# Venous Thromboembolism: An Insidious Hazard Part II: Prophylaxis and Treatment

*Venu Chalasani M.B B.S. and Donald G. MacLellan B.Sc., M.D., F.R.A.C.S.*

## Introduction

Venous thromboembolism (VTE) is a relatively common and largely preventable condition, particularly afflicting the hospital population. The long term sequelae of VTE are pernicious, with one study showing that after 8 years, the post-phlebitic syndrome occurred in almost one third of patients following their first deep venous thrombosis [1]. In many of these patients, chronic venous ulceration is a long-term consequence.

In the first review article of this series, the incidence, prevalence and sequelae of VTE were discussed [2]. The incidence of VTE can be considerably reduced by appropriate prophylaxis and thus, hopefully, the sequelae of venous ulceration can also be decreased. This article will review the guidelines for prophylaxis and treatment of VTE.

## Risk of VTE without prophylaxis

Appropriate prophylaxis is dependant on assessing an individual patient's risk for VTE. The risk of VTE is related to predisposing factors as well as the acute problem precipitating the hospital admission. Common predisposing factors include [3]:

- age over 40;
- prior episodes of VTE;
- malignancy;
- obesity;
- hypercoagulable states, and
- immobility or paralysis.

*Venu Chalasani M.B B.S. and*
*Donald G. MacLellan B.Sc., M.D., F.R.A.C.S.*

*Canberra Clinical School*
*University of Sydney*
*The Canberra Hospital*
*PO Box 11 Woden ACT 2606*

*Tel: (02) 6244 3037*
*Fax: (02) 6244 3042*

Hospitalised patients can be subdivided broadly into surgical, orthopaedic, medical and gynaecological groups. It has been increasingly recognised that the risk of VTE varies between these groups.

For orthopaedic patients, both total hip replacement and total knee replacement are considered high risk. Patients with multiple trauma or hip fracture are also considered high risk. There is less data regarding other orthopaedic conditions [4].

In surgical patients, the risk is dependent on the type of surgery (e.g. type of anaesthesia, post operative immobility, major or minor procedure), the presence of sepsis and the level of hydration, in addition to the aforementioned risk factors.

Gynaecological procedures have similar risk levels for VTE as general surgical procedures. However, the risk appears to be less for benign gynaecological and vaginal procedures [5]. Oral contraceptive agents (both low dose estrogen and combined pills) are an additional risk factor.

The number of published studies examining VTE in medical patients is less than those in other specialties, although medical patients have the highest risk [6]. Three out of every four fatal pulmonary emboli in hospital occur in medical patients. Prophylaxis can prevent up to two thirds of DVT in medical patients. The highest risk are those in ICU, those with acute stroke and those with congestive cardiac failure. Moderate risk medical patients include those with nephrotic syndrome, inflammatory bowel disease, respiratory failure, chest infection, heart failure, malignancy and polycythaemia.

Patients generally can be subdivided into low, moderate or high risk groups for VTE whilst in hospital. This risk scale was developed by Salzman and Hirsh in 1982 [7] and a modified version is presented in Table 1.

Low risk patients have a risk of DVT of less than 10 per cent, moderate risk patients 10-40 per cent and high risk patients 40-80 per cent. This risk categorisation will be dependant both on the reason for admission and additional risk factors such as those described above.

**Table 1. Prevalence of venous thromboembolic events according to a patient's level of risk (adapted from Salzman and Hirsch [7]).**

| | Deep vein thrombosis | Proximal vein thrombosis | Fatal pulmonary embolism |
|---|---|---|---|
| **High risk groups** | 40-80 per cent | 10-30 per cent | 1-10 per cent |
| **Moderate risk groups** | 10-40 per cent | 1-10 per cent | 0.1-1 per cent |
| **Low risk groups** | <10 per cent | <1 per cent | 0-0.1 per cent |

## Prophylaxis

There are three main avenues for the addressing the problem of VTE. These are:

- Treat established VTE.
- Screen for VTE.
- Primary prevention of VTE.

Of these available avenues, primary prophylaxis is the most preferable and will be the initial focus of this article. There is a significant reduction in the incidence of VTE with prophylaxis. In general surgery, there is a 67 per cent reduction, orthopaedic surgery 68 per cent and urology 75 per cent. Overall, there is a 68 per cent reduction in VTE in surgical units with prophylaxis.

In the last two decades, many different methods of prophylaxis have been trialled. These include low dose unfractionated heparin (UFH), adjusted low dose unfractionated heparin, low molecular weight heparin (LMWH), warfarin, aspirin, dextran 70, hydroxychloroquine, graduated compression stockings (GCS) and sequential compression devices (SCD).

The currently recommended methods of prophylaxis are based on the International Consensus Statement (1997) [5] and the Australian and New Zealand guidelines for practice [4]. They are UFH, LMWH, GCS and SCD. In certain high risk groups, warfarin is also recommended.

### Low Dose Unfractionated Heparin (UFH)

UFH has been shown in numerous randomised controlled trials to reduce significantly the incidence of VTE [8]. It is usually administered every 12 hours subcutaneously, at a dose of 5000 international units.

The recognised complications of UFH include wound haematomas, heparin induced thrombocytopaenia syndrome (HITS) and local bruising at the site of injection. Advantages include the fact that no anticoagulant monitoring is required and it is relatively inexpensive.

### Low Molecular Weight Heparin (LMWH)

LMWH has been shown in trials to be at least as effective or even more effective than UFH in moderate risk surgical patients and in orthopaedic patients [8]. There have been five trials involving general surgery patients comparing enoxaparin to UFH, all showing similar rates of DVT [9]. The Thrombo-prophylaxis Collaborative Group [10] found both to be equally efficacious, but the incidence of major bleeding episodes was twice as common in the UFH group.

A meta analysis by Mismetti [11] involving medical patients compared LMWH to UFH and found no significant difference in the incidence of DVT or PE. There was, however, a 52 per cent reduction in the risk of major haemorrhage with LMWH. The advantages of LMWH (Table 2) include once daily administration and lower rates of bleeding [11]. It is, however, more expensive than UFH.

**Table 2. Clinical advantages of low molecular weight heparins (LMWH) compared with un-fractionated heparin (UFH) [12].**

- Similar or improved efficacy
- A lower incidence of bleeding complications
- A lower incidence of heparin-induced thrombocytopaenia syndrome (HITS)
- Increased bioavailability (almost complete following subcutaneous administration)
- Substantially reduced interindividual variation
- Reduced dosing frequency
- No need for laboratory monitoring
- Increased convenience and patient acceptability
- A greater potential for outpatient use

### Graduated Compression Stockings (GCS)

GCS have been shown to reduce the risk of DVT [13]. They are also relatively inexpensive and easy to use. Studies have also shown that they are effective when used in combination with other prophylactic methods [14]. They are contraindicated in patients with significant peripheral vascular disease.

### Sequential Compression Devices (SCD)

These devices provide intermittent pneumatic external compression of the lower limbs. They work by increasing blood flow in the deep veins of the legs and by increasing fibrinolytic activity thereby thought to reduce fibrin levels and risk of clot formation. They have no significant side effects and so are useful in patients in whom other forms of prophylaxis may be contraindicated. Like GCS, they are contraindicated in patients with significant peripheral vascular disease. Recently, foot compression devices have become available which also have been shown to effectively improve venous return, but whether they prevent DVT formation is unknown.

### Warfarin

Warfarin, an oral anticoagulant, has been shown to be effective in both gynaecological and orthopaedic patients. However, warfarin has a higher risk of bleeding compared with other pharmacological options and requires daily haematological monitoring [6].

## Recommendations for prophylaxis

The following recommendations are from the current guidelines for practice in Australia and New Zealand (Tables 3, 4, 5) [4]. Patients have been conveniently categorised as medical, surgical or orthopaedic.

Despite these current recommendations, VTE remains a significant cause of morbidity and mortality. This is because prophylaxis only decreases the risk, without expunging it. In certain high risk patients (e.g. trauma and orthopaedic surgery), this risk of VTE may be as high as 45 per cent, despite strict adherence to the above guidelines [15].

## Duration of prophylaxis

The optimum duration of prophylaxis has yet to be established. Currently, prophylaxis ends when the patient is discharged from hospital. The risk, however, carries on beyond the immediate post-operative period [16].

**Table 3. Recommended prophylaxis in medical patients.**

| Risk category | Clinical features | Recommended prophylaxis |
|---|---|---|
| **High** | • Age >70 years<br>• Stroke<br>• Presence of shock<br>• History of DVT/PE<br>• Congestive cardiac failure<br>• Thrombophilia | Low-dose subcutaneous heparin and GCS, SCD |
| **Moderate** | • Immobilised patient with acute disease<br>• Cardiac failure | Low-dose subcutaneous heparin or GCS, SCD |
| **Low** | • Minor medical illness | Early ambulation and adequate hydration; consider GCS, SCD |

**Table 4. Recommended prophylaxis in surgical patients.**

| Risk category | Clinical features | Recommended prophylaxis |
|---|---|---|
| **High** | • Major surgery & age >60 years<br>• Major surgery & age 40-60 years with cancer or history of DVT/PE<br>• Thrombophilia | Low-dose subcutaneous heparin and GCS, SCD |
| **Moderate** | • Major surgery & age 40-60 years without other risk factors<br>• Minor surgery & age >60 years<br>• Minor surgery & age 40-60 years with history of DVT/PE or on oestrogen therapy | Low-dose subcutaneous heparin or GCS, SCD if heparin contraindicated |
| **Low** | • Major surgery, age <40 years & no risk factors<br>• Minor surgery & age 40-60 years with no other risk factors | Early ambulation & adequate hydration; consider GCS, SCD |

**Table 5. Recommended prophylaxis in orthopaedic patients.**

| Condition | Average risk of DVT without prophylaxis | Prophylaxis |
|---|---|---|
| • Elective hip - replacement | 51 per cent | LMWH & GCS, SCD |
| • Hip fracture | 45 per cent | |
| • Total knee replacement | 47 per cent | |
| • Multiple trauma | 50 per cent | Subcutaneous heparin (if low risk of bleeding) and GCS, SCD |

A study by Bergqvist [17] involving 232 patients undergoing total hip replacement, compared prophylaxis for 10-11 days with prophylaxis for 30 days. The incidence of DVT was significantly lower in the group receiving extended prophylaxis. A similar study by Planes [18], involving patients undergoing total hip replacement, compared extended prophylaxis (for 21 days) versus prophylaxis up until discharge from hospital. They too found a lower rate of DVT in the extended prophylaxis group, with no significant bleeding episodes.

Hull *et al* [19] have recommended that outpatient prophylaxis should at least be offered for a short period if patients are discharged early (to achieve a total treatment duration of 7-10 days). For high risk patients, however, the accumulating evidence suggests that extended outpatient prophylaxis (29-35 days) is warranted.

## Future prophylactic trends

The future prophylactic agents are aimed at decreasing the unwanted side effects of bleeding, whilst increasing the effectiveness of the prophylaxis. The goal is to improve the benefit:risk ratio [15]. In certain high risk patients (e.g. trauma surgery), the incidence of VTE is still high despite using currently available methods of prophylaxis.

The current focus is on thrombin, as it has a crucial role in the formation of clot. There are two main classes of new drugs being trialled: indirect thrombin inhibitors and direct thrombin inhibitors.

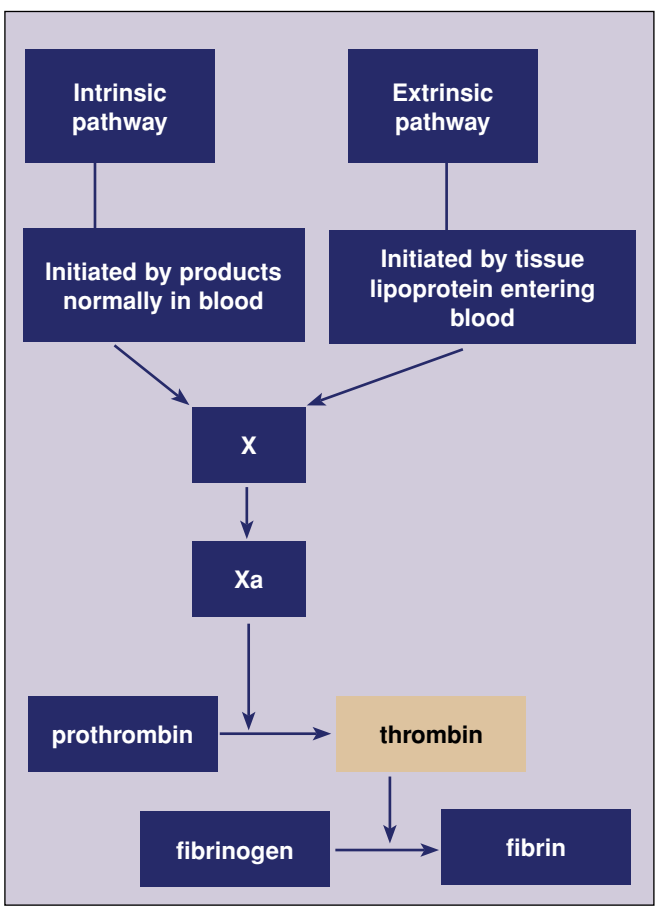
Indirect thrombin inhibitors prevent the formation of thrombin by blocking the actions of enzymes required for the formation of thrombin (Figure 1). Indirect thrombin inhibitors under trial include danaparoid, pentasaccharide and dermatan sulphate. Danaparoid has anti-Xa and anti-IIa activity, however, half of the antithrombotic effect is due to an unknown mechanism. Pentasaccharide has a very specific anti-Xa activity, whilst dermatan sulphate interacts with and activates heparin cofactor II. Of the indirect thrombin inhibitors, pentasaccharide appears to have most promise for the future.

Direct thrombin inhibitors under trial include desirudin and lepirudin. These agents bind directly to thrombin. Desirudin has been shown in early trials to have prevented more DVT than either UFH [20] or LMWH [21]. In the first study, involving over 800 patients undergoing total hip replacement, desirudin significantly reduced the frequency of total and proximal DVT when compared to UFH [20]. In the latter study, involving 1500 patients undergoing total hip replacement, the frequency of DVT was 18 per cent for patients taking desirudin as against 25 per cent for those in the LMWH [21] group.

## Treatment of VTE

The principles of treatment of DVT have been unchanged since the 1940s. The drugs used, however, are gradually changing.

**Figure 1. Coagulation pathway**



### DVT

The options for treatment include anticoagulation (with LMWH, heparin, or warfarin), thrombolytic therapy (with streptokinase, tissue plasminogen activator (TPA), or urokinase) or surgery. Traditionally, patients have been treated with a continuous infusion of intravenous heparin followed by an oral anticoagulant such as warfarin for 3-6 months. Numerous randomised controlled trials have now shown that LMWHs can be used in place of intravenous heparin, allowing the majority of patients to be treated as outpatients [22].

The optimal duration of treatment with warfarin has yet to be established. However, for patients with a transient risk factor, oral anticoagulation is recommended for at least 3 months; for patients with idiopathic VTE, 6 months is preferable to 3 months [23].

Alternative therapies which may be useful include thrombolysis, caval filters and surgical thrombectomy. Thrombolysis has the advantage of dissolving the thrombus, the disadvantage being a higher risk of bleeding. Caval filters are usually reserved for use in patients with a contraindication to anticoagulation [24], whilst surgical thrombectomy is used in those patients with massive thrombosis in whom thrombolysis is contraindicated [25].

### P.E.

The options are similar to those used for DVT. They include anticoagulation (with heparin and then warfarin), thrombolytic therapy (with streptokinase, TPA, or urokinase) or surgery (pulmonary embolectomy or caval interruption). Heparin via a continuous intravenous infusion has been the mainstay of treatment for acute PE. Recent trials involving LMWH instead of intravenous heparin have been promising (THESEE Study Group [26] and Columbus Investigators [27]) and this may be the way of the future for acute PE as well as DVT.

Two randomised trials of note have assessed the use of thrombolytic therapy in acute PE. The first, a NIH sponsored multicentre trial [28], showed benefits for the pulmonary vasculature in both the short and long-term, although there was a higher bleeding rate.

The second trial, by Goldhaber [29], used TPA and found similar results. Further studies are needed in this area before recommendations can be made. The indications for pulmonary embolectomy and caval filters are similar to those used in the treatment of DVT, namely contraindications to thrombolysis and anticoagulation respectively.

## Conclusions

All patients should have a DVT risk group assessment when they are admitted to hospital. This would include considering the reason for their admission (e.g. acute myocardial infarct) as well as any pre-existing risk factors (e.g. thrombophilia). When determining what prophylaxis to use, potential contraindications should also be assessed.

High risk patients should receive LMWH or UFH as well as GCS or SCD. Moderate risk patients should receive UFH and GCS. Low risk patients should be mobilised early, be well hydrated and use GCS. When patients are discharged from hospital, high risk patients should be advised to wear GCS for an extended period of time.

By preventing VTE from occurring, a significant cause of mortality and morbidity will be reduced. The incidence of post-phlebitic syndrome will also be diminished, hence, hopefully, the incidence of venous ulcers. Venous ulcers significantly affect a patient's quality of life, as well as posing a significant burden on the health budget. Prophylaxis is a relatively simple way of minimising these insidious hazards.

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