far greater risk of recurrence than the general population (up to 25% of all cases of VTE occur in those who have previously had VTE). The risk of VTE recurrence is greatest 6-12 months after the initial episode, then decreases with time, but never disappears.\textsuperscript{19}

**New oral anticoagulants for DVT**

Since 1940, warfarin has been the only oral anticoagulant available for the treatment of VTE. Two newly introduced oral anticoagulants, dabigatran (Pradaxa®) and rivaroxaban (Xarelto®), have shown promise in the treatment of DVT.\textsuperscript{3}

The RE-COVER trial concluded that a fixed dose of dabigatran in the treatment of acute VTE is as effective as warfarin, has a similar safety profile and does not require laboratory monitoring.\textsuperscript{20} The results of the Einstein-DVT trial were reported in 2010. The trial showed that oral rivaroxaban is as effective in preventing the recurrence of symptomatic VTE as well-managed patients receiving the standard therapy of LMWH, enoxaparin or fondaparinux, and an oral vitamin K anticoagulant (mainly warfarin).\textsuperscript{21}

**Conclusion**

DVT is a relatively common condition with potentially fatal sequelae. In addition to surgical procedures, several patient factors are associated with an increased risk of DVT. Currently, warfarin is the mainstay of long-term therapy; however newer agents have shown promise and may change the face of DVT treatment in the future.
Table V: Dosage adjustments for patients on maintenance warfarin therapy\textsuperscript{16}

<table>
<thead>
<tr>
<th>International normalised ratio (INR)</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>Increase weekly dose by approximately 20%</td>
</tr>
<tr>
<td>1.5-1.9</td>
<td>Increase weekly dose by approximately 10%</td>
</tr>
<tr>
<td>2-3</td>
<td>None</td>
</tr>
<tr>
<td>3.1-3.9</td>
<td>None, recheck weekly If persisting, decrease weekly dose by approximately 10-20%</td>
</tr>
<tr>
<td>4-5</td>
<td>Skip one dose Decrease weekly dose by approximately 10-20% and recheck in five to seven days</td>
</tr>
</tbody>
</table>

5-9 without significant bleeding

Stop warfarin
Consider low-dose vitamin K 1-2.5 mg per os, monitor and repeat if necessary
Monitor INR every two to three days
Restart warfarin once INR is within target range
Decrease weekly dose by approximately 10-20% and recheck in five to seven days

> 9 without significant bleeding

Stop warfarin
Give vitamin K 5 mg per os, and repeat if necessary
Monitor INR daily
Restart warfarin once INR is within target range
Decrease weekly dose by approximately 20% and recheck in five to seven days
Monitor frequently until stable

Prolonged INR and significant bleeding

Stop warfarin
Give prothrombin complex concentrates (50 U/kg) or fresh frozen plasma (15-20 ml/kg) or Bioplasma FDP\textsuperscript{\textregistered} (fresh human plasma)
Give vitamin K 1-2 mg intravenous injection slowly
Monitor INR daily

References