"The Prevention of Post-Operative Deep Vein Thrombosis"

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Abstract

Background

In a university hospital, disparate and unsatisfactory thromboprophylaxis in surgical patients was found. No hospital consensus was in place for the prevention of postoperative deep vein thrombosis (DVT). Literature review suggested low molecular weight heparin (LMWH) and anti-embolic stockings were the best prophylaxis, however the optimal length of stocking was unknown.

Method

An audit of thromboprophylaxis in surgical patients and surgical doctors was performed.

A randomised controlled trial investigated the efficacy and safety of a new single protocol of LMWH and the best length of stocking, for every patient requiring surgery under general anaesthesia. Of 426 patients interviewed, 376 were randomised into three stocking groups, Medi Thrombexin® Climax™ thigh-length, Thrombexin® Climax™ knee-length and Kendall TED™ thigh-length. All patients received LMWH. DVT incidence was assessed by duplex ultrasonography. Complications of thromboprophylaxis were recorded. Compliance and health outcome measures were developed to assess patient stocking acceptability.

Results

Audit of thromboprophylaxis revealed inadequate surgical thromboprophylaxis. A simple ‘single protocol’ improved doctors’ thromboprophylaxis compliance on replicate audit.
The randomised trial assessing the ‘single protocol’ showed no postoperative DVT occurred in the low or moderate-risk patients (n=85). Twenty-one DVT occurred in nineteen patients, all were high-risk patients (n=291): two with Thrombexin® Climax™ thigh-length stockings and eleven with Thrombexin® Climax™ knee-length (p<0.05). Six patients wearing TED™ thigh-length stockings developed DVT. Groups were similar for age, gender, thromboembolic risk, surgical type and protocol compliance. One significant bleeding complication occurred. A validated health outcome measure showed patient satisfaction with knee-length stockings was significantly greater than with thigh-length. However, stocking compliance for in-patients was equal. Whereas patients’ compliance with knee-length was significantly greater after hospital discharge.

**Conclusion**

A single protocol employing LMWH and thigh-length stockings abolished DVT (diagnosed by duplex) in low and moderate-risk patients and reduced DVT to 2% in high-risk patients. The ‘Blanket LMWH/thigh-length stocking protocol’ was effective, safe and the length of stocking proved significant. A new single protocol and hospital consensus to prevent postoperative DVT was achieved.
Chapter 1  - Introduction

1.1 Definition of deep vein thrombosis
1.2 Historical review of deep vein thrombosis
1.3 Epidemiology of deep vein thrombosis
   1.3.1 Size of the problem
   1.3.2 Prevalence and incidence
1.4 Pathophysiology of venous thrombosis
   1.4.1 Aetiology and risk factors
   1.4.3 Prognosis
1.5 Current attitudes towards the prevention of deep vein thrombosis in surgical patients
   1.5.1 Current recommendations for thromboembolic prophylaxis
   1.5.2 Reported application of thromboembolic prophylaxis
1.6 Aims of study and hypotheses
1.7 Statistical analysis
1.8 Computer equipment, software and database
Chapter 2 - A review of the literature: The prevention of deep vein thrombosis in surgical patients

2.1 Introduction

2.2 Why prevent deep vein thrombosis?

2.3 Types of prophylaxis: mechanisms of action, efficacies and complications

2.3.1 The mechanical methods of prophylaxis

2.3.2 The pharmacological methods of prophylaxis

2.3.2.1 Subcutaneous heparin

2.3.2.2 The recent orthopaedic literature comparing unfractionated to low molecular weight heparin for thromboprophylaxis.

2.3.2.3 Oral anticoagulants

2.3.2.4 Dextran infusion

2.3.2.5 Antiplatelet agents

2.3.2.6 Others

2.4 Recommendations for the use of prophylaxis in clinical practice

2.5 Cost-effectiveness

2.6 Commencement and Duration of Prophylaxis

2.7 Conclusions
Chapter 3  - A review of the literature: The prevention of deep vein thrombosis with graduated compression stockings

3.1 Background

3.2 Mechanism of action

3.3 Efficacy of graduated compression stockings in the prevention of post-operative deep vein thrombosis

3.4 Complications of graduated compression stockings

3.5 Cost-effectiveness of graduated compression stockings

3.6 A review of the evidence for using thigh or knee-length graduated compression stockings in the prevention of post-operative deep vein thrombosis

3.6.1 Methods

3.6.2 Results

3.7 Summary
Chapter 4 - An audit of surgical thromboembolic prophylaxis in a teaching hospital and the response of medical staff to an education and awareness program promoting a single blanket protocol.

4.1 Background

4.1.1 The evolution of medical audit

4.1.2 Essential properties of medical audit

4.1.3 The audit cycle

4.1.4 Audit and quality of care

4.1.5 Focus of audit

4.1.6 The audit protocol

4.1.7 Summary

4.2 Methods

4.3 Results

4.4 Conclusions
Chapter 5 - The disparity in the practice of DVT prophylaxis and the difficulties in achieving a general consensus for the prevention of deep vein thrombosis in surgical patients

5.1 Introduction

5.2 A Teaching Hospital Questionnaire Audit: Disparity and Errors in the Practice of DVT Prophylaxis

5.2.1 Introduction

5.2.2 Methods

5.2.3 Results

5.2.4 Conclusions

5.3 Instigating change in a large teaching hospital

5.3.1 Communications to departments

5.3.2 Feedback from departments

5.3.3 The use of LMWH and graduated compression stockings ‘across the board’ for patients undergoing surgery

5.4 Discussion
Chapter 6 - A randomised controlled trial to develop a new blanket protocol of low molecular weight heparin and the best – thigh or knee-length – stocking for the prevention of post-operative DVT

6.1 Introduction
6.1.1 The need for a randomised controlled trial
6.1.2 Aims of the study
6.1.3 Hypothesis and study end-points
6.1.4 Ethics approval
6.1.5 Sources of funding
6.1.6 Venous colour duplex scanning
6.1.7 Sample Size and Statistical Analysis

6.2 Patients and methods
6.2.1 Patients and data collection
6.2.2 Recruitment and randomisation
6.2.3 Patient information and informed consent
6.2.4 Colour duplex scanning for deep vein thrombosis in trial patients
6.2.5 Commencement and maintenance of trial prophylaxis
6.2.6 Treatment of patients who developed DVT

6.3 Results
6.3.1 Patient Series
6.3.2 Colour Doppler ultrasound scanning for DVT
6.3.3 Trial Results
6.3.3.1 Postoperative deep vein thrombosis
6.3.3.2 LMWH prophylaxis commenced before and after surgery
6.3.3.3 Complications resulting from the blanket use of LMWH and stockings
6.3.3.4 The compression profiles of the stockings
6.3.3.5 Clinical aspects of deep vein thrombosis
6.4 Conclusions

Chapter 7 - The development and validation of a health related quality of life (HRQL) measure to assess patient satisfaction with compression stockings

7.1 Background – Health outcome assessment
7.1.1 Health outcomes measurement
7.1.2 Measuring health outcomes in surgery
7.1.2.1 Types of HRQL
7.1.2.2 Medical Outcomes Study Short Form 12 Item Health Survey

7.2 Developing a specific health outcome questionnaire
7.2.1 Development of instrument ‘questions’ (items)
7.2.2 Selection of the items for use in the questionnaire
7.2.2.1 Face validity
7.2.2.2 Frequency of endorsement
7.2.2.3 Homogeneity of items
7.2.2.3.1 Cronbach’s Alpha
7.2.2.3.2 Split-half homogeneity
7.2.2.3.3 Item-total-correlation
7.2.3 Multifactor inventories
7.2.4 Summary of item selection
7.2.5 Scale construction

7.3 Testing a specific health outcome questionnaire
7.3.1.1 Reliability
7.3.1.2 Validity
7.3.1.3 Responsiveness
7.3.1.4 Acceptability

7.4 The development and testing of a questionnaire to assess patients’ satisfaction with thigh and knee length stockings
7.4.1 Methods and patient series
7.4.1.1 Development of instrument ‘questions’
7.4.1.2 Selection of the items for use in the questionnaire
7.4.1.2.1 Frequency of endorsement
7.4.1.2.2 Homogeneity of items
7.4.1.3 Scale construction
7.4.1.4 Testing for use as a satisfaction measure
7.4.1.4.1 Reliability
7.4.1.4.2 Validity
7.4.1.4.3 Responsiveness

7.4.1.4.4 Acceptability

7.4.1.5 Use of the questionnaire assessing patient satisfaction with thigh and knee length stockings

7.5 Results

7.5.1 Development of instrument ‘questions’

7.5.2 Selection of the items for use in the questionnaire

7.5.2.1 Frequency of endorsement

7.5.2.2 Homogeneity of items

7.5.3 Scale construction

7.5.4 Validity

7.5.5 Test-Retest Reliability

7.5.6 Acceptability

7.5.7 Patient satisfaction with thigh and knee length stockings

7.5.8 Conclusions

7.6 The assessment of patient stocking compliance

7.6.1 Methods and patient series

7.6.2 Compliance diary sheets

7.6.3 Results

7.7 Conclusions
Summary

Chapter 8  - Summary of the development and evidence for the Charing Cross Hospital guidelines to prevent post-operative deep vein thrombosis

8.1 The need for change in DVT prophylaxis practice

8.2 Preliminary arguments for a single protocol

8.3 Achieving a hospital consensus for a large randomised clinical trial

   investigating a single protocol and the optimal stocking length

8.4 The optimal length of stocking

8.5 LMWH for all patients undergoing surgery

8.6 Health outcome assessment of stocking satisfaction and compliance

8.7 The impact of this study on clinical practice at a large university hospital

8.8 Future research
List of Tables

Chapter One

Table 1a  The inherited venous thrombotic disorders
Table 1b  Risk factors for venous thromboembolism in hospitalised patients
Table 1c  Risk categories in surgical patients
Table 1d  Recommended thromboembolic prophylaxis for surgical patients
Table 1e  The sample sizes for certain differences in an equivalence study

Chapter Two

Table 2a  The different types of thromboembolic prophylaxis
Table 2b  Summary of DVT prophylaxis efficacies
Table 2c  The properties of heparin
Table 2d  Risk categories and recommended prophylaxis in surgical patients
Table 2e  Summary of the ‘International Consensus Statement’ recommendations for thromboembolic prophylaxis in surgical patients

Chapter Three

Table 3a  The effect of GCS on DVT after general and gynaecological surgery
Table 3b  Effect on DVT of GCS alone versus GCS with subcutaneous heparin in general and orthopaedics surgery
Table 3c  Effect on DVT of subcutaneous heparin alone and in combination with GCS
Table 3d  Articles excluded from analysis
Table 3e  Articles included for analysis
Table 3a Summation of data for thigh and knee length stockings

Chapter Four

Table 4a Thromboembolic risk categories and recommended prophylaxis for surgical patients.
Table 4b Patient demographics
Table 4c Surgical specialities of patients
Table 4d Prophylaxis given to surgical patients
Table 4e Patient demographics
Table 4f Improvements in surgical DVT prophylaxis after education and introduction of single blanket prophylaxis protocol

Chapter Five

Table 5a Different types of stocking used by surgical wards
Table 5b Beliefs of surgical doctors about the best prophylactic modalities

Chapter Six

Table 6a Entry and exclusion criteria for the study
Table 6b Surgical specialities of recruited patients
Table 6c The demographic details of the trial patients
Table 6d Similarity of stocking groups for ‘DVT risk factors’
Table 6e The values required for the calculation of specificity, sensitivity, positive and negative predictive values of clinical diagnosis of DVT
Chapter Seven

Table 7a  Summary of properties for quality of life assessments
Table 7b  Matrix method for content validity
Table 7c  The assessment of questionnaire for comprehension using visual analogue and Likert scales.
Table 7d  Mean item scores for each stocking group
List of Figures

Chapter Four

Figure 4a  The audit cycle
Figure 4b  The risk categories
Figure 4c  DVT prophylaxis given to patients
Figure 4d  DVT Prophylaxis by each surgical speciality
Figure 4e  DVT prophylaxis by each surgical ward
Figure 4f  DVT risk categories of patients
Figure 4g  Improvements in DVT prophylaxis after education and introduction of single protocol

Chapter Five

Figure 5a  The different grades of the surgical doctors who answered the questionnaire
Figure 5b  The variety of surgical specialities
Figure 5c  The sources of information used by doctors to guide prophylaxis prescription
Figure 5d  The surgical doctors that prescribed prophylaxis
Figure 5e  The sources of information used by each grade of doctor to guide prophylaxis prescription
Figure 5f  The prophylaxis routinely prescribed by the surgical doctors
Figure 5g  Beliefs of surgical doctors about the best heparin and stocking types for prophylaxis.
Figure 5h  Actions of surgical doctors when in doubt about the correct prophylaxis to prescribe for a patient
Figure 5i  The preferred time of commencement of prophylaxis

Chapter Six

Figure 6a  Recruitment consort diagram
Figure 6b  Flow diagram of the trial methodology
Figure 6c  Rate of recruitment of trial patients
Figure 6d  Trial consort diagram
Figure 6e  Similarity of stocking groups for DVT risk
Figure 6f  Similarity of stocking groups for surgical speciality
Figure 6g  Similarity of stocking groups for aspirin usage
Figure 6h  Accuracy of duplex scanning for DVT
Figure 6i  Postoperative DVT rates for each stocking group
Figure 6j  Anatomical distribution of DVT with each stocking type
Figure 6k  DVT occurred with 'bone-cutting' and abdominal cancer surgery
Figure 6l  Operation associated with DVT
Figure 6m  DVT rates with and without preoperative heparin
Figure 6n  DVT rates with and without preoperative heparin for each stocking group
Figure 6p  Complications associated with LMWH and stockings
Figure 6q  Stocking compression profiles
Figure 6r  The incidence of symptomatic DVT and those detected by duplex ultrasound
Figure 6s  The distribution of clinical findings and there relationship to DVT diagnosed by duplex
Chapter Seven

Figure 7a  The endorsement of questions by patients
Figure 7b  Mean scores for odd and even questions
Figure 7c  Sum of questions scores for odd and even questions
Figure 7d  Patients' weighting by importance
Figure 7e  Satisfaction scores for compression hosiery
Figure 7f  Satisfaction scores for 'Extreme' groups wearing stockings
Figure 7f  Satisfaction scores for three and four layer bandaging
Figure 7h  Correlation between physical SF-12 scores and stocking satisfaction scores
Figure 7i  Correlation between mental SF-12 scores and stocking satisfaction scores
Figure 7j  Reliability test-retest assessment
Figure 7k  Stockings satisfaction questionnaire assessment
Figure 7l  Mean item scores for each stocking group
Figure 7m  Stocking compliance in hospital and after discharge

Appendix

Abbreviations

List of presentations and publications resulting from this study

Acknowledgements

References
Chapter One

Introduction

List of contents

1.1 Definition of deep vein thrombosis
1.2 Historical review of deep vein thrombosis
1.3 Epidemiology of deep vein thrombosis
   1.3.1 Size of the problem
   1.3.2 Prevalence and incidence
1.4 Pathophysiology of venous thrombosis
   1.4.1 Aetiology and risk factors
   1.4.3 Prognosis
1.5 Current attitudes towards the prevention of deep vein thrombosis in surgical patients
   1.5.1 Current recommendations for thromboembolic prophylaxis
   1.5.2 Reported application of thromboembolic prophylaxis
1.6 Aims of study and hypotheses
1.7 Statistical analysis
1.8 Computer equipment, software and database
1.1 Definition of Deep Venous Thrombosis

The term thrombosis refers to the formation within the vascular system (in a living animal) of an abnormal mass made up of blood constituents. Thrombosis is defined as a mass of aggregated platelets immobilised within fibrin, adherent to the vessel wall. There is variable content of red cells and entrapped leucocytes and the proportions and arrangements of these various components are dependent on local and general conditions. Venous thrombi are composed of large amounts of fibrin and erythrocytes that form a loose friable mass called the red thrombus, which randomly enmeshes platelets and leucocytes. The most proximal portion often contains prominent platelet masses and is paler than the distal coagulum of red cells and fibrin (De Gruchy 1990). Venous thrombi differ from arterial thrombi by their early obstructive nature within the vessel whereas the latter enlarge progressively by deposition of new layers of platelets and fibrin to produce the lines of Zahn with eventual partial or complete obstruction of the arterial flow. However the most serious consequence of venous thrombosis is embolisation to the pulmonary circulation, which is not uncommonly fatal. The thrombosis of veins and arteries, and the resultant embolic complications, together produce the largest cause of morbidity and mortality in the western world.

Venous thrombosis is classified according to the anatomical distribution of the affected vein. The veins of the lower extremity are subdivided, like those of the upper extremity, into two sets; superficial and deep. The superficial veins are placed beneath the integument between the two layers of superficial fascia. The deep veins accompany the arteries and their branches, frequently in pairs that are referred to as venae commitantes. Venous thrombi may occur in the superficial or deep venous systems, the former may cause local symptoms as a result of superficial
thrombophlebitis. Where as, deep venous thrombosis (DVT) may cause local and systemic complications. Deep vein thromboses are classified as ‘proximal’ when they involve the popliteal vein or more proximal deep veins of the lower limb and pelvis. Distal DVT are classified as major calf thrombi, when they are more than five centimetres in length but confined to the deep veins of the calf, or as minor calf thrombi when they are less than five centimetres in length (Fordyce & Ling 1992). The importance of this classification is underlined by evidence to suggest that the minor calf thrombi of less than five centimetres may resorb spontaneously (Kakkar et al. 1969) which is in stark contrast to the potential clinical outcome of proximal thrombi that have been shown to produce pulmonary embolism (PE) in as many as fifty percent of cases (Moser & Le Moine 1981).

Both superficial and deep veins are provided with valves, these are more numerous in the deep venous systems. Deep vein thrombosis more commonly occurs within the deep veins of the leg rather than the arm. This is probably related to the fact that valves are more numerous in the veins of the leg than in those of the upper limb (Gray 1918). Authors have reported the importance of blood stagnation behind deep venous valve cusps that encourages the formation of DVT (Lewis 1976 & Kalebo et al. 1990). Venous thrombosis develops under conditions of slow blood flow and is augmented by further retardation and stagnation of flow in the venous system.

The development of an ‘early’ surgical DVT is thought to begin during the surgical procedure, with any clinical manifestations usually evident during the first postoperative week, where as prolonged immobility in the convalescing patient may lead to the formation of a ‘late’ DVT” that may not be directly related to the operation itself. Successful prophylaxis against the surgical complication of venous thromboembolism (VTE), in the first instance needs to prevent the development of
the ‘early’ DVT around the time of surgery and then continue until the patient is fully ambulant to prevent the development of a ‘late’ DVT.

1.2 Historical review of the venous thrombosis

The notion of blood transport by two types of vessels (phlebos) was described as early as the sixth century BC by Alcmeon of Croton, the first Greek known to practice dissection. The separation of vessels into two types was also found in the Hippocratic Corpus (5th century BC), where the term ‘artery’ refers to the trachea, bronchi and vessels originating from the heart, these were described as transporting blood to the connecting ‘veins’. Early reports of blood clotting were found in the writings of the Greek philosophers of the 4th century B.C. Plato described fibres within the blood that caused clotting when blood left the body and cooled, this view was held until the 18th century. Aristotle added that the fibres were solid and blood removed from the fibres did not clot. Observations made through the act of blood letting which was active in the Hippocratic school and dates back to the early Egyptian times, was the basis for the Greek humoral hypothesis of the four humours which is set out in the treatise on the ‘Nature of Man’ of the Hippocratic code (400 BC). The clotting of blood emptied into a container was assumed to be the normal behaviour of blood within the body and was reported to slowly separate in to the four humours. The upper portion clearing to become a transparent yellow colour (named yellow bile), the bottom would form a thick red almost black layer (black bile), at the surface a thin bright red layer formed (blood) and in disease a greeny white layer (phlegm) would separate from the black layer at the bottom. It was the separation of clotted blood and formation of the phlegm in disease that formed the basis of pathology for over two thousand years. The phlegm layer was renamed innumerable
times and also known as the crusta sanguinis, inflammatoria, phlogostica, the buffy coat. Even today, the interplay of fibrinogenesis and fibrinolysis, and erythrocyte sedimentation rate have important roles in clinical practice.

King Ptolemy who ruled from 323 to 282 BC established his library and museum in the Egyptian capital Alexandria in order to install Greek learning in the new Egyptian environment. The library became the wonder of the scholarly world, attracting distinguished medical talent, notably Herophilus of Chalcedon (330-260 BC). Herophilus improved Aristotelian anatomy by distinguishing between arteries and veins through the dissection of living humans. Four centuries later the anatomical and physiological discoveries of the Alexandrian physicians were utilised and improved upon by Galen, born in AD 129 in Pergamon (now Bergama, Turkey). He affirmed that the two systems of arteries and veins were anastomosed, however there is no evidence in Galen’s work that he saw the possibility of blood circulating from the former to the latter. Galen supported and elaborated on the humoral pathology, he was a great advocate of phlebotomy, described the ‘buffy coat’ and founded ‘Galenic’ anatomy. For fourteen centuries Galenic concept of anatomy prevailed despite continued criticism and correction. The arguments over blood letting caused anatomists to pay more attention to venous anatomy. Hieronymus Fabricius ab Aquapendente (c. 1533-1619), a great comparative anatomist described the valves of the veins and their possible function by reporting that the valves helped the central and upper parts of the body to get blood thus preventing the extremities from gathering excessive blood (Porter 1997). His work was a major influence on William Harvey who performed demonstrations on the blood circulation. William Harvey (1578-1657) of Folkestone, England, praised Galen for his evidence for pulmonary blood circulation however he questioned Galen’s account of transit of air
and waste in opposite directions through the venous artery. Through his dissection, Harvey found that blood travelled from the vena cava, through the pulmonary circulation via the right ventricle and into the aorta via the left ventricle. As a favoured pupil of Hieronymus Fabricius, he deduced from studies of the venous valves that blood must flow from the arteries to veins and back to the heart. 

Franciscus Sylvius (1614-1672) introduced clinical bedside teaching and the first chemical laboratory in Europe. Sylvius assigned a prominent part of disease to the chemical properties of the blood. Inflammation of the blood was dependent on stagnation of the blood in the vessels, which he felt could result in the production and deposition of pus. The lay term ‘inflammation of the blood’ most probably dates back to the work of Sylvius.

By the middle of the 17th century, early microscopists were studying the composition of the blood. In 1658, Jan Swammerdam (1637-1680) was the first to describe (during microscopic studies of frogs blood) the red corpuscle floating in serum. Richard Lower (1631-1691) was famous for his work on transfusion and the uptake of ‘air’ by the blood in the lungs with its resultant change in colour form dark to bright red. He also noted the similar colour change on the upper side of a venous blood clot exposed to the air compared to the dark underside, which would then become florid if turned over. A pioneer anatomist, Marcello Marpighi in 1666 washed clotted blood to reveal white fibrous strands (Ratnoff & Wintrobe 1980). A great clinician and teacher, Herman Boerhaave (1668-1738) began the first formal lectures in physiology, the “Institutiones Medicae”, that were the origins of the “Institutes of Medicine”. Boerhaave held that blood coagulated if it ceased to move due to the natural tendency of cells within the blood to cohere one with another, with some intermixed serum. He believed that disease was due to stagnation and
coagulation of blood in the blood vessels, either due to alterations in the vessels themselves or the blood.

Up until this time, a frequent error of the blood coagulationist was to assume that the behaviour of the blood in the bleeding bowl was the same as the blood in the body. The eighteenth century saw the beginnings of the modern ideas on the formation and behaviour of the blood. Joseph Lieutaud (1703-1780) described the condition of "anaemia", an exhaustion of the blood vessels associated with blood lost and starvation. In 1760 Richard Davies wrote essays in which he described his scrupulous experimental techniques to examine the fractions of the blood in its fluid and coagulated states and initiated studies on clot retraction. He showed quite clearly that red blood cells themselves have no power of coagulation.

The first 'haematologist' William Hewson (1739-1774) was born in Hexam, England. He is principally remembered for his work on coagulation, where he proved that blood serum was the main coagulant of the blood by skimming off the plasma from a ligated vein. The clear plasma that he called "coagulable lymph" - later to be known as "fibrinogen" - then clotted. He observed that blood in fact slowed its rate of clotting if cooled contrary to the teachings of Plato. In the 1770s, Hewson localised the source of coagulation fibres to the liquid part of the blood known today as plasma. He also showed that the walls of the blood vessel exert a 'remarkable influence' on restraining coagulation (Hewson 1846).

The early nineteenth century led to a definite regression in the study of the functions of the blood with much of the 18th century's findings forgotten. Phlebotomy as part of therapy slowly but steadily disappeared. Jean Cruveilhier (1791-1874), the first professor of pathological anatomy in Paris, revived interest in the blood. Inflammation of the veins or phlebitis occupied the centre of his concept of disease.
He distinguished adhesive phlebitis or thrombosis, from suppurative phlebitis, areas of infarction were called fibrinous deposits or capillary phlebitis, however he failed to recognised the possibility of embolism. William Addison (1802-1881) was the first to reveal some of the functions of the leucocytes in inflammation and pus and he recognised platelets and their relationship to the formation of fibrin.

Rudolph Virchow (1821-1902), a graduate from Berlin, dominated German biomedical research for half a century. Through his studies of blood coagulation and the chemical nature of the fibrin clot, he found that fibrin was only found in the blood stream after the onset of coagulation and he named its precursor fibrinogen. Through animal experiments, autopsies and clinical observations, he elucidated the nature of phlebitis. He described that in most cases of vascular inflammation associated with blood clots, the clot usually formed first which led to local inflammatory and obstructive effects. The emboli commonly found in the pulmonary circulation at autopsy did not result from a general disease but originated from the venous clot elsewhere in the body and travelled via the venous and right cardiac circulatory systems to the lungs, which in turn set off local vascular and respiratory reactions that were often fatal. In 1846, he published his first paper on embolism, noting the frequent association of infected venous thrombi and lung abscesses. In 1856, he described the pathogenesis of venous thrombosis, and emphasised the importance of changes to the composition of the blood to increase coagulability, changes in the vessel wall, in particular endothelial damage, and disturbances to blood flow, especially stasis (Virchow 1858, Porter 1997).

Only at the end of the nineteenth century, the studies of Bizzozero, Eberth and Schimmelpbusch, and others found that platelets, the last of the blood cells to be discovered, provided a significant contribution to thrombus formation (Ratnoff &
Travers of St. Thomas’s Hospital in cooperation with Cooper of Guy’s Hospital, wrote a historical account of the surgery of the veins, noting the occasional suppuration of the ligated veins, occasionally accompanied by fatal pulmonary embolism. In the 1920s to 30s, pulmonary embolectomy was performed regularly as an emergency procedure. Crawford and Kirschner achieved international recognition for this procedure despite only limited successes. John Homans (1941) of Boston stressed the importance of division of the deep veins of the leg in circumstances of thromboembolism. For repetitive episodes of thrombus migration surgeons would occasionally interrupt the vena cava below the renal veins by ligature or insertion of a screen filter that prevent further clot migration centrally. T.J. Fogarty and associates devised a catheter with an inflatable balloon that could assist in the removal of thrombus from veins or arteries (Krause et al 1966).

The discovery in 1916 of heparin by McLean and William H Howell and dicoumarin by Campbell and Link in 1939 provided anticoagulant substances that could be used in the treatment and prophylaxis of thrombotic and embolic states (Beck 1984). Early clinical studies carried out before the routine use of anticoagulant therapy demonstrated that in the region of six percent of patients with untreated deep vein thrombosis died of pulmonary embolism (Zilliacus 1946). The prophylactic and therapeutic use of anticoagulants and venous compression techniques, has largely eradicated the need for emergency surgical intervention for the treatment of venous and pulmonary thrombi. However, pulmonary embolism is still a major cause of death in hospitalised patients in the developed world. The root of the problem stems from the development of deep vein thrombosis, which still commonly occurs in our hospitals today.
1.3 Epidemiology of Venous Thromboembolic Disease

1.3.1 Size of the problem

Surgical practice continues to be complicated by venous thromboembolic disease, despite continued efforts over the last four decades to reduce its occurrence. In the face of the increased use of thromboprophylaxis, rates of VTE have not reduced significantly since the 1980's. Patients are continuing to suffer from the severe complications of DVT and PE; ten percent of hospital deaths have been associated with PE (Sandler & Martin 1989). Although a fatal PE may be the first presentation, a DVT may propagate to produce a PE and up to seventy percent of patients with proven PE have venographic evidence of peripheral deep venous thrombosis (Hull et al 1983). Venous thromboembolism is a common complication among hospital inpatients and is known to contribute to longer hospital stays, increased morbidity and mortality.

1.3.2 Prevalence and Incidence

Venous thromboembolism is a major health problem affecting at least one person per thousand annually. In people below the age of forty the incidence of VTE episodes (DVT and PE) is approximately one in 10,000 people per year, which increases to one in 100 per year for those aged 75 years and over (Anderson et al 1991 & Martinelli 2001). Epidemiological data shows the annual rate of symptomatic DVT to be around 160 per 100,000 in the general population. Deep vein thrombosis ranks third as the most common cardiovascular disease behind acute ischaemic coronary disease and stroke and affects approximately 8 in every 10,000 individuals per year (Anderson et al 1991). Reports from the United States Vital Statistics and the National Hospital Discharge survey from 1970 to 1985 demonstrated an age-adjusted
DVT rate of 79 per 100000 and for pulmonary emboli, 51 per 100000 (Gillum 1987). The prevalence, defined as the number of cases of a disease existing in a given population at a specific period of time (period prevalence) or a particular moment in time (point prevalence) and incidence, the number of new specified events of disease during a specific period in a specified population are hard to establish with regard to VTE. Because, in the general population and hospitalised patients the limited published evidence and the clinically silent nature of the disease prevents the identification of all of the victims. The prevalence has been reported for asymptomatic DVT in adult patients on admission to hospital to be around five and a half percent with a rise to 17.8 percent in patients aged over eighty years (demonstrating the increased risk with age) (Oger et al 2002). The development of VTE in patient populations with specific risk factors has also been demonstrated by the high prevalence in patients suffering from malignancy; DVT (5.5%) and PE (7.6%) with the recurrence of VTE reaching approximately fifty percent (Joung & Robinson 2002). The prevalence of DVT in hospice patients with advanced cancer was in the region of fifty percent (Johnson et al 1999). In critically ill patients admitted to Critical care units, the prevalence of objectively determined DVT ranged from 13 to 31 percent (Geerts et al 2002).

The majority of fatal PE arise from DVT in the lower limb. Pulmonary embolism continues to be a major cause of death in hospitalised patients in the United Kingdom; nine percent of all patients admitted to hospital died and of these ten percent were due to PE - 0.9% of all admissions (Sandler and Martin 1989). In surgical patients, the incidence of fatal PE in low-risk patients is approximately 0.5%, and in high risk-patients; such as elective hip surgery patients (1.5%) and as high as 5% in patients undergoing surgery for hip fracture (Gallus 1993).
1.4 Pathophysiology of venous thrombosis

1.4.1 Aetiology and risk factors

Excessive activation of coagulation or inhibition of the normal anticoagulant mechanisms may result in hypercoagulability and thrombosis. The abnormalities of the vessel wall, alterations in blood flow and changes in the composition of the blood are major factors involved in the development of thrombosis that were recognised in the nineteenth century by Virchow and other authors as previously discussed. These three main aetiological factors are considered, they are frequently referred to as the triad of Virchow.

Abnormalities of the vessel wall

In venous thrombosis, in contrast to arterial thrombosis, the vessel wall is usually histiologically normal however an exception to this generalisation is direct venous trauma or venous vascular disease. A reduction in venous tone may be an important factor in the increased incidence of deep vein thrombosis in pregnancy or in women taking oral contraceptives (Goodrich and Wood 1964). Studies have reported the over-distension of the vein wall during surgery which has been linked to an increase in venous thrombosis (Coleridge Smith et al 1990, Comerota et al 1989, Goldsmith 1972, Thomas et al 1985).

Abnormalities in blood flow

Venous thrombosis develops in an environment of stagnant or slow venous blood flow. The pathophysiological role of stasis in the creation of venous thrombosis is theorised to be due to the impaired removal of activated coagulation factors due to
inadequate venous blood flow (Strandeness et al 1977). The venous circulation does
not require an abnormality, pathological or mechanical, to reduce the blood flow to
prothrombotic levels. Physiological venous stasis can occur in relation to disrupted
retrograde currents in venous valve pockets of normal veins and in the arcades of the
soleus muscle of the calf. These effects may be compounded by the effects of ageing
that may cause venous enlargement and reduced tone in these areas of the venous

**Abnormalities of the blood composition**

The ability of the blood from certain patients’ to coagulate at an abnormally rapid
rate has led to the concept of hypercoagulability which implies that prethrombotic
changes exist in the blood due to its composition that are important in the
pathogenesis of thrombosis (Hirsh 1977, Kitchens 1985, Thomas 1988). Platelets are
incorporated into all forms of thrombus, however they appear to play a more
important role in the formation of arterial rather than venous thrombi. Antiplatelet
agents have not been shown to offer any major clinical use in the prevention of deep
vein thrombosis (Fourth ACCP consensus 1995, Hirsh & Hoak 1996); the effective
methods of thromboembolic prophylaxis will be discussed later.

The hypercoagulability of the blood is found mainly in relation to acquired or
inherited disorders that predispose to deep vein thrombosis, these conditions are
summarised in table 1a. Acquired elevation of coagulation factors, such as
fibrinogen and factors V and VIII have been reported in patients with thrombosis,
prothrombotic disorders, pregnancy and women receiving oral contraceptives, and as
a result of an acute-phase reaction to inflammation or tissue damage. However,
increased activation of coagulation in animal studies is a major factor in
experimental venous thrombosis rather than increased levels of coagulation factors (Deykin & Wessler 1964, Wessler et al 1967). Venous stasis in addition to activation of coagulation consistently lead to the formation of thrombosis, which appears to be a more potent stimuli than damage to the vein wall (Thomas et al 1985, Wessler et al 1967).

Tissue factor (TF) is thought to be a primary initiator in the development of in vivo thrombosis (Nemerson 1988), in the absence of TF, endothelial cells maintain thromboresistance whereas immunological injury to the endothelium may lead to expression of tissue factor (Vermylen et al 1986). Patients with carcinoma are known to be more susceptible to venous (and arterial) thrombosis, adenocarcinomas can express TF (Callender & Rapaport 1993) and other tumours substances, such as cancer procoagulant A, that activate factor X (Gordon & Cross 1981).

Pregnancy and oestrogen medication produce a hypercoagulable state (Weiner et al 1984) that can increase the risk of venous thromboembolism (Daly et al 1996, Grodstein et al 1996). Pregnancy has been described as a physiological chronic form of disseminated intravascular coagulation (DIC) (Woodfield et al 1972). Oestrogens therapy is known to induce activation of coagulation with reduction of inhibitors of coagulation such as antithrombin III and protein S, and has been reported to induce an acquired protein C resistance (Quehenberger et al 1996; Rosing et al 1997; Vanderbroucke et al 1994).
<table>
<thead>
<tr>
<th><strong>Classification &amp; Disorders</strong></th>
<th><strong>Mechanism of Thrombosis</strong></th>
<th><strong>Inheritance</strong></th>
<th><strong>Estimated Prevalence (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated protein C deficiency (Factor V Leiden)</td>
<td>APC fails to inactivate factor Va due to highly conserved point mutation</td>
<td>AD</td>
<td>20-60</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Failure to generate APC; failure to inactivate factors Va and VIIIa</td>
<td>AD</td>
<td>5-6</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Failure of APC to inactivate factors Va and VIIIa</td>
<td>AD</td>
<td>5-6</td>
</tr>
<tr>
<td>Thrombomodulin deficiency</td>
<td>Failure to generate APC</td>
<td>AD</td>
<td>5</td>
</tr>
<tr>
<td>ATIII deficiency</td>
<td>Failure to inhibit thrombin, factor Xa, and other activated factors</td>
<td>AD</td>
<td>1-2</td>
</tr>
<tr>
<td>Heparin cofactor II deficiency</td>
<td>Failure to inhibit thrombin</td>
<td>AD</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>Elevated prothrombin level</td>
<td>AD</td>
<td>5-10</td>
</tr>
<tr>
<td>Impaired clot lysis Dysfibrinogenaemia</td>
<td>Abnormal fibrin resists fibrinolysis</td>
<td>AD</td>
<td>1-2</td>
</tr>
<tr>
<td>Plasminogen deficiency t-PA deficiency</td>
<td>Failure to generate plasmin (AR)</td>
<td>AD</td>
<td>?</td>
</tr>
<tr>
<td>Excess PAI-1 activity</td>
<td>Neutralisation of t-PA</td>
<td>AD</td>
<td>?</td>
</tr>
<tr>
<td>Homocysteinaemia</td>
<td>Endothelial cell cytotoxicity and perturbation of vascular haemostatic mechanisms</td>
<td>AR</td>
<td>1 in 335,000 live births (homozygous) 25% of patients with recurrent arterial or venous thrombosis 10% of patients with first episode of arterial or venous thrombosis</td>
</tr>
</tbody>
</table>

**Table 1a:** The inherited venous thrombotic disorders. (Adapted and modified from Florell & Rodgers 1997). Abbreviations: AD, autosomal dominant; AR, autosomal
Hereditary tendency to thrombosis, now known as thrombophilia, was first described by Egeberg in 1965, when he discovered a deficiency of antithrombin III. In the 1980s, both protein C deficiency and protein S deficiency were associated with VTE, and over the last decade numerous other inherited abnormalities in the clotting system that predispose to venous thrombosis have been discovered, including the highly investigated mutation in the clotting factor V, known as factor V Leiden. The inherited disorders of coagulation that may lead to venous thromboembolism are numerous and complex (table 1a). Many patients who suffer a thrombotic event are found to have a combination of inherited and iatrogenic aetiological factors, such as the oral contraceptive pill. The incidence of thrombosis due to inherited conditions alone is small, therefore patients should only be considered for evaluation of these inherited disorders if they are less than 45 years with recurrent thrombosis or in the primary episode with a family history (Rodgers & Chandler 1992). This is based on the fact that the majority are autosomal dominant and therefore most patients would have a positive family history.

1.4.2 Prognosis

The large majority, greater than ninety percent of venous thromboses occur in the deep veins of the legs, with the remainder usually involving the veins of the pelvis and approximately one percent in the upper limb. Most venous thrombi begin in the calf veins, usually in the sinuses above the venous valves. In this location, venous thrombi have several potential fates. In the short term the following may take place:
• **Lysis** - Venous thrombi generally remain small and are eventually lysed, posing no further threat to health.

• **Organisation** - Many thrombi undergo organisation similar to thrombi of arterial origin. Small organised venous thrombi may be incorporated into the wall of the vessel, whereas larger thrombi can obstruct venous outflow.

• **Propagation** - Venous thrombi may form a nidus for further thrombosis and more proximal propagation of thrombus into the larger iliofemoral veins. Proximal extension of calf vein DVT occurs in approximately 20-50% of cases (Huisman et al 1989, Kakkar et al 1969).

• **Embolisation** - Large venous thrombi or proximal iliofemoral thrombi represent a significant threat to the pulmonary circulation via embolisation and may be fatal. Pulmonary emboli have been detected in as many as 50% of the cases with proximal DVT (Kakkar et al 1969) and 10-13% of patients with postoperative asymptomatic deep calf vein thrombosis (Giannoukas et al 1995).

In the long term, obstructive venous thrombi may undergo canalisation, with partial restoration of venous drainage, commonly with incompetent valves in the affected segment of vein. The long-term sequelae represent a major burden to the modern health services with the frequent complications of post-phlebitic syndrome and venous ulceration. The prevalence of symptomatic post-thrombotic syndrome (PTS) in patients who have suffered previous DVT appears to vary between 29 and 79% (Lindner et al 1986, Johnson et al 1999, Prandoni et al 1996, 1998). The symptoms and signs of PTS, which include pain, swelling, skin discoloration and hyperpigmentation, development or progression of varicose veins, and ulceration have been reported to be mild, moderate and severe in 55%, 4% and 4% of patients.
respectively (Biguzzi et al 1998). Other reports have documented a higher symptomatic rate of 78% in patients with previous DVT (Bergqvist et al 1997). The prevalence of venous insufficiency in patients with PTS has been shown to be as high as 88.9% (McColl et al 2000, Lindhagen et al 1986). Moderate PTS has been reported more often (44%) in patients with recurrent DVT (McColl et al 2000). Recurrent thrombosis in patients that are adequately treated for DVT occur in up to thirty percent at 8 years and PTS may develop in up to twenty eight percent at five years (Prandoni et al 1996). The treatment of PTS is difficult due to its chronic nature and gradual worsening of venous insufficiency leading to the eventual development of venous ulceration in 2-10% of patients. Surgery is usually reserved for the extreme cases of PTS due to the sensitivity of the deep veins to surgical manipulation causing further thrombosis. The mainstay of treatment is the use of compression hosiery for life, which is aimed at palliation rather than cure.

1.5 Current attitudes to the prevention of deep vein thrombosis in surgical patients

1.5.1 Current recommendations for thromboembolic prophylaxis

Numerous recommendations for effective venous thromboprophylaxis have been published over the last fifty years. Over forty years ago the evidence was emerging for the routine use of graduated compression stockings (GCS) in surgical patients and more than fifteen years ago a review of over seventy randomised trials investigating the preoperative use of subcutaneous heparin recommended its use in
### Patient factors | Disease or Surgical factors
--- | ---
Age | Trauma, surgery, especially of hip, pelvis, lower limb.
Obesity | Malignancy, especially pelvic, abdominal, metastatic.
Immobility | Heart failure or recent myocardial infarction
(bed rest over 4 days) | 
Pregnancy | Lower limb paralysis
Puerperium | Infection
High dose oestrogen therapy | Inflammatory bowel disease
Previous VTE | Nephrotic syndrome
Thrombophilia, deficiency of antithrombin III, protein C or S, Antiphospholipid antibody or lupus anticoagulant | Paraproteinaemia Polycythaemia Paroxysmal nocturnal haemoglobinuria Behcet’s disease Homocysteinaemia

**Table 1b – Risk factors for venous thromboembolism in hospitalised patients** (modified from THRIFT consensus group 1992.)

general, urology and orthopaedic surgery due a significant reduction in the rate of DVT, PE, fatal PE and overall surgical mortality (Collins et al 1988). The results of this review confirmed the findings of the first large international multicentre trial assessing the use of perioperative subcutaneous heparin in the prevention of VTE (IMT 1975, 1997). In 1992 the Thromboembolic Risk Factors (THRIFT) consensus group advocated that all surgical and medical patients should receive specific
preoperative thromboprophylaxis in accordance with their risk of developing VTE.

This idea was modified from some of the first authors to separate the thromboprophylactic requirements of patients into categories in relation to their thromboembolic risk (Salzman & Hirsh 1982).

The risk of VTE in hospitalised patients is not only dependent on the patients’ current illness, planned treatment or operation, but also on pre-existing patient variables that predispose to VTE. Epidemiological studies have demonstrated that age is an important risk factor with forty years designated as a threshold to separate risk groups, however other factors are also important that can place patients at high risk even if they are younger than forty (table 1b). The THRIFT group recommended that all patients admitted to hospital should be assessed for thromboembolic risk and then the intensity of the prophylaxis they receive should be tailored accordingly so that low-risk patients should be encouraged to mobilise as early as possible, moderate and high-risk should receive additional specific prophylaxis together with early mobilisation, such as GCS, intermittent pneumatic compression (IPC) and subcutaneous heparin injections.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calf DVT</td>
</tr>
<tr>
<td>High-risk</td>
<td>40-80%</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>10-40%</td>
</tr>
<tr>
<td>Low-risk</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Table 1c – Risk categories in surgical patients. (Modified from the European Consensus Statement 1993 and Salzman & Hirsh 1982)
The recommendations of the THRIFT group were reinforced by the European consensus statement (Haas 1993), the risk to each of the groups were more clearly defined (table 1c) with their recommended prophylaxis requirements. High-risk patients should receive a combination of pharmacological and mechanical methods of prophylaxis, namely low molecular weight heparin (LMWH) or low dose unfractionated heparin (LDUH) subcutaneous injections and GCS (and/or IPC) respectively. Moderate risk patients should receive one or a combination of the above ‘high-risk’ prophylaxis. Low-risk patients may be given prophylaxis, such as GCS on the basis of a risk-benefit ratio, however there was insufficient data at this time (1993) for guidance in this risk group. The author emphasized the need for comparisons of LMWH to LDUH, and pre- and post-operative commencement of pharmacological and mechanical modalities.

There are numerous large and small consensus groups that produce guidelines for prescribing effective prophylaxis against VTE in hospitalised patients. The majority rely on the theoretical basis of VTE risk categories for patients who require increased prophylaxis according to their increased risk. The majority of surgical patients that stay in hospital for treatment do so because of the severity of their illness, as a product of their comorbidity this results in most patients falling into the high and moderate risk groups with very few low thromboembolic risk in-patients. The common theme of ‘risk proportional thromboprophylaxis’ means that the majority of surgical in-patients are therefore recommended subcutaneous heparin and GCS (or IPC) for the high or moderate risk patients (Table 1d). In other words, heparin and stockings for any patients with one or more risk factors or an age over thirty-nine years undergoing more than minor surgery. The recommendations for low-risk patients are not proven as RCTs for this group have not been performed, however
these patients undergoing minor surgery are commonly treated in hospital day-surgery facilities, or if hospitalised for a more major procedure they are usually anecdotally recommended early mobilisation with or without GCS.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical Features</th>
<th>Recommended DVT Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Major surgery, &gt;60 years and &gt;40 with risk factors. Major Orthopaedic leg surgery</td>
<td>Subcutaneous Heparin and GCS, or IPC</td>
</tr>
<tr>
<td>Moderate</td>
<td>Major surgery; &gt;40 yrs Minor surgery; &gt;60 yrs and &gt;40 with risk factors</td>
<td>Subcutaneous Heparin and/or GCS, or IPC</td>
</tr>
<tr>
<td>Low</td>
<td>Major surgery; &lt;40 yrs Minor Surgery; &lt;60 yrs No risk factors</td>
<td>Early Mobilisation or GCS</td>
</tr>
</tbody>
</table>

Table 1d - Recommended thromboembolic prophylaxis for surgical patients. Modified from the International Consensus Statement (Nicolaides et al 2001)

*Abbreviations: DVT; deep vein thrombosis, GCS; graduated compression stockings, IPC; intermittent pneumatic compression. Additional risk factors include: malignancy, previous DVT or pulmonary embolus, varicose veins, oestrogen medication, thrombophilia, ongoing sepsis, morbid obesity and general immobility. Operations: Minor Surgery; less than 30 minutes, Major Surgery; more than 30 minutes operating time.*
The most recent and comprehensive guidelines for the prevention of VTE in surgical patients is from the International Consensus Statement (Nicolaides et al 2001 & 2002). The recommended prophylactic requirements for general surgical and orthopaedic patients are summarised in table 1d.

At the time this study was performed (2001-2003), the current edition of the International consensus (Nicolaides et al 2002) provided more evidence for the use of GCS, IPC and LMWH in specific surgical groups of patients, these will be discussed in more detail in chapter two. However, in general the international consensus guidelines rely on the relationship between the risk of VTE and an increase in the intensity of recommended prophylaxis.

1.5.2 Reported application of thromboembolic prophylaxis

The use of thromboprophylaxis by surgeons has reportedly increased over the last two decades, however rates of VTE episodes have not decreased significantly since the 1980s. At this time, surveys of the prophylactic methods used by surgeons have shown that in the United Kingdom and North America, only about 25% of general surgeons and 5% of orthopaedic surgeons reported using perioperative administration of subcutaneous heparin routinely (Morris 1980, Simon 1974, Conti & Daschbach 1982). Since this time, numerous investigators have provided a substantial amount of evidence to show that prophylaxis against venous thromboembolism is effective by reducing the incidence of DVT and PE by as much as two-thirds. Despite the apparent benefits of prophylactic measures Anderson and colleagues showed that only one-third of patients received prophylactic therapy (Anderson et al 1991). Evidence has laid the foundations for the numerous comprehensive guidelines and frameworks for prophylactic practice that have been published in recent years (see
1.5.1 Current recommendations for thromboembolic prophylaxis). However, there is still controversy over the correct prophylactic methods for surgical patients from different surgical specialties (Jones 1991). This uncertainty is may partly explain the frequent occurrence of inadequate clinical application of thromboembolic prophylaxis in many centres in the UK and globally (George et al 1998, Jones 1991, Stephens et al 1995, Audet et al 1998, Fletcher et al 1992, Conti & Daschbach 1982, Bratsler et al 1998). These reports have demonstrated a lack of prophylaxis administered to surgical patients despite an abundance of excellent prophylactic techniques and international guidelines. The failure of the prophylaxis reaching the patients was shown to be related to the inability of clinicians to understand guidelines with the resultant poor application of prophylactic methods (Ahmad et al 2002).

1.6 Aims of study and hypotheses

With the aid of literature analysis and investigative results, the overall objective of this study was to establish a new evidence-based policy in order to improve the prevention of post-operative DVT in a large multidisciplinary teaching hospital. The original objectives set out in the thesis application were as follows,

1. Assess whether knee-length stockings are as effective as thigh-length at preventing postoperative DVT through incidence of DVT and stocking satisfaction and compliance
2. Assess the VTE prophylactic practices in Charing Cross Hospital
3. Compare the venous flow characteristic of knee and thigh-length stockings to determine whether these may account for different efficacies of the stockings
However, during the preparation for the clinical trial required for the comparison of the knee and thigh-length stockings it soon became apparent that the state of surgical DVT prophylaxis in our hospital was in disarray. This led to a formal audit assessment of the status of thromboembolic prophylaxis in our surgical departments and research of the literature to develop a possible solution. Failure by the surgical departments in our hospital to use or implement the current European or International guidelines for the prevention of DVT lead us to believe that a simplified protocol was necessary to improve the application of DVT prophylaxis. Hence, the first two original objectives set out in the thesis application became a larger study than originally anticipated due to the major failures in DVT prophylaxis in our institution. The main study objectives were therefore changed accordingly:

1. Assess the state of thromboembolic prophylaxis in surgical patients in our multidisciplinary teaching hospital.

2. Report to each surgical department the status of thromboembolic prophylaxis in surgical patients with an overview of the current evidence in order to achieve a hospital consensus.

3. Assess the impact of a new single blanket protocol on hospital prophylaxis compliance.

4. Development of the new single protocol for DVT prophylaxis through a randomised clinical trial to compare knee to thigh-length stockings and the blanket application of LMWH for all surgical in-patients undergoing surgery.

5. The development of a specific HRQL and compliance questionnaire to assess satisfaction of patients wearing GCS.
6. Introduction of the new single protocol to all surgical departments to achieve a hospital consensus for patients admitted to a large teaching hospital for surgery.

The following plan of investigations for the study were undertaken:

1. Literature review and summation-analysis
   An overview of the literature assessing pharmacological and mechanical prophylaxis. A summation analysis of the current literature comparing the efficacy of knee to thigh-length graduated compression stockings for the prevention of post-operative DVT.

2. Audit of current practice
   An audit of the current status of venous thromboprophylaxis in a large teaching hospital. An education and awareness program to improve practice where needed prior to repeat audit.

3. Questionnaires
   The development of a questionnaire to formally assess the status of DVT preventive practice by surgical firms in Charing Cross Hospital.

4. Investigations
   a) A randomised controlled trial (RCT) to compare the efficacy of knee to thigh length GCS for the prevention of post-operative DVT
   b) Assess the safety of LMWH used across the board as part of a single blanket protocol for all surgical in-patients undergoing surgery.
c) The development and use of a specific HRQL questionnaire and compliance assessments to assess satisfaction and compliance respectively of patients wearing GCS.

The ultimate study goal was to develop a new single ‘blanket’ protocol to prevent post-operative DVT, in a university hospital, suitable for all surgical patients undergoing surgical procedures. In our hospital this included low, moderate and high-risk patients from breast and oncology, ear, nose and throat (ENT), gastrointestinal, neurosurgery, orthopaedic, urology and vascular surgical specialities. If proven to be safe and effective for all surgical specialities, a single protocol - as a product of its simplicity - would theoretically improve hospital prophylaxis compliance.

1.6.1 Study hypotheses and end-points

The primary study hypothesis was,

'Provided all patients receive LMWH, thigh-length anti-embolic stockings are equivalent to knee-length of the same design in the prevention of post-operative deep vein thrombosis'

The primary end-point of the study was the incidence of post-operative deep vein thrombosis diagnosed by duplex scanning.

The secondary study hypothesis was,

'A protocol of low molecular weight heparin and anti-embolic stockings
is safe and effective to implement as blanket prophylaxis to prevent post-operative deep vein thrombosis in all surgical patients and procedures requiring general anaesthesia.'

The secondary end-point was the incidence of complications associated with the use of low molecular weight heparin and anti-embolic stockings. The tertiary study hypothesis was,

'The satisfaction and compliance of patients wearing knee-length anti-embolic stockings is greater than with thigh-length stockings.'

The tertiary end-points were the specific HRQL measurement for patient stocking satisfaction and the patient stocking compliance.

1.7 Statistical analysis

Statistical analysis was performed using STATA 6.0 statistical package (Stata Corporation, College Station, USA). Logistic regression analysis was used to estimate crude odds ratios (ORs) between Medi thigh-length and Medi knee-length and between Kendall thigh-length and Medi knee-length stocking groups. These crude ORs were also adjusted for the use of preoperative LMWH.

1.8 Computer equipment, software and database

A Dell® Optiplex™ Gxi computer was used (Pentium III 800MHz) with 128Mb of ram for the majority of the study work, all patient data was kept in offline storage databases. A database of all patients entered into the study was completed using
Microsoft® 2000 Professional (Microsoft Corporation, Seattle, USA) Access™ database. The Access database was used as the primary database from which information could be taken for analysis in other databases for statistical analysis and graphs, namely Microsoft® Excel™, SPSS® (SPSS Inc, USA) and STATA 6.0 statistical package (Stata Corporation, College Station, USA). Reference Manager (Research Information Systems) was used to store and compile references.
Chapter 2

A review of the literature:
The prevention of deep vein thrombosis in surgical patients

List of contents

2.1 Introduction
2.2 Why prevent deep vein thrombosis?
2.3 Types of prophylaxis: mechanisms of action, efficacies and complications
   2.3.1 The mechanical methods of prophylaxis
   2.3.2 The pharmacological methods of prophylaxis
      2.3.2.1 Subcutaneous heparin
      2.3.2.2 The recent orthopaedic literature comparing unfractionated to low molecular weight heparin for thromboprophylaxis.
      2.3.2.3 Oral anticoagulants
      2.3.2.4 Dextran infusion
      2.3.2.5 Antiplatelet agents
      2.3.2.6 Others
   2.4 Recommendations for the use of prophylaxis in clinical practice
   2.5 Cost-effectiveness
2.6 Commencement and Duration of Prophylaxis
2.1 Introduction

A vast amount of literature and studies involving the prevention of venous thrombosis have been published over the last fifty years. The aim of this chapter is to provide the reader with a succinct overview on the prophylaxis of DVT in surgical practice and an update on the latest evidence for recommendations and advances in this area. In recent years, meta-analysis has been applied as a means of bringing together the large collection of data on VTE prophylaxis. However meta-analysis has its potential pitfalls through its nature of combining information from smaller studies to produce an overall result, hence these articles should be interpreted with caution, especially with regard to the inclusion criteria. Traditional reviews of the literature offer insights into possible trends within the disease pattern, however they rarely offer new evidence as the data from studies is usually kept in the original form and not summated. The foundation of evidence-based practice is the prospective randomised controlled trial, of which many have been performed over the last five decades on the prevention of VTE.

2.2 Why prevent deep vein thrombosis?

Deep vein thrombosis causes considerable harm to the patient, acutely it can propagate and embolise to form a fatal pulmonary embolus and in the long term may progress in at least thirty percent of cases to the chronic and incurable condition of post-thrombotic syndrome which can lead to venous ulceration (Kakkar et al 1969, Giannoukas et al 1995 & Prandoni et al 1996). The alternative to primary prevention is secondary prevention that involves screening, diagnosis and treatment of DVT. Deep vein thrombosis is not only a dangerous disease, but also elusive and difficult to treat, less than half of all DVT are symptomatic, and these symptoms, when
present are non-specific. The long-term anticoagulation treatment of DVT is not always absolute, as some patients continue to suffer from the acute – recurrent DVT and pulmonary emboli – and the chronic sequelae of VTE and in addition it is not uncommon for patients to suffer severely from the side effects of long-term anticoagulation. Among the patients that are adequately treated for DVT, recurrent thrombosis may occur in up to thirty percent at 8 years and PTS may develop in up to twenty-eight percent at five years (Prandoni et al 1996)

In general the burden to patients and professional staff, the inability of treatment to reliably resolve the effects of DVT and the huge costs of screening and treatment (Bergqvist 1988) has led to primary prevention of DVT (and therefore VTE in general) being the only viable mode of action followed by secondary prevention for the relative few that escape the prophylactic net.

2.3 Types of prophylaxis: mechanisms of action, efficacies and complications

The prophylaxis of DVT can be achieved by using a variety of different means; these can be divided in to mechanical or pharmacological methods. Each method targets one or more of the areas of Virchow’s aetiological triad, the mechanical methods in general prevent the stasis of venous blood and damaging effects of venous over-distension. Whereas the pharmacological agents combat the increased coagulability of the blood. The different types of established prophylaxis are summarised in table 2a.
### Table 2a – The different types of thromboembolic prophylaxis

<table>
<thead>
<tr>
<th>Mechanical Prophylaxis</th>
<th>Pharmacological Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graduated compression stockings</td>
<td>Subcutaneous low dose heparin</td>
</tr>
<tr>
<td></td>
<td>(unfractionated or low molecular weight)</td>
</tr>
<tr>
<td>Intermittent pneumatic compression</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Early mobilisation and leg elevation</td>
<td>Dextran</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

#### 2.3.1 The mechanical methods of prophylaxis

The mechanical methods of prophylaxis include graduated compression stockings and intermittent pneumatic compression devices, which are thought to prevent DVT through increasing the emptying of blood from venous valve pockets, increase the velocity of distal to proximal venous blood flow and reduced over-distension of the veins during surgery. Mechanical methods have a number of advantages over pharmacological modalities:

- They do no alter the clotting mechanisms within the blood and therefore the bleeding tendency,
- Simple to use,
- Cheap and cost-effective,
• Can be combined with pharmacological methods to increase the efficacy of prophylaxis,

• Can be considered for use in low risk patients due to their low complication rate and minimal cost.

However, there are a number of disadvantages:

• They have not been shown to reduce the risk of PE unlike anticoagulant prophylaxis (Nicolaides et al. 2002).

• Effectiveness is reliant on compliance which may be decreased in patients who find them uncomfortable

• Mechanical methods are contraindicated in patients with peripheral vascular disease due to risk of producing limb ischaemia

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Mean incidence of DVT (%) by $^{125}$I fibrinogen scanning [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>25.1 [23.9,26.5]</td>
</tr>
<tr>
<td>Low dose unfractionated heparin</td>
<td>8.7 [7.8-9.7]</td>
</tr>
<tr>
<td>Graduated compression stockings</td>
<td>9.3 [6.4-13.3]</td>
</tr>
<tr>
<td>Intermittent pneumatic compression</td>
<td>9.9 [6.9-13.9]</td>
</tr>
<tr>
<td>Dextran</td>
<td>16.6 [13.1-18.4]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20.4 [16.5-25.0]</td>
</tr>
</tbody>
</table>

Table 2b – Summary of DVT prophylaxis efficacies. Modified table from meta-analysis in general surgical patients (Clagett & Reisch 1988)
The specific characteristics and properties of graduated compression stockings are reviewed in chapter three of this thesis, with particular attention paid to the efficacies of the thigh and knee-length designs. The efficacy of GCS in the prevention of postoperative DVT in general surgical patients was calculated by meta-analysis performed by Clagett and Reisch (1988), the results are shown in table 2b. 

*Intermittent pneumatic compression* has been recognised as a useful inhibitor of postoperative DVT formation, on a par with GCS stockings and recommended for prophylactic use as an alternative to GCS (Nicolaides et al 2001). However, IPC has been shown to have limited prophylactic benefit in patients undergoing surgery for malignancy (Clagett et al 1988). Graduated compression stockings have the benefit of improved practicality as IPC requires an electrical supply and thereby limits mobility on the ward and is more expensive. However, IPC can be used simultaneously over GCS, especially on the operating table.

### 2.3.2 The pharmacological methods of prophylaxis

In the forty-five years since the pioneering randomised clinical trial investigating the efficacy of anticoagulation in the management of venous thromboembolism (Barritt & Jordan 1960), there has been substantial progress in the management of VTE with major advances in anticoagulation therapy used for the primary prevention of VTE. Venous thrombosis usually occurs at the vessel wall with stasis or hypercoagulability as predisposing factors. Venous thrombosis, unlike the ‘platelet-dependent’ arterial thrombosis, relies more on the formation of thrombin and fibrin. Therefore anticoagulant medications that reduce the formation of thrombin and hence reduce the initiation and the extension of fibrin-rich venous thrombi are of major importance.
in the prevention of deep vein thrombosis and pulmonary embolism. The mainstream pharmacological methods of prophylaxis are summarised in table 2b.

2.3.2.1 Subcutaneous heparin

In 1916, W. H. Howell discovered heparin and its ability to prevent the clotting of blood. Heparin is a naturally occurring glycosaminoglycan normally present in human tissues, the properties of heparin are summarised below in table 2c. Heparin was first isolated from ox liver by J. McLean who also identified its anticoagulant capabilities (McLean 1916). Unfractionated heparin is obtained commercially from either bovine lung or porcine intestinal mucosa, and consists of a heterogeneous mixture of polysaccharides with a range of molecular weights from 4,000 to 30,000, with a mean molecular weight of approximately 12,000.

Most commercial heparins have specific activities usually around 150 U/mg, however the calcium salts of heparin are thought to have decreased local bleeding with subcutaneous injections and greater bioavailability than sodium heparin (Hirsh et al. 1970). The heparin structure consists of alternating residues of uronic acid and glucosamine that are variably sulphated, this sulfation of residues is a major determinant of heparin’s anticoagulant activity. By itself, heparin is not an anticoagulant but a catalyst with a high binding affinity for anti-thrombin III (ATIII). ATIII regulates coagulation by inactivating coagulation proteases, such as thrombin and Xa, whose activity is enhanced by the binding of heparin. Low molecular weight heparins primarily inhibit factor Xa and have a lesser effect on the inhibition of thrombin. In addition to its anticoagulant properties, heparin has other biological effects, such as; hydrolysis of triglycerides from chylomicrons, activation of
platelets, suppress cell-mediated immunity, and affect the metabolism of aldosterone and thyroxine.

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### The Properties of Heparin

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Negatively-charged glycosaminoglycan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Intravenous, subcutaneous</td>
</tr>
<tr>
<td>Site of action</td>
<td>Blood, vascular endothelium</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Catalyses antithrombin III inactivation of serine proteases (thrombin, factor Xa)</td>
</tr>
<tr>
<td>Dosage for prophylaxis</td>
<td>5000 U subcutaneous 8-12 hr</td>
</tr>
<tr>
<td>Dosage for treatment of thromboembolism</td>
<td>5000-10000 U initial intravenous bolus, 30,000 U/24 hr continuous infusion until oral anticoagulation established</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Activated partial thromboplastin time (aPTT), Heparin levels for patients receiving very high doses or for patients in which aPTT is unreliable, for example lupus anticoagulant.</td>
</tr>
</tbody>
</table>

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**Table 2c** **The Properties of Heparin**

*Pharmacokinetics.* The highly charged nature of heparin prevents its passage through cell membranes and thus prevents the oral use of heparin. Heparin is active when given parenterally, either intravenously or subcutaneously. The half-life of heparin increases with increasing dosage and decreases with increased clearance. Heparin is cleared by the reticuloendothelial system, metabolised by the liver, and the metabolic products are excreted in the urine. Clearance is also increased secondary to the extent of thromboembolism. Finally, the activity of heparin is also affected by its
binding to plasma proteins and the endothelium. Therefore the anticoagulation achieved by heparin has a number of dependent variables so that the therapeutic use has to be closely monitored to maintain a range that is effective but without over-anticoagulation to reduce risk of bleeding. Low dose subcutaneous unfractionated heparin for prophylaxis of VTE usually does not require monitoring with the standard twelve or eight hourly subcutaneous injection regimes. The standard unfractionated heparin has a number disadvantages when compared to the more recently developed LMWH, which has led to the increasing use of the latter in clinical practice (discussed later).

*Low dose unfractionated heparin* (LDUH) - usually prescribed 5000 units 8-12 hourly - has been the most common form of anticoagulant prophylaxis used over the last four decades. Its use has been advocated for the moderate and high-risk patients. In general, it is a safe and effective form of prophylaxis proven to reduce not only the rate of DVT but also fatal PE and overall patient mortality (Collins et al 1988, Hyers et al 1989, Salzman & Hirsh 1977). Despite the promising results from large RCTs investigating the prophylactic benefits, LDUH prevents only about two-thirds of DVT and two-thirds of fatal PE (Collins et al 1988 & International multicentre trial 1975).

The prevention of postoperative DVT with pharmacological methods is unfortunately achieved with infrequent but occasionally serious side effects from the treatment, however with careful administration of heparin the risks can be kept to a minimum. Bruising at the injection site can be minimised by using a concentrated solution (25000 units/ml), a small bore needle and good injection technique. With LDUH there have reports of increased risk of intra- and postoperative bleeding complications of around two percent (Collins et al 1988, Clagett et al 1988 & IMT
1975, 1997), however an equal number of reports have detected no difference in bleeding complications from placebo, and even less with the more contemporary LMWH. In the majority of studies, of which many are from orthopaedic and neurosurgery specialities who particularly fear operative bleeding complications, LDUH was shown to not increase the incidence of operative bleeding when compared to placebo (Dunn & Goa 1996, Freedman et al 2000, Howard & Aaron 1998, Palmer et al 1997, Koch et al 1997). Operative bleeding complications have a number of causes and distinguishing those due to heparin coagulopathy maybe difficult and for this reason many randomised clinical trials have investigated this phenomena. Randomised controlled trials, some with double-blinding have shown rates of bleeding complications for LMWH, LDUH and placebo in orthopaedic surgery that ranged between 1.5-6%, 6-9% and 2.4-8% respectively (Levine et al 1991 & 1996, Menzin et al 1994, Turpie et al 1986, Leclerc et al 1996). Likewise, in neurosurgery bleeding complications occurred at 2-3%, 0-1.8% and 0-3% respectively (Raab et al 2001, Macdonald 1999, Agenlli 1988, Nurmondamed 1996), and results from gastrointestinal surgery studies were very similar (Ockelford et al 1989, Gallus et al 1993). Contraindications to subcutaneous heparin include bleeding disorders such as thrombocytopenia, haemophilia, hepatic or renal failure; potential or ongoing bleeding, such as from peptic ulceration or varices; history of hypersensitivity to heparin or heparin induced thrombocytopenia. Heparin induced thrombocytopenia occurs in approximately 0.3% of patients given prophylactic porcine heparin, the Committee on the safety of medicines advises that heparin activity and platelet levels should be monitored after five days of prophylaxis and stopped if thrombocytopenia is detected. Other unfavourable reactions include skin
necrosis, raised serum concentrates of serum transaminases, osteoporosis with long-term heparin especially in pregnancy (Hirsch 1991)

Low molecular weight heparin, like unfractionated heparin exerts its anticoagulant function by potentiating the action of antithrombin against its target proteases (thrombin and factor Xa) and by mobilising the tissue factor pathway inhibitor (TFPI) from the vascular endothelium into the circulation. In contrast to unfractionated heparin, LMWH has little effect on factor II but has a similar effect on factor X. The ability of LMWH to inhibit factor ten is the cornerstone of its anticoagulant properties. TFPI is a potent inhibitor of the extrinsic coagulation cascade, which exerts its function by neutralising the catalytic activity of factor Xa and by feedback inhibition of the factor VIIa-TF complex in the presence of factor Xa. The observed superior efficacy of LMWH over unfractionated heparin in clinical trials assessing prophylaxis and treatment of VTE may be explained by the decreased circulating antithrombin and TFPI (free- and bound) found with unfractionated heparin but not with subcutaneous LMWH treatment (Hansen & Sandset 1998). The monitoring of the anticoagulant activity of LMWH is through measurement of antifactor Xa levels, however this not necessary with the low dose required for VTE prophylaxis. During the last two decades several LMWHs have been developed by chemical or enzymic degradation of unfractionated heparin. The LMWHs currently available for use in clinical practice are produced by different techniques and therefore have varied pharmacological properties, which may have important clinical implications such as associated bleeding complications. Examples of LMWH that have been investigated in clinical trials include, enoxaparin, certoparin, dalteparin, nadroparin, parnaparin, tinzaparin and clivarine. In the UK, only Enoxaparin (20-40 mg/d), tinzaparin (3500 units/d) and dalteparin are currently licensed for use in VTE
prophylaxis in the UK. Enoxaparin and tinzaparin are LMWH with an average molecular weight of about 4500 daltons (Kakkar et al 1993). They have better bioavailability by the subcutaneous route and a longer half-life in the circulation than unfractionated heparin, allowing a once daily administration for prophylaxis and treatment. The anti-Xa/anti-IIa ratio ranges from 1.5 to 1.8 for tinzaparin and around 3.2 for enoxaparin, these ratios theoretically would be important in predicting the antithrombotic efficacies and bleeding risk of the LMWH (Bara et al 1999). Low molecular weight heparin has been heavily investigated over the last decade to establish its efficacy and safety when compared to LDUH and placebo. A large of number of trials and meta-analyses have demonstrated that LMWH is undoubtedly no worse and in many instances better at preventing thromboembolic complications than LDUH. A meta-analysis by Mismetti and colleagues (2001) comprehensively updated the surgical profession on the efficacies and complications of LMWH compared to placebo and LDUH. Previous meta-analysis have demonstrated a reduction of asymptomatic DVT with LMWH and LDUH that was associated with a reduction in the risk of PE or death (Leizorovicz et al 1992 & Jorgensen et al 1993). Mismetti and colleagues found 82 studies from 1984 to 1999 evaluating LMWH in general surgery, urology, gynaecology, and cancer surgery, of which 21 were excluded for poor techniques of randomization, methodology, or use of heparinoids. In comparison to placebo, LMWH was found to significantly reduce the risk of DVT by 72 percent (relative risk (RR) 0.28(95% CI 0.14,0.54) p<0.001), clinical PE by 75 percent (RR 0.25 (0.08,0.79); p = 0.018) and clinical VTE by 71 percent (RR 0.29 (0.11,0.73); p = 0.009). Haemorrhage was found to be more frequent in patients with preoperative LMWH than placebo, the incidence of major haemorrhage was 2.8 percent and wound haematoma was 10.3 percent. Individual LMWH groups were
not analysed due to small numbers of studies. In comparison to LDUH, LMWH reduced the risk of DVT, clinical PE by a non-significant margin, 10% and 12% percent respectively. However, LMWH was significantly better at reducing clinical VTE ($p = 0.049$). As far as haemorrhagic complications were concerned, with LMWH there was a reduced risk of major haemorrhage and wound haematoma, but not significantly less than LDUH. When the dosage of LMWH was introduced into the analysis, low-dose LMWH (3400 anti-Xa units or less) achieved an equal efficacy to LDUH, but with significantly less risk of haemorrhage (RR 0.76 (0.63,0.92); $p = 0.005$). Conversely, high-dose LMWH (more than 3400 anti-Xa units) appeared to be more effective than LDUH, especially with clinical PE, however this was counterbalanced with by a significant increased risk of haemorrhagic complications. Other more recent meta-analyses have reinforced the argument for LMWH over LDUH and placebo in the prevention of VTE with minimal bleeding complications (Counsell & Sandercock 2002, Will-Jorgensen et al 2002 & Handoll et al 2002).

In addition to improved efficacy, LMWH has other advantages in terms of patient acceptability, practicality and cost. Patient acceptability is improved with only one daily subcutaneous injection compared to a possible three injections with LDUH. The single daily administration is more practical for health professionals and at the time writing LMWH daily cost (e.g. enoxaparin 20mg - 90 pence) was less than the daily cost for LDUH (from 98 pence/day). The fact that LMWH requires only a once daily dose, permits the injection to be given on the evening before surgery, which allows the peak plasma anti-Xa activity that occurs one to four hours after the injection to pass during the night, therefore reducing further any risk of peroperative bleeding. Many anaesthetists also prefer LMWH prophylaxis to be given
up to twelve hours before placement of spinal and epidural anaesthesia (Bergqvist & Wiklund 2000). Therefore LMWH should be administered on the ‘evening’ before surgery to allow these patients to safely receive regional anaesthesia and LMWH prophylaxis. LMWH has other potential side effects apart from the ‘bleeding’, which include allergy; inducing skin necrosis and heparin induced thrombocytopenia. In contrast to unfractionated heparin, in cases reviewed from the literature, the LMWH induced minimal thrombocytopenia or thromboembolic complications and skin necrosis usually only occurred after previous heparin exposure. Whereas in cases with unfractionated heparin that induced skin necrosis, the patients were rarely pretreated with heparin and showed greater tendency towards thrombocytopenia and thromboembolism. This would suggest that LMWH is less immunogenic than unfractionated heparin and requires repeated exposure to initiate skin necrosis (Fureder et al 1998).

2.3.2.2 The recent orthopaedic literature comparing unfractionated to low molecular weight heparin for thromboprophylaxis

The main area of controversy with the use of LMWH has been in orthopaedic surgery, some of these surgeons argue that the potential risk prosthetic joint infection secondary to haematomae caused by the bleeding tendency of LMWH far outweigh the benefits of preventing ‘asymptomatic DVT and the occasional PE’. A summary of the literature assessing the incidence of bleeding complications after orthopaedic surgery with heparin thrombo-embolic prophylaxis is included. An search of electronic databases, Medline and Pubmed, for orthopaedic meta-analyses or randomised controlled trials (RCT) published over the last 10 years has produced the following studies assessing heparin for the prophylaxis of deep vein
thrombosis and pulmonary embolism in patients undergoing orthopaedic surgical procedures. Their conclusions about efficacy of LMWH and LDUH and bleeding complications are summarised below.

**Freedman et al.** *A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. J.BJS July 2000; 82-A: 929-38.*

(1) In this study LDUH was the least effective and least safe pharmaceutical prophylaxis, LMWH was second to warfarin for efficacy and safety.  
(2) Significant bleeding risks were associated with both LDUH (minor and major bleeding complications) and LMWH (minor only). Major bleeding complications included gastrointestinal, spinal/epidural anaesthesia related or wound haematomas requiring surgical decompression.


(1) LMWH is more efficacious than LDUH or warfarin for DVT prevention.  
(2) No excess of bleeding was recorded in the LMWH group.

(1) In orthopaedic surgery LMWH is significantly superior to both LDUH and warfarin in the prevention of DVT.

(2) LMWH results in significantly less bleeding complications when compared to LDUH and warfarin.


(1) LMWH was superior to LDUH with respect to efficacy and safety in orthopaedic surgery (safety analysis reported wound haematomas and other bleeding complications).

(2) Low dose LMWH was equally efficacious to LDUH and provided increased safety over LDUH.

(3) High dose LMWH did not provide an increase in efficacy of prophylaxis.


(1) All treatments except aspirin reduced the risk of DVT.

(2) Only LMWH and stockings reduced the risk of pulmonary embolism.

(3) Percentage of patients with clinically important bleeding was 1.8% and 2.6% with LMWH and unfractionated heparin respectively.

(1) LMWH is more effective in DVT prevention than LDUH
(2) No significant differences in minor and major bleeding complications were found between the two groups.
(3) The use of LMWH results in an overall saving in cost.

In summary, the issue of bleeding complications is controversial because some studies have shown fewer wound haematomas and bleeding complications with LMWH while other studies have shown the opposite. Summations of the available data by meta-analyses show a trend towards LMWH having an increased efficacy with fewer postoperative bleeding complications. A large European trial (Leyvraz et al 1991) showed that LMWH with adjusted dose for weight showed no increase in bleeding complications. A recent review of VTE prophylaxis found that the discrepancy between trials reporting different rates of bleeding complications with LMWH was related to the doses used (Agnelli & Sonaglia 2000). It has been shown that doses of LMWH greater than 3400 anti-Xa IU/day were associated with higher rates of bleeding than experienced with LDUH. In contrast, LMWH used in doses lower than 3400 anti-Xa IU/day produced similar levels of VTE prevention with less bleeding.
2.3.2.3 Oral anticoagulants

In the 1920's, it was found that cattle fed on spoiled sweet clover developed a severe bleeding tendency. The active agent was later identified as bishydroxycoumarin (dicoumarol) (Campbell & Link 1941) and from this, synthetic derivatives - including warfarin - were developed. The therapeutic efficacy of vitamin K antagonists led to their widespread use in the 1970s, however drug associated bleeding disorders became troublesome. The subsequent acceptance of the International Normalised Ratio (INR) has improved the clinical application of warfarin. Commercially available warfarin is a racemic mixture of levorotatory and dextrorotary forms, which has a half-life of approximately 36 hours. Warfarin inhibits the synthesis of γ-carboxylated vitamin K dependent proteins (prothrombin, factors VII, IX, X) and this leads to the anticoagulant effect in the circulation.

Complications of warfarin include haemorrhagic complications; there is a direct relationship with bleeding and the intensity of anticoagulation. And non-haemorrhagic complications, such as alopecia, abdominal discomfort, liver dysfunction and skin necrosis, these are rare. Warfarin induced skin necrosis an uncommon but devastating complication that usually occurs in the first week of treatment. Thrombosis of skin vessels results in skin necrosis that frequently requires plastic surgery or even amputation.

Warfarin is effective in the prevention of DVT after orthopaedic surgery (Francis et al 1983, Morris & Mitchell 1976, Powers et al 1989) and gynaecological surgery (Taberner et al 1978 & Poller et al 1987). It has been shown to be effective, whether started preoperatively or post-operatively (Hirsch 1990 & 1991, Gallus 1990). Due to the potential bleeding risk with the recommended general use of an international normalised ratio (INR) of 2-2.5 and 2-3 for orthopaedic hip operations, some authors
have advocated using a preoperative low-dose of warfarin or commencing prophylaxis after surgery (Francis et al 1983, Poller 1987 & Hirsch 1991). Warfarin is usually reserved for high-risk patients due to the required daily laboratory INR assessments and increased risk of bleeding (Hirsch 1990 & 1991, Gallus 1990). Warfarinisation if contraindicated in patients with bleeding disorders or bleeding pathology (as for heparin) and in pregnancy due to risk of fetal abnormalities. Caution should be taken with spinal or regional anaesthesia due to the risk of haemorrhagic complications (Wille-Jorgensen P et al 1991 & Wildsmith & McClure 1991). Warfarin has been shown to be effective for orthopaedic surgery but is not practical for other specialities that involve abdominal surgery because post-operative ileus would prevent its administration.

Oral forms of LMWH are currently under investigation, which would avoid the cost and patient discomfort of the subcutaneous route of administration. The relative large size and negative charge of the molecule has lead to the unreliable absorption of LMWH via the gastrointestinal tract. A compound has been developed (Emisphere Technologies, Tarry-town, New York, USA) to act as a ‘carrier’ for LMWH to be administered orally; sodium N-[10-(2-hydroxybenzoyl)amine decanoate (SNAD). LMWH and SNAD are bound by a noncovalent interaction that allows the compound to pass through the gastrointestinal mucosa. Once in the bloodstream the complex dissociates to leave the free LMWH molecule. Animal experimental studies have demonstrated a significant anti-Xa activity with decreased thrombosis after oral LMWH treatment (Salartash et al 2000). In future years oral LMWH may become the treatment of choice for the prevention of VTE in the large proportion of hospitalised patients who can receive oral medication, the remainder
who are only tolerant of parental medications, would therefore receive subcutaneous form of LMWH.

2.3.2.4 Dextrans infusion

Dextrans 70 has been shown to exert antithrombotic effects on the lysability of fibrin, platelets and the endothelium (Bergentz 1978). However, it has limited ability to prevent DVT, more so in orthopaedic patients, and it seems to have achieved better results in preventing PE, possibly due to its fibrin lysing ability (Clagett & Reisch 1988, Hirsch 1990, Gallus 1990, Wille-Jørgensen 1991). Dextran has been shown to reduce fatal PE in data summated from 29 randomised studies, the controls (n=2981) had an incidence of 1.5% compared to the patients treated with dextran (n=2964) the fatal PE rate was 0.34% (Relative risk 0.22; 95% confidence interval (CI) 0.11-0.44), however the effect on preventing DVT was small (RR 0.76; 95% CI 0.64-0.91).

Dextran has the risk of bleeding complication, as for heparin, requires intravenous infusion with risk of fluid overload in the susceptible, and noteworthy allergic reactions, which include anaphylaxis (THRIFT consensus 1992).

2.3.2.5 Antiplatelet agents (Aspirin)

Aspirin exerts its antithrombotic effect by irreversibly inhibiting (by acetylation) platelet cyclooxygenase, preventing synthesis of thromboxane A2, and impairing platelet secretion and aggregation. Non-steroidal anti-inflammatory drugs (NSAID) such as aspirin have the well-documented complication of damaging the gastrointestinal (GI) mucosa, commonly resulting in gastric ulceration causing perforation or GI haemorrhage. Other side effects include abdominal discomfort, systemic bleeding and blood loss. Aspirin (acetylsalicylic acid) and
hydroxychloroquine have been shown to offer only minimal protection from VTE (Clagett & Reisch 1988, Gallus 1990). The antithrombotic effects of aspirin occur at low doses around 75mg, however these antithrombotic effects are mainly on the arterial side of the circulation.

2.3.2.6 Others

Hirudin, and its synthetic analogues are direct thrombin inhibitors that do not require antithrombin III for their activity consequently making them more efficient at inhibiting clot-bound thrombin (Weitz et al 1990). The advantages of hirudin include good bioavailability after subcutaneous injections, weak immunogenicity and ease of monitoring with activated partial thromboplastin time (aPTT) or thrombin time. Disadvantages include the lack of reversing agent and expense. Recombinant hirudin has been shown to be a possible alternative to subcutaneous heparin in two level one orthopaedic hip surgery studies (Eriksson et al 1994 and 1997).

Other novel anticoagulants include Tick anticoagulant peptide isolated from the Soft Tick, antistasin isolated from the Mexican leech, pro-uronase, and tissue plasminogen activators such as those isolated from the Vampire bat (Desmodus rotundus). These substances have limited human studies to provide evidence for their efficacy and safety.

Caval filters are used to prevent imminent PE and not DVT and together with their invasive nature, they are not indicated as part of routine VTE prophylaxis.

Drugs that stimulate fibrinolysis, such as anabolic steroid have only limited efficacy for VTE prophylaxis (THRIFT consensus 1992).
2.4 The recent recommendations for the use of prophylaxis in clinical practice

As previously discussed in chapter one, over the last four decades the continued development of evidence-based guidelines for surgeons to practice effective prophylaxis of VTE has lead to the protocols found in the THRIFT, European and International Consensus Statements. These guidelines advocated that all surgical and medical patients should receive specific thromboprophylaxis in accordance with their risk of developing VTE. This idea was modified from some of the first authors to separate the thromboprophylactic requirements of patients into categories in relation to thromboembolic risk (Salzman and Hirsh 1982). The risk of VTE in hospitalised patients is not only dependent on the patients’ illness, planned treatment or operation, but also on pre-existing patient variables that predispose to VTE. The patient factors that increase the risk of VTE include; age, obesity, immobility, increases in oestrogen levels, varicose veins, previous history of VTE, systemic infection, acquired and hereditary thrombophilias. Epidemiological studies have demonstrated that age is an important risk factor with forty years designated as a threshold to separate risk groups, however the other factors mentioned can unite to place patients at high risk even if they are younger than forty years of age.

The THRIFT group recommended that all patients admitted to hospital should be assessed for thromboembolic risk and then the intensity of the prophylaxis prescribed should be tailored accordingly. This resulted in the recommended prophylaxis for low-risk patients was early mobilisation, the moderate and high-risk patients were recommended combinations of prophylaxis such as GCS, IPC and subcutaneous heparin, together with early mobilisation.
The European consensus statement (Haas 1993) separated the risk of each group more clearly and allocated their recommendations for the prophylactic requirements of each group (table 2d).

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk of VTE</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calf DVT</td>
<td>Proximal DVT</td>
</tr>
<tr>
<td>High</td>
<td>40-80%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-40%</td>
<td>2-10%</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;10%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Table 2d – Risk categories and recommended prophylaxis in surgical patients (Modified from the European Consensus Statement. Haas 1993). Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolic disease; PE, pulmonary embolism; LMWH, low molecular weight heparin; LDUH, low dose unfractionated heparin; GCS, graduated compression stockings; IPC, intermittent pneumatic compression.

A number consensus groups have recommended very similar guidelines for the prescription of effective prophylaxis against VTE in surgical patients. The majority base their protocols on the theory of thromboembolic risk categories for which an increasing intensity of prophylaxis is recommended for a patient deemed to be at increased risk. This common premise results in the majority of patients staying in hospital for surgical treatment are usually of high or moderate risk of developing DVT or PE (any patients with one or more risk factors or over the age of forty years.
having more than minor surgery) and therefore receive subcutaneous heparin and/or GCS or IPC.

However, there are a number of potential flaws in the risk category system for prescribing VTE prophylaxis:

- Firstly, each different consensus uses slightly different risk factors for their risk categories which may lead to the inconsistent and disparate use of prophylaxis by doctors in hospital practice,

- Secondly, the evidence for the correct prophylaxis for one of the three risk groups is not available, i.e. the low risk patients.

- Thirdly, the risk categorisation depends on the characteristics of the individual patient and the type of surgery planned. If some of these factors used to ‘predict’ the correct prophylaxis inadvertently change intra- or post-operatively, then the patient will receive sub-optimal prophylaxis; such as the planned duration of surgery, the malignant status of a presumed benign lesion, and the patients’ postoperative mobility and infective status.

Despite these potential problems, the most recent and comprehensive guideline for the prevention of VTE in surgical patients is from the International Consensus Statement (Nicolaides et al 2002). The guidelines issued in this statement are summarised below (Table 2e). For the majority of patients from all of the specialities shown in the table, the evidence suggests that the most frequently effective modalities of prophylaxis are LMWH, for which the evidence is continually accumulating to make LMWH the drug of choice in VTE prevention, and GCS or IPC. Combinations of LMWH with GCS have been shown to be more effective than single prophylaxis, however more evidence is required. In comparison to IPC, GCS are cheaper, more acceptable to patients, easier to use, and more practical patients.
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>General Surgery</th>
<th>Orthopaedic Surgery</th>
<th>Neurosurgery</th>
<th>Gynaecology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>LMWH or LDUH (I)</td>
<td>TKR – LMWH (I), GCS &amp; IPC</td>
<td>Combinations of LMWH and GCS (III) or IPC</td>
<td>LMWH or LDUH (I), and IPC (I), GCS (III), or IPC</td>
</tr>
<tr>
<td></td>
<td>GCS or IPC (I)</td>
<td>THR – LMWH (I), Adjusted dose warfarin for neurosurgery patients in general</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combinations of above (II)</td>
<td>TKR – LMWH (I), IPC (I), recombinant Hirudin (I), and GCS (III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>LMWH or LDUH (I)</td>
<td>As above by extrapolation</td>
<td>LMWH of LDUH (I), and IPC (I) or GCS (III)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GCS or IPC (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Early ambulation</td>
<td>Early ambulation</td>
<td>GCS (III), Ambulation (III), Hydration (III)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydration</td>
<td>Hydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GCS</td>
<td>GCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Insufficient evidence)</td>
<td>(Insufficient evidence)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2e – Summary of the ‘International Consensus Statement’
recommendations for thromboembolic prophylaxis in surgical patients
(Nicolaides et al 2002) Abbreviations: Levels of evidence, (I) – from sound clinical
trials, (II) – from studies with some inconsistencies, (III) – Extrapolated evidence or
small or poorly designed trials; LMWH, low molecular weight heparin; LDUH, low
dose unfractionated heparin; GCS, graduated compression stockings; IPC,
intermittent calf or foot compression; TKR, total knee replacement; THR, total hip
replacement.

and staff. Thus GCS in the majority of instances are the preferred choice of
mechanical prophylaxis, however IPC used with GCS adds supplementary
protection.

2.5 Cost effectiveness of prophylaxis

In every part of the health service, whether state-run or self-funded, health
economics are an important part of health care practice. Without the efficient and
effective use of available resources the quality of care would soon deteriorate.
In medium and high-risk surgical patients the costs of screening, diagnosis and
treatment of VTE are so high that the current recommendations of primary
prevention utilise the resources most efficiently and therefore cost effectively (Haas
1993). VTE prophylaxis becomes less cost effective as age progresses due to the
decreasing life expectancy. There is no data available as yet for low-risk patients and
unfortunately this situation may not change as due to the low incidence of VTE in
this group the very large RCT’s required to attain the necessary data. Despite the
lack of data, the prophylaxis of low-risk patients should not be ignored as there is
firm evidence demonstrating that this group develop VTE complications even if
infrequently.
The cost effectiveness of DVT prophylaxis has been reported (Bergqvist 1997 & 1988, Anderson & O'Brien 1997, Menzin 1994), and because the cost of LMWH has reduced - to less than LDUH - since its conception it is now more cost effective. Though LMWH is 5 to 10 times more expensive than unfractionated heparin for the treatment of established DVT, it is now the cheaper heparin for prophylaxis at 90 pence per day (single daily injection of enoxaparin) compared to 98 pence per day for the twice daily regime of LDUH, thus making LMWH more economically acceptable than unfractionated heparin. The prices – at the time of study (2001-2003) - for Hammersmith Hospitals NHS Trust (Charing Cross Hospital) are summarised below:

➤ LMWH

- Clexane (enoxaparin) 90p per day (one injection)
- Fragmin (dalteparin sodium) 83.5p per day (one injection)
- Tinzaparin 3500u 85p per day (one injection)

➤ LDUH

- 98p per day (12 hourly: two injections per day at 49p per injection of mini-heparin)
- £1.47p per day (8 hourly: three injections per day at 49p per injection of mini-heparin)

2.6 Commencement and duration of prophylaxis

The best time for the commencement and the duration of thromboembolic prophylaxis is unknown. Many authors have investigated both sides of the dispute over commencing prophylaxis before or after surgery and for continuing prophylaxis for different periods of time post-operatively. There is some evidence in the existing
literature, but only very little from RCTs investigating this particular area of VTE prophylaxis. There are two main questions that need to be answered:

i. Should DVT prophylaxis be started before or after surgery?

ii. For how long does DVT prophylaxis need to be continued in the postoperative period?

The European consensus (1993) states clearly that 'prophylaxis should be initiated before operation in all groups. The current recommendation is to continue prophylaxis for 7-10 days. Although the evidence is weak, consideration should be given to extending prophylaxis when the hospital stay is prolonged or the risk continues.

Other authors have made similar recommendations that the prophylaxis of DVT should continue at least until discharge, and only in some selected high-risk cases after they have left hospital; therefore not for a predetermined time after surgery which may not be best for the individual needs of the patient (THRIFT consensus group 1992 & Scurr et al 1988). Three RCTs in orthopaedic surgery have investigated the optimal duration of prophylaxis after elective hip replacement surgery, which showed a marked reduction of venographically detected DVT – from 19-26% to 7-12% - in patients treated with one month of LMWH anticoagulant prophylaxis (Bergqvist et al 1996, Planes et al 1996, Dahl et al 1997). Conversely in a review of 29 general surgical trials involving over eight thousand patients, subcutaneous heparin was given to the majority of patients for only seven days. The authors of this recent comprehensive review on the methods of DVT prophylaxis recommended that 'prolonged prophylaxis with either LMWH or adjusted-dose warfarin (INR 2-3) can be adopted in patients with additional risk factors such as leg
paralysis, malignancy, or previous episode(s) of venous thromboembolism’ (Agnelli & Sonaglia 2000)

2.1 Conclusions

A number of conclusions can be drawn from the literature,

- Primary prevention is better for the patient and more effective than secondary prevention as the mainstay of VTE management.
- In general, graduated compression stockings are the preferred mechanical prophylactic modality in terms of efficacy, safety, cost, practicality and patient acceptability.
- Overall, low molecular weight heparin is the better pharmacological prophylaxis for the prevention of postoperative DVT again in terms efficacy, safety, cost, practicality and patient acceptability.
- Consensus groups recommend combination prophylaxis for high and moderate risk patients. The low risk recommendations are without evidence, however complication-free prophylaxis would be beneficial if not cost-effective.
- Risk categorisation of patients for thromboprophylaxis suffers a number of failings that can potentially result in inadequate prophylaxis.
- As surgery initiates the VTE process, it is probably more beneficial to start prophylaxis prior to surgery if safety can be guaranteed, however this is theoretical and yet unproven. The optimal duration of postoperative prophylaxis is unknown.
A number of areas for future research in the prevention of postoperative DVT were highlighted by the literature. If one considers the variety of patient characteristics and surgical procedures, together with the continuing advances in prophylactic methods, the whole subject of VTE prevention is vast. However, the key questions in surgical VTE prophylaxis that have arisen time and time again from many authors will require investigation via prospective randomised clinical trials in the future. These include:

- The efficacy of above-knee compared to below knee compression stockings (see chapter three)
- The efficacy of pre-operative compared to post-operative subcutaneous heparin prophylaxis
- The optimal duration of prophylaxis after surgery
- The best methods of improving the rate of application of protocols/guidelines for VTE prophylaxis in our hospitals
Chapter Three

A review of the literature:

The prevention of deep vein thrombosis with graduated compression stockings

List of contents

3.1 Background
3.2 Mechanism of action
3.3 Efficacy of graduated compression stockings in the prevention of post-operative deep vein thrombosis
3.4 Complications of graduated compression stockings
3.5 Cost-effectiveness of graduated compression stockings
3.6 A review of the evidence for using thigh or knee-length graduated compression stockings in the prevention of post-operative deep vein thrombosis
3.6.1 Methods
3.6.2 Results
3.7 Summary
3.1 Background

The use of external lower limb compression devices were first reported in the 17th century by Pierre Dionis, the surgeon-in-ordinary to the Queen of France and to the Empress Maria Theresa of Austria. The application of GCS to the lower extremity for the prevention of venous thromboembolism was formerly investigated as early the 1950’s (Wilkins et al 1952; Wilkins & Stanton 1953). Since then, the use of GCS has been varied and inconsistent, largely due to the dispute over their exact mechanism of action and their effectiveness in the myriad of patients undergoing a wide range of surgical procedures in our hospitals. There is evidence to suggest that GCS increase the velocity of distal to proximal venous flow in the leg (Meyerowitz & Nelson 1964; Makin et al 1969) and reduce the distension of the deep veins of the calf during surgery (Coleridge Smith et al 1991). However, other studies have shown conflicting evidence against the beneficial effects of GCS in terms of alterations in venous flow and prevention of venous thrombosis. What is certain is the practicality, ease of use, low cost and safety of GCS that have ensured that GCS with the help of encouraging results from continued research are at the forefront of DVT prophylaxis in surgical patients.

Graduated compression stockings are available in a number of designs, which include varying lengths and compression profiles. Sigel and coworkers (1975) found the optimal degree of graduated compression to be a pressure of 18 mmHg at the ankle and 8 mmHg over the upper thigh in order to produce the best gradient to encourage distal to proximal venous blood flow. Interestingly, the optimal length of stocking has still not been decided despite the use of GCS for over thirty years in hospitals worldwide. Stockings are available in a number of ‘lengths’ that in general equate to either above-knee or below-knee designs. The below-knee stockings are
applied to the leg from the distal foot over the ankle to just proximal to the knee joint and are commonly referred to as 'knee-length' GCS. Whereas, the above-knee stockings, referred to as 'thigh-length' GCS are applied from the distal foot, over the ankle and knee joint up to the proximal thigh. Varying mechanisms enable the above-knee stockings to stay in place, the most commonly used design in hospital practice are those with a 'band' around the upper thigh. Other forms of above-knee stockings have waist 'bands' or 'belts' that keep the stockings in place, however these are less common as they cause some interference with the wounds from inguinal, hip, pelvic and lower abdominal surgery without any added benefit of increased area of compression to the leg. Essentially, the above-knee stockings apply pressure to the calf and thigh whereas the knee-length stockings compress only the calf.

3.2 Mechanism of action

In the early 1940's, Hunter and his colleagues reported on three hundred and fifty one autopsies and concluded from their findings that sudden immobilisation in bed of previously ambulant elderly patients was a major contributor to the development of DVT by altering the function of the venous circulation (Hunter et al.1941). In the same decade, studies went on to investigate preventive measures for DVT by determining the effects of external compression on the flow of venous blood in the deep veins of the leg. Initially, the increase in venous flow with compression was demonstrated by observing the time taken for blue dye injected into the foot to be cleared from the common femoral vein, external compression was shown to increase venous blood flow velocity in the leg by as much as 45% (Stanton et al 1949).
Subsequent clinical studies using radioactive isotopes added further information by confirming the reduced transit time from foot to femoral vein in the presence of lower extremity compression. In 1960, using radiolabelled human albumin Meyerowitz and Crook showed that an external calf compression of 10 mmHg could increase blood flow by as much as 60% when compared to the unstockinged contralateral leg. Meyerowitz and Nelson demonstrated similar results in a repeat of this study. (Meyerowitz et al 1964). On theoretical grounds the application of elastic compression to the legs soon became the main mechanical method of DVT prevention. However the effect of greater external compression to the leg was investigated in animal and human studies by Spiro et al (1970) and Sabri et al (1971). These studies demonstrated that excessive pressure was detrimental to venous blood flow and external compression for DVT prevention should be less than 20 mm Hg. Early designs of stockings were flawed and hence offered little benefit and in some instances were detrimental. Due to the ‘inverted cone’ shape of the leg, a stocking of uniform compression along its length actually applies greater external pressure proximally because of the wider circumference of the thigh compared to the calf. These ‘tubular’ or ‘tubigrip’ stockings failed to prevent DVT as they produced a reverse pressure gradient which inhibited the flow of venous blood out of the leg and actually increased the risk of venous stasis (Makin et al 1969 & Rosengarten et al 1970). Sigel and his colleagues (1973) subsequently demonstrated that although external elastic compression decreased venous capacitance of the lower limb, the resultant alteration in the venous blood flow is dependent on an inverse pressure gradient. Correctly applied graduated compression, with a greater pressure distally that gradually reduced proximally along the length of the leg increased the velocity of venous flow in the direction of the decreasing pressure gradient (Sigel et al 1975).
These findings have subsequently been supported by Lawrence and Kakkar (1980), the venous clearance of radioisotopic substances injected into the foot of recumbent subjects was substantially enhanced to between 2-5 cm/s by graduated compression. The mode of application of graduated compression was found to be of critical importance, the use of elastic bandages was unreliable with regard to the pressure applied, even with the greatest care of application. Bandages were found to easily produce a tourniquet effect and an inverse pressure gradient that delayed rather than enhanced the venous emptying (Lewis 1976). On the basis of these studies an above-knee (thigh-length) GCS was developed which was seamless with a circumferential knit and one-way stretch, the stocking is shaped to the foot and calf, with a gusset at the top to fit over the femoral triangle and prevent gartering. The stocking was manufactured in nine sizes, classified in length as short, regular and long and in circumference as small, medium and large which enabled the stocking to suitably fit ninety five percent of the population. A below-knee stocking was later available that fitted the remaining five percent of the population that were unable to get an adequate fit with the above-knee variety. Holford (1976), Scurr et al (1987) and Turner et al (1984) showed by randomised controlled prospective studies that this thigh-length GCS reduced the occurrence of the postoperative DVT after major surgical and gynaecological operations. The earlier studies by Rosengarten et al (1970) and Browse et al (1974) failed to show any prophylactic benefit from elastic compression stockings that were of the two-way stretch material, not contoured to fit the leg and had no gusset. Subsequent studies have shown that the stocking must provide a graduated compression, no garter at the top and the fit is of critical importance (Lewis et al 1976). More recently, an increased rate of postoperative
DVT has been demonstrated in the presence of poor fitting stockings that do not achieve the required distal to proximal pressure gradient (Best et al 2000). Graduated compression stockings are thought to prevent the development of DVT via their acceleration of venous emptying from the superficial to deep and from distal to proximal veins in the leg. This increased venous velocity was found to persist for thirty minutes after the stockings were removed in bedresting patients (Sigel et al 1973). Additionally, GCS produced faster clearance of venographic contrast from behind venous valve cusps, which are known to be an important site of venous stasis and subsequent DVT development (Lewis 1976 & Kalebo et al 1990).

It has been speculated that damage to the vessel wall, one of the elements of Virchow’s aetiological triad of venous thrombosis, is also prevented by GCS. Passive dilatation of the veins to such an extent that the media no longer provides support for the endothelium, resulting in endothelial tears was thought to be an integral part of DVT development (Stewart et al 1980). During surgery, the presence of venous stasis and activated clotting factors, with endothelial tears that allow the migration of white cells underneath the venous endothelium leads to the exposure of the underlying thrombogenic subendothelial collagen. In the study by Comerota et al (1985) this relationship was demonstrated between venous distension (in the upper limb) during surgery and the occurrence of post-operative DVT (in the lower limb). Coleridge-Smith et al (1990) confirmed the development of venous distension in the lower limb during surgery. Further investigation into this phenomena has shown that GCS (Kendall TED Stockings, Tyco Healthcare) produced a significant reduction in the median gastrocnemius vein diameter immediately after stocking application at the start of surgery and progressively during the surgical procedure. The total reduction in vein diameter was forty-eight percent in the group wearing GCS,
whereas the control group experienced significant venous distension by nineteen percent (Coleridge Smith et al 1990). This study demonstrated that GCS protected against the venodilation effects of surgery that were suggested by Comerota et al (1989) as a cause of prothrombotic endothelial injury.

3.3 Efficacy of graduated compression stockings in the prevention of post-operative deep vein thrombosis

Until the last decade, the effectiveness of GCS in the prevention of postoperative DVT has been in some doubt despite the use of compression stockings in surgery since the 1950's. A large number of clinical studies have been conducted in order to assess the efficacy of GCS, however many of these failed in their objectives due to the lack of randomisation, suitable control groups and poor diagnostic techniques. A meta-analysis performed by Wells et al (1994) employed strict inclusion and exclusion criteria for the studies investigating GCS to be included for the final analysis. Their search of the literature between 1966 and 1992 found 122 studies, of these only thirty-one were properly randomised. A further twelve studies were ineligible due to the lack of suitable control groups, and seven used inaccurate or inadequately evaluated diagnostic methods to detect postoperative DVT. Overall, from the original 122 studies published prior to June 1992, only twelve articles were judged eligible for analysis. The results of this meta-analysis provided strong evidence that GCS produce a significant risk reduction in the development of post-operative DVT in patients undergoing abdominal, gynaecological and neurosurgery. The risk reduction was sixty eight percent (p value less than 0.0001). Their results were inconclusive for orthopaedic surgery and for the overall prevention of pulmonary embolism. In all of the studies analysed it was reported that thigh-length
GCS were used in all patients. The literature available at this time was unable to provide evidence for the efficacy of below-knee GCS compared to thigh-length GCS. The available good quality studies comparing knee to thigh-length GCS were small and hence did not exclude a possible true difference between stocking lengths (Williams & Palfrey 1988 & Porteus et al 1989). The data on GCS in general was insufficient for Wells et al to draw conclusions about the efficacy of GCS as a prophylactic method when used singularly or in combination with another prophylactic modality such as heparin, intermittent pneumatic compression or dextran 70 (Wells et al 1994).

A comprehensive review by Jefferey and Nicolaides (1990) of the ‘stocking’ literature over a similar period; between 1974 and 1987 found the rate of postoperative DVT in general surgical and orthopaedic patients using GCS ranged from zero to twenty three percent compared to a DVT rate of between thirteen and fifty-four percent in patients without prophylaxis.

Graduated compression stockings used in conjunction with LDUH in three studies showed a DVT rate of between two and four percent compared to patients using LDUH alone with a DVT rate of between twelve and twenty seven percent. The results from one study using intermittent calf compression (Scurr et al. 1987) and another using dextran 70 (Bergqvist & Linblad. 1984) displayed a similar trend of improved efficacy with ‘combination prophylaxis’. The realisation by Virchow (1858) that multiple factors are involved in the pathogenesis of venous thrombosis led to the advancement of present day theories for DVT prophylaxis in surgical patients. The fact that combined prophylaxis may show improved efficacy of DVT prevention over solo modalities may be related to the targeting of different parts of Virchow’s triad, so that if one method fails the other is still acting on another part of
the ‘triad’ to reduce DVT. More recent literature has since reinforced the evidence for these trends shown in the earlier studies. The Cochrane library was set up in order to provide an accurate source of information to guide clinicians in the pursuit of ‘evidence-based’ practice. A recent Cochrane review on the use of elastic compression for the prevention of DVT in hospitalised patients (Amarigini & Lees 2000) identified sixteen RCT eligible for assessment. All but one of these trials were surgical; they included general, orthopaedic, neurosurgery or gynaecological surgery. The one medical trial (Kierkgaard & Norgren 1993) investigated patients who had suffered acute myocardial infarction. The patients from this study all received aspirin and some from one other trial by Barnes et al (1975), however these studies were included because current evidence indicated that aspirin has little effect on the venous side of the circulation (Amarigiri & Lees 2000). The reviewers sought to ascertain from a meta-analysis; the effectiveness of GCS in preventing DVT when used alone or in combination, the prophylactic requirements of low-risk patients and the complications associated with the use of GCS. The use of GCS alone in post-surgical patients was found to significantly lower the risk of DVT, the incidence in the control group (of 581 patients) was twenty seven percent compared to thirteen percent in the treatment group of 624 patients: odds ratio 0.34 (95% CI 0.25, 0.46). The use of GCS on a background of another prophylactic modality, demonstrated a DVT incidence of two percent in 501 patients compared to fifteen percent in 505 control patients who received only the background prophylaxis and no GCS: odds ratio 0.25 (95% CI 0.15, 0.37). This ‘observed’ evidence, as compared to evidence gleaned directly from RCTs suggests that GCS combined with another method of DVT prophylaxis are more effective than when use alone. None of the patients in these trials were of low thromboembolic risk and therefore no conclusions could be
taken for the prophylactic requirements of this group. The GCS were predominantly of the thigh-length design, which highlights the need to formerly compare the efficacy of above-knee to below-knee GCS. None of the trials mentioned the complications associated with the use of GCS. To date, the most extensive evaluation of the literature covering the prevention of VTE is available from The International Consensus Statement (ICS), which was established during the International Union of Angiology World Congress in London, April 1995. Subsequent regular consensus meetings involving leading authors from the USA, UK and the rest of the world ensure the most recent major advances and supporting evidence are included in each edition published. The latest edition (at the time of writing), published in 2002, recommends certain clinical practices in accordance to the levels or grades of evidence available; levels I to III or grades A to C (Nicolaides et al 2002). The use of GCS for preventing DVT in general surgical and urology patients is recommended by level I evidence (table 3a). The numbers of subjects in the studies are too small to assess the effects of GCS on pulmonary embolism. The recommendation for the use of GCS in other areas of surgery is extrapolated from the evidence from general surgery and the limited numbers of studies within their own speciality, therefore the evidence currently available for neurosurgery, orthopaedics and gynaecological surgery is level III.

There is more recent evidence from RCT that combining GCS with another prophylactic modality is more effective than when each agent is used separately (Nicolaides AN 1994). These include studies that employed GCS and LDUH (see tables 3b & 3c), GCS and LMWH (Kalodiki et al 1996, Lassen et al 1991, Leyvraz et al 1991 & Nurmohamed et al 1992), GCS and Dextran (Bergqvist & Lindblad 1984), GCS and IPC (Scurr et al 1987).
<table>
<thead>
<tr>
<th>Author</th>
<th>Control Groups</th>
<th>GCS Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>DVT (%)</td>
</tr>
<tr>
<td>Allan et al, 1983</td>
<td>103</td>
<td>37 (36)</td>
</tr>
<tr>
<td>Borow &amp; Goldson, 1981</td>
<td>89</td>
<td>32 (36)</td>
</tr>
<tr>
<td>Holford 1976</td>
<td>48</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Scurr et al, 1977</td>
<td>70</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Tsapogas et al, 1971</td>
<td>44</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Turner et al, 1984</td>
<td>92</td>
<td>4 (4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>446</strong></td>
<td><strong>128 (29)</strong></td>
</tr>
</tbody>
</table>

Table 3a – The effect of GCS on DVT after general and gynaecological surgery.

*Modified from the International consensus statement (Nicolaides et al 2002)*

The evidence is good for LDUH and LMWH combined with GCS, however the numbers of studies for other combinations are too small to offer valid recommendations. Therefore the ICS in general recommends the combined use of
GCS with LMWH (with other prophylactic modalities in some specific instances) for the prevention of DVT in high and moderate risk patients in general surgery, urology, neurosurgery, orthopaedics and gynaecological surgery.

<table>
<thead>
<tr>
<th>Author</th>
<th>GCS</th>
<th>Number of patients</th>
<th>DVT (%)</th>
<th>Heparin &amp; GCS</th>
<th>Number of Patients</th>
<th>DVT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borow &amp; Goldson 1983</td>
<td>106</td>
<td>15 (14)</td>
<td>63</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moser &amp; Froidevaux 1976</td>
<td>20</td>
<td>5 (25)</td>
<td>20</td>
<td>2 (10)</td>
<td></td>
<td></td>
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<tr>
<td>Nicolaides et al 1972</td>
<td>122</td>
<td>29 (24)</td>
<td>122</td>
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<tr>
<td>Rasmussen et al 1988</td>
<td>74</td>
<td>22 (30)</td>
<td>89</td>
<td>23 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>322</strong></td>
<td><strong>71 (22%)</strong></td>
<td><strong>294</strong></td>
<td><strong>28(9.5%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3b – Effect on DVT of GCS alone versus GCS with subcutaneous heparin in general and orthopaedics surgery. Modified from the International consensus statement (Nicolaides et al 2002)
<table>
<thead>
<tr>
<th>Author</th>
<th>Heparin</th>
<th>Heparin &amp; GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>DVT (%)</td>
</tr>
<tr>
<td>Borow &amp; Goldson 1983</td>
<td>86</td>
<td>23 (26)</td>
</tr>
<tr>
<td>Moser &amp; Froidevaux 1976</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Rasmussen et al 1988</td>
<td>85</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Torngren 1980</td>
<td>98</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Wille-Jorgensen et al 1985</td>
<td>86</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Wille-Jorgenesen et al 1991</td>
<td>81</td>
<td>12 (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>451</strong></td>
<td><strong>83 (18)</strong></td>
</tr>
</tbody>
</table>

Table 3c – Effect on DVT of subcutaneous heparin alone and in combination with GCS. Modified from the International consensus statement (Nicolaides et al 2002)

The evidence for recommendations in low risk patients is insufficient (Nicolaides et al 2002) and due to the low incidence of DVT in this group, extremely large RCTs
would be required to attain level-one verification. Nevertheless, these 'low-risk' patients do suffer from postoperative DVT and very occasionally die from PE, hence an almost 'complication-free' prophylactic modality, such as GCS may be advisable for this group.

3.4 Complications of Graduated Compression Stockings

Mechanical means of DVT prevention have been preferred in certain surgical specialities where bleeding complications secondary to pharmacological prophylactic treatments may result in potentially catastrophic postoperative intra-cranial haemorrhage or prosthetic joint haematomas. Graduated compression stockings have been reported to cause very few complications, rarely they cause minor abrasions or blisters and for this reason are regarded as generally 'safe'. However in some very rare instances, severe complications of limb ischaemia have been reported (Heath et al 1987) with thigh-length stockings without a gusset, however in this report other causes of limb ischaemia could not be completely ruled out. Since this time, many stocking manufacturers have modified their stocking design and introduced a gusset into the thigh band. No similar severe complications have been reported in gusseted stockings.

3.5 Cost-effectiveness of graduated compression stockings

A number of studies have investigated the cost-effectiveness of prophylaxis for venous thromboembolism (Salzman et al 1980, Oster et al 1987 & 1987, Bergqvist et
al 1988, Hull et al 1982). Prevention of DVT is recommended as cost-effective (Nicolaides et al 2002) due to the very high cost of the alternative; screening, diagnosis and treatment of DVT. Prophylaxis has the obvious advantage of potentially preventing the majority of acute and possibly fatal complications of VTE and the long-term problems experienced by patients who develop post-thrombotic syndrome. The economic evidence for low risk patients is again insufficient and may never be available due to the large studies required to investigate the low incidence of DVT in these patients. Knee-length stockings are in general two-thirds of the price of the thigh–length variety and therefore would be more economical if found to be equally effective at preventing postoperative DVT (Agu et al 1999).

3.6 A review of the evidence for thigh-length or knee-length graduated compression stockings in the prevention of deep vein thrombosis

The majority of recent meta-analyses and reviews of DVT prophylaxis have highlighted the need for information regarding the comparative efficacies of thigh and knee-length stockings. Investigations into the optimal length of compression devices have revealed that knee-length stockings may be equal to the thigh length GCS in terms of efficacy. Lawrence and Kakar (1980) provided further evidence for graduated compression with a multi-compartment pneumatic sleeve and demonstrated that venous velocity changes with compression to the lower leg, below the knee alone, was not significantly different from full-length compression. Sparrow et al suggested from their scintigraphic investigation of leg blood volumes with elastic compression stockings that thigh compression may be detrimental to
performance of stockings. In some patients thigh length compression can produce a reverse of venous flow. Wilkins et al (1950) suggested that after large clinical trials with full-length compression hosiery for DVT prophylaxis that knee length stockings would be acceptable to patients. Porteous et al (1989) demonstrated that patients more readily accepted knee length stockings.

The most recent International Consensus Statement (Nicolaides et al 2002) lists the difference between thigh and knee-length stockings as one of the ‘Key Questions to be Answered’. Authors who have reviewed the current literature state that there is insufficient data from RCT to recommend one over the other in the prevention of postoperative DVT (Agu et al 1999). In light of reports about the knee-length version of compression stockings achieving greater acceptability and patient compliance at a lower cost (Agu et al 1999), a proven equivalent efficacy would most likely lead to a widespread change in stocking prescription for surgical patients.

The data from published studies assessing the efficacies of thigh compared to knee-length GCS in the prevention of postoperative DVT was reviewed and summated.

3.6.1 Methods

Studies were obtained from an electronic search of Medline and Pubmed and secondary hand searches of article reference lists. The search was performed using key words; ‘graduated compression stockings’, ‘anti embolic stockings’, ‘thigh length’, ‘knee length’, ‘above-knee’, ‘below-knee’, ‘efficacy’, and ‘deep vein thrombosis’ for studies in all languages. The inclusion and exclusion criteria for studies to undergo summation analysis was as follows:
Inclusion/exclusion, studies were required to have the following:

- Records of the incidence of DVT in patients under study
- Prospective randomised trial in surgical patients
- Sound methodology
- Clear interpretation of the results for knee and thigh length groups

The following data from each study was recorded (if stated):

- Number of patients treated with GCS and included in study analysis
- Thromboembolic risk of subjects
- Method of randomisation
- Brand and compression profile of stockings
- Type of surgery performed
- Method of DVT diagnosis
- Incidence and percentage of postoperative DVT for each stocking length
- Areas of possible controversy
3.6.2 Results

A total of eleven studies were found from the search of the literature, of which eight studies were excluded (Table 3d).

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal, Year</th>
<th>Reason for exclusion</th>
</tr>
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<tbody>
<tr>
<td>Tsapogas et al</td>
<td>Arch Surg, 1971</td>
<td>No comparison to thigh GCS</td>
</tr>
<tr>
<td>Williams et al</td>
<td>JBJS [Br] 1994</td>
<td>No investigation of DVT incidence</td>
</tr>
<tr>
<td>McNally et al</td>
<td>JBJS [Br], 1995</td>
<td>No investigation of DVT incidence</td>
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<tr>
<td>Berridge et al</td>
<td>Phlebology, 1999</td>
<td>No investigation of DVT incidence</td>
</tr>
<tr>
<td>Benko et al</td>
<td>Phlebology, 1999</td>
<td>No investigation of DVT incidence</td>
</tr>
<tr>
<td>Best et al</td>
<td>JBJS [Br] 2000</td>
<td>No comparison to thigh GCS</td>
</tr>
<tr>
<td>Benko et al</td>
<td>Clin Orth Rel Res, 2001</td>
<td>No investigation of DVT incidence</td>
</tr>
<tr>
<td>Hameed et al</td>
<td>S Afr J Surg, 2002</td>
<td>No investigation of DVT incidence</td>
</tr>
</tbody>
</table>

Table 3d - Articles excluded from analysis

Two studies assessed only knee-length stockings for DVT incidence and six of the studies did not compare the two stocking lengths for DVT incidence but for other properties such as venous blood flow and velocity, acceptability and wrinkling. The data from the remaining three studies (Table 3e) was summated in order to produce an overall efficacy for thigh and knee-length GCS (Table 3f).
<table>
<thead>
<tr>
<th>Author</th>
<th>Patents with Thigh &amp; Knee Length GCS</th>
<th>Risk and Surgery type</th>
<th>Method of DVT Diagnosis</th>
<th>DVT incidence (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams &amp; Palfrey 1988</td>
<td>44 &amp; 44</td>
<td>High Abdo</td>
<td>Isotopic Fibrinogen Uptake</td>
<td>6(13.6) 8(18.2)</td>
</tr>
<tr>
<td>Porteus et al 1989</td>
<td>56 &amp; 58</td>
<td>High Abdo</td>
<td>Isotopic Fibrinogen Uptake &amp; Venography</td>
<td>3(5.4) 1(1.7)</td>
</tr>
<tr>
<td>Hui et al 1996</td>
<td>44 &amp; 40</td>
<td>High Ortho</td>
<td>Venography</td>
<td>THR THR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ipsi (22) Ipsi (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cont (9) Cont (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TKR TKR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ipsi (65) Ipsi (68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cont (12) Cont (10)</td>
</tr>
</tbody>
</table>

Table 3e - Articles included for analysis

The patient numbers in each of the studies were small, however the summation of the data produced a total of 288 legs in the thigh-length group and 284 in the knee-length group. All of the information required to convert the numbers of patients into numbers of legs for each study was clear without discrepancies. However, the study by Hui et al stated that they could only provide valid data from the ipsilateral legs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Thigh Length</th>
<th>Knee Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Legs</td>
<td>DVT</td>
</tr>
<tr>
<td>Williams 1988</td>
<td>88</td>
<td>9</td>
</tr>
<tr>
<td>Porteus 1989</td>
<td>112</td>
<td>3</td>
</tr>
<tr>
<td>Hui 1996 (THR)</td>
<td>48</td>
<td>Ipsilateral 5</td>
</tr>
<tr>
<td></td>
<td>(Contralateral 2)</td>
<td>(Contralateral 1)</td>
</tr>
<tr>
<td>Hui 1996 (TKR)</td>
<td>40</td>
<td>Ipsilateral 13</td>
</tr>
<tr>
<td></td>
<td>(Contralateral 2)</td>
<td>(Contralateral 2)</td>
</tr>
<tr>
<td><strong>Total Number of Legs &amp; DVT</strong></td>
<td>288</td>
<td>34</td>
</tr>
<tr>
<td><strong>DVT Percent</strong></td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 3f - Summation of data for thigh and knee length stockings

because some of the patients were unable to have venograms on the contralateral legs (n=12). All of the studies were randomised; either by envelope (Williams & Palfrey 1988) or by number (Porteus et al 1989 & Hui et al 1996). None of the studies were able to show a significant difference between the two stocking lengths, however the numbers of subjects in each trial were small so a difference cannot be ruled out.
addition, there were some discrepancies (shown below) in the data that makes their results questionable.

i. Non of the trials demonstrated a statistically significant difference in overall DVT for either stocking length,

ii. Williams et al used different brands of thigh and knee-length stockings,

iii. Hui et al used a Robert-Jones bandage under the stockings after TKR which would probably change the compression profile exerted on the leg, and only found statistical significance for the knee-length stocking in the prevention of proximal and major calf thromboses in patients having total knee replacements.

3.7 Summary

Within the literature there are a small number of published studies comparing the properties of thigh to knee-length stockings that provide some evidence to explain the behaviour of each stocking type. Benko et al (1999) showed good evidence for the ability of thigh length stockings to increase venous velocity to a greater extent than the knee-length design. Colour Doppler measurements of peak velocity in the femoral vein of patients (n=15) with thigh-length GCS was significantly greater (p<0.002 paired t-test) than in the control group (n=15). The thigh group also showed a significantly (p<0.05) reduced popliteal vein diameter, which is thought to limit vein wall damage and thus the development of popliteal DVT. Another study by the same author, (Benko et al 2001) demonstrated in a study with 200 adults that thigh and knee length stockings all significantly increased venous capacitance and
venous outflow when compared to control subjects (p<0.001 Wilcoxon). Although there was no significant difference between mean changes in venous capacitance and outflow, the knee length stockings increased venous outflow less than the thigh length stockings. Similar changes in venous haemodynamics where publicized in a small study by Berridge et al (1999), where only the thigh length stockings produced an increased deep venous velocity. Conflicting evidence has been reported that show no benefit of thigh-length over knee-length GCS in terms of venous haemodynamics and indeed suggest an advantages of the knee-length for patient acceptability and compliance. Work performed by Lawrence and Kakkar (1980) suggested that thigh-length stockings effect no greater increase in femoral vein blood flow than knee-length. A knee-length stocking of 18 mmHg compression at the ankle gradually reducing to 14 mmHg in the upper calf, was equally effective at augmenting deep venous velocity as a full length stocking of 18 mmHg ankle compression and 8 mmHg upper thigh compression. This evidence together with Kakker’s report in the Lancet (1969) that most deep vein thromboses following major abdominal surgery originate in the calf veins led to the theory that the knee length GCS were not inferior to thigh-length in the prevention of DVT. McNally et al (1995) reported in a study of two hundred patients that the increases in venous blood flow, assessed by plethysmography, achieved by thigh and knee-length stockings were not dissimilar, and that the knee-length design were more acceptable to patients, caused less uncomfortable wrinkling and improved stocking compliance. In other studies, knee-length stockings have been found by the use of simple tests to be more acceptable to patients and nursing staff and to roll down and wrinkle less (Porteus et al 1989, Benko et al 2001). Indeed the trivial sounding problem of rolling down and wrinkling experienced more commonly with above knee stockings can produce
severely detrimental effects by causing a reversal of the pressure gradient and tournique effects. An increased external pressure of 28 mmHg in the popliteal fossa has been shown to develop with thigh-length stockings and the knee flexed, which predisposed to a reverse pressure gradient in seventy percent of the subjects wearing thigh-length GCS (Wildin et al 1998). Not only has the reverse pressure gradient effect been demonstrated to cause excessive pressure, increase venous congestion and contribute to the development of DVT (Best et al 2000), but limb ischaemia has been reported in two cases secondary due to a tournique formed by a ‘rolled-down’ gussetless thigh-length stocking (Heath et al 1987). The thigh stocking when compared to the knee-length stocking, has been found to be more difficult to achieve an adequate fit which then leads to more rolling down and wrinkling with resultant changes in the external compression gradient upon which the function of stockings is reliant (Williams et al 1994). The patient acceptability has an important role, it is reported to be greater for the knee length stockings and a GCS is only effective in preventing DVT as long as it is worn by the patient and correctly applied.

The results from the trials assessing the different lengths of GCS for the prevention of DVT have demonstrated no difference in the prevention of DVT in each study and the summation of the data from all three trials has produced the same result. However, a steadfast conclusion cannot be taken from three small trials and further work in this important area is required. The comparative efficacies of thigh and knee length stockings is important to clarify in order to improve patient care with regard to the prevention of DVT. It is clear from this summation of the available data that a reliable and valid answer to this question could only be achieved through a large prospective RCT, this major undertaking became a large part of the investigations in this study.
Chapter Four

An audit of
surgical thromboembolic prophylaxis in a teaching hospital
and the response of medical staff to an education and awareness
program promoting a single ‘blanket’ protocol

List of contents

4.1 Background

4.1.1 The evolution of medical audit
4.1.2 Essential properties of medical audit
4.1.3 The audit cycle
4.1.4 Audit and quality of care
4.1.5 Focus of audit
4.1.6 The audit protocol
4.1.7 Summary

4.2 Methods

4.3 Results

4.4 Conclusions
4.1 Background

4.1.1 The evolution of medical audit

The King of Babylon, who had drawn up a set of rules for doctors, known as the
Code of Hammurabi, first introduced the assessment of the effectiveness of health
care nearly four thousand years ago. The ancient Greeks regulated their health care
through medical ethics and codes, with onus on the doctor to deliver a standard of
care. The Hippocratic oath sets the requirement for health care through good
knowledge about the treatment efficacies and results. The modern literature on
medical audit first started to evolve in the 1950s on the west coast of America
(Lembcke 1967). It is only over the last two decades that audit has become regarded
as an important component in surgical practice in the United Kingdom. A major
stimulus was the Confidential Enquiry into Peri-Operative Deaths, which
demonstrated the amount of variation in practice and outcomes for similar
populations of patients in the National Health Service (Buck et al 1987). Medical
audit has now becomes an integral part of maintaining the standards of care within
the health service, since its formal introduction in the White Paper Working for
Patients (Department of health 1989) and by the Standing Medical Advisory
Committee in 1990.

Medical audit is an ongoing process of evaluation and development of health care
processes. Early on, audit results are often mistaken for apportioning blame, and
doctors were initially hesitant with the use of audit. Audit data must therefore be
collected with a view to improving the service in that particular area, hence reluctant
doctors will see the benefits. Audit should be a series of planned short studies in the
target area of interest, the results of which should move the practice forward as
required in a health service with ever increasing demands and expectations.
4.1.2 Essential properties of medical audit

Medical audit has five essential properties:

- **Peer Review** – the standards of medical care are set by the professionals who utilise clinical results, research and feedback from the patients.

- **Standards and Quality** – The specification of required standards and quality of care at a local level allows inadequate performance to be identified. Utilisation of national professional standards and evidence-based medicine is a necessity.

- **Patient Based and Multi-dimensional** – the focus of any health care intervention is the patient and therefore audit should encompass patient’s treatments and outcomes in a holistic manner.

- **Systematic Approach** – a clear and systematic approach is required to perform good quality audit studies. The patient selection should be from a defined population.

- **Commitment to Change Practice** – audit is designed to improve the service of care and achieve an optimum level of care at a local level. A commitment to change practice in accordance with audit findings is essential to its success.

It is important to recognise the differences in the principles of medical audit and medical research. Medical audit defines the requisite local standards of clinical practice and hypothesises that these standards of health care should be in place. Thus, there is no experimental component in medical audit, just a process to ensure that the patients receive a quality of care set by predetermined standards. Medical research however investigated a new or experimental treatment or seeks to establish a cause for a condition. The results are unknown and therefore research requires close supervision, ethical approval and informed consent. In clinical practice the
results of audit may be unpredictable and therefore audit may still contribute to the medical literature.

4.1.3 Audit cycle

Shaw first described the audit cycle in 1980, which has frequently been used to illustrate the processes of audit (Figure 4a). The audit cycle summarises the information requirements for completing a successful audit.

Figure 4a - The audit cycle

- *Setting standards* – predefined criteria to allow accurate data collection
- *Recording practice* – Collection of specified data and data analysis to enable comparison to the set standards and highlight the deficiencies
Effecting change – professionals and management combine efforts to improve the care to the required level and then re-audit to record any change in practice. If the standards are still not met then further change followed by re-audit is required until the requisite standards are met. This process may take months to years for department alterations in practice because of resistance to change and increased funding required to support these changes. Audit should be re-run on regular basis (audit cycle) to ensure the maintenance of standards.

4.1.4 Audit and quality of care

Audit involves the assessment of the quality of care assuming quality can be assessed reliably and accurately. Despite setting standards of quality to be achieved through audit, defining the actual quality of the care may be difficult with the multi-faceted nature of healthcare. Maxwell (1984) defined a recognised set of quality criteria:

- Access to service
- Relevance to need
- Effectiveness
- Equity
- Social acceptability
- Efficiency
- Economy

Each criteria must be viewed from the standpoint of the professional and the patients, especially as the patient is the focus of quality in the care process. The patients’ views on the quality of care may not be informed, however their views are still important.
4.1.5 Focus of audit

Audit can easily become complex and convoluted due to the multiple requirements described above. Hence in order to minimise this, audit must be focused appropriately. Various approaches are available to achieve this:

- **Problem selection** – Problems that are amenable to change as perceived by peers and patients
- **Prioritisation** – processes that are higher priority can be defined by one of Shaw’s criteria (1989):
  - High risk
  - High volume
  - High cost
  - Wide variation in clinical practice
  - Local clinical anxiety
- **Optimising benefits** – Audit focuses on areas in which maximal benefit can be achieved. Improvements to practice should be in line with evidence based principals and national framework guidelines.

The duration of audit should also be targeted in order to achieve an accurate and compact data assessment. True outcomes of any treatment encompass early and late complications and benefits, hence the duration of audit assessment needs to be tailored accordingly. There is no defined time span for audit activities and the duration is dependent on the chosen area of practice.

Finally, the feasibility of audit was highlighted by Fowkes (1982), the properties of the audit should be as follows:

- Common practice to produce adequate numbers
- Significant effect on outcome/resources
4.1.6 The audit protocol

The audit protocol forms the definition of the information requirements that should be agreed before the commencement of the audit. The protocol delivers the information necessary to instigate change in the practice and therefore has to be laid out in a clear and succinct fashion to avoid analysis problems of the results. Clinical protocols set the benchmark for the agreed practice at a local level and often lead to clinical audit. The audit may then influence the clinical practice and protocols depending on the audit results. Audit may be retrospective, prospective or concurrent. The latter allows changes to the clinical practice before the end of the audit process. Concurrent audit has the advantages of being preventive by preventing bad practices or limiting suboptimal outcomes by introducing clinical practice alterations as the current audit is performed. However, the use of data concurrently has the disadvantage of having only a limited part of the data set when compared to the end results of a prospective audit. The audit protocol is used to record patients details and outcomes and therefore must confidential. Audit has now developed so that it is a normal part of clinical practice and therefore patient information is kept confidential similarly to patients’ clinical notes.

4.1.7 Summary

This introduction to audit has highlighted the necessary requirements for a successful audit. Over the last three decades, the importance of prophylaxis against post-
operative DVT has been recognised, however its use and compliance is variable and
in many hospitals very poor. In light of the vast wealth of literature and guidelines
available to clinicians it is confusing to find that surgical patients are still not
receiving adequate prophylaxis to prevent DVT. This may be due to complexity of
recommendations in the literature and the lack of consensus between clinicians. A
commentary by John Bergan (1997) discussed the reasons for ‘physicians to
underplay the value of prophylaxis’, these included:

1. An individual clinician’s experience suggests a low level of occurrence of
fatal PE and therefore they forget the need for DVT prophylaxis
2. Failure of education – continuing medical education programs dramatically
increase the awareness of DVT and prophylaxis (John Bergan 1997,
Anderson et al 1994)

The use of DVT prophylaxis has been audited in the surgical patients of this
multidisciplinary teaching hospital in order to gauge the overall status of
prophylaxis. It was clear that the majority of our surgical patients came under an
‘umbrella’ of DVT risk - the majority were high risk and very few were of low risk
for developing postoperative VTE - that could therefore be treated with a ‘single
prophylaxis protocol’ of graduated compression stockings and subcutaneous heparin
in accordance to International and European consensus guidelines for the prophylaxis
of DVT in high and moderate risk surgical patients. An assessment was then
performed that highlighted the inadequacies of the current DVT prophylaxis,
measured the effect of an education program and proposed a ‘single prophylaxis
protocol’ to achieve a consensus between the doctors of different surgical specialities
and healthcare staff in our hospital.
4.2 Methods

The audit process was carried out in three phases:

1. Audit of existing practice
2. Education of hospital medical staff
3. Re-audit of surgical patients after the completion of an education and awareness programme and introduction of the new single prophylaxis protocol.

**Phase One** - All of the surgical patients at Charing Cross Hospital, already occupying a ward bed or admitted to a hospital bed over a period of forty-eight hours, were assessed for the audit on venous thromboprophylaxis. The inclusion criteria for the audit study, were that the patients were:

- Under the care of a surgical consultant
- Admitted to a surgical ward.

Patients were excluded from risk analysis and therefore the audit if:

- They had not undergone an operation during that admission, as the current recommendation from the International Consensus (Nicolaides et al 2002) requires the details of the operation to be included in the risk categorisation.
- Patients that had just arrived in the hospital ward at the time of the audit and the nursing staff and/or doctors had not had sufficient time to implement their DVT prophylaxis.

Patients were recorded as having optimal prophylaxis if they had received subcutaneous heparin in combination with GCS. However, optimal prophylaxis for patients with contraindications to heparin or GCS was recorded if the patient had received the maximal appropriate prophylaxis for that particular patient. Relevant contraindications to certain methods of prophylaxis were as follows:
- Any history of peripheral vascular disease (PVD) or diagnosis of PVD in the hospital notes and the presence of dressings or external fixators on lower limbs.
- Allergy to subcutaneous heparin,
- Concurrent use of other forms of anticoagulation such as warfarin or intravenous heparin
- Surgery in the previous 12 hours for orthopaedic and neurosurgery specialities (as these specialities refused peri-operative heparin within twelve hours).

All patients were interviewed and assessed for their DVT risk and prophylaxis of VTE. The data for each patient was recorded by using a pre-defined audit proforma sheet (Appendix). The proforma documented the patient’s age, sex, speciality, consultant, surgical procedure, risk factors for VTE disease in accordance to the International Consensus statement 2001 (table 4a). All data was stored on a secure computer site. All audit was performed without prior warning to medical staff to avoid last minute changes to prophylactic practice.

Phase Two - An education program was given to surgical house officers, senior house officers, registrars and surgical nurses via thirty-minute verbal presentations and the use of handouts and posters for the ward notice boards. The surgical consultants were informed by the use of postal letters. Information regarding the findings of the VTE prophylaxis in the surgical patients at Charing Cross hospital, a summation of the literature covering VTE disease and how a single protocol for the prevention of DVT in surgical patients could be applied in our hospital was given.
### Table 4a - Thromboembolic risk categories and recommended prophylaxis for surgical patients

Information and recommendations from the International Consensus Statement on the Prevention of Venous Thromboembolism (Nicolaides et al 2001). *Additional risk factors include:* malignancy, previous DVT or pulmonary embolus, varicose veins, oestrogen medication, thrombophilia, ongoing sepsis, morbid obesity and general immobility. *Abbreviations:* DVT; deep vein thrombosis, GCS; graduated compression stockings, IPC; intermittent pneumatic compression.

*Surgery:* Minor Surgery; less than 45 minutes, Major Surgery; more than 45 minutes operating time.

The new single protocol advocating a ‘blanket’ approach to DVT prophylaxis – that negates the need for risk categorisation - using subcutaneous heparin and anti-embolic stockings for all surgical patients. The ‘single protocol’ was implemented.
with the permission from consultants from the Gastrointestinal, Urology, Vascular, Breast and Oncology surgical specialities. All of the junior surgical doctors and nursing staff were made aware of the introduction of the new protocol for the prevention of postoperative DVT. Approximately three months later, without warning medical staff, the audit was repeated for DVT prophylaxis and the accuracy of implementation for all surgical patients on surgical wards who had received, or were due to receive surgery on that admission.

4.3 Results

Phase One Results - A total of 178 patients under the care of surgical consultants were identified for inclusion into the audit. The demographics of the patients are displayed in table 4b, the mean age of the patients demonstrated a generally elderly population that remained in hospital for an average of 23 days, with an approximately equal gender ratio.

One hundred and six of these patients had undergone one or more surgical procedures during the current hospital admission so the risk of VTE and the correct application of prophylaxis as recommended by the International Consensus statement could be assessed in these patients. These patients had very similar demographics to overall group (table 4b), with an mean age of sixty-one years, equal sex ratio and average hospital stay of 32 days. These patients had received surgery from a wide range of surgical specialities; Ear nose and throat (ENT), Breast and Oncology, Gastrointestinal (GIT), Neurosurgery, Orthopaedics, Plastics, Urology, and Vascular surgery (table 4c).
<table>
<thead>
<tr>
<th>Number of patients</th>
<th>178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients</td>
<td>62 years (range 19-94)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>56% Male</td>
</tr>
<tr>
<td>Average hospital stay</td>
<td>23 days (range 1-365)</td>
</tr>
</tbody>
</table>

Table 4b - Patient demographics

Thromboembolic risk categories (according to the International Consensus) of these 106 patients showed that the majority of the patients were of high risk for developing postoperative DVT and PE (75 patients, 71% high risk), twenty percent were of moderate risk (21/106), and only a small proportion were (10/106, 9%) of low risk. These risk proportions are displayed in graphical form (Figure 4b).

The numbers of patients who had received adequate physical prophylaxis against DVT, either adequately fitted GCS or intermittent pneumatic compression (IPC), were found to be low with only 35 patients wearing correctly fitted GCS and one patient with IPC out of a total of 82 patients who had no contraindication to lower limb external compression. These findings equate to only 43 percent of patients were correctly fitted and appropriately prescribed GCS and overall a total of only 44 percent of patients received mechanical prophylaxis (GCS and IPC) (table 4d and figure 4c). The patients that received subcutaneous heparin injections totalled fifty-two out of a total of 96 patients who were eligible to receive subcutaneous heparin. (Ten patients were contraindicated subcutaneous heparin; one due to allergy and nine patients were already undergoing anticoagulant therapy with either warfarin or intravenous heparin for non--prophylactic reasons.) This equates to only 54 percent of the patients who appropriately received subcutaneous heparin and 58 percent of
patients received some form of pharmacological prophylaxis (subcutaneous heparin or full anticoagulation) out of the total 106 patients.

<table>
<thead>
<tr>
<th>Surgical Specialities</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT</td>
<td>4</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
</tr>
<tr>
<td>GIT</td>
<td>9</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>12</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>31</td>
</tr>
<tr>
<td>Plastics</td>
<td>14</td>
</tr>
<tr>
<td>Urology</td>
<td>7</td>
</tr>
<tr>
<td>Vascular</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>106</strong></td>
</tr>
</tbody>
</table>

Table 4c – Surgical specialties of patients

In addition, amongst the patients who received subcutaneous heparin, the use of unfractionated low dose heparin (LDUH) and fractionated low molecular weight heparin (LMWH) was inconsistent with less than half (48%) of the surgical patients undergoing surgery received the preferential LMWH and 52% received LDUH. The International consensus recommends that high and moderate risk patients should receive subcutaneous heparin in combination with GCS or IPC for the optimal prophylaxis of postoperative DVT (the evidence for recommendations in the low risk patients is not yet available). In this cohort of patients, 91 percent of the patients were high or moderate risk (n=96) and should consequently have received mechanical and pharmacological prophylaxis in combination, some of the patients were protected by full anticoagulant therapy (n=9) for reasons other than for
prophylaxis. The total number of patients who received optimal prophylaxis in line with the current international recommendations (Nicolaides et al 2002) amounted to forty-seven percent (Table 4d).

The optimal prophylaxis given to each risk category of patients was worst for the moderate and high-risk patients with only 38% and 44% of these patients respectively receiving the correct prevention therapy. The results for individual specialities and wards may indicate areas of weakness with regard to DVT prophylaxis in our institution, however the numbers are small for individual specialities and therefore must be interpreted with caution (Figure 4d).

**Figure 4b- The Risk Categories**
Figure 4c - DVT Prophylaxis Given to Patients

Percentage of Patients (n=106)

Type of Prophylaxis

- Mechanical
- Pharmacological
- Optimal Prophylaxis

Figure 4d - DVT Prophylaxis by Each Surgical Speciality

Percentage of patients

Speciality

- Mechanical
- Pharmacological
- Optimal Prophylaxis
<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Number of Patients (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Number of patients fitted with GCS</td>
<td>39</td>
</tr>
<tr>
<td>Number of patients fitted with stockings of incorrect size</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients fitted with IPC</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients with a contraindication to GCS or IPC</td>
<td>24</td>
</tr>
<tr>
<td>Number of Patients correctly fitted with GCS</td>
<td>39</td>
</tr>
<tr>
<td>Percentage correctly fitted with mechanical prophylaxis</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Pharmacological Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Number of patients administered subcutaneous heparin</td>
<td>52</td>
</tr>
<tr>
<td>Number of patients with allergy to heparin</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients with other medical prophylaxis</td>
<td>9</td>
</tr>
<tr>
<td>Percentage of patients correctly administered s.c heparin</td>
<td>54%</td>
</tr>
<tr>
<td>Number of patients correctly administered pharmacological prophylaxis</td>
<td>61</td>
</tr>
<tr>
<td>Percentage correctly administered pharmacological prophylaxis</td>
<td>58%</td>
</tr>
<tr>
<td><strong>Optimal Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Total number of patients with optimal DVT prophylaxis</td>
<td>50</td>
</tr>
<tr>
<td>(combination prophylaxis or full anticoagulant therapy)</td>
<td></td>
</tr>
<tr>
<td>Total percentage of patients with optimal DVT prophylaxis</td>
<td>47%</td>
</tr>
</tbody>
</table>

Table 4d – Prophylaxis given to surgical patients

The Breast and GIT surgical specialities were the only specialities that achieved optimal prophylaxis in fifty percent or more of their patients, the remaining specialities achieved very unsatisfactory levels of prophylaxis.
The data for each of the surgical wards revealed a marked variation in the efficiency of applying DVT prophylaxis, however in some of the wards, the number of patients who had undergone a surgical procedure during the hospital stay was small (Figure 4e). The wards with the worst performances were 7 West and 10 South, these consist mainly of orthopaedic and neurosurgery patients respectively, where the poor compliance with prophylactic recommendations may stem from the fear of using subcutaneous heparin with some of their operations.

**Figure 4e - DVT Prophylaxis by Each Surgical Ward**
Phase Two Results – The results of the first phase of the audit that demonstrated the substandard DVT prophylaxis in our hospital, were received with surprise; many of the staff had assumed that the general status of prophylaxis was good. The education sessions to junior doctors and nursing staff were received with enthusiasm. The consultants were concerned about the inadequate DVT prophylaxis used in their patients and many showed interest towards developing a hospital consensus for the protection of patients from the complications of postoperative VTE. However, there was still debate on the use of subcutaneous heparin in certain patients, namely those undergoing orthopaedic prosthetic surgery, spinal surgery and neurosurgical cranial procedures - despite the high risk of these patients for developing VTE. The length and type of stocking was also raised as an uncertainty that was important to clarify. At this early stage of the proceeding the consultants from the breast and oncology, GIT, urology and vascular specialities agreed to the use of a new single blanket protocol of subcutaneous LMWH and GCS for all of their patients undergoing or who may undergo surgery. The consultants from the other specialities; ENT, neurosurgery, orthopaedics and plastic surgery recognised the need for change, but required more evidence from the awaited RCT that would assess the use of blanket LMWH and different lengths of GCS in surgical patients (see chapter 6).

After the education program, the second phase audit showed the application of prophylaxis - in the patients who had undergone surgery, from the specialities that agreed to a single blanket protocol (breast and oncology, GIT, urology and vascular), significantly improved (p<0.05). The demographic data and ‘risk’ of patients from phases one and two audits are summarised below in table 4e and figure 4f. The patient populations were very similar with regard to numbers of patients, age, gender ratio, length of hospital stay and risk of VTE disease (according to the International
Consensus Statement). The use of mechanical (p=0.1), pharmacological (p=0.03) and overall optimal prophylaxis (p=0.003) improved considerably in accordance with the international consensus statement, over a three-month period (table 4f and figure 4g).

<table>
<thead>
<tr>
<th>Audit Phase One</th>
<th>Audit Phase Two</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Before Education’</td>
<td>‘After Education and Single Protocol’</td>
</tr>
<tr>
<td>45 patients</td>
<td>34 patients</td>
</tr>
<tr>
<td>Mean age 65 years</td>
<td>Mean age 63 years</td>
</tr>
<tr>
<td>Males 65%</td>
<td>Males 59%</td>
</tr>
<tr>
<td>Mean hospital stay 49 days</td>
<td>Mean stay 22 days</td>
</tr>
</tbody>
</table>

Table 4e – Patient demographics

Figure 4f - DVT Risk Categories of Patients
<table>
<thead>
<tr>
<th>Types of Prophylaxis</th>
<th>Phase One ‘Before Education’</th>
<th>Phase Two ‘After Education’</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mechanical prophylaxis:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical prophylaxis fitted appropriately</td>
<td>54% (n=28)</td>
<td>81% (n=16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[p=0.1]</td>
</tr>
<tr>
<td><em>Pharmacological prophylaxis:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous heparin administered appropriately</td>
<td>67% (n=37)</td>
<td>92% (n=26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[p=0.03]</td>
</tr>
<tr>
<td>Full Warfarin or Intravenous heparin administered</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td><em>Combined Prophylaxis:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous heparin with stockings</td>
<td>24%</td>
<td>32%</td>
</tr>
<tr>
<td>Subcutaneous heparin (No stockings due to contraindication to compression)</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td><em>Optimal Full ‘DVT’ Prophylaxis:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number with stockings and s.c heparin or full anticoagulation for other clinical reasons</td>
<td>56% (n=45)</td>
<td>88% (n=34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[p=0.003]</td>
</tr>
</tbody>
</table>

Table 4f - Improvements in surgical (breast and oncology, GIT, urology and vascular) DVT prophylaxis after education and introduction of single blanket prophylaxis protocol
Figure 4g - Improvements in DVT Prophylaxis after Education and Introduction of Single Protocol

These changes were due to increased compliance by doctors and nurses, with respect to prescribing and application of GCS and subcutaneous LMWH in all patients undergoing surgery. The introduction of a simple single protocol negates the need for complex VTE risk assessment. The breakdown of the changes in prophylactic practice before and after the education and introduction of a single blanket protocol is shown in table 4f and figure 4g.
4.4 Conclusions

A simplified ‘blanket’ approach to DVT prophylaxis led to a significantly improved use of DVT prophylactic measures. A single protocol using GCS and subcutaneous heparin, preferably LMWH, was acceptable for all surgical in-patients having an operation in our hospital for a number of reasons:

1. The majority of the surgical patients undergoing surgery at Charing Cross Hospital were of high and moderate risk for developing complications of VTE.

2. The International consensus (Nicolaides et al 2002) and many other published guidelines such as the European consensus and THRIFT guidelines advocate the use of subcutaneous heparin and GCS for high and moderate risk patients.

3. The evidence to recommend venous thromboembolic prophylaxis in low risk patients is not reported in the literature.

4. Current guidelines in the literature recommend the separation of patients into risk categories – high, moderate and low risk - followed by the prescription of increasing amounts of prophylaxis according to the patients’ risk. This method has a number of weaknesses:
   a. Doctors are unable to reliably separate patients into the correct risk categories (see chapter 5; ‘A Teaching Hospital Audit: Errors of DVT Prophylaxis at the Bedside’)
   b. The separation of patients into risk categories relies on the summation of preoperative risk factors, which may change during or after the surgery with a resultant upgrading of the patients’ risk.
Therefore, low risk patients may easily become moderate or high risk after surgery if the patient undergoes prolonged surgery (greater than 45 minutes) or becomes immobile, infected, thrombophilic, or if malignancy is unexpectedly found on histological examination of the surgical specimen.

5. The complications of low dose subcutaneous heparin and compression stockings are rare and usually minimal. Additionally the low risk of complications can be minimised by the use of a clear hospital protocol that highlights the absolute and relative contraindications to heparin and stockings.

6. The cost of low dose subcutaneous heparin and compression stockings is low and has been shown to be cost effective in the moderate and high-risk patients for the prevention of DVT. (The economic data for DVT prevention in low risk patients has not been reported.)

This study demonstrates how the use of audit with structured education and reaching a consensus on an area of clinical practice can improve the quality of patient care. This has been demonstrated in the realm of DVT prophylaxis in previous studies (Jones 1991). The importance of a simple solution to a clinical problem is highlighted by this audit, other authors have demonstrated that protocol compliance is improved if the protocol is not complicated (George et al 1998). The consensus achieved at Charing Cross Hospital promoting the use of a single blanket application of low dose subcutaneous heparin and compression stockings for all surgical inpatients undergoing any surgical procedure (with specific exclusions) is simple and easy to use in every day clinical practice. This resulted in the majority of patients receiving prophylaxis and those patients who were unable to receive either
subcutaneous heparin or GCS still received their optimal prophylaxis. A single protocol allows a simple blanket application of prophylaxis to all patients, however continued audit and education is a necessity for the sustained effectiveness of any new protocol.
Chapter Five

The disparity in the practice of DVT prophylaxis and the difficulties in achieving a general consensus for the prevention of deep vein thrombosis in surgical patients

List of Contents:

5.1 Introduction

5.2 A Teaching Hospital Questionnaire Audit: Disparity and Errors in the Practice of DVT Prophylaxis

5.2.1 Introduction

5.2.2 Methods

5.2.3 Results

5.2.4 Conclusions

5.3 Instigating change in a large teaching hospital

5.3.1 Communications to departments

5.3.2 Feedback from departments

5.3.3 The use of LMWH and graduated compression stockings ‘across the board’ for patients undergoing surgery

5.4 Discussion
5.1 Introduction

Since its conception, the practice of prophylaxis against deep vein thrombosis in surgical patients has been notorious for its controversy and debate. Many consultants and junior doctors try to adhere to the guidelines published in the literature that undergo continual change due to advancing science, while others use anecdotal evidence taken from past experience. Past experience may highlight the immediate complications of anticoagulant prophylactic therapy and grossly underestimate the rate of VTE episodes, many of which present after the ever-shortening hospital stays. During the course of this study, work has been directed towards improving the overall standard of the VTE prophylaxis in surgical patients in Charing Cross hospital. The weaknesses, failures and ways to improve venous thromboprophylaxis in our acute multidisciplinary university hospital were investigated. A number of surveys, audits, questionnaires, departmental presentations, teaching sessions and a randomised clinical trial were performed in order to provide evidence to enable the advancement of prophylactic practice in this hospital. The information gathered during the course of this work has been presented at international surgical meetings and was received with much interest; hopefully this work may then be used to help other hospitals address the same problems with thromboprophylaxis. In a 'nutshell', the main deficiency locally (and similarly described elsewhere in the literature) is a lack of a consensus between surgeons on the correct prophylaxis modalities and regimen to use. After more than forty years of scientific progress in this field, many hospitals and medical institutions still lack a consensus on how to manage the prophylaxis of DVT in their patient population.

A number of observations in this hospital were made that exemplify the disparity in prophylactic practice. The diverse opinions of surgical consultants in charge of
surgical firms led to uncertainty in the prescribing and application of prophylaxis by junior doctors and nursing staff. The results from the audit of thromboprophylaxis (chapter 4) demonstrated the poor application of prophylactic measures in surgical patients, with many patients not receiving any pharmacological prophylaxis at all. This was because consultants preferred not use subcutaneous heparin in certain operations, for example, total knee and hip replacements, spinal and intracranial surgery, despite published evidence indicating that these are the very patients that required prophylaxis due to their high risk of VTE. In addition, the use of LDUH and LMWH was inconsistent, with approximately only one quarter of the surgical patients undergoing surgery receiving the preferential LMWH (chapter 4).

The use of GCS was also disparate with many different brands and lengths of stocking found on different surgical wards, the choice of which was largely governed by cost, not evidence (table 5.1). To date only one make of stocking has level-one evidence to prove its efficacy in the prevention of postoperative DVT, namely Kendall thigh-length TED graduated compression stockings. Authors have demonstrated the importance of an optimal external graduated compression achieved by the stocking to reduce venous stasis (Sigel 1973 & 1975, Lawrence and Kakkar 1980). Thomas et al (2000) has since shown that many of the other stockings on the market do not achieve the optimal external compression profiles.

The audit performed in chapter four highlighted the inadequacies and the need for change, however there was still considerable resistance to running a RCT with subcutaneous LMWH used across the board (chapter 6), let alone reaching an agreement on a hospital consensus for all surgical patients involving the use of LMWH and GCS (as recommended by the International consensus statement for
high and moderate risk patients who made up the majority of our in-patient population).

<table>
<thead>
<tr>
<th>Surgical Ward</th>
<th>Type of GCS (length)</th>
<th>Compression Profile (ankle/calf/thigh) mm Hg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 South</td>
<td>Kendall TED (thigh length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>7 South</td>
<td>Kendall TED (thigh and knee length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>7 West</td>
<td>Kendall TED (thigh and knee length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td></td>
<td>Preventex (thigh and knee length)</td>
<td>14/13/3</td>
</tr>
<tr>
<td>7 North</td>
<td>Kendall TED (thigh and knee length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>8 South</td>
<td>Preventex (thigh and knee length)</td>
<td>14/13/3</td>
</tr>
<tr>
<td></td>
<td>Parama (thigh and knee length)</td>
<td>17/15/7</td>
</tr>
<tr>
<td>8 North</td>
<td>Kendall TED (thigh and knee length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>10 South</td>
<td>Kendall TED (thigh length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>11 West</td>
<td>Kendall TED (thigh and knee length)</td>
<td>13/11/3</td>
</tr>
<tr>
<td>ITU</td>
<td>Kendall TED (thigh length)</td>
<td>13/11/3</td>
</tr>
</tbody>
</table>

Table 5a – Different types of stocking used by surgical wards at Charing Cross Hospital. Legend: Intensive care unit (ITU), (* Average scores taken from Thomas et al 2000)
Despite readily available prophylactic guidelines from electronic literature sources and the prophylactic modalities are readily available if prescribed, however the prophylaxis was not reaching the patients. An audit questionnaire of the surgical doctors at Charing Cross hospital was performed to investigate the nature of the differing views on prophylactic practice and the consequence of the lack of a hospital consensus on prescribing prophylaxis.

5.2 A teaching hospital questionnaire audit: disparity and errors in the practice of DVT prophylaxis

5.2.1 Background

In our multidisciplinary university hospital a disparate and unsatisfactory use of thromboprophylactic measures in surgical patients undergoing surgical procedures was found (chapter 4). An investigation via a questionnaire audit of the thromboprophylaxis prescription procedures and the use of evidence-based guidelines by surgical doctors of all grades was carried out.

5.2.2 Methods

A questionnaire was developed to assess the thromboprophylaxis practice of surgical doctors. The questionnaire items were developed through interviews with ten doctors from all grades. Twenty-four questions made up the questionnaire (Appendix) that assessed the individual and departmental practices and the use of thromboprophylaxis guidelines. The questionnaire was given to surgical doctors at Charing Cross Hospital over the period of one week, doctors completed the
questionnaire under supervision without reference to any sources of information that could have influenced their answers. Results were collated anonymously.

5.2.3 Results

A total of fifty-six surgical doctors were asked to answer the questionnaire, 98 percent completed the questionnaire; one consultant refused. Of those who completed the questionnaire, thirteen were house-officers, twenty were senior house-officers, fifteen were registrars and seven were consultants (figure 5a). The doctors belonged to a wide variety of surgical specialities (figure 5b). The answers given in the questionnaire by all of the doctors, showed the majority followed their consultant’s or their own personal opinion when prescribing thromboprophylaxis, only 7% used guidelines published in the literature (figure 5c).

Figure 5a - The different grades of the surgical doctors who answered the questionnaire
The most junior members of surgical teams were reported by 87% to most frequently prescribe the surgical thromboprophylaxis (figure 5d). The questionnaire revealed that literature guidelines were not used by any of the firms’ most junior doctors (n = 21) who answered the questionnaire (figure 5e). Interestingly some doctors stated that they referred to the hospital guidelines for assistance with prophylactic practice, however at this time no hospital guidelines actually existed. Doctors were asked to place the single and combined prophylactic methods in order of efficacy, the first being the most efficacious. The majority of doctors believed that subcutaneous heparin in combination with antiembolic stockings was the best ‘combination prophylaxis’ and more efficacious that using heparin alone (table 5b). Despite this, only 42% of the doctors routinely prescribed subcutaneous heparin with GCS (figure 5f). Forty seven percent of all doctors who answered the questionnaire stated that they routinely prescribed subcutaneous heparin alone.
Figure 5c - The Sources of Information Used by Doctors to Guide Prophylaxis Prescription

- Personal Knowledge: 42%
- Hospital Guidelines: 36%
- Literature Guidelines: 7%
- Consultant Opinion: 15%

Figure 5d - The Surgical Doctors that Prescribed Prophylaxis

- Junior Grade: 13%
- Middle Grade: 0%
- Consultant: 87%
Figure 5e - The sources of information used by each grade of doctor to guide prophylaxis prescription.

Table 5b - Beliefs of surgical doctors about the best prophylactic modalities.

<table>
<thead>
<tr>
<th>'Best' Single Prophylaxis</th>
<th>'Best' Combined Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1st</td>
</tr>
<tr>
<td>Subcutaneous Heparin</td>
<td>Heparin &amp; GCS</td>
</tr>
<tr>
<td>2nd</td>
<td>2nd</td>
</tr>
<tr>
<td>Intermittent Pneumatic</td>
<td>Heparin &amp; IPC</td>
</tr>
<tr>
<td>Compression (IPC)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td></td>
</tr>
<tr>
<td>Dextran</td>
<td></td>
</tr>
</tbody>
</table>

Table 5b – Beliefs of surgical doctors about the best prophylactic modalities.
Most doctors believed that low molecular weight heparin was better than LDUH but their choice was governed by firm policy (figure 5g). The surgical doctors were asked which type of subcutaneous heparin was better, LMWH or LDUH and which GCS type was better, thigh or knee-length.

When using subcutaneous heparin alone or in combination with another prophylactic modality, twenty four percent of doctors routinely prescribed unfractionated subcutaneous heparin and 34% used the fractionated LMWH. More than half of the doctors also believed that thigh-length GCS were better than the knee-length design.
The separation of patients into high, moderate or low risk categories is a necessity required by current International and European guidelines for the successful prescription of prophylaxis for surgical patients. This was poorly performed by the doctors who answered the questionnaire, only 45% of doctors correctly identified the thromboembolic risk of three case scenarios. Interestingly, in the event of inaccurate risk assessment; GCS with heparin was prescribed regardless in 66% of cases.
The current guidelines are complex due to multiple risk factors that must be considered before prophylaxis can be correctly prescribed. According to the results from this questionnaire, the complexity of guidelines has led to confusion and uncertainty in the prescription practices of many doctors. Ninety-one percent of doctors experienced confusion on regular occasions over the correct prescribing of DVT prophylaxis and 51 percent felt uncertain when actual DVT prophylaxis prescriptions were given. When in doubt about the correct prescription; 73% of doctors referred to colleagues or seniors doctors for advice on prophylaxis, only twenty-four percent referred to the literature guidelines (figure 5h).

**Figure 5h – Actions of surgical doctors when in doubt about the correct prophylaxis to prescribe for a patient.**
Most doctors (96%) were in favour of simplifying DVT prophylaxis and agreed that a single 'blanket' protocol of subcutaneous heparin and stockings for all surgical patients with a small number of designated exclusions would be beneficial. Most doctors also agreed that a prophylaxis protocol with subcutaneous heparin and GCS should be commenced preoperatively rather than postoperatively, these included some consultants from orthopaedic and neurosurgery who often commence their pharmacological prophylaxis after surgery for fear of increasing bleeding complications (figure 5i).

**Figure 5i - The Preferred Time of Commencement of Prophylaxis**

![Bar chart showing the preferred time of commencement of prophylaxis](image)
5.2.4 Conclusions

This audit questionnaire has revealed a marked disparity in the prophylactic practices of the surgical doctors at Charing Cross Hospital. Within the different surgical specialities, there appears to be no particular structure or framework to explain these variations in practice. A number of salient conclusions were drawn from this survey:

- Throughout the specialities there is disparity of prescription practice.
- Very few of the surgical doctors use guidelines published in the literature
- The least experienced doctors in surgical teams most frequently prescribe the majority of the thromboembolic prophylaxis for their firm’s patients.
- None of these junior doctors audited used literature guidelines
- Subcutaneous heparin and GCS were the most frequently prescribed prophylaxis regime
- LMWH and thigh length stockings were the preferred varieties
- Surgical doctors were poor at separating patients into risk categories as required for the use of published guidelines in the literature
- The majority of doctors were in favour of a blanket protocol with preoperative LMWH and GCS for all surgical patients with exclusion of patients with specific medical contraindications.

The results of this study were combined with those from the previous audit (chapter 4) to give an overall appraisal of the thromboprophylaxis in Charing Cross Hospital. This information was used to provide evidence to each surgical department. It was explained that there was a desperate need for an improvement in our prophylactic practice.
5.3 Instigating change in a large teaching hospital

The advent of clinical governance has led to a change in the professional environment in which all doctors carry out their clinical duties; the standards of patient care are foremost on the list of clinical outcome criteria. The quality of care is improved firstly, by the use of national frameworks and local protocols that have been developed through the use of evidence-based principals, and secondary through the regular appraisal of the service quality by audit and instigating improvements to the areas of deficiency. However, even with clinical governance, there are still areas of practice throughout the National health service (NHS) that are resistant to change and regular audit. Such as venous thromboprophylaxis, which has proved unremittingly difficult to keep up to date and compliant in many hospitals throughout the NHS.

5.3.1 Communications to departments

The collective results from audit (chapter 4) and this questionnaire survey were analysed to produce information in order to help understand and deal with the difficulties in achieving good thromboprophylactic practice through the development of a hospital consensus for the prevention of postoperative DVT in surgical patients. Presentations were prepared and presented at specially arranged meetings to each surgical department. At this stage only nominal interest for improving the overall status of DVT prophylaxis was shown among surgical consultants. There existed a certain inertia to any suggestions for changing practice, in fact this began with the extreme difficulty experienced when trying to gather together all the senior and junior doctors of any one surgical speciality for a presentation. In general, the surgical consultants were happy with there own DVT prophylaxis within their firms.
and were unaware – prior to the presentations - of the overall picture of disparity that was made up of unstructured ‘firm-led’ DVT prophylaxis regimes. The junior doctors were in favour of improving the system of prophylaxis as long as it was recognised by their individual consultants. A few consultants, from a variety of specialities, showed enthusiasm for updating their practice; provided the evidence was clear and of good quality, these consultants (see acknowledgements) were instrumental in helping to organise meetings and instigate change.

The presentations made use of PowerPoint (Microsoft® Office 2000) to convey the information to the audience. Each presentation lasted for approximately forty minutes, followed by twenty minutes of discussion and questions from the ‘floor’.

Presentations were delivered to each department on more than one occasion to allow further questions and ‘departmental issues’ to be addressed. The presentations contained the following information:

- Background information
  - Epidemiology of VTE disease
  - The need for DVT prophylaxis; acute complications of DVT and PE and the long term effects of post-thrombotic syndrome

- The state of surgical DVT prophylaxis in our hospital,
  - Audit and questionnaire results

- An update on the published literature,
  - National and International consensus guidelines
  - Specific prophylactic recommendations for surgical specialities; comparisons of the published evidence for LMWH versus LDUH, and GCS versus other mechanical prophylaxis
Developing a hospital consensus for prevention of DVT in surgical patients at Charing Cross Hospital,

- Recommendations for LMWH and GCS
- Unanswered questions
  - Is LMWH safe and effective to use across the board?
  - Which length of GCS, thigh or knee-length, is the best in terms of efficacy and patient acceptability and compliance?
- The potential benefits of introducing a new single protocol
- Proposing a RCT investigating the use of a single blanket application of LMWH with GCS across the board and which is the best length of GCS in patients from all surgical specialities.

5.3.2 Feedback from departments

Presentations made to all surgical departments; breast and oncology, ENT, GIT, neurosurgical, plastics, urology and vascular, were received with enthusiasm. The poor state of the thromboprophylaxis in most surgical departments was found to be a surprise to many consultants who had assumed that the prophylaxis in their patients was adequate. The information provided from the current literature reassured many of the surgeons that subcutaneous heparin and GCS were the best combination of prophylaxis to use in general. All consultants without objection accepted the need to set up a RCT to resolve the important issue of which is the optimal length of stocking. However the use of LMWH for patients in the RCT was somewhat more controversial. Some consultants believed, despite evidence to the contrary from the current literature, that LMWH offered no prophylactic advantage over unfractionated heparins with the added detriment of increased bleeding complications. It was
mainly the orthopaedic and neurosurgeons who feared the potentially devastating outcome of bleeding complications in prosthetic joint and intracranial surgery respectively. The ENT, urology and vascular surgeons agreed to change from unfractionated to LMWH for the purposes of the proposed RCT. The breast and GIT surgeons had by this stage already incorporated LMWH into the prophylaxis of their patients. A final agreement was reached; firstly with the orthopaedic and neurosurgical teams that LMWH could be used in their patients recruited into the trial on the proviso that the LMWH was commenced twelve hours postoperatively. And secondly by the majority of consultants that the introduction of a new single protocol of LMWH and GCS for all in-patients undergoing surgery would be considered depending on the results from the RCT.

5.3.3 The use of LMWH and graduated compression stockings

‘across the board’ for patients undergoing surgery

The introduction of LMWH over a decade ago, for the prophylaxis of DVT in hospitalised patients has been met with some resistance. This was related to queries over its efficacy and bleeding complications when used in surgical patients and the initial expense of LMWH compared to unfractionated heparins. Since this time, numerous randomised clinical trials have been performed to evaluate the performance of LMWH in comparison to unfractionated heparin and its cost has gradually reduced to such an extent that it is now cheaper per day than its unfractionated counterpart. Low molecular weight heparin is the heparin of choice for the prophylaxis of the majority of surgical patients for a number of reasons:

1. Efficacy
2. Reduced complications
3. Patients acceptability
4. Cost
5. Other benefits, such as reduced hypersensitivity and anti-neoplastic effects

Graduated compression stockings have been commonplace in the prevention of DVT in surgical patients for over forty years. However, it is still not known which length of stocking, thigh or knee-length is more effective. This is a relevant and important uncertainty to resolve because of the high frequency of their application in surgical (and medical) practice. On the surgical wards in the majority of NHS hospitals one would expect to see a large proportion of the patients wearing GCS. The International and European consensus recommend their use in combination with subcutaneous heparin (mainly LMWH), for a large proportion of patients (those of high or moderate risk) from many different surgical specialities. However, even with numerous guidelines DVT prophylaxis in surgical patients in our hospital and many others is still inadequate (Anderson et al 1991, Bratsler et al 1998, Conti & Daschbach 1982, Ahmad et al 2002). Assessment of the literature and the failures of DVT prophylaxis in this institution has led me to strongly believe that in order to ensure that every patient undergoing surgery appropriately receives prophylaxis against DVT a simplified single protocol of LMWH and GCS for all surgical patients is the answer to this widespread problem.

The argument for a single ‘blanket’ protocol of LMWH and GCS is as follows:

1. LMWH and GCS have been shown to be the best combination prophylaxis in terms of efficacy, practically and patients acceptability.
2. Low dose LMWH and GCS are safe and rarely cause complications
3. The majority of patients staying in hospital to undergo surgery are of high or moderate risk for VTE and are recommended LMWH and GCS by the International and European consensus.

4. Some low risk patients in hospital have the potential to increase their risk to moderate or even high risk through surgical complications or unexpected histological diagnosis of malignancy.

5. Many of the surgical doctors administering prophylaxis do not use guidelines.

6. A single blanket protocol does not require the separation of patients into risk categories prior to administering prophylaxis, which is an advantage as many of the surgical doctors administering prophylaxis cannot risk assess the patients correctly.

7. LMWH can be given on the evening before surgery and the patients can still receive epidural and spinal anaesthesia on the morning of surgery without missing any of the required heparin prophylaxis.

8. LMWH is a single daily injection that is more acceptable to patients than twice or thrice daily injections.

9. LMWH is cheaper than unfractionated heparin for a daily prescription.

10. A simplified single protocol has been shown to improve the rate and compliance of DVT prophylaxis prescription (chapter 4).

The arguments against a DVT single blanket protocol for surgical patients are relatively few. These include factors such as the complications and cost of giving low risk patients LMWH and GCS. This query can be answered by the fact that low risk patients are known to suffer DVT and PE, the evidence for low risk patients with regard to the required prophylaxis and its cost effectiveness is not available in the
literature, and low risk patients can easily increase their risk status unexpectedly through prolonged or complicated surgery.

5.4 Discussion

The need for a new and fresh approach to the prevention of VTE in our surgical patients is clear. This approach must incorporate the evidence and work completed in the many studies and guidelines currently available in the literature. The international consensus recommends the use of subcutaneous heparin, in most cases LMWH, and GCS for high and moderate risk patients (Nicolaides et al 2002). This new single protocol of LMWH and stockings for all surgical patients undergoing surgery (in hospital) incorporates these recommendations from the International consensus and applies them to the population of surgical patients in a large teaching hospital in a simplified manner that has been shown to improve prophylaxis compliance (chapter 4). A large RCT was set up to assess the proposed new single protocol for efficacy, safety and to investigate which is the optimal length of GCS.
Chapter Six

A randomised controlled trial

to develop a new blanket protocol of low molecular weight
heparin and the best – thigh or knee length – stocking

for the prevention of postoperative DVT

List of Contents:

6.1 Introduction

6.1.1 The need for a randomised controlled trial

6.1.2 Aims of the study

6.1.3 Hypothesis and study end-points

6.1.4 Ethics approval

6.1.5 Sources of funding

6.1.6 Venous colour duplex scanning

6.1.7 Sample Size and Statistical Analysis

6.2 Patients and methods

6.2.1 Patients and data collection

6.2.2 Recruitment and randomisation

6.2.3 Patient information and informed consent

6.2.4 Colour duplex scanning for deep vein thrombosis in trial patients

6.2.5 Commencement and maintenance of trial prophylaxis

6.2.6 Treatment of patients who developed DVT
6.3 Results

6.3.1 Patient Series

6.3.2 Colour doppler ultrasound scanning for DVT

6.3.3 Trial Results

6.3.3.1 Postoperative deep vein thrombosis

6.3.3.2 LMWH prophylaxis commenced before and after surgery

6.3.3.3 Complications resulting from the blanket use of LMWH and stockings

6.3.3.4 The compression profiles of the stockings

6.3.3.5 Clinical aspects of deep vein thrombosis

6.4 Conclusions
6.1 Introduction

Surgical practice continues to be complicated by venous thromboembolic disease, despite continued efforts over the last four decades to reduce its occurrence. Patients are continuing to suffer from the severe complications of DVT and PE; ten percent of hospital deaths have been associated with PE (Sandler & Martin 1989). Although a fatal PE may be the first presentation, a DVT may propagate to produce a PE and up to seventy percent of patients with proven PE have venographic evidence of peripheral venous thrombosis (Hull et al 1983). In general, the most appropriate methods for the prevention of DVT in the surgical patient are subcutaneous heparin and graduated compression stockings (GCS) (Nicolaides et al 2001, Wille-Jørgensen et al 2002, Amarigiri & Lees 2000). Other pharmacological and physical prophylactic modalities however, are either less effective, less safe or impractical.

6.1.1 The need for a randomised controlled trial

In Charing Cross hospital, a large university hospital, there was considerable variation in the use of prophylactic methods with regard to types and regimen of heparin, GCS and their implementation, was found. None of the surgical specialities had a specific departmental protocol for the prevention of post-operative thromboembolism. Subcutaneous heparin prophylaxis was disparate, LDUH and different brands and doses of LMWH were prescribed inconsistently. The status of thromboprophylaxis was audited in Charing Cross hospital to establish the areas of practice that required improvement (chapter 4). In one hundred and six patients who had undergone surgery in our hospital, subcutaneous heparin prophylaxis was omitted in forty-six percent. The use of AES was omitted or deficient in fifty-four percent of patients. Many of the patients given stockings, received a variety of
stocking lengths, ‘unproven’ brands and with inadequate fitting in many cases. The majority of patients in hospital for surgical treatment were found to be of high thromboembolic risk (ICS. Nicolaides et al 2001). The combined use of subcutaneous heparin and stockings was evident in only twenty-four percent of patients (Howard et al 2002). Our findings are similar to other reports from the literature describing poor compliance of DVT prevention. In order to correct the poor compliance of thromboprophylaxis in our hospital the junior doctors and nurses were educated about the merits of a simple protocol of ‘heparin and stockings for all’ surgical patients, the re-audit showed a significant improvement of adequate thromboprophylaxis to 88% of patients (P=0.003) (Howard et al 2002). Information was fed back to the surgical specialities from our audit and the merits of a single protocol were discussed. After presentations to departments, the majority of surgeons felt that there was no doubt that LMWH was effective, more acceptable to patients due to the single daily injection, and cheaper than LDUH. However, surgeons and nurses were not certain of the safety of LMWH and what length and design of anti-embolic stocking should be applied.

6.1.2 Aims of the study

The goal was to develop a single and safe ‘blanket’ protocol to prevent post-operative DVT, in a university hospital, suitable for all surgical procedures for low, moderate and high-risk patients (ICS. Nicolaides et al 2001) from a wide range of specialities including breast and oncology, ear, nose and throat (ENT), gastrointestinal (GIT), neurosurgery, orthopaedic, urology and vascular. Recent Cochrane reviews gave encouragement for the combined use of subcutaneous heparin and GCS (Wille-Jørgensen et al 2002, Amarigiri & Lees 2000). A single
protocol that recommended a ‘blanket’ application of LMWH and GCS was investigated for safety and efficacy of DVT prophylaxis when prescribed to every patient admitted to hospital (excluding day-surgery patients) for any surgical procedure that requires a general anaesthetic. The best length of GCS was investigated for efficacy on a background of LMWH and stocking satisfaction with a health related quality of life (HRQL) and a compliance assessment (chapter seven).

6.1.3 Hypothesis and study end-points

The study hypothesis; ‘provided LMWH is given to all patients, thigh length anti-embolic stockings are equal to knee-length of the same design in the prevention of post-operative deep vein thrombosis’, was based on the limited evidence comparing thigh to knee-length stockings. The primary end-point of the study was the incidence of post-operative deep vein thrombosis by duplex scanning. The secondary end-point was the incidence of bleeding complications associated with LMWH.

6.1.4 Ethics approval

The study involved the recruitment of patients undergoing surgery at Charing Cross Hospital and therefore ethical approval was gained from the local Riverside Research Ethics Committee (Chelsea Westminster Hospital, London). A copy of the approval is appended in this manuscript (appendix). The ethical committee reference number is RREC 2447.

6.1.5 Sources of funding

Funding for this research came from a number of sources, these included the payment of my salary for Clinical Tutor in Surgery by Imperial College and the
Hammersmith Hospitals NHS Trust, additional costs from the Charing Cross
vascular surgical department research fund, and we are very grateful for the free
donation of GCS and partial funding of colour duplex scanning costs by Medi UK
Ltd.

6.1.6 Venous colour duplex scanning

The ability to visualise directly the superficial and deep venous systems by non-
invasive means with colour duplex scanning has revolutionised the approach to the
investigation of venous disease. In the early 1980's, 'B' mode compression
ultrasonography of the veins in the lower limb was introduced for the diagnosis of
DVT. Since this time, venous ultrasound scanning has been the subject of numerous
studies assessing its applications and accuracy. The earlier studies assessed the use
of compression ultrasonography for the detection of DVT. However accuracy has
improved over the last two decades as the technology has advanced with the
introduction of colour Doppler ultrasound in the mid 1980's and with the more recent
addition of enhanced computer software and power Doppler (colour Doppler
ergy). Today, state of the art ultrasound machines now provide high levels of
accuracy when compared to venography and isotopic fibrinogen scans for the
detection of DVT. For some time the detection of proximal (popliteal, femoral and
iliac vein) DVT has reached good levels of sensitivity and specificity with additional
safety employed by repeated scanning within one week. The duplex detection of calf
vein DVT however, has been controversial. The perceived minor relevance of the
calf vein DVT together with inferior diagnostic imaging from early ultrasound has
often led to this pathology being ignored. More recently the improved software for
pre and post processing of the B mode image, such as high definition zoom, together
with Doppler and now power Doppler, has enabled good visualisation of small calf veins and low flow scenarios can reliably be assessed. The accuracy has been reported to reach between 94 and 97.9% for detecting acute isolated calf DVT and 97% (confidence interval (CI) 96-98%) for the diagnosis of proximal DVT (Baumgartner et al 1998 & Keearon et al 1998). The sensitivity has been reported to reach one hundred percent, specificity 71%, positive predictive value 71%, achieved with 100% of scans completed successfully (Forbes & Stevenson 1998). Colour duplex scanning for DVT is non-invasive, time efficient, acceptable to patients, harmless and repeatable. Contrast venography on the other hand, is expensive, uncomfortable to the patient, occasionally painful, technically difficult to perform and is inadequate or impossible to perform in up to ten percent of patients. In addition, disagreements over the interpretation of venographic results for diagnosing DVT have been reported to occur in approximately ten percent of cases. Therefore, although in the past this test has been considered the gold standard for the detection of DVT, it is not ideal to use in the clinical environment. Isotopic fibrinogen scanning suffers similar set backs to venography as it is invasive, uncomfortable for the patients, technically difficult to interpret and in patients it has limited ability to image proximal DVT in patients with knee and hip replacements due to artefact. Burn et al (1997) reported how duplex ultrasonography has become increasing prevalent as a first line diagnostic instrument for the diagnosis of lower limb DVT in UK hospitals and that venography is used in only a minority of departments as the principal diagnostic technique.

The accuracy of detecting postoperative DVT by duplex scanning is dependent on a number of factors:

- The ultrasound machine and its capabilities
The ultrasonographer and techniques employed

The use of a ‘serial strategy’ of colour Doppler scanning before and after the surgery and within one week after an equivocal DVT scan.

The colour Doppler ultrasound (CDU) machine that was used for this study was an ATL/HDI (High Definition Imaging) 5000 (Advanced Technology Laboratory, USA), which is a state of the art colour Doppler machine with power Doppler and high definition zoom capabilities. All of the ultrasound scans for this study were performed by myself after completing a venous duplex training course of three months duration. Scanning for DVT with ultrasonography is known to be operator dependent, however errors can be limited if the operator is trained to perform a strict scan protocol. I was trained by our principal clinical vascular technological scientist (acknowledgements) to perform scans in this manner (see methods 6.2.4).

In the diagnosis of postoperative DVT, it is important to scan all of the patients for the presence of DVT before their operation to ensure that the patients have not recently suffered an undiagnosed acute DVT just prior to surgery and to record any deep venous scarring or occlusions secondary to previous ‘old’ DVT, that could potentially be mistaken for acute venous thrombosis after the surgery. All of the three factors – hypercoagulability, vein wall damage and venous stasis - described by Rudolph Virchow (1858) in the pathogenesis of venous thrombosis, are potentially present during and immediately after a surgical procedure. These are secondary to the stress response, calf vein wall distension and muscle paralysis, respectively. The development of an ‘early’ surgical DVT is thought to begin during the surgical procedure, with any clinical manifestations becoming evident during the first postoperative week, where as prolonged immobility in the convalescing patient may lead to the formation of a ‘late’ DVT’ that may not be directly related to the
operation itself. Hence, the second postoperative duplex scan should be carried out at five to seven days after the surgery. If the patient has not developed a DVT by 5-7 days after surgery then any venous thrombosis that develops after this time can be assumed to be related to thrombogenic factors taking effect to produce a ‘late’ DVT. However, for follow up purposes, I duplex scanned any patients who experienced any symptoms of DVT up to six weeks after their operation.

6.1.7 Sample size and statistical analysis

Studies provide evidence for improved venous haemodynamic properties of thigh over knee-length stockings (Benko et al 1999, 2001 & Berridge et al 1999). Sample size calculations for detecting a theoretical difference between thigh and knee-length GCS enabled the recruitment numbers to be estimated. Therefore, sample size calculations were based on detecting a possible difference in postoperative DVT rates of 20% in the knee-length stocking group and 5% in each of the thigh-length stocking groups. These calculations - based on 90% power at the 5% significance level - required 114 patients per group (342 patients in total).

The sample size calculations for equivalence of above-knee GCS to below-knee stockings for the prevention of DVT, based on hypothetical assumptions taken from the limited evidence from small trials in the published literature showing minimal differences between the stocking lengths in terms of efficacy. After testing for equivalence of treatment it was assumed that $\pi(1)=\pi(2)$ for all practical purposes although they may differ by a small amount. In conducting such a test for equivalence to show, with a given probability $1$-beta (power in table), that the trial will rule out any difference in proportions greater than some prespecified, usually small, difference epsilon. Sample size calculations based on testing for equivalence,
to detect a difference of 7% in a one-sided test, at the 0.05 significance level and
with 90% power, recruitment required 315 patients per group. The table 1e, gives the
sample sizes for differences in an equivalence study.

Statistical analysis was performed using STATA 6.0 statistical package (Stata
Corporation, College Station, USA). Logistic regression analysis was used to
estimate crude odds ratios (ORs) between Medi thigh-length and Medi knee-length
and between Kendall thigh-length and Medi knee-length stocking groups. These
crude ORs were also adjusted for the use of preoperative LMWH.

<table>
<thead>
<tr>
<th>Difference (epsilon)</th>
<th>Sig level=0.1, power = 0.9</th>
<th>Sig level=0.05, power=0.9</th>
<th>Sig level=0.1, power=0.8</th>
<th>Sig level=0.05, power=0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>n=2956 per</td>
<td>n=3854 per</td>
<td>n=2029 per</td>
<td>n=2782 per</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>group</td>
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</tr>
<tr>
<td>0.05</td>
<td>n=473 per</td>
<td>n=616 per</td>
<td>n=325 per</td>
<td>n=445 per</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>group</td>
<td>group</td>
<td>group</td>
</tr>
<tr>
<td>0.06</td>
<td>n=328 per</td>
<td>n=428 per</td>
<td>n=225 per</td>
<td>n=309 per</td>
</tr>
<tr>
<td></td>
<td>group</td>
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</tr>
<tr>
<td>0.07</td>
<td>n=242 per</td>
<td>n=315 per</td>
<td>n=166 per</td>
<td>n=227 per</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>group</td>
<td>group</td>
<td>group</td>
</tr>
</tbody>
</table>

Table 1e – The sample sizes for certain differences in an equivalence study. Sig level = significance level, n = number of patients.
6.2 Patients and methods

6.2.1 Patients and data collection

All patients were recruited from the surgical departments of Charing Cross hospital, the specialities included breast and oncology, ENT, gastrointestinal, neurosurgery, orthopaedic, urology and vascular surgery. Patients were given trial information sheets on the day before their proposed surgery (Appendix). A record of patient details were recorded on a trial baseline sheet (see below) in order to gain information for DVT risk categorisation and stratified randomisation. Data sheets were compiled to made a trial booklet for each patient. Other sheets recorded information from each stage of the patients’ participation in the trial, these included a randomisation, surgery and post-surgery, venous duplex scan findings, patients’ stocking satisfaction questionnaire and compliance assessment (Appendix).

All completed patient trial booklets were stored and not inspected until the completion of the trial. At the end of the trial, all patient data was entered and stored in secure offline computer databases. The risk factors for venous thrombosis were recorded on the ‘baseline’ sheet, these factors included:

- Age
- Male/Female
- Past medical history of:
  - Deep vein thrombosis
  - Pulmonary embolus
  - Coagulopathy
  - Coagulopathy family history
  - Smoking
- Obesity
- Varicose veins (CEAP classification)
- History of leg fracture or joint prosthesis surgery
- Mobility at time of trial (bed bound/chair bound/housebound/full)
- Recent - last six weeks - aeroplane flight (duration/date)
- Malignancy (type, date of diagnosis)

* Medications* (warfarin, aspirin, oral contraceptive pill, hormone replacement therapy, steroids, others).

The stratified randomisation details of each patient were recorded. The treatment data was recorded regarding the length of the surgery (greater or less than 45 minutes as recommended by the international consensus, and the type of surgery. A record of peri-operative prophylaxis complications was made for each case.

The findings from colour Doppler scanning, clinical assessment for DVT and PE and the compliance of patients wearing stockings and receiving LMWH injections were recorded. The compression profiles of each of the stocking designs were assessed randomly on patients throughout the duration of the trial. External pressure (compression profile) applied by the stocking was measured with an Oxford pressure monitor equipped with three skin/stocking interface pressure transducers. The transducers were positioned at specific points on the patients’ limbs between the skin and the stocking: the level of the maleoli of the ankle joint in the midline, on the lateral aspect of the lower leg at the midpoint between the maleoli and the tibial tuberosity and at the level of the tibial tuberosity (as described in the operator instructions). Care was taken not to position the transducers over boney prominences as this may produce falsely elevated readings. After the wearing of GCS for 5-7 days, the patients were asked to complete an HRQL ‘stocking satisfaction
questionnaire' developed for the assessment of patient acceptability using lower limb compression therapies (chapter 7).

6.2.2 Recruitment and randomisation

Patients were interviewed at surgical pre-admission clinics or on admission to surgical wards at Charing Cross Hospital for planned elective surgery, before entry into the study, patients were checked to ensure they fitted the entry criteria as detailed in table 6a.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A random allocation of all patients undergoing any elective surgical procedure whilst admitted as an in-patient at Charing Cross hospital.</td>
<td>1. Patients unable to give informed consent</td>
</tr>
<tr>
<td></td>
<td>2. Patients unable to receive LMWH or anti-embolic stockings</td>
</tr>
<tr>
<td></td>
<td>3. Patients receiving full oral or intravenous anticoagulation</td>
</tr>
<tr>
<td></td>
<td>4. Patients undergoing surgery in the Day Surgery Unit</td>
</tr>
</tbody>
</table>

Table 6a Entry and exclusion criteria for the study

The interview provided verbal information and ethics-committee-approved information sheets describing deep vein thrombosis, the study protocol and ethics approval. Informed consent (Appendix) was gained after the patient had had sufficient time to digest the information and ask further questions.
426 Patients Assessed for Eligibility to Commence Trial

11 patients did not meet inclusion criteria
39 patients refused to participate

376 Patients Randomised to Commence Trial Protocol
All Patients Received LMWH

- Kendall T.E.D. Thigh-length AES 127 Patients
- MEDI Thrombexin Thigh-length AES 121 Patients
- MEDI Thrombexin Knee-length AES 128 Patients

Figure 6a Recruitment consort diagram. Low molecular weight heparin (LMWH), Antiembolic Stockings (AES)

The patients that volunteered to take part in the trial were randomised via computer into one of the three stocking groups (figure 6a):

2. Medi Thrombexin® Climax™ (Medi UK, Hereford, England) thigh-length stockings,

Computer randomisation was stratified for surgical speciality and thromboembolic risk, in line with the International Consensus Statement for the Prevention of Venous Thromboembolism (Nicolaides et al 2001).

6.2.3 Patient information and informed consent

Trial information sheets were provided to all patients, these were developed in accordance to the recommendations of the Riverside ethics committee (London). General information describing deep vein thrombosis, its development in relation to surgical procedures and potential complications of a lower limb DVT. Specific information describing the randomised controlled trial and the influence that enrolment in the trial may have on the patients’ surgical care in hospital. Patients were interviewed during admission to surgical pre-admission clinics and surgical wards, information sheets were provided with a verbal explanation of the trial, sufficient time was allowed to assess the information and ask further questions. The patients who were interested in taking part in the study signed an informed consent sheet prior to taking part in any trial procedures. Patients who were unable to understand the trial information fully due to illness or otherwise were unable to give informed consent and therefore were unable to take part in the study.
6.2.4 Colour duplex scanning for deep vein thrombosis in trial patients

The incidence of DVT was assessed by colour Doppler ultrasound scanning as described previously in this chapter (6.1.6 Colour duplex scanning). All duplex scans were performed by myself with an ATL/High definition imaging 5000 (Advanced Technology Laboratory, USA) ultrasound machine with power Doppler and high definition zoom capabilities. All patients received a pre-operative venous duplex scan on the evening before surgery and a further duplex assessment on the fifth to seventh day after the surgical procedure. The preoperative scan was performed in order to check for clinically silent DVT or old post-thrombotic scarring or occlusions. As an undiagnosed preoperative DVT would potentially produce a false positive result during the second duplex after surgery. Any patients with preoperative DVT had their operations cancelled for safety reasons and rescheduled to a time that it was deemed appropriate to carry out the required elective surgery.

Due to the long time delay and the possibility of the patient no longer undergoing their planned operation these patients were removed from the study. However if the patients returned for surgery during the trial period then these patients would then be enrolled with the patients' permission.

A postoperative venous duplex was performed on all patients, the results of this second scan were compared to results from the preoperative CDU scans taking into account any preoperative detection of ‘old’ prothrombotic scarring or occlusions. The vascular department’s principal vascular technology scientist supervised and verified the venous duplex scans. Prior to commencement of the trial, I underwent a three-month period of training to learn the techniques for venous duplex scanning of the lower limb for diagnosing DVT, this training was carried out under the guidance
of the principal vascular technology scientist. During this training I achieved a high standard of DVT duplex scanning and thereafter during the trial venous scans were regularly supervised and checked by the principal vascular technology scientist, Mrs Mary Ellis. The DVT scans were frequently graded for accuracy by the principal vascular technologist. During this assessment, my scan results were not revealed to the principal vascular technologist until she had completed and finalised the outcome of the scan that she performed on the same patient.

Scanning for DVT with ultrasonography is known to be operator dependent, however errors can be limited if the operator is trained in a strict scan protocol. I was trained by our principal clinical vascular technological scientist to perform scans in the following manner:

1. With the patients in the supine position with the knee slightly flexed, longitudinally scan the iliac to the distal popliteal veins of both legs with frequency-based colour coded duplex ultrasound

2. Valsalva manoeuvre is performed by the patient whilst insonnating over the femoral triangle to ensure free venous flow from the inferior vena into the iliac veins

3. Scan in cross-section the iliac to distal popliteal veins with compression non-colour ultrasound.

4. In the sitting patient with the lower legs dependent, scan the proximal popliteal (to ensure an overlap of scanned areas) to the distal ends of the calf veins, namely the anterior tibial, posterior tibial, peroneal, gastrocnemius and soleus veins, in longitudinal CDU and cross-sectional non-colour compression ultrasound.
5. Power Doppler was used for small veins with low flow

6. Magnified imaging with high definition zoom mode was used for areas of suspected abnormality

7. Six criteria were required to be fulfilled for all areas of the deep venous circulation in order to exclude acute DVT –
   i. Colour fill
   ii. Spontaneous flow
   iii. Phasic flow
   iv. Augmentation
   v. No visible thrombus
   vi. Complete venous compression

8. If all of the six above criteria were not adequately fulfilled or if poor images were produced secondary limb pathology such as oedema, cellulitis, lymphoedema or obesity; the duplex scans were checked during that current scan by the principal vascular technology scientist and repeated within 7 days with the principal vascular technology scientist in attendance, as part of a serial scanning strategy.

Power Doppler and high-resolution zoom imaging modes were used for areas of suspected abnormality and for small veins with low flow rates.

For follow up purposes, any patients who experienced any symptoms of DVT up to six weeks after their operation were duplex scanned.

6.2.5 Commencement and maintenance of trial prophylaxis

Subcutaneous LMWH and graduated compression stockings were prescribed and administered to the patients on the evening before surgery (see figure 6b for a flow
diagram of the trial methodology). Stockings were expertly fitted to patients using the manufacturers guidelines; measurements with a tape measure were performed at the necessary points on the leg to achieve the best possible fit. All patients received stockings on the evening before surgery unless the surgical intervention involved the lower extremity and for these cases the stocking was fitted to the leg undergoing surgery on the first postoperative day.

**Figure 6b - Flow diagram of the trial methodology**
Patients were checked each day to ensure that stockings were being worn and maintained there fit, patients also completed diary cards to record stocking compliance. Patients were free to chose whether they wore their allocated stockings. A record of complications associated with the use of stockings and LMWH was made for all patients. A complication was classified as significant if it caused death, required surgical correction or other morbidity such as infection or wound dehiscence. Minor complications were regarded as those that were uncomplicated and resolved without additional treatment. Patients were allowed to leave the trial at any point if they wished as a result of complications secondary to a trial intervention or for other personal reasons.

6.2.6 Treatment of patients who developed DVT

All patients who developed a DVT during the trial were treated with full anticoagulation, initially using subcutaneous LMWH (Tinzaparin 175 Units/kg/day) until daily oral anticoagulation (Warfarin) achieved an International Ratio (INR) level of greater than two. Patients were also prescribed level-two compression hosiery to wear on a daily basis and referred for haematological follow-up care with a planned six months period of warfarin treatment.
6.3 Results

6.3.1 Patient series

A total of 426 patients were interviewed for introduction into the trial, thirty-nine refused and eleven were medically unable to wear AES or receive subcutaneous heparin prophylaxis, because they suffered from peripheral vascular disease or received other anticoagulation such as intravenous heparin or warfarin. The remaining three hundred and seventy six patients were randomised into the three stocking groups, the overall mean age was 58 years (range 16-88) and forty-two percent were males. The recruitment of patients during the trial is shown in figure 6c, limitations to the rate of recruitment were found to be due to the following:

- Patients admitted to hospital on the afternoon/evening before surgery still required multiple medical investigations
- Many patients were admitted on morning of surgery
- Shortage of hospital beds for elective surgery led to many cancellations
- Foreign and very elderly patients had difficulty understanding trial information
- Some patients were not prepared to return for 2nd duplex scan.

Patients were recruited from a variety of surgical specialities that included: breast and oncology (n=73), ENT (n=13), gastrointestinal (n=122), neurosurgery (n=34), orthopaedic (n=62), urology (n=58) and vascular surgical patients (n=14) (table 6b). Thromboembolic risk assessment in accordance with the International consensus (Nicolaides et al 2001) revealed 291 patients were high risk, fifty-nine patients were moderate risk and twenty-six patients fell into the low risk category. Stratified randomisation allocated patients into three similar stocking groups (see table 6c) consisting of patients wearing Medi Thrombexin thigh-length stockings (n=121),
Medi Thrombexin knee-length stockings (n=128) and Kendall T.E.D. thigh-length stockings (n=127) (figure 6d).

**Figure 6c - Rate of recruitment of trial patients**  
*(Dec 2000 - June 2002)*

Precise stratified randomisation resulted in each group being statistically very similar in terms of age (P=0.850), gender (P=0.998) (table 6c), thromboembolic risk (P=0.230) (figure 6e) and surgical speciality (figure 6f). There was no significant difference between groups for compliance with the trial protocol i.e. receiving injections of LMWH and wearing stockings (P=0.277).
<table>
<thead>
<tr>
<th>Surgical Speciality</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>73</td>
</tr>
<tr>
<td>ENT</td>
<td>13</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>122</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>34</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>62</td>
</tr>
<tr>
<td>Urology</td>
<td>58</td>
</tr>
<tr>
<td>Vascular</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 6b – Surgical specialities of recruited patients

<table>
<thead>
<tr>
<th></th>
<th>Kendall Thigh Stocking</th>
<th>Medi Thigh Stocking</th>
<th>Medi Knee Stocking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>127</td>
<td>121</td>
<td>128</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>42%</td>
<td>41%</td>
<td>42%</td>
</tr>
<tr>
<td>[Pearson Chi² p=0.99]</td>
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<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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</tr>
<tr>
<td>Mean</td>
<td>58</td>
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</tr>
<tr>
<td>Median</td>
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<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td>Std Dev</td>
<td>15.3</td>
<td>16.2</td>
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<td>[Kruskal-Wallis Test; p=0.85]</td>
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</table>

Table 6c – The demographic details of the trial patients
426 Patients Assessed for Eligibility to Commence Trial

11 patients did not meet inclusion criteria
39 patients refused to participate

376 Patients Randomised to Commence Trial Protocol
All Patients Received LMWH

Kendall T.E.D. Thigh-length AES
127 Patients

102 (80%) Patients Completed Trial Protocol

6 Patients with Postoperative DVT (5 unilateral and 1 bilateral DVT)

MEDI Thrombexin Thigh-length AES
121 Patients

93 (77%) Patients Completed Trial Protocol

2 Patients with Postoperative DVT (2 unilateral DVT)

MEDI Thrombexin Knee-length AES
128 Patients

99 (77%) Patients Completed Trial Protocol

11 Patients with Postoperative DVT (10 unilateral and 1 bilateral DVT)

Figure 6d - Trial consort diagram. Low molecular weight heparin (LMWH), Antiembolic Stockings (AES), Deep vein thrombosis (DVT)
Figure 6e - Similarity of stocking groups for DVT risk

Figure 6f - Similarity of stocking groups for surgical speciality
Table 6d – Similarity of stocking groups for ‘DVT risk factors’

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Kendall Thigh Stockings (% patients)</th>
<th>Medi Thigh Stockings (% patients)</th>
<th>Medi Knee Stockings (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous DVT/PE</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>History of Thrombophilia</td>
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<td>0</td>
</tr>
<tr>
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<td>26</td>
</tr>
<tr>
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<td>5</td>
<td>11</td>
</tr>
<tr>
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<td>3</td>
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<tr>
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</tr>
<tr>
<td>Malignancy</td>
<td>51</td>
<td>55</td>
<td>48</td>
</tr>
</tbody>
</table>

Figure 6g - Similarity of stocking groups for aspirin usage
As previously mentioned the VTE risk category for each patient was calculated using the guidelines in the International Consensus Statement (Nicolaides 2001). However, separate VTE risk factors for patients in each stocking group were very similar (table 6d). Aspirin usage was found to statistically similar [Pearson Chi^2; p>0.05] for each group (figure 6g). Malignancy is thought to be an important risk factor and interestingly the Medi thigh GCS group had the highest malignancy rate (see later).

6.3.2 Colour Doppler ultrasound scanning for DVT

The accuracy of the trial scans with colour Doppler was assessed by the principal vascular technologist, these were graded out of a total score of five. All scanned diagnosed by myself as positive for DVT were checked by a vascular scientist, additional scans were checked randomly each week of the trial and any scans found difficult to interpret by myself and the vascular scientist were brought back for a ‘re-scan’ after four days. My results were scored as follows; half a mark was awarded for each of the six factors required for the diagnosis of a DVT; colour fill, spontaneous flow, phasic flow, augmentation, no visible thrombus and complete venous compression.

One mark was awarded for correctly assessing the anatomical extent of the DVT and a final mark for detecting or excluding other synchronous DVT at all sites of the deep venous system. The recorded scores are shown in figure 6h, there were no scans in which the overall diagnosis of DVT made by Mary Ellis, the chief vascular technologist, was different from the DVT diagnosis by my scans. In summary, all scans checked proved to be correct in their diagnosis of lower limb DVT.
6.3.3 Trial results

6.3.3.1 Postoperative deep vein thrombosis

No DVT occurred in the low or moderate DVT risk patients (n=85) using this protocol. All postoperative DVT occurred in the patients from the high-risk group, nineteen patients developed DVT from two hundred and ninety one high-risk patients; two of these suffered bilateral DVT.

There were two patients wearing Medi Thrombexin thigh-length stockings that developed unilateral postoperative DVT with significantly more, eleven patients from the Medi Thrombexin knee-length group developed DVT (Fisher’s Exact Chi²; P=0.039), one with bilateral DVT. Kendall thigh-length stockings were associated with five patients with unilateral DVT and one with bilateral DVT, neither significantly more than Medi Thrombexin thigh nor less than Medi Thrombexin knee-length stockings (Fisher’s Exact Chi²; P=0.190) (figure 6i). Although significant differences were found with Chi², clearer interpretation of the results was
possible with logistic regression analysis. Logistic regression found an 81% reduction in DVT with Thrombexin thigh-length stockings (OR 0.18 [95% CI 0.04 – 0.82] p=0.026) and a 50% reduction with Kendall thigh-length (OR 0.5 [95% CI 0.18 – 1.41] p=190), when compared to Thrombexin knee-length stockings. The DVT that developed with the thigh-length stockings were all found in the posterior tibial and peroneal veins of the calf. The knee-length stockings were associated primarily with calf vein DVT, however one DVT was found in the superficial femoral vein of the thigh (figure 6j).

Age and malignancy were found by logistic regression analysis to be positive risk factors for DVT, the average age of the nineteen patients with DVT was 68 years (range 45-83) and twelve of these had a history of malignancy. The patients with postoperative DVT included, six orthopaedic patients, six patients from gastrointestinal surgery, five urology patients and two neurosurgical patients. The DVT were associated with two main types of surgery, firstly ‘bone cutting’ operations which included hip (n=3) and knee replacements (n=2), spinal surgery (n=3) and craniotomy (n=1). And secondly with major abdominal surgery: upper gastrointestinal operations (n=3), lower gastrointestinal operations (n=3), nephrectomy (n=2), cystectomy (n=3) and radical prostatectomy (n=1), (figure 6k). The specific surgical procedures that resulted in the patient suffering a postoperative DVT are detailed in figure 6l.
Figure 6i - Postoperative DVT rates for each stocking group

<table>
<thead>
<tr>
<th>Percent</th>
<th>Kendall Thigh-length</th>
<th>Medi Thrombexin Thigh-length</th>
<th>Medi Thrombexin Knee-length</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
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<td>2</td>
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<tr>
<td>100</td>
<td>102</td>
<td>94</td>
<td>99</td>
</tr>
</tbody>
</table>

(OR 0.18
[95% CI 0.04–0.82]
p=0.026)

Figure 6j - Anatomical distribution of DVT with each stocking type

<table>
<thead>
<tr>
<th>Number of DVT</th>
</tr>
</thead>
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<td>10</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Peroneal Vein  Posterior Tibial Vein  Superficial Femoral Vein

<table>
<thead>
<tr>
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<th>Medi Thigh</th>
<th>Medi Knee</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>8</td>
</tr>
<tr>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 6k - DVT occurred with 'bone-cutting' and abdominal cancer surgery

![Graph showing the percentage of patients with postoperative DVT across different surgical specialties.]

- **Number of patients with postoperative DVT**
- **Percentage of patients with postoperative DVT**
The VTE risk factors of the patients who developed post-operative DVT were minimal apart from twelve or nineteen patients (63%) had a history of malignancy. Otherwise, none of the patients had previously suffered VTE, only two had a family history of DVT, three were smokers, five had varicosities, three had previous joint replacements and six had limited mobility. However, most interestingly six patients with DVT had deep venous scarring on preoperative duplex scanning, but this factor and all others were spread evenly across the stocking groups.
6.3.3.2 LMWH prophylaxis commenced before and after surgery

Thirteen percent of the patients that underwent neurosurgical and orthopaedic surgical procedures, who all received their LMWH twelve hours after surgery, developed postoperative DVT compared to only five percent of the patients from the other specialities; breast, ENT, GIT, urology and vascular, who all commenced the LMWH prophylaxis preoperatively on the evening before surgery. This difference was found to be statistically borderline but not significant (OR 0.41 [95% CI 0.16 - 1.06] P=0.066), (figures 6m), however this possible trend was reciprocated across each stocking group (figure 6n).

**Figure 6m - DVT rates with and without preoperative heparin**

![DVT rates graph](image.png)

- Pre- and Postoperative LMWH
- Postoperative LMWH only
Complications resulting from the blanket use of LMWH and stockings

A record of complications associated with the use of subcutaneous LMWH and AES showed that only one significant bleeding complication occurred, other complications included minor haematomas (n=2) not requiring further management and minor foot abrasions from stockings (n=3), (figure 6p). The significant bleeding complication developed when a drain was removed on the second day after parotid surgery, the resultant haematoma required further general anaesthesia for evacuation. The patient made a rapid and uncomplicated recovery before discharge back to community.
6.3.3.4 The compression profiles of the stockings

The compression profiles of the stockings showed that the Medi designs produced a greater mean external pressure at all three measurement points on the lower limbs of a total of thirty-one patients. All three types of stocking produced graduated pressure profile reducing from distal to proximal in the lower limb (figure 6q).
6.3.3.5 Clinical aspects of deep vein thrombosis

Deep vein thromboses of the calf have a range of non-specific clinical symptoms and signs that makes the simple clinical diagnosis historically unreliable. The advent of venography for the diagnosis of DVT highlighted the inaccuracies of clinical examination alone (Barnes et al 1975). However, if risk factors are present in combination with consistent symptoms and signs, then the probability of a correct clinical diagnosis is increased (Wells et al 1997, Wells & Anderson 2000). Authors have developed ‘clinical prediction indexes’ to improve the diagnosis of DVT to help physicians with limited access to objective diagnostic means such as venography or duplex. There are four published clinical prediction indexes by Vine et al (1981), Landefeld et al (1990), Wells et al 1995, and a revised version by Wells et al (1997). The latter index has been reported to be the most useful, however none of these
indexes can safely replace the need for diagnostic testing (Kahn 1998). It is important to successfully diagnose a DVT, because if left untreated the patient can suffer a fatal PE. Proximal extension of calf vein DVT occurs in approximately 20-30% of cases and PE (symptomatic and asymptomatic) have been detected in as many as 50% of the cases with proximal DVT (Huisman et al 1989 & Kakkar et al 1969).

I recorded the clinical findings in the lower extremities of all of our trial patients in order to investigate further the relationship between clinically diagnosed DVT and those DVT diagnosed by Duplex ultrasound. The criteria for the clinical diagnosis of DVT was based on the presence of lower limb swelling confirmed by calf circumference measurement, calf/thigh pain confirmed by tenderness on palpation and a change in discolouration confirmed by the presence of erythema. The proportion of symptomatic and asymptomatic DVT (detected by duplex ultrasound after surgery) were approximately equal (figure 6r), around fifty percent.

A small proportion of patients from the total recruitment of 376 patients entered into the trial experienced one or more of the symptoms or signs mentioned above in one or two legs. The distribution of clinical findings and their relationship to DVT diagnosed by duplex is displayed in figure 6s. Of the original 376 patients (752 legs) recruited into the trial, 79 patients did not attend their postoperative duplex scan because their operation was cancelled or they chose to decline. Of the remaining 297 patients (594 legs), 62 patients (64 limbs) experienced limb swelling, eleven patients (twelve limbs) suffered calf or thigh erythema and 43 patients (44 limbs) had calf or
thigh pain and tenderness and 287 patients (574 limbs) did not have any symptoms. One patient experienced all three symptoms of swelling, erythema and pain in both legs.

Of these symptomatic limbs (total 78), 10 legs suffered DVT diagnosed by duplex and the remaining 68 symptomatic limbs had no duplex evidence of DVT. Of the 516 asymptomatic limbs, 11 legs suffered DVT by duplex (505 limbs had no evidence of DVT by duplex).

The accuracy of clinical diagnosis can be assessed by calculating the specificity, sensitivity, positive and negative predictive values (assuming duplex DVT diagnosis as the gold standard). The values required for the calculations are displayed in table 6e.
376 patients recruited into the trial (752 legs)

79 patients did not attend second postoperative duplex scan

297 patients completed the trial (594 legs)

78 legs experienced 'DVT' symptoms

516 legs were asymptomatic for DVT

10 legs with DVT by duplex

11 legs with DVT by duplex

68 legs with no DVT by duplex

505 legs with no DVT by duplex

Figure 6s - The distribution of clinical findings and there relationship to DVT diagnosed by duplex
Table 6e - The values required for the calculation of specificity, sensitivity, positive and negative predictive values of clinical diagnosis of DVT

The combination of all three clinical findings, the triad of swelling, pain and erythema were present in only nine legs (eight patients), however only one patient (one limb) from this group suffered a post-operative DVT. However, of the legs
without the complete clinical triad (n=586 legs), 20 were diagnosed with DVT by duplex and 573 legs were free of thrombosis. The specificity, sensitivity, positive and negative predictive values of clinical diagnosis using the 'clinical triad' of swelling, pain and erythema are as follows:

Specificity \[= \frac{573}{573 + 8} = 98\%\]

Sensitivity \[= \frac{1}{1 + 19} = 5\%\]

Positive Predictive \[= \frac{1}{1 + 8} = 11\%\]

Negative Predictive \[= \frac{573}{573 + 20} = 97\%\]

Clinical diagnosis by examination alone is specific but not sensitive for the diagnosis of DVT. These calculations indicate that clinical diagnosis of DVT is moderately accurate at detecting those without DVT, with improved specificity if a clinical triad model is applied. However, clinical appraisal alone is poor at diagnosing patients with DVT and will miss a large proportion of patients with DVT if the clinical triad is used alone.

6.4 Conclusions

Although numerous investigators have provided evidence to show that prophylaxis against venous thromboembolism is effective by reducing the incidence of DVT and PE by as much as two-thirds, there is still a lot of confusion and controversy over the correct prophylactic methods for surgical patients (George et al 1998). This uncertainty has led to the frequent occurrence of inadequate compliance of
thromboembolic prophylaxis in many centres globally (George 1998, Jones 1991, Stephens et al 1995, Audet et al 1998, Fletcher et al 1992). Hence, we may not be alone in our regional centre where the use of prophylaxis in surgical patients was alarmingly disparate (Howard et al 2002). There was no single policy for any of the departments, specialities or even consultant firms. The doctor initiating a patient’s treatment in hospital usually prescribed the DVT prophylaxis, which was more often than not the most junior member of the team. Low molecular weight and unfractionated heparins and antiembolic stockings of thigh-length and knee-length designs were prescribed to surgical patients in an incongruent manner.

In our establishment the poor adherence to thromboembolic prophylaxis was generally not realised until audit presentations to each speciality were given to explain the existing deficiencies. Education has proved beneficial to prophylaxis of venous thromboembolism (Howard et al 2002, George et al 1998, Jones 1991, Stephens et al 1995, Audet et al 1998, Fletcher et al 1992, Anderson et al 1994) and is required on a regular basis with support from frequent audit. A general consensus between departments would not have been reached without this education and audit. Any information conveyed to the medical staff has to be based on evidence-based principals. Unfortunately, the complexity of the abundant recommendations for surgical thromboembolic prophylaxis in the literature adds to the general uncertainty and consequent loss of coordinated and agreed practice. A clear and simple plan for venous thromboembolic prophylaxis was proposed in order to improve its application and therefore overall efficacy. This plan was based on our audit findings that most surgical ‘in-patients’ are of high or moderate thromboembolic risk. And despite the copious methods available for the prevention of venous thromboembolism, low-dose heparin and AES are the most frequent combination in
use (Conti & Daschbach 1982). Antiembolic stockings have proved effective in the surgical patient with a reduction in the incidence of postoperative DVT to approximately eleven percent and subcutaneous low dose heparin is slightly more effective, reducing the DVT incidence to around nine percent (Wille-Jørgensen et al 2002). Furthermore, the combined effects of GCS and subcutaneous heparin are thought to be synergistic (Kalodiki et al 1996, Nurmohamed et al 1992, Leyvraz et al 1991, Nicolaides et al 2002). The efficacy, safety and acceptability of these two methods have led to their popularity in surgical practice.

It was proposed that LMWH should be given to all patients undergoing surgery with general anaesthesia, bar those with medical contraindications. This policy was accepted throughout the surgical specialities. However the orthopaedic and neurosurgery specialities feared bleeding at the time of surgery and insisted on delayed heparin administration for their patients.

The question arose as to which type of stocking and heparin is best in combination. Until our randomised controlled trial, no conclusive evidence was available to distinguish between knee and thigh-length GCS to guide practitioners on their prescription (Hui et al 1996, Porteous et al 1989, Williams et al 1996, Williams et al 1988). Our study has provided level one evidence that the thigh-length version of GCS is better at preventing postoperative DVT than the knee-length design with the same graduated compression profile. We have also demonstrated that the manufacture specifications of the stocking are important, but there is no significant difference between the two thigh-length stockings. Certainly, we can be sure that the full thigh length stocking is a vital factor.

Low molecular weight heparin has been heavily investigated over the last decade to establish its efficacy and safety when compared to LDUH and placebo. A large
number of trials and meta-analyses have demonstrated that LMWH is undoubtedly no worse and in many instances better at preventing thromboembolic complications than LDUH (Handoll et al 2002, Koch et al 1997). On the balance of published evidence we felt that it was right to attempt to convince all surgical specialities to use LMWH for all patients and they did. We believed that we could investigate which stocking was optimal, but on current evidence LMWH should be given to every surgical patient undergoing general anaesthetic except in day surgery, and continued daily till discharge. In addition to efficacy, LMWH has other advantages in terms of patient acceptability, practicality and cost. Patient acceptability is improved with only one daily subcutaneous injection compared to a possible three injections with LDUH. The fact that LMWH requires only a once daily dose, permits the injection to be given on the evening before surgery, which allows the peak plasma anti-Xa activity that occurs one to four hours after the injection to pass during the night, therefore reducing further any risk of per-operative bleeding. Many anaesthetists also prefer LMWH prophylaxis to be given up to twelve hours before placement of spinal and epidural anaesthesia (Bergqvist et al 1997); the preoperative ‘evening’ LMWH injection allows these patients safely to receive regional anaesthesia with heparin prophylaxis. The cost effectiveness of DVT prophylaxis has been reported (Oster et al 1987, Dunn et al 1996, Freedman et al 2000), and because the cost of LMWH has reduced since its conception it is now the cheaper option, making it more economically acceptable than unfractionated heparin (Freedman et al 2000). Very few complications were associated with the combined use of LMWH and GCS. The potential side effect of postoperative bleeding has been a frequent criticism of LMWH, especially by orthopaedic and neurosurgery consultants who fear the devastating postoperative complications of joint prosthesis infection and intracranial
haemorrhage. The controversy surrounding heparin prophylaxis is evident from the large number of studies investigating the fine balance of the reduction in thromboembolic complications opposed to the potential increase in perioperative bleeding. However, in the majority of studies, of which many are from orthopaedic and neurosurgery specialities, LMWH does not increase the incidence of operative bleeding when compared to placebo, let alone LDUH (Freedman et al 2000, Howard et al 1998, Palmer et al 1997, Levine et al 1991, Menzin et al 1994). Operative bleeding complications have a number of causes and distinguishing those due to heparin coagulopathy maybe difficult and for this reason the clinical trials required randomisation. Randomised controlled trials, some with double-blinding have shown rates of bleeding complications for LMWH, LDUH and placebo in orthopaedic surgery that ranged between 1.5-6%, 6-9% and 2.4-8% respectively (Turpie et al 1986, Agnelli et al 1998, Macdonald et al 1999, Nurmohamed et al 1996, Raabe et al 2001). Likewise, in neurosurgery bleeding complications occurred at 2-3%, 0-1.8% and 0-3% respectively, and results from gastrointestinal surgery studies were very similar (Gallus et al 1993, Ockelford et al 1989). In our study, the orthopaedic and neurosurgical teams at least had the reassurance that the major bleeding problems they feared did not occur. For them to allow LMWH to be given twelve hours before surgery could potentially increase this complication but the balance could be a lower DVT rate. Surgery requiring ‘bone cutting’ and tumour resection are at high risk of thromboembolic complications and therefore require optimal prophylaxis. The surgical procedure initiates the thromboembolic process and therefore we feel that starting the heparin prophylaxis after surgery is suboptimal and interestingly in our study, the neurosurgery and orthopaedic patients suffered the highest rate of
postoperative DVT (figure 6m), approximately twice that of the other specialities whose patients received LMWH prior to their surgery.

The combination of a good quality thigh-length stocking and LMWH for hospitalised patients requiring surgery produced a low postoperative DVT rate of two percent in the high-risk patients and no DVT in the moderate and low-risk patients. We have recommended a simple and safe protocol for DVT prophylaxis in a busy university hospital by prescribing LMWH and GCS to all surgical in-patients. To have a hospital protocol means that prophylaxis against DVT is less likely to be forgotten and its simplicity improved compliance (chapter 4). If a speciality insists on a LMWH delay, this can be accommodated. Those patients with medical contraindications to heparin or stockings would receive their permitted prophylaxis.

A ‘blanket’ treatment of perioperative LMWH and good quality thigh-length AES is safe and effective to use in surgical patients for the prophylaxis of postoperative DVT, with very few disadvantages.
Chapter Seven

Assessment of patient satisfaction with compression stockings:
the development and validation of the a health outcome measure
and the assessment of stocking compliance

List of contents

7.1 Background – Health outcome assessment

7.1.1 Health outcomes measurement

7.1.2 Measuring health outcomes in surgery

7.1.2.1 Types of HRQL

7.1.2.2 Medical Outcomes Study Short Form 12 Item Health Survey

7.2 Developing a specific health outcome questionnaire

7.2.1 Development of instrument ‘questions’ (items)

7.2.2 Selection of the items for use in the questionnaire

7.2.2.1 Face validity

7.2.2.2 Frequency of endorsement

7.2.2.3 Homogeneity of items

7.2.2.3.1 Cronbach’s Alpha

7.2.2.3.2 Split-half homogeneity

7.2.2.3.3 Item-total-correlation

7.2.3 Multifactor inventories

7.2.4 Summary of item selection
7.2.5 Scale construction

7.3 Testing a specific health outcome questionnaire

7.3.1 Reliability

7.3.2 Validity

7.3.3 Responsiveness

7.3.4 Acceptability

7.4 The development and testing of a questionnaire to assess patients' satisfaction with thigh and knee length stockings

7.4.1 Methods and patient series

7.4.1.1 Development of instrument 'questions'

7.4.1.2 Selection of the items for use in the questionnaire

7.4.1.2.1 Frequency of endorsement

7.4.1.2.2 Homogeneity of items

7.4.1.3 Scale construction

7.4.1.4 Testing for use as a satisfaction measure

7.4.1.4.1 Reliability

7.4.1.4.2 Validity

7.4.1.4.3 Responsiveness

7.4.1.4.4 Acceptability

7.4.1.5 Use of the questionnaire assessing patient satisfaction with thigh and knee length stockings

7.5 Results

7.5.1 Development of instrument 'questions'

7.5.2 Selection of the items for use in the questionnaire

7.5.2.1 Frequency of endorsement
7.5.2.2 Homogeneity of items
7.5.3 Scale construction
7.5.4 Validity
7.5.5 Test-Retest Reliability
7.5.6 Acceptability
7.5.7 Patient satisfaction with thigh and knee length stockings
7.5.8 Conclusions

7.6 The assessment of patient stocking compliance
7.6.1 Methods and patient series
7.6.2 Compliance diary sheets
7.6.3 Results

7.7 Conclusions
7.1 Background – Health outcome assessment

With the advent of clinical governance, practitioners are now increasingly accountable for the quality of health care provision. This chapter outlines the importance of the measurement of health outcomes and summarises the currently available outcomes measures in surgery. The development of an outcome measure for patients using lower limb compression treatments is described.

There are many ways to measure outcomes of care. An improvement in a patient’s condition needs to be demonstrated in order to determine the benefit of a surgical treatment or intervention. In surgery, audit and follow-up appraisals are used to record a number of outcome variables such as: improvement in symptoms, survival, specific and general changes in morbidity, for example in vascular surgery; patency of vessel or graft, healed or non-healed, amputation and stroke rate. Patient satisfaction and quality of life outcome measurements represent an essential adjunct to these largely objective ‘standard’ outcomes measures. Many patients have been found to grade symptom relief higher than healing on their list of treatment priorities. For example, in patients with near intractable venous ulceration, which are commonly treated by compression, improvements in the patients’ quality of life - which is closely related to patient acceptability and satisfaction with therapy - is as important as achieving healing (Harmer et al 1994). Any treatment with the capability to cure and improve quality of life would be the ideal therapy. In order to prove whether a new or established treatment is optimal; a valid, responsive, acceptable and reliable health outcome measure is required alongside the ‘standard’ outcomes measures.

Until recently, health outcome assessment has been slow to permeate clinical surgical principles. The popularity of health outcome assessment was minimal in the
1970's (Bardelli & Saracci 1978). In the 1980's a review of surgical trials showed that only 3% mentioned quality of life (O'Young & McPeek 1987). In the early 1990's the importance of health outcome assessments was recognised, it has taken many years to infiltrate into surgical practice:

"It is important that we join with colleagues in other disciplines to develop measures of the outcome of surgery, ‘Quality of Life’ and ‘patient satisfaction’ after surgery are important outcome measures and in our daily work we should attempt to measure our success in these ways. Many of the technical decisions in clinical surgical management are based on the weighting of different outcomes, and we should ensure that these incorporate patient values. Patient opinions are important in determining these relative values." (Devlin 1990)

The reporting of health outcomes has increased from 0.63% in 1980 to 4.2% in 1997 for trials of all disciplines (Sanders et al 1998). Currently, the majority of surgical, medical and pharmaceutical trials measure quality of life and treatment acceptability or satisfaction as an outcome variable alongside morbidity and mortality.

7.1.1 Health outcomes measurement

Traditionally, the assessment of health outcomes in care involved the use of objective biomedical measures that focused on the disorder, where the outcome is defined as the presence or absence of the disease. At the population level the influence of disease is defined in terms of morbidity, incidence and prevalence and mortality. Although simple, these measures are now thought to be incomplete
measures of health outcome due to improvements in general living standards and health care (McDowell & Newell 1987). The many different aspects of a patient's life, such as cultural, economic, social and environmental factors are taken into account in the measurement of health outcomes. Objective biomedical measurements are easier to measure than the complex influences of these factors. Surgical interventions may functionally improve the affected organ or the overall physical state of the patient, however with a detrimental effect on the quality of life. The goal of medical care for most patients is the achievement of a more effective life and the preservation of function and well-being (McDermot 1981). In this new era of clinical governance and applying evidence-based medicine, the sole use of biomedical measures is no longer adequate and information about quality of life, patient satisfaction as well as functional status is required to fully assess a treatment's success. Over the last fifty years, the introduction of numerous treatments for each disease has lead to many studies comparing new treatments to established treatments. Chronic conditions are rarely cured, hence health care commonly focuses on limiting or improving the impact of the condition on the patient's life by improving the health related quality of life (HRQL). The patient's subjective perceptions of their health are therefore an important measure of health outcome along with the objective measures. The approach to assessing the subjective outcomes is grounded in the theory that the patient is the best judge of their health and can accurately report these subjective outcomes (Fitzpatrick 1984, Albrecht 1994). There are a number of health outcome measures and their development has increased over recent decades. These now include measures of patient satisfaction, functional disability, psychological well-being, social health and HRQL (McDowell & Newell 1987).
Health related quality of life is a concept that assesses the patient’s perceptions relating to health care, rather than the influences on health of environmental factors. The measurement of HRQL is now recognised as a core component in the assessment of health care outcomes (Albrecht 1994, Geigle & Jones 1990). A Medline search over the last two decades using ‘health outcomes’ or ‘HRQL measurement’ as key words in the titles of articles demonstrates a gradual yearly increase in related articles. Furthermore health care reforms in the UK now require the use of health outcome measures.

Measurement of HRQL - The World Health Organisation defined health as a state of “complete physical, mental and social well-being, and not just the absence of disease” (1958). HRQL helps to complete the assessment of a patient’s health by focusing on the person and their experiences of the disease and treatment. Price offered a simple but clear definition of HRQL as “the impact of an illness and its treatment on disability and daily living” (Price 1996).

Early attempts to size quality of life were primitive in comparison to their present day equivalents, for example: they recorded the numbers able to ‘resume paid employment’ or ‘perform household duties’ (Ebbs 1989). A comprehensive HRQL instrument must have multiple dimensions; these usually assess physical, mental or cognitive, emotional or psychological, social and role functions, disease symptoms and perceptions of well-being. The applicability of HRQL instruments are diverse and numerous. HRQL can be used to improve health outcome evaluation of:

1. The efficacy of a new or established treatment.
2. Results in research and clinical studies.
4. Clinical decisions, prioritising waiting lists, treatment guidelines and health policies (Coons & Kaplan 1993),

5. Symptoms that are otherwise difficult to assess objectively, for example fatigue in sarcoidosis (Wirnsberger et al 1998),

6. Health care delivery to the wider community (Martin & Stockler 1998),

7. Finally to help individual patients with difficult clinical choices over their treatment options offering different outcomes in quality of life (Casali et al 1997).

Beattie et al described the ‘ideal’ HRQL measure as one that produced constant validity when used by any healthcare employee, in any location and for any disease or treatment (Beattie et al 199).

7.1.2 Measuring health outcomes in surgery

The concurrent assessment of the clinical outcomes and HRQL in patients undergoing a surgery provides a complete overall assessment of the benefits of that treatment. The recognised way of assessing the quality of life is by using a generic and specific measure of health outcome (Garratt 1993, Ware et al 1993). The properties of these outcome measures are summarised in table 7a.

7.1.2.1 Types of HRQL

A wide range of instruments for measuring HRQL have been developed during the last decade that fall into two broad categories: generic and disease specific tools. The selection of an instrument depends upon its measurement properties but also upon the particular context in which the instrument is to be used.
<table>
<thead>
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<th>GENERIC INSTRUMENTS</th>
<th>SPECIFIC INSTRUMENTS</th>
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<td></td>
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<tr>
<td>Health Profiles</td>
<td>Utility Measures</td>
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<td>Single index</td>
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<td>May detect different aspects of HRQL</td>
<td>representing HRQL</td>
</tr>
<tr>
<td>Enable comparison across different conditions</td>
<td>Can be used for cost-utility analysis</td>
</tr>
<tr>
<td>Can be used for cost effectiveness analysis</td>
<td></td>
</tr>
<tr>
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<td>Attribution problems of single index</td>
</tr>
<tr>
<td>May not be responsive</td>
<td>May not be responsive</td>
</tr>
<tr>
<td>Do not take account of values attached to levels of HRQL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td></td>
</tr>
<tr>
<td>Sickness impact profile</td>
<td>EuroQol</td>
</tr>
<tr>
<td>Nottingham health profile</td>
<td></td>
</tr>
<tr>
<td>Short form 36 item health survey</td>
<td>Aberdeen back pain scale</td>
</tr>
<tr>
<td>Short form 12 item health survey</td>
<td>Asthma quality of life questionnaire</td>
</tr>
<tr>
<td></td>
<td>Sabbatsberg sexual rating scale</td>
</tr>
<tr>
<td></td>
<td>Child health questionnaire</td>
</tr>
<tr>
<td></td>
<td>Pain perception profile</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7a - Summary of properties for quality of life assessments

Generic instruments are designed to assess multiple conditions and measure generalised effects. These characteristics lend to the ability to assess a new intervention or treatment for which the medical outcomes are uncertain. Generic instruments can measure the broad range of effects and co-morbidity of multiple diseases which enables comparisons of quality of life between different population
groups, normal and those with disease (Stewart et al 1989, Ware & Sherbourne 1992). The age and sex matched population ‘normal scores’ are available for such established tools as the Medical Outcomes Study SF-36 (Ware & Sherbourne 1992), the Nottingham Health Profile (NHP) (Hunt et al 1985) and the Sickness Impact Profile (SIP) (Bergner et al 1976). The SF-36 and NHP have been used to gauge outcomes in many conditions in many different countries. The SF-36 continues to be validated for use in more countries, languages and conditions (Ware 1999, Chang et al 2000).

There are two major classes of generic instruments: Health profiles that measure HRQL across a number of designated dimensions and Utility measures that take account of values or preferences attached to HRQL states (Davies et al 1999). The 36 item short form (SF-36) is a health profile that was designed for use in clinical practice and research, health policy evaluation and general population health surveys. The SF-36 assesses eight health domains: limitations in physical activity, social activity, role activities due to physical and emotional health problems, bodily pain, general mental health (psychological distress and well-being), vitality (energy and fatigue) and general health perceptions (Ware & Sherbourne 1992). Another commonly used generic instrument is the 12-Item Short-Form Health Survey (SF-12), which was developed from the SF-36 to form the Physical Component Summary and Mental Component Summary measures (Ware et al 1996). The wide-range of applications of health profiles enables their use in assessing cost-effectiveness in the treatment of disease, however cost-utility assessment requires utility instruments for this purpose. Utility instruments take account of preferences associated with HRQL states. Through weighting of HRQL states and their durations the quality adjusted life years (QALYs) can be calculated (Williams 1985). A commonly used utility
instruments for cost-benefit analysis is the EuroQol (EuroQol Group 1990), which assesses the health effects of all interventions in units of utility via five items (mobility, self care, main activity, pain/discomfort and anxiety/depression).

Specific HRQL instruments have a more restricted application, the focus of the assessment is specific to a certain condition, disease, function, population or problem which in-turn produces greater responsiveness or sensitivity to clinical changes associated with that particular disease (Davies et al 1999). Specific instruments can be designed or selected to assess specific areas of interest in the quality of life of a population, for example venous ulceration (Smith et al 2000), varicose veins (Garrat 1993), back pain (Ruta 1994), asthma (Juniper 1992). Disease specific tools have the advantage of being more responsive to small changes in health produced by the disease under investigation, for example: the Dutch questionnaire for Klippel-Trenaunay syndrome (van der Ploeg et al 1995) and the Diabetes Quality of Life Measure (Jacobson et al 1994).

Both specific and generic measures have their strengths and weaknesses, which are products of their design; generic tools can detect changes in comorbidity but are less specific, whereas specific HRQL instruments may fail to detect changes occurring outside the primary interest. However, generic and specific HRQL instruments when used in combination may compliment each other by joining their general and specific attributes, which has now become a recognised process (Garratt 1993, Ware 1993). Whatever HRQL tool is employed, particular attention needs to be paid to the translation and validation of instruments for use in different countries, cultural contexts and diseases (Holcik 1999). The increasing appreciation of the need for disease specific measures in surgery, especially in vascular surgery when maintaining the quality of life is of great importance amidst incurable chronic disease
processes. Quality of life measures have been and are now frequently employed to assess outcomes in chronic venous disease. Outcomes after treatment of deep vein thrombosis (DVT) have been assessed by HRQL for short term benefits such as: after catheter directed thrombolysis of iliofemoral DVT (Comerota 2000) and for long term follow-up of post-thrombotic syndrome for up to eight years (Beyth et al 1995). The SF-36 has been applied in combination with a specific instrument (Hicken et al 2000) for simultaneous assessment of common conditions including varicose veins (Ruta et al 1999).

Recent reviews of quality of life assessments in vascular disease came to the conclusion that the SF-36 (Beattie 1997, Howard & Davies 2001) or its shorter version the SF-12 was the best generic tool for ‘vascular’ patients particularly as it is translated for use in a number of different countries. The combined use of generic and specific instruments is required to achieve an overall assessment of health outcome. In this study the patients were asked to wear anti-embolic stockings for prophylactic reasons rather than for the treatment of a specific condition. We needed to assess the acceptability of the trial stockings for each patient and not their quality of life in relation to their disease for which they were undergoing surgery. Patient stocking satisfaction measurement would help to understand compliance variations and chose the ‘best’ of two functionally similar GCS. Until this study there was not available tool to access patient satisfaction with compression stockings, therefore I needed to develop a questionnaire to measure patient satisfaction with lower limb compression therapies which could be used in this study and in future studies comparing compression treatments. This new specific HRQL tool was developed for use alongside a generic instrument; hence the Charing Cross Stockings Satisfaction
Questionnaire (CSSQ) was employed with the SF-12 to ensure that the measure of stocking acceptability and not influenced by the patients’ illness.

7.1.2.2 Medical Outcomes Study Short Form 12 Item Health Survey

The 12-Item Short-Form Health Survey (SF-12) was developed from the SF-36 by regression methods to form the Physical Component Summary and Mental Component Summary measures (Ware et al 1996). The SF-12 is a generic instrument that provides an overall assessment of HRQL. The SF-12 has been employed in combination with the SF-36 (Hawk et al 1998, Besette et al 1998) and individually (Johnson & Coons 1998). The SF-12 is a general health survey with a shorter respondent time and improved respondent acceptability compared to SF-36. It generates physical and mental health summary scores equivalent to SF-36. The SF-12 was also more sensitive than the EuroQol EQ-5D in low morbidity conditions (Johnson & Coons 1998).

7.2 Developing and testing a specific health outcome questionnaire

The methods described below explain the development and validation of a specific health outcome measure to assess the patient satisfaction associated with the wearing of lower limb compression therapies, such as GCS. The development of a health outcome instrument relies on item selection through the empirical testing in relation to the objectives and proposed application as recommended by Streiner and Norman (Streiner & Norman 1990). There are a number of approaches to develop a specific instrument, either by the modification of a generic instrument, addition of specific qualities to a generic measure or development of a separate specific instrument.
(Patrick & Deyo 1989). The modification of a generic instrument requires the adjustment of the content or removal of items to make the measure more specific to the area of concern (Temkin et al 1989). Specific supplements to generic instruments add specific domains to the existing domain of the generic instrument, this approach reduces the effort of the patient by negating the simultaneous use of a generic and specific instrument and by reducing the repetition found in any overlap between domains. Separate specific instruments aim to assess specific areas of a condition (Juniper et al 1992, Ruta 1994), however if the specific instrument is used alongside a generic instrument there may be areas of repetition.

The assessment of patient satisfaction for lower limb compression therapies is a small and very specific area of health outcome to investigate, prior to the development of our instrument in this study there was no existing measure generic or specific for this health outcome. Therefore it was necessary to develop a new specific health outcome measure.

### 7.2.1 Development of instrument ‘questions’ (items)

The selection of items for an HRQL instrument should be guided by theories of HRQL measurement taken from the literature, clinical practice, and interviews with health professionals and patients (Streiner & Norman 1990). The first stage involves a detailed search of the literature to investigate previous similar assessments. Following this, interviews with patients using the treatment highlights the areas of patient interest to form items in the health outcome questionnaire. These interviews should be composed of open and closed questions. There is no set number of interviews required, the criteria often used is ‘sampling until redundancy’, in other words until no new subject are uncovered. Interviews should also be carried out with

206
a number of health professionals in the field such as doctors and nurses. Again there is no set rule as to how many and who is interviewed from the medical staff. Clinical observation alone may be enough to establish the items for an instrument in a new area or field, this can be attained through preliminary research in the specialist area. The number of domains or items construed from these sources described above will usually be more than what is required in the final questionnaire. In the process of reducing the number of items to a suitable number, one must ensure that the remaining items cover the specific area being measured. This is known as 'content validity' and will be discussed in more detail later in this chapter. The simplest method of assessing the content is by the matrix method (see table 7b). The left hand column of the matrix contains the questions and the row at the top contains the areas to be assessed, each question should address one or more of the areas otherwise the questionnaire will not be comprehensive.

<table>
<thead>
<tr>
<th>Question</th>
<th>Area 1</th>
<th>Area 2</th>
<th>Area 3</th>
<th>Area X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

Table 7b - Matrix method for content validity

Once the subjects for the questions have been decided, then the method of obtaining an accurate response to each question must be decided. A large amount of research into this area has been performed (Streiner & Norman 1990). The questions can be in two forms, categorical or continuous. Categorical answers 'yes' or 'no' produce a
nominal scale for the questionnaire. The simple binary answer provides a definite positive or negative but may miss detail available from a continuous scale. There are many varieties of continuous scales such as visual analogue, likert scales and adjectival scales.

The scales should be of a reading age of twelve years unless the questionnaire is planned for use in specific population whose reading level is known, hence technical terminology should be avoided. Microsoft word has a useful application to assess the reading age of the any document. The questions should not be ambiguous. The questions should also ask one question only, double-barrelled questions asking for the answers to more than one subject within the same question can produce inconsistent answers. The length of the questions should be short as possible without losing the comprehensibility.

Once a pilot format of the questionnaire has been formulated with the chosen questions and answer scales, the questionnaire can tested for simple understanding on a population comparable to intended population.

7.2.2 Selection of the items for use in the questionnaire

The pilot instrument is tested and adjusted when necessary in order to meet a number of requirements necessary for the final development of a fully effective and validated questionnaire.

7.2.2.1 Face validity

Face validity refers to the ability of items to measure ‘on the surface’ what they aim to ask. In other words does the question make sense when read. If the respondent does not fully understand the question this may lead to the person answering
incorrectly or omitting the question completely. Open face validity makes the question's meaning and relevance clear to the respondent and this can be easily be subjected to the patient making a 'fake' answer in order to influence the doctor's management of that patient.

7.2.2.2 Frequency of endorsement

The endorsement frequency provides a discriminatory value for a question. The endorsement value \( p \) is the number of people \( n \) who answer yes or no (for a dichotomous question) over the total number of people answering the questionnaire \( q \).

\[
P = \frac{n}{q}
\]

In other words; the proportion of people that answer the question with a particular response. If a question has an endorsement frequency greater than 80% then the majority of subjects are answering yes to that question, and likewise if the value is less than 20% then few are answering no, this indicates that the question has little discriminatory value. However if the question has a number of answer choices then the endorsement values will be lower due to the spread, in these cases lower endorsement values but not higher endorsement values may be accepted. In some questionnaires it may be necessary to include questions with high endorsement values \( p \geq 0.95 \) if it is suspected that patients are faking their answers or not reading the reading the questions correctly. These questions should be predictable and the scores from these questions should not be included in the overall scale.
7.2.2.3 **Homogeneity of items**

In order to assess a specific condition or patient’s behaviour, the instrument should be homogeneous with regard to its items, in other words the items assess different parts but be moderately correlated to each other and the total scale score. Too high a correlation between items could result in redundancy of questions, or conversely poor correlation could result in the items assessing different traits. There are a number of statistical tests that can be available for the assessment of internal consistency that provides a measure for the homogeneity of the instrument.

7.2.2.3.1 **Cronbach’s Alpha**

Cronbach’s Alpha determines the reliability of a scale using dichotomous responses and when more than two response options are available. Cronbach’s Alpha assesses the average level of reliability between all of the items that make up the questionnaire (Cronbach 1951). If all of the items are focused on measuring the outcome for a specific problem then a moderate to high level of correlation should be attained; alpha should exceed 0.7 for a reliable instrument (Cronbach 1951). Generally, the greater the reliability of a questionnaire the higher the coefficient. If the questions are too diverse and measure more than one trait then the reliability coefficient will be poor. However, if the alpha is too high it can indicate that there are too many redundant and similar repetitive questions (Boyle 1991). Thus alpha should be greater than 0.7 (Nunally 1975, Cronbach 1951) and approximately below 0.9. The equation for Cronbach’s alpha is as follows:

$$\alpha = \frac{n}{n-1} \left(1 - \frac{\sum \hat{\sigma}_i^2}{\sigma_r^2}\right)$$
The value \( n \) is the number of items, \( \sigma_i \) is the standard deviation of the item and \( \sigma_r \) is the standard deviation of the total score.

### 7.2.2.3.2 Split-half homogeneity

Another approach to testing the homogeneity of a scale is called split-half reliability. Here the items are divided into two halves, also referred to ‘odd-even’ homogeneity, if the scale is internally consistent then the split-halves should be very similar. This form of test should not be applied to a timed achievement test or to an instrument in which the items are serially linked in a ‘chain’, where the next answer is dependent on the former.

### 7.2.2.3.3 Item-total correlation

This is the correlation of the item with the scale total not including the score from that item, it is best calculated using statistics (Nunally 1975), using the formula:

\[
\rho_{i(t-1)} = \frac{\rho_{it} \sigma_t - \sigma_i}{\sqrt{\sigma_i^2 + \sigma_t^2 - 2 \sigma_i \sigma_t \rho_{it}}}.
\]

The value \( \rho_{i(t-1)} \) is the correlation of the item \( i \) with the total, with the effect of the item \( I \) removed. The value \( \rho_{it} \) is the correlation of item \( I \) with the total score. The value \( \sigma_i \) is the standard deviation of \( i \) and \( \sigma_t \) is the standard deviation of the total score. Items with lower correlation than 0.20 should be discarded. The correlation used depends on the distribution of data, if parametric – Pearson’s coefficient - or non-parametric – Spearman’s coefficient – tests should be applied (Kline 1986).
7.2.3 Multifactor inventories

More sophisticated analysis – factor analysis - is required of a scale that is part of an inventory that contains a number of scales. Factor analysis looks for relationships within a set of questions, using the method of ‘principal components’ where the first component describes the maximum variance and successive components describe further the smaller portions of variance that are not correlated with each other (Joliffe 1986, Joliffe & Morgan 1992 & Stewart et al 1988). The total variance explained by each component is expressed in terms of an Eigenvalue. If the Eigenvalue is greater than one then this component is considered important (Joliffe & Morgan 1992). The Eigenvalues express the variance in a standardised form with a mean of zero and a standard deviation of one. Those factors with Eigenvalues greater than one will explain the majority of the variance, as the number of factors increases the total variance will decrease. The questions with the highest loadings within these latter factors have poor face validity then they are discarded. The overall aim of this analysis is not to reduce the number of questions, however this commonly is the end result. This process of instrument assessment is for an inventory and not a single questionnaire, and therefore is not required for the assessment of our instrument.

7.2.4 Summary of item selection

The requirements for the selection of questionnaire items are as follows:

- Thorough literature review for initial questions
- Patient and expert interview
- Pre-test the questions for comprehensibility and lack or ambiguity
- Elimination of any items without face-validity and not fulfilling the necessary endorsement criteria (described above).
- Pretest again after any eliminations
- Check for internal consistency

Once the above stages have successfully been completed then method of scoring the scale will need to be developed.

### 7.2.5 Scale construction

The development of a scoring system for the questionnaire will allow the results to be compared, for example, between populations or before and after an intervention or treatment. The simplest method of scoring is to assume that each question has an equal ‘weight’ and to simply add the scores of each question to produce a final overall score. If it is deemed necessary to weight the scoring system then two methods are available, theoretical or empirical. Theoretical weighting adjusts the scores of the questions, thought by a panel of experts, to be the most important. Empirical weighting relies on multiple regression to produce weighted scores for the questions. The equation is as follows:

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \ldots \text{etc}
\]

The value ‘Y’ is the predicted score that is based on the product of the items ‘X’ with the weights ‘\(\beta\)’, where \(\beta_0\) is a ‘weight’ constant.

Weighting has potential problems by changing the ‘true’ outcome of the instrument and some authors have shown that weighting makes little difference to the final outcome (Steiner et al 1981). In questionnaires with less than 40 questions, weighting may have some benefit (Nunally 1975).
In order to allow scores of different questionnaires to be comparable the final score can be transformed. Transformation of the score can be performed using percentiles or by using the formula for standardised scores:

\[ z = \frac{X - X_m}{SD} \]

Where \( z \) is the transformed score, \( X \) is the total questionnaire score by an individual, \( X_m \) is the mean score for the sample and \( SD \) the standard deviation for the sample. This results in the scale having a mean of zero and a standard deviation of one. A simpler method of transformation is to convert the score to range from 0 – 100 by using the formula:

\[ z = \frac{100x}{y} \]

Where ‘x’ is the individual’s score and the maximum questionnaire score of is ‘y’.

### 7.3 Testing a specific health outcome questionnaire

A questionnaire of any practical use must be valid, reliable, responsive and acceptable to the population being questioned. Validity refers to the ability of the questionnaire to assess what it is meant to assess. Reliability refers to the ability of the questionnaire to consistently measure an outcome over repeated testing. Responsiveness is the ability to measure the important changes in the outcome. Questionnaires should be easy to administer and easy for the patient to complete, in other words they should be acceptable.
7.3.1 Validity

A health outcome measure must assess the health related outcome in order to be valid. Validity is defined as the ability of a test to measure what it is intended to measure (Streiner & Norman 1990). There are many types of validity, these are usually classified under content, criterion and construct validity. Not all forms of validity are required for the assessment of questionnaires validity.

Content validity refers to the adequacy of the items in the questionnaire. Simple observation of the questionnaire assesses the adequacy of the items for content validity. The more representative the items are with respect to the condition, the more valid the conclusions that can be drawn from the questionnaire outcome.

Criterion validity refers to the instrument's direct comparison to another instrument that has been deemed to be the 'gold standard' or criterion. The comparison can be made concurrently (concurrent validity) or in the future (predictive validity).

Criterion validity is rarely applied to health outcome measures as more often than not they are novel instruments assessing new areas of medicine. Criterion validity is more commonly used in health instruments to validate a shorter version of the same instrument to ensure that its performance is equivalent.

Construct validity is used in the absence of a 'gold standard'. Construct validity is further subdivided into trait, discriminant and convergent validity. The 'constructs' are variables that are not directly observable, in medicine these are usually known as 'hypothetical constructs' due to their often subjective nature. Construct validation assesses the question for measuring a health outcome in line with a predicted theory. It can be assessed by comparison to 'extreme groups' and convergent and discriminant validation. Statistically the groups can be assessed by the simple
parametric and non-parametric tests however correlation may be employed if necessary.

7.3.2 Reliability

Reliability is calculated by internal consistency, (which assesses the level of correlation or 'agreement' between questions), and test-retest which demonstrates the questionnaire's stability during repeated application. For outcome measures, test-retest assessment is recommended as the most appropriate assessment of reliability (Kirshner & Guyatt 1985). Reliability testing provides the evidence for the ability of the questionnaire to produce consistent results during different occasions or with different observers – *reproducibility*. Internal consistency is measured using item-total correlations, Cronbach’s alpha or Split-half homogeneity as described previously in this chapter. It is not adequate to use internal consistency alone as an indicator of reliability and testing should also involve the use of 'test-retest' (Streiner & Norman 1990, Kirshner & Guyatt 1985). Internal consistency will assess the questionnaire at any one time and therefore cannot take into account any variations in the patients' health on a day-to-day basis, therefore test-retest is required to assess stability of the questionnaire over a period of time. A sample of the population is given a second questionnaire after a period of time and the scores from the two tests are compared for their similarity. This period of time should be long enough to prevent the patient from simply remembering the answers and short enough so that the patient's health has not significantly changed. Two weeks is thought an appropriate period of time (Streiner & Norman 1990). Statistical analysis allows the level of similarity between the scores before and after the lag period to be formally assessed.
7.3.3 Responsiveness

Until recently the need for the assessment of responsiveness was underestimated in comparison to the appraisal of reliability and validity (Tuley et al 1991). This may be due partly to the lack of formal assessments for responsiveness (Deyo et al 1991). Responsiveness measures the questionnaires ability to detect important changes in health outcome (Deyo & Centor 1986, Guyatt et al 1987). A number of methods exist; firstly by using transition questions that ask patients to rate their current health compared to a period in the past. Other methods include using mean differences and significance levels (Guyatt et al 1989), receiver operating characteristic curves (Mackenzie et al 1986), index of responsiveness, effect size and standard response means (Laing 1992). The standard response mean is a form of effect size measurement, which is calculated by dividing the standard deviation of score differences by the mean change in scores. A standard response mean equal to or greater than 0.2, 0.5 and 0.8 imply small, moderate or large health changes respectively (Liang et al 1990). The standard response mean has the advantage over the other methods described above as it is a standardised measure that can analysed statistically and used for comparison between different instruments.

7.3.4 Acceptability

The ease of use for the patients and the observer together with acceptability to patients ensures good response rates and reliable outcomes. A lengthy and difficult questionnaire reduces the acceptability to patients which in turn reduces its use in routine clinical situations restricting the use of the instrument to research situations. There are numerous different modes of administration of the questionnaire; self-
completion by the patients results in a lower response rate compared to interview administration using face-to-face or telephone techniques.

7.4 The development and testing of a questionnaire to assess patients' satisfaction with thigh and knee length stockings

The application of compression hosiery and bandaging is an integral part of conservative treatments for a variety of venous disorders, such as:

- Superficial and deep venous insufficiency
- Post-phlebitic syndrome
- Venous ulceration
- Prophylaxis against deep vein thrombosis

To date there is no health outcome measure to assess the patient acceptability of different compression treatments that are commonly used in patients with chronic venous insufficiency (and lymphoedema). The patient acceptability of this treatment modality is important to assess as many patients have chronic disease requiring long term treatment. Although many patients understand that compression treatment is an integral part of their therapy, some patients find stockings and bandaging restricts their normal daily activities and are cosmetically unappealing. The effectiveness of any external compression treatment is critically dependent on whether it is worn or tolerated by the patient. The influence of external compression treatments on quality of life can be assessed by a specific assessment of patient satisfaction. Quality of life data together with the evaluation of clinical efficacy would provide an overall appraisal to establish which is the best GCS for prevention of postoperative DVT. Therefore, a validated a specific questionnaire to formerly assess patient satisfaction
and quality of life in patients receiving compression treatment for venous disease was developed.

7.4.1 Methods and patient series

7.4.1.1 Development of instrument ‘questions’

Questionnaire items were developed via interviews with patients and experts in venous disease. Thirty interviews with patients were carried out and expert opinion was obtained from vascular consultants and stocking manufacturers. Patients were asked which characteristics of compression stockings and bandaging they ‘liked’ or ‘disliked’ and, were ‘important’ or ‘unimportant’. The experts were asked to give their opinions on the factors that they believed made up an effective and acceptable stocking.

The comprehension and ease of completing the questions was assessed by pre-testing of pilot questionnaires in two formats; visual analogue scale and Likert scale format. Face validity was assessed by questioning the patients about their understanding of the questions. All of the patients who answered the questionnaire during its development were recruited during their treatment at Charing Cross hospital as outpatients and/or inpatients.

7.4.1.2 Selection of the items for use in the questionnaire

7.4.1.2.1 Frequency of endorsement

One hundred and eighty three surgical in-patients, wearing GCS, were ask to complete the questionnaire for the purposes of assessing the endorsement of the questions. A number greater than 50 subjects is required for this assessment. No patients refused to answer the questionnaire.
7.4.1.2.2 Homogeneity of items

The internal consistency of the questionnaire was assessed by statistically comparing the means and total scores from the ‘odd’ and ‘even’ questions of the questionnaires (Split-half homogeneity) answered by a cohort of 127 surgical in-patients wearing GCS. No patients refused to answer the questionnaire.

7.4.1.3 Scale construction

Thirty patients wearing GCS admitted to hospital for surgical care were asked to complete the questionnaire and rate the questions in order of importance. Patients were asked to indicate the four most important items out of the total of eight. The ‘importance’ of a question was graded by the patients depending on how important they believed the item to be with regard to the properties of the stockings.

7.4.1.4 Testing for use as a satisfaction measure

7.4.1.4.1 Validity

The stocking satisfaction questionnaire was assessed for content and construct validity. The content validity was assessed by applying the question to a cohort of 26 patients wearing different types of compression stockings. Construct validity was assessed by applying the questionnaire to ‘extreme’ groups of compression therapy in 80 patients wearing extremes of compression stocking and 24 wearing Charing Cross four layer or three layer bandaging (4LB and 3LB). Criterion validity was not possible to assess with no similar questionnaires or health outcome measures currently published for comparison as a ‘gold standard’. However the stocking satisfaction scores of 31 patients wearing compression stockings or bandages, were correlated with the scores in the same patients who completed the general health
outcomes measure SF-12, in order to assess the effect of the status of their general health on stocking satisfaction scores.

7.4.1.4.2 Reliability

Reliability was assessed by calculating the test-retest assessment and internal consistency (Split-half homogeneity and Cronbach’s Alpha). The questionnaire’s test-retest stability was assessed over a period of two weeks before the repeat assessment.

7.4.1.4.3 Responsiveness

The formal assessment of responsiveness for this new health outcome instrument was not possible as this involves testing the instrument for its ability to measure changes of health outcome over a period of a patient’s treatment. The use of transition questions and the comparison of previous and current scores to evaluate standard response means and effect size was not applicable to a new questionnaire that investigates stocking satisfaction and not a disease process.

7.4.1.4.4 Acceptability

The acceptability of the questionnaire was assessed by two criteria, firstly the time for completion and secondly the response rate of the patients asked to answer the questionnaire. Twenty patients were timed without warning whilst answering the questionnaire and the number of patients who refused to complete or failed to return a completed questionnaire during this study was recorded.
7.4.1.5 Use of the questionnaire assessing patient satisfaction with thigh and knee length stockings

All patients recruited to the study RCT for comparing thigh to knee-length GCS (chapter 6) were asked to complete the stockings satisfaction questionnaire at the time of the second postoperative duplex DVT scan. By this time in the study, the patients had worn their stockings for 5-7 days.

7.5 Results

7.5.1 Development of instrument ‘questions’ (items)

The results of patient interviews provided information for the development of the domains or items for the questionnaire. A combination of the most frequently mentioned characteristics and ‘most important’ factors together with the experts’ opinions were used to produce the following domains:

- Discomfort
- Tightness
- Temperature
- Itch
- Falling down
- Hygiene
- Unsightliness
- Difficulty of application
The domains were found to express negative experiences with compression. In general, patients did not enjoy wearing their compression stockings or bandaging and they preferred the therapies that caused less of the symptoms described in these domains. The questionnaire items were designed to be simple to read and understand without ambiguity and asked the patients to grade their experiences. The Likert scale format proved to be fully comprehensive and face validity (correct understanding of the items) was good. The visual analogue scale format proved to be inadequate due to poor understanding of the mechanism of completing the answer, especially by the elderly patients. Table 7c summarises these results:

<table>
<thead>
<tr>
<th>Patients Responses</th>
<th>Visual Analogue Scale (n=12)</th>
<th>Adjectival Scale (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients correctly completing questions</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Number confused by questionnaire layout</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Number unable to complete due to illness</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 7c - The assessment of questionnaire for comprehension using visual analogue and Likert scales.
The item questions and their ‘Likert scale’ layout to make up the questionnaire were as follows:

**Question 1 - Do you feel the stockings cause you discomfort?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

**Question 2 - Do you feel the stockings make your legs itch?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

**Question 3 - Do you feel the stockings make your legs feel hot?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

**Question 4 - Do you feel the stockings are too tight?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

**Question 5 - Do you feel the stockings slip down around your thigh or knee?**

<table>
<thead>
<tr>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Question 6 - Do you feel the stockings are unhygienic to wear?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

**Question 7 - Do you feel your stockings look unsightly to wear?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

**Question 8 - Do you feel your stockings are difficult to remove and put back on, (if performed by yourself without the help of another person)?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

The questionnaire was accompanied by simple introductory instructions. Patients were asked to answer questions by placing a single mark in the box that most accurately described their experience whilst wearing the trial stockings for each question. As this questionnaire was intended for use compression bandage therapies as well as stockings, the term ‘stockings’ was interchanged with bandages if assessing compression bandaging – as general term for both therapies such as compression appliance was found to be poorly understood by patients. Each question was scored without weighting from 0-4 for ‘Not at all’ to ‘Extremely’ respectively. The minimum questionnaire total score was zero and the maximum was 32. The questionnaire total scores were transformed into percentages, where zero percent corresponded to no satisfaction and 100% to maximal satisfaction.
7.5.2 Selection of the items for use in the questionnaire

7.5.2.1 Frequency of endorsement

The endorsement of the questions answered by a cohort of 183 patients is represented by the endorsement value: the percentage of questions answered in a particular manner by the patient group. This group of patients (n=183) was approximately equal for gender (53% female) and the mean age was 60 years (range 21-86). The endorsement values (%) demonstrated that the items were answered with the most negative choice, 'extremely' by less than eighty percent of patients and answered positively, i.e. 'not at all' by greater than twenty percent of the patients for all items (figure 7a). These values indicated that all questions were satisfactory with regard to patient endorsement.
7.5.2.2 Homogeneity of items

The questionnaire was completed by 144 patients staying in hospital wearing GCS for homogeneity (or internal consistency) assessment with Split-half homogeneity and Cronbach’s alpha. The population was approximately equal for gender (52% female) and the mean age of the group was 60 years.

7.5.2.2.1 Split-halve homogeneity

The statistical comparison (t-test) of the means and totals of the ‘odd’ and ‘even’ questions from the questionnaire were very similar (figures 7b and 7c) (p=0.698), which implies good internal consistency for the questionnaire. This was also confirmed by split-halves reliability analysis using SPSS® (SPSS Inc, USA).

<table>
<thead>
<tr>
<th>Statistics for</th>
<th>Mean</th>
<th>Variance</th>
<th>Std Dev</th>
<th>Number of Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>6.6597</td>
<td>6.9114</td>
<td>2.6289</td>
<td>4</td>
</tr>
<tr>
<td>Part 2</td>
<td>8.2778</td>
<td>7.4188</td>
<td>2.7237</td>
<td>4</td>
</tr>
<tr>
<td>Scale</td>
<td>14.9375</td>
<td>19.6254</td>
<td>4.4301</td>
<td>8</td>
</tr>
</tbody>
</table>

Reliability Coefficients 8 items,

Guttman Split-half = .5396,

Equal-length Spearman-Brown = .5399,

Unequal-length Spearman-Brown = .5399.
Figure 7b - Mean Scores for Odd and Even Questions

P = 0.698, N = 144, Mean Age = 60 yrs. Females 53%

Figure 7c - Sum of Questions Scores for Odd and Even Questions

Odd Questions: 975, Even Questions: 968
7.5.2.2 Cronbach's alpha

Cronbach's alpha calculated for the eight item questionnaire achieved borderline reliability of 0.6, an alpha value between 0.7 and 0.9 is optimal and a level of greater than one indicates some redundant items and less than 0.5 demonstrates an unsatisfactory reliability. Cronbach's alpha calculated using SPSS software is displayed below:

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std Dev</th>
<th>Cases</th>
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</thead>
<tbody>
<tr>
<td>1. Q1</td>
<td>1.6875</td>
<td>.9998</td>
<td>144.0</td>
</tr>
<tr>
<td>2. Q2</td>
<td>1.4861</td>
<td>.7754</td>
<td>144.0</td>
</tr>
<tr>
<td>3. Q3</td>
<td>1.9306</td>
<td>1.1072</td>
<td>144.0</td>
</tr>
<tr>
<td>4. Q4</td>
<td>1.5556</td>
<td>.8753</td>
<td>144.0</td>
</tr>
<tr>
<td>5. Q5</td>
<td>1.9306</td>
<td>1.1556</td>
<td>144.0</td>
</tr>
<tr>
<td>6. Q6</td>
<td>1.5694</td>
<td>.9727</td>
<td>144.0</td>
</tr>
<tr>
<td>7. Q7</td>
<td>1.9028</td>
<td>1.2079</td>
<td>144.0</td>
</tr>
<tr>
<td>8. Q8</td>
<td>2.8750</td>
<td>1.4430</td>
<td>144.0</td>
</tr>
</tbody>
</table>

N of Cases = 144.0

Statistics for Mean Variance Std Dev N of Variables
Scale
14.9375 19.6254 4.4301 8

Item Means
Mean
1.8672
Range
1.3889
Minimum
1.4861
Max/Min
1.9346
Variance
.1983

Item Variances
Mean
1.1772
Range
1.4810
Minimum
.6012
Max/Min
3.4633
Variance
.2160

Inter-item Covariances
Mean
.1823
Range
.5250
Minimum
-.0223
Max/Min
-22.5000
Variance
.0170

Inter-item Correlations
Mean
.1646
Range
-.0239
Minimum
.4955
Max/Min
Variance
Reliability Coefficients 8 items

Alpha = .5944  Standardized item alpha = .6119.

7.5.3 Scale construction

The patients who completed and graded the questions in order of importance numbered thirty, twelve were male and the mean age was 52 years (range 22-83). The relative importance of each of the questions is displayed in figure 7d, with question eight assessing application regarded as the most important and question seven assessing unsightliness of the stockings as the least important to the patients. Although this investigation together with patients endorsement, provided an indication of the usefulness of the questions, it was not considered necessary to weight the scores of individual items as this may alter the ‘true’ outcome. Empirical weighting was deemed unnecessary when discussed with two experts in quality of life and health outcome measures.

7.5.4 Validity

The content validity was found to be satisfactory, indicated by the different scores produced by the questionnaire of three different types of compression therapy when worn by 26 patients.
The theoretical assumption that patient acceptability of stockings would decrease with increase compression and length of the stocking was reflected in the better scores for the lower compression class one (CCL1) knee length compared to the longer higher compression class two (CCL2) thigh length stockings (figure 7e). Construct validity, was assessed by applying the questionnaire to eighty patients wearing extremes of compression stocking or bandaging, i.e. ‘extreme’ groups. The ‘extremes’ of GCS that are frequently used in clinical practice are GCS and CCL2 stockings. A ‘zero’ compression (cosmetic) stocking was also assessed by the questionnaire as an extreme (figure 7f). The satisfaction scores reduced with the stockings of greater compression.
Figure 7e - Satisfaction Scores for Compression Hoisery

Figure 7f - Satisfaction scores for 'Extreme' groups wearing stockings
The questionnaire was also applied in order to assess the 'extremes' of compression bandages, in twenty-four patients wearing three and four layer bandaging. The satisfaction scores decreased similarly with increased compression (figure 7g).

The questionnaire scores from patients (n=31) who also simultaneously completed the SF-12 health outcome assessment showed that there was no correlation between these two health outcome measures (p=0.6, r=1.04) (figures 7h & 7i). The SF-12 assessed the general health quality of life of the patients, but not the acceptability or satisfaction with compression stockings or bandages. Therefore the lack of correlation indicates that the stocking satisfaction questionnaire scores are not a mere reflection of the overall health of the patients.
Figure 7h – Correlation between physical SF-12 scores and stocking satisfaction scores

1. PCS = 17.27 + 0.27 * cxssq
   R-Square = 0.36

2. PCS = 51.04 - 0.15 * cxssq
   R-Square = 0.07

3. PCS = 155.64 - 2.48 * cxssq
   R-Square = 1.00

4. PCS = 32.33 + 0.09 * cxssq
   R-Square = 0.03
Figure 7i – Correlation between mental SF-12 scores and stocking satisfaction scores

Linear Regression

MCS = 48.73 + -0.07 * cxssq  
R-Square = 0.03

MCS = 54.18 + -0.00 * cxssq  
R-Square = 0.00

MCS = 161.50 + -2.69 * cxssq  
R-Square = 1.00

MCS = 28.11 + 0.29 * cxssq  
R-Square = 0.28
7.5.5 Test-Retest reliability

Test-retest assessment and reliability expressed as a product of the questionnaire’s homogeneity or internal consistency was found to be good. The internal consistency of the questionnaire was described previously. The test and retesting of the questionnaire by 39 patients wearing GCS separated by a two-week period proved to be very similar with no significant difference (paired t-test) between mean scores of the first ‘test’ and the second ‘retest’ assessment (figure 7j).

![Figure 7j - Reliability test-retest assessment](image)

7.5.6 Acceptability

This instrument was developed as a self-completion questionnaire, which is theoretically less responsive than telephone or interview completion questionnaires. However the acceptability of the questionnaire was found to be more than adequate because:
i. The mean completion time was less than the recommended five minutes. The mean time for completion was 3 minutes and twenty seven seconds (range 54 to 634 seconds).

ii. The number of patients who voluntarily completed the questionnaire was excellent, no patients refused.

7.5.7 Patient satisfaction with thigh and knee length stockings

All 376 patients in the trial were asked and successfully completed the questionnaire. No patients refused. The median satisfaction scores for each stocking group (figure 7k)

![Figure 7k - Stockings Satisfaction Questionnaire Assessment](image)

The Kendall Thigh group demonstrated a greater patient satisfaction score of 90% with the Medi thrombexin® climax™ knee-length stockings compared to 78% satisfaction with Medi.
thrombexin® climax™ thigh-length (Kruskal-Wallis Test, p=0.001) and 78% satisfaction with Kendall T.E.D.™ thigh-length stockings (Kruskal-Wallis Test, p=0.001). There was no significant difference between Medi and Kendall thigh-length stockings (Kruskal-Wallis Test, p>0.05).

The median of question scores (range 0-4) from each questionnaire item for each stocking type demonstrated that the thigh length stockings scored higher (worse) for all items (questions) when compared to knee-length stockings (figure 71 & table 7d).

Figure 71 - Median item scores for each stocking group
Both thigh length stockings scored particularly badly with 'Unsightliness' and 'Application difficulty' and Kendall thigh-length stockings produced a markedly high (bad) score for falling down. The worse scores for application with Medi thigh and falling down with Kendall thigh may be related to the greater and lesser compression profiles of these stocking respectively (chapter 6).

<table>
<thead>
<tr>
<th>Questionnaire Item</th>
<th>Mean Item Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kendall Thigh (n=101)</td>
</tr>
<tr>
<td>Discomfort</td>
<td>0.57</td>
</tr>
<tr>
<td>Tightness</td>
<td>0.46</td>
</tr>
<tr>
<td>Temperature</td>
<td>1.18</td>
</tr>
<tr>
<td>Itch</td>
<td>0.65</td>
</tr>
<tr>
<td>Falling down</td>
<td>1.74</td>
</tr>
<tr>
<td>Hygiene</td>
<td>0.50</td>
</tr>
<tr>
<td>Unsightliness</td>
<td>1.04</td>
</tr>
<tr>
<td>Difficulty of application and removal</td>
<td>2.13</td>
</tr>
</tbody>
</table>

*Table 7d - Mean item scores for each stocking group*
7.5.8 Conclusions

This stocking satisfaction questionnaire was found to be a valid and useful tool for the specific assessment of satisfaction in patients with lower extremity compression appliances. Its use in clinical practice and future research will enable practitioners to assess patient acceptability of new or alternative compression treatments. This health outcome measure may be used in conjunction with a generic HRQL instrument to investigate clinical or trial patients receiving treatments involving compression therapy. The necessity for this satisfaction questionnaire is based on the theory that the efficacy of a compression device is highly dependent on patient compliance. The stocking compliance of the patients in this study is discussed in the next part of this chapter. The stockings effectiveness has been shown to dependent on the length of the stocking (chapter 6), the thigh length stockings reduced postoperative DVT significantly more than the knee-length variety of the same compression profile. The DVT prevention by the Kendall thigh stockings fell approximately half way between the two Medi stockings (thigh and knee-length), this may be related to finding of the Kendall stocking falling down markedly more than the Medi thigh stocking. As expected, the stocking satisfaction questionnaire revealed overall a significantly improved satisfaction with knee-length stockings, but the breakdown into individual domains showed much better scores for unsightliness and difficulty of application compared to the thigh stockings. The next part of this chapter reveals whether these differences in satisfaction are associated with differences in stocking compliance.
7.6 The assessment of patient stocking compliance

Compliance is defined as the consistency and accuracy with which a patient follows the regimen prescribed by a physician or other health professional. There are numerous methods of assessing the compliance of a regimen depending on the nature of the treatment. Patients can either be asked to record their use of the therapy or a timing device may be used to record the actual use of the treatment. In clinical trials, bias can be introduced with both of these methods; the patient may increase their use of the therapy or adhere more to a specific regime if they know their performance or behaviour is recorded by the physician. Some timing devices have the advantage that compliance can be recorded unknown to the patients, however in many instances this is not possible with simple mechanical therapies such as GCS. The effectiveness of GCS is heavily dependent on the actual use of the stocking by the patients, hence in a randomised controlled trial such as this, it was important to ensure that each stocking group received the same instructions regarding stocking use.

7.6.1 Methods and patient series

To all 376 patients, information regarding the DVT and the purpose and use of stockings was given in the ethically approved trial information sheets and verbally at two stages in the trial; initially when the stockings were first applied and subsequently after the postoperative duplex scan. All patients were given the following advice:

i. To wear their allocated stockings day and night during the trial until the postoperative duplex scan. Patients were free to remove their stockings if they wished for any reason.
ii. After the postoperative duplex scan, the patients were advised that the continued wearing of stockings for approximately four weeks after surgery had been shown to be beneficial in the prevention of DVT. Their decision to continue wearing their stockings or not would not affect the trial results. They were also informed that they were free to remove their stockings at any time for any reason.

If the patients wished to continue wearing their stocking then a compliance diary sheet with a stamped addressed envelope and another pair of GCS was supplied for wash-and-wear purposes. All patients were shown how to apply and remove their stockings.

Patient compliance diary sheet was developed for the purposes of the trial, this involved a literature search for similar instruments (none was found), expert opinion and a trial of pilot compliance assessment sheets with ten patients. The patients’ compliance diary sheets consisted of a different sheet for each postoperative week. In the event of any difficulties with compliance sheet completion, patients were given a telephone number to call for advice.

7.6.2 Compliance diary sheets

The pilot version of the compliance diary sheet proved easy to use with a maximal response rate – no patients refused to answer the questions and all successfully completed the compliance assessment. The layout of the compliance is shown in the appendix. The total approximate number of hours that the stockings were worn could simply be summated from the compliance sheet entries. The compliance score was calculated as a percentage of the total time available for the stockings to be worn.
This was divided into hospitalised in-patient stay and time in the community after discharge from hospital.

7.6.3 Results

All trial patients who attended their postoperative duplex scan completed their compliance sheets for the first week of the trial. Eighty five percent of patients who chose to wear their stockings after the postoperative scan, returned the completed compliance sheets. There was no significant difference for stocking in-patient compliance for each stocking group (Chi² p>0.05), the percentage of time worn was 99% for Kendall thigh, 92% for Medi thigh and 98% for Medi knee (figure 7m).

![Figure 7m - Stocking compliance in hospital and after discharge](image)

7.7 Conclusion
7.7 Conclusion

The compliance for the knee length stockings was significantly better than for the thigh-length stockings after the patients had left hospital ($\chi^2 p>0.05$). The greater patient acceptability and comfort of knee over thigh-length stockings has been reported before by a number of authors (McNally et al 1995, Porteus et al 1989, Benko et al 2001). However the formal comparison of the thigh to knee-length stocking satisfaction and compliance has not been previously carried out. This health outcome and compliance study has confirmed a number of important characteristics of thigh and knee-length stockings:

- The patients’ satisfaction with knee length stockings was better than with thigh-length. Thigh stockings differed most markedly in the characteristic of ‘falling down’, unsightliness and difficulty of application.

- A similar trend of stocking compliance was shown after discharge from hospital, with the knee-length stockings performing considerably better.

- The stockings compliance of patients while staying in hospital was not significantly different. This may be due to influence of nurses and doctors enforcing stockings prophylaxis.

- The stocking satisfaction and compliance was very similar for the two different brands of thigh-length stocking, implying that it is the length of stocking that is important to patients and not the different materials of manufacture.

Stocking efficacy in the reduction of DVT is dependent on the stocking being worn by the patient. Despite improved acceptability to patients of the knee-length design, the thigh-length is the preferred GCS due to the fact that patient compliance is equivalent for thigh and knee stockings in hospital and thigh-length stockings were
proven to be more effective. The optimal in-patient GCS is the thigh-length, however the knee-length stocking could be considered for use as a 'post-hospital-discharge stocking' in view of its better compliance outside of hospital.
Chapter Eight

Summary of the development and evidence for the charing cross hospital guidelines to prevent post-operative deep vein thrombosis

List of contents

8.1 The need for change in DVT prophylaxis practice
8.2 Preliminary arguments for a single protocol
8.3 Achieving a hospital consensus for a large randomised clinical trial investigating a single protocol and the optimal stocking length
8.4 The optimal length of stocking
8.5 LMWH for all patients undergoing surgery
8.6 Health outcome assessment of stocking satisfaction and compliance
8.7 The impact of this study on clinical practice at a large university hospital
8.8 Future research
8.1 The need for change in DVT prophylaxis practice

In Charing Cross hospital, a large university multidisciplinary hospital, and in many other centres in the developed world, continued reports of poor thromboembolic prophylaxis have occurred (George et al 1998, Jones 1991, Stephens et al 1995, Audet et al 1998, Fletcher et al 1992, Conti et al 1982). In Charing Cross hospital, the proportion of surgical patients who effectively received GCS was only 44%, subcutaneous heparin was 54%, and overall optimal prophylaxis was found to be present in only 47%. The dangers of protecting only ‘half’ of the surgical patients against DVT or PE are substantial. Without prophylaxis, the incidence of DVT in unprotected general surgical patients ranges from 25 to 30 per cent and up to 70 percent in orthopaedic patients (Colditz et al 1986, Hull et al 1986, Clagett & Reisch 1988, Stamatakis et al 1976). Optimal prophylaxis using a combination of mechanical and pharmacological agents, most commonly GCS and subcutaneous heparin, reduces the risk of DVT by 60-80 percent in general surgery and 50-64 per cent in orthopaedics patients (Stulberg et al 1984, Jeffrey & Nicolaides 1988, Parker-Williams & Vickers 1991, THRIFT consensus group 1992). Most lower extremity thromboses are subclinical and some may resolve, although a significant amount do produce permanent valvular damage and chronic venous insufficiency. A small number of these DVT extend proximally and embolise to the lungs and depending on the amount of pulmonary circulation obstructed may produce mild, moderate or fatal effects. Pulmonary embolism accounts for a substantial proportion of postoperative deaths (Berqvist & Lindblad 1985). Pulmonary embolism and DVT may be difficult to detect before the patient clinically deteriorates and treatment may be unsuccessful, hence prophylaxis is the best means of reducing complications and death from VTE disease.
With over forty years of research highlighting the dangers and the need for the prevention of thromboembolic disease, it is unacceptable to find inadequate and disparate thromboembolic prophylactic practice in a modern hospital. Especially with an abundance of guidelines and numerous effective, safe and cheap methods of prophylaxis available. Therefore an investigative process was commenced in order to find out where, why and how the prophylaxis was lacking in Charing Cross hospital. The plan was to use this information to rectify and improve the overall status of thromboembolic prophylaxis in surgical patients.

8.2 Preliminary argument for a single protocol

Poor prophylactic practice continues despite continued efforts by consensus bodies to provide the optimal regime guidelines (Nicolaides et al 2001, THRIFT 1992, Haas 1993). These authors went to great lengths to publish consensus statements containing accurate and up to date evidence-based recommendations for the prevention of postoperative DVT. However, the reported insufficient use of prophylaxis may represent a breakdown in the intended and actual implemented prophylaxis. The published guidelines utilize the process of obligatory categorisation of patients into risk groups prior to prescribing the appropriate thromboembolic prophylaxis. This process has two main weaknesses with regard to DVT prophylaxis:

i. Preoperative thromboembolic risk-factors that decide the thromboprophylaxis may change intra- and post-operatively with a resultant change in the prophylactic requirements of that patient that are not met. Surgery and complications that increase DVT risk need to have optimal prophylactic cover in place at the time of these events.
ii. One of the three risk category patient groups - low risk - has minimal randomised controlled evidence to support clinical or economic prophylactic recommendations, thus evidence-based practice for this group is difficult to apply.

Our new protocol is based on the guidelines produced by these consensus groups, which are based on years of collated evidence and expert opinion that recommend subcutaneous heparin and GCS (or IPC) for high and moderate-risk patients. In a large university hospital such as Charing Cross, the majority of patients are of high-risk, some moderate and only a small proportion of patients undergoing surgery are low risk. Therefore, this permits ‘stockings and heparin use across the board’ and negates the need for risk categorisation in our hospital. In this era of clinical governance, health professionals are increasingly encouraged to perform evidence-based practice and maintain the quality of the care. The best way of unifying the practice of the many different health professionals is via the implementation of guidelines, healthcare frameworks or protocols. George et al (1998) demonstrated that the number of thromboprophylactic protocol violations increased with the complexity of the protocol. The questionnaire audit assessing prophylactic practice of surgical doctors (chapter 5) demonstrated that complex guidelines, that are readily available in the literature, were either not being used or used with incorrect risk assessment (with resultant incorrect prophylaxis prescriptions). Hence it was concluded that in order to achieve successful compliant DVT prophylaxis in Charing Cross hospital, the new recommendations needed to be simple, evidence-based, without risk assessment, and laid out in a clear protocol that was the same for all patients (unless medically contraindicated) undergoing surgery by all surgical specialities - a single blanket protocol.
8.3 Achieving a hospital consensus for a large randomised clinical trial investigating a single protocol and the optimal stocking length

In general, as demonstrated by the questionnaire survey in chapter five, the junior doctors were keen to improve and simplify the surgical DVT prophylaxis in their hospital, however their practice was governed by the wishes of their surgical consultants in charge. A small number of surgical consultants, from a variety of specialities, showed enthusiasm for updating their practice as long as the recommendations were evidence-based; these consultants were influential in arranging meetings and instigating change within each department. In order to set up a hospital consensus for an area of practices such as DVT prophylaxis, the agreement by all heads of departments, surgical consultants, trainee doctors, nursing sisters, pharmacists and management staff is required for a consensus to be reached. If a collection of any of these professionals - as experienced in this study - are opposed to the consensus then the whole process becomes hindered. In the early stages only nominal interest was shown for improving the overall status of DVT prophylaxis by a large proportion of surgical consultants. Details of the opinions and reactions of individual consultants will not be detailed as part of this thesis. The nursing sisters and chief pharmacists were in favour of a hospital protocol that would unify surgical prophylactic practice in the hospital. Management expressed their wishes to use evidence-based and proven cost-effective means of DVT prophylaxis. A number of different approaches were employed to reach an agreement between consultants and departments, namely by personal meetings, letters and departmental presentations. The latter proved to be the most effective method for communicating information
and commencing debate on important issues. Presentations containing audit results and literature reviews were prepared and presented to each surgical department (chapter 5). The main points that were raised against achieving a surgical consensus during these meetings were as follows:

- In general, the surgical consultants assumed that their own DVT prophylaxis regimes were adequate.
- Consultants were unaware of the overall disparity of the DVT prophylaxis in the hospital and how prophylaxis overall was made up of unstructured ‘firm-led’ regimes.
- Orthopaedic consultants were in favour of not using subcutaneous heparin at all in spinal surgery and only post-operatively in hip and knee replacements. They were in favour of using LDUH rather than LMWH due to suspected increased risk of bleeding complications with the latter.
- Neurosurgeons were not in favour of using subcutaneous heparin preoperatively in any cranial or spinal surgery. They also preferred unfractionated heparin to LMWH for the bleeding risk.
- Some consultants preferred to use either no GCS or knee length types for certain patients and operative procedures
- Many varieties of GCS were in use in the hospital, many of which had no randomised clinical trial evidence to support their use.

A second round of presentations provided the evidence from the literature for the use of LMWH rather than LDUH, in terms of improved efficacy, lower cost and safety from bleeding and other complications. These presentations also outlined the need for a randomised controlled trial to investigate the best length of stocking and the
efficacy and safety of a ‘single LMWH with stockings protocol’ for all surgical patients.

An agreement was reached to allow the trial to commence with LMWH in trial patients only, postoperatively in orthopaedic and neurosurgical patients, and preoperatively in the remaining specialities with randomisation to either knee or thigh length GCS. Attaining a consensus on prophylaxis for all surgical patients in the hospital would then depend on the evidence provided by this trial.

8.4 The optimal length of stocking

The best length of stocking was investigated by the means of a large randomised controlled trial with 376 patients randomised into three stocking groups. Two groups with Medi thrombexin® climax™ stockings, one with thigh length and the other with knee-length GCS. The third group wore Kendall T.E.D.™, the original and most frequently prescribed graduated compression anti-embolic stocking used in the NHS and the stocking with the most level one evidence demonstrating its efficacy in the prevention of postoperative DVT (Holford 1976, Scurr et al 1977, Turner et al 1984). These stockings groups were investigated for incidence of postoperative DVT by serial pre- and post-operative duplex scanning, stocking acceptability with a validated stocking satisfaction health outcome assessment, and patient compliance. The Medi thigh-length stockings proved to be significantly better at reducing postoperative DVT than the Medi knee-length stocking with an equivalent compression. This was found to be in the order of a five-fold reduction (ORs=0.18 [95%CI 0.04-0.82] P=0.026). The Kendall T.E.D.™ stockings were found to be neither significantly better than the knee-length or significantly worse than the Medi thigh-length stockings. However, this study did not have sufficient power to show
differences between the two types of thigh stockings. The two lengths of Medi thrombexin® climax® are manufactured from the same materials and produced comparable compression to the calf, the dissimilarity in DVT prevention between these stockings can therefore be assumed to be due to the differences in their length. The health outcome findings (discussed later in this chapter) of stocking satisfaction and compliance also revealed significant differences and important similarities to support the use of thigh length stockings as part of a single protocol.

8.5 LMWH for all patients undergoing surgery

The use of LMWH for thromboprophylaxis was controversial at the time of its introduction - over a decade ago - to clinical practice due to the lack of true evidence and use of anecdotal evidence regarding bleeding complications, efficacy and expense. Some of these old beliefs were found to remain at Charing Cross hospital, however a simple review of the recent literature and published prophylaxis guidelines clearly demonstrates that LMWH is the heparin of choice for the use in the majority of surgical patients. Compared to unfractionated heparins, low molecular weight heparins have been shown to perform equally and in many instances better at preventing postoperative DVT and PE with less bleeding complications when used at the optimal dosage. And as far as cost, it is now the cheaper option when administered once daily compared the twice or thrice daily injections with unfractionated heparin regimes. The once daily subcutaneous LMWH injection has the added benefit of improved patients acceptability. Even with the abundance of evidence in the literature, many surgeons at Charing Cross hospital still required reassurance that LMWH was safe and effective to use across the board in a blanket protocol. This study verified that daily enoxaparin (20mg) given on the
evening before surgery, and postoperative in orthopaedic and neurosurgery patients, was effective and safe when used across the board for the prevention of postoperative DVT. In the RCT, no DVT occurred in the low and moderate risk patients and with the best thigh-length stockings the DVT rate was only two percent. Only one significant bleeding complication occurred from which the patient made a full recovery. The timing of administering LMWH in this trial was on the evening before surgery for a number of important reasons:

- Firstly, the peak activity of LMWH is at one to four hours after subcutaneous injection. Therefore if administered on the morning before surgery, may increase bleeding during surgery. This may explain many surgeons dislike of LMWH with regard to bleeding. However if given on the evening before surgery this allows the peak activity to pass and the prophylactic activity to continue during surgery.

- Secondly, the evening dose permits the required twelve hours to pass before anaesthetists are happy to insert epidural or spinal catheters for regional anaesthesia. The evening dose is therefore part of the single protocol regimen making LMWH available for use in all patients undergoing surgery.

There are a number of different LMWH dosage regimes that have been investigated in the literature. These involve doses adjusted to the weight of the patient and increased doses for high-risk patients. However, studies have shown that increasing the dose of LMWH increases the risk of bleeding without added efficacy in DVT prevention (Koch et al 1997). In order to avoid complex prescribing regimes in the ‘single blanket protocol’, a single dose of 20mg of enoxaparín was investigated for efficacy in this study. The low incidence of DVT (2%) in only high risk patients proved this to be a reliable and effective dose in line with similar results from the
Cochrane reviews (Wille-Jorgensen et al 2002). If a speciality or health professional insists on a LMWH delay or increased dosage for certain patients, this can be accommodated. The single protocol is the basis for DVT prophylaxis in patients undergoing surgery in this university hospital, it should encompass the prophylactic requirements of all surgical patients. It can be ‘upgraded’ or ‘added to’ in specific cases but not ‘downgraded’ or omitted unless there is a medical contraindication to stockings or LMWH. Those patients with medical contraindications to LMWH or stockings would only receive appropriate safe prophylaxis.

In summary, a simple and safe new protocol for DVT prophylaxis in a busy university hospital is recommended. The combination of a good quality thigh-length stocking and LMWH for hospitalised patients requiring surgery produced a low postoperative DVT rate in the high-risk patients and no DVT in the moderate and low-risk patients. To have a single hospital protocol means that prophylaxis against DVT is less likely to be forgotten; confirmed by the audited improvement (p<0.05) in prescribing optimal prophylaxis to 88% of surgical patients (chapter four). This study provides evidence that a single ‘blanket’ protocol of LMWH and a good quality thigh-length anti-embolic stockings is safe and effective to use all surgical patients (bar medical contraindications) for the prophylaxis of postoperative DVT, with very few disadvantages.

8.6 Health outcome assessment of stocking satisfaction and compliance

Prior to this study the evidence to support the choice of stocking for general DVT prophylaxis and for use in a new protocol was limited, only three randomised clinical trials assessing DVT prevention comparing knee to thigh length stockings were
available in the published literature. These studies as previously mentioned in chapter three contained small numbers of patients and failed to show any differences in the efficacy between knee and thigh-length stockings. Despite these limitations, the study primary hypothesis was based on the available published evidence,

'Provided all patients received LMWH, thigh-length anti-embolic stockings are equivalent to knee-length of the same design in the prevention of post-operative deep vein thrombosis'.

If this hypothesis had been shown to be correct then the stocking with the greater patient acceptability and compliance would be the stocking of choice. This principle also applies to other compression therapies with similar efficacies used to treat venous and lymphatic disorders of the limb. Hence a validated instrument to assess patient satisfaction with lower limb compression therapies has uses outside of this study in clinical practice and other research.

Stocking acceptability assessed with a new validated instrument demonstrated that patients were more satisfied (p<0.05) with knee-length stockings (satisfaction score 90%). The satisfaction levels for the two types of thigh length stocking were very similar (satisfaction score 78%) and at an acceptable level so as not to prevent their use. The similarity in the scores achieved by the two different thigh-length stockings brands suggested that it was the length of the stocking and not the materials of manufacture that was important to the patients.

The trends discovered in stocking acceptability were mirrored in the compliance scores achieved by each stocking type when used after discharge from hospital, with
the knee-length stocking performing considerably better than the thigh-length stockings. However, the compliance was good and not significantly different for each stocking type when worn by patients staying in hospital. These findings provide guidance on the GCS to use in a new single protocol - the most efficacious thigh-length stocking with equal in-patient compliance and acceptable levels of patient satisfaction.

8.7 The impact of this study on clinical practice at a large university hospital

In the early stages of this research, the status of thromboprophylaxis in this hospital was disparate and inadequate. Only about one half of the patients were receiving optimal prophylaxis and only a quarter the better LMWH, as recorded by a hospital wide audit of surgical patients (chapter 4). Many different brands and regimes of subcutaneous heparin were prescribed. The use of GCS was also in disarray with a variety of unproven brands and an inconsistent use of knee and thigh-length stockings on many of the surgical wards.

Since this time, the use of audit, surveys, reviews of the literature, and a large randomised controlled trial has provided evidence to instigate change in a large university hospital with many surgical specialities and academic surgical consultants. With the approval of the surgical and medical directorates and the help of the consultants in charge of clinical governance, the new Charing Cross single protocol was implemented in October 2003 for use in all surgical patients staying in hospital to undergo surgery. The medical consultants have used the latest evidence from the medical literature and extrapolated these findings concerning the benefits of thigh-length stockings to develop a similar single protocol for all medical patients. In
summary the status of thromboprophylaxis practice in Charing Cross hospital is as follows:

- All consultants from all specialities have agreed a consensus to use a single blanket protocol of thigh-length stockings (Kendall and Medi) and LMWH (enoxaparin) in all surgical in-patients undergoing surgery (and all medical patients)
- The LMWH used, is subcutaneous enoxaparin 20mg prescribed in the evening at 6pm, as prescribed during the RCT. A single type and dose of LMWH was chosen to maintain the simplicity of the single protocol.
- Thigh stockings used, are either Medi thrombexin® climax™ or Kendall T.E.D.™.
- LMWH/thigh stockings prophylaxis is given preoperatively in all surgical specialities, except in certain specific procedures that require LMWH to be commenced postoperative, namely spinal surgery, intracranial surgery and joint replacements. However, some orthopaedic and neurosurgery consultants have agreed to use preoperative LMWH in all of their patients.
- A list of specific contraindications to the use of either LMWH or GCS is available on all wards and on the hospital intranet.
- The published hospital single protocol ‘LMWH/thigh stockings’ is published on the Hammersmith Hospitals NHS Trust intranet.

The single LMWH/thigh-stockings protocol published on the intranet gives clear and simple instructions for thromboprophylaxis with guidance for relative and absolute contraindications. The thromboprophylaxis practice in Charing Cross hospital will be audited at regular intervals by the department of clinical governance. These audits
will record and report the future influence of this study on prophylactic compliance at Charing Cross Hospital.

8.8 Future research

The use of the single protocol needs to be audited to complete the assessment of the changes made as a result of this work on DVT prophylaxis in Charing Cross hospital; this was not possible during this study due the prolonged time taken to achieve a consensus and to establish the new single protocol in all surgical departments.

However the significant improvements to 88% optimal prophylaxis in surgical patients achieved by using the ‘single protocol’ in the breast and oncology, gastroenterology, urology and vascular surgery specialities (chapter four) indicates that a simple single DVT protocol improves overall prophylactic compliance.

Future work is required to find if this protocol is applicable to other similarly sized hospitals that would probably have similar patient populations. However the thromboembolic risk of the patient population would require formal assessment through similar audit processes, to confirm that the majority of patients were of high and moderate risk. The evidence based recommendations for the DVT prophylaxis of these patients is LMWH and GCS (Nicolaides et al 2001) and therefore the single protocol would be indicated.

A ‘grey’ area in the prophylactic recommendations published in the literature is the optimal prophylactic requirements of low risk patients. Currently there is no good evidence to guide practitioners and this evidence may not become readily available due to the large numbers of these patients that would be required in a randomised study. Many protocols simply recommend no prophylaxis apart from early mobilisation. However even if the incidence is low, this group of patients are at risk
from fatal PE and debilitating DVT after surgery. The protocol developed in this study recommends the same prophylaxis for these patients as the other patients in higher risk groups on the basis of their small proportion of the total in-patient population and the ease at which these low-risk patients may become higher risk during their hospital stay. There is certainly no evidence in the literature to suggest that these patients should be withheld DVT prophylaxis. However more evidence is required for this low risk group in terms of DVT prophylaxis requirements and cost-effectiveness.

The protocol developed in this study recommends the use of preoperative prophylaxis when safe, however the evidence comparing the efficacies of prophylaxis implemented before or after surgery needs to be improved.

The actual mechanism(s) by which GCS achieve prophylaxis of DVT has never been fully evaluated. Stockings are known to counteract two parts of Virchow’s triad by increasing venous velocity and reducing vein wall distension. However is this their actual mechanism of action? Further work is required in this area to explain the differences in efficacy of knee to thigh-length stockings.
Appendix

Appendix A  Ethical committee approval
Appendix B  Audit proforma
Appendix C  Patient information sheets
Appendix D  Patient consent form
Appendix E  Trial baseline sheet
Appendix F  Randomisation sheet
Appendix G  Surgery and post-surgery sheet
Appendix H  DVT duplex sheet
Appendix I  Patient stocking satisfaction questionnaire
Appendix J  Patient stocking compliance diary sheet
Appendix A  Ethical committee approval

RIVERSIDE RESEARCH ETHICS COMMITTEE
Pharmacy Offices  Lower Ground Floor
CHELSEA & WESTMINSTER HOSPITAL
369 Fulham Road  London SW10 9NH
Tel: 020 8846 6855  Fax: 020 8846 6860

Professor R Greenhalgh
Department of Vascular Surgery
Imperial College of Science, Technology and Medicine
4th Floor
Charing Cross Hospital
Fulham Palace Road
London, W6 8RF

Dear Professor Greenhalgh,

RREC 2447 - The development of Charing Cross guidelines for the prevention of venous thrombosis after surgery with subcutaneous low dose heparin and anti-embolic stockings in high, medium and low risk patients

Thank you for sending us this submission. Following your response to the four points raised, I am pleased to inform you that approval has now been granted by the Committee.

Please note the following conditions which form part of this approval:

[1] This approval is for one year only. For projects with an expected duration of more than one year, a letter from the principal investigator will be required in order to further extend consent. This will enable the Committee to maintain a full record of research.

[2] Any changes to the protocol must be notified to the Committee. Such changes may not be implemented without the Committee's approval.

[3] The Committee should be notified immediately of any serious adverse events that are believed to be study related or if the entire study is terminated prematurely.

[4] You are responsible for consulting with colleagues and/or other groups who may be involved or affected by the research, e.g., extra work for laboratories. Approval by the Committee for your project does not remove your responsibility to negotiate such factors with your colleagues.

Cont/2.

262
Cont/2... RREC 2447 - The development of Charing Cross guidelines for the prevention of venous thrombosis after surgery with subcutaneous low dose heparin and anti-embolic stockings in high, medium and low risk patients

[5] You must ensure that nursing and other staff are made aware that research in progress on patients with whom they are concerned has been approved by the Committee.

[6] Pharmacy must be told about any drugs and all drug trials, and must be given the responsibility of receiving and dispensing any trial drug.

[7] The Committee must be advised when a project is concluded and should be sent one copy of any publication arising from your study, or a summary if there is to be no publication.

[8] All documents relating to the study, including Consent Forms for each patient (if applicable), must be stored securely and in such a way that they are readily identifiable and accessible. The Committee will be conducting random checks on the conduct of studies, and these will include inspection of documents.

May I take this opportunity to wish you well in your research. If any doubts or problems of an unexpected nature arise, please feel free to contact me at any time.

Yours sincerely

C G Mackworth-Young MA MD FRCP
Chairman - RREC

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<tr>
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<td>Letter of Indemnity</td>
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</table>
Appendix B  Audit proforma

Consultant

Speciality:  
Operation:  Ward  In-patient stay  Day post-op

Patient details
Age:  years
Male  Female

Risk Factors
Previous Deep vein thrombosis  Yes  No
Previous Pulmonary embolus  Yes  No
Coagulopathy  Yes  No  Type:
FHx Coag  Yes  No  Type:
Smoker  Yes  No
Hx of VVs  Yes  No
Hx of # leg/Sx  Yes  No
Recent flight  Yes  No  Duration
Malignancy  Yes  No  Diagnosis  Date:
Obese  Yes  No  Kg  Ht  BMI:

Medication
Warfarin  Aspirin  HRT  OCP  Steroids
Others:

Stockings
None  One  Both legs  Suitable Size Fitted  Yes  No
Known contra-indication: Yes/No

Heparin

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</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (BD=1, OD=2, Nocte=3)</td>
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<td></td>
</tr>
<tr>
<td>Pre-op</td>
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<td></td>
</tr>
<tr>
<td>Post-op</td>
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</table>

Mobility level attained
Bed  Chair
Walking with aid  Walking unaided

Other DVT Prophylaxis  Yes  No  Type:
THE DEVELOPMENT OF CHARING CROSS GUIDELINES FOR THE
PREVENTION OF
VENOUS THROMBOSIS AFTER SURGERY WITH ANTI-EMBOLIC LEG
STOCKINGS
AND LOW DOSE HEPARIN

2. Invitation

You are being invited to take part in a research study. Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and medical staff if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled ‘Medical Research and You’. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

3. What is the purpose of the study?

In patients who have had an operation there is a risk of developing a thrombosis in the deep veins of the leg. There are a number of measures, which can be used to help prevent this from occurring; these include using anti-embolic leg stockings and an injection of low dose heparin just under the skin once a day. However the exact type of stockings that are best for this purpose is not yet known.

The Department of Vascular Surgery of Imperial College of Science, Technology and Medicine, led by Professor R. M. Greenhalgh has set up a study to compare the
effectiveness of different types of leg stockings, used to stop deep vein thrombosis (DVT) occurring after surgery.

A second part of the study will also involve a testing two small samples of blood. These blood tests will not require any additional 'needles' or 'injections', the samples will be taken at the same time as your routine blood tests on admission to hospital and in the operating theatre anaesthetic room before your surgery. The analysis of the blood samples will help us to develop a test that may be able to predict if you are going to develop a deep vein thrombosis after your surgery and therefore help to prevent DVT in the future.

With the information from the trial, we will develop guidelines for the prevention of deep vein thrombosis; to be used in our trust for every surgical procedure performed under general anaesthetic involving at least one night stay in hospital. Subcutaneous heparin will be recommended for all, but type of stocking is under scrutiny.

4. Why have I been chosen?

You are due to have an operation in the next few days, and as part of the usual post operative treatment, you would normally be asked to wear leg stockings and receive daily injections of low dose subcutaneous heparin. If you agree to take part, we would like to decide for you which of the three types of stocking to wear after the operation. You would still receive the standard heparin injections.

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving any reason. This will not affect the standard of care you receive.

5. What will happen to me if I take part?

Before your operation, a specialist vascular nurse will measure and fit your new stockings, which you should then wear day and night until seven days after your operation. The stockings that you receive will be one of three types, Kendall ‘TED’ thigh length anti-embolic stockings, Medi thigh length anti-embolic stockings or Medi knee length stockings. This is a ‘Randomised trial’, which means that people will be put into one of three groups and then compared. As we do not know which
are the best stockings to use, patients are randomly assigned by computer to wear one of the stocking types and then each group is compared. The computer has no information about the individual, so that each patient is assigned by chance. *At this stage we would like to take a small blood sample (1 ml) when your routine pre-operative blood tests are taken and another just before your operation when the anaesthetist is routinely required to insert a needle for venous access.*

On the 5-7th day after your operation the vascular research fellow or a vascular technician will carry out an ultrasound scan on the veins in your legs, looking for deep vein thromboses. This test is completely painless, and is not dangerous to you at all, but it will require you to lie still for approximately 30 minutes. If you have left hospital before the fifth day after your operation, we would give you an appointment to come to have the ultrasound scan in the Department of Vascular Surgery at Charing Cross Hospital as part of your post operative management.

When an adult patient wears stockings and receives low dose heparin injections after an operation, the risk of developing a deep vein thrombosis is between 1 and 10%. This depends on whether your are in the low, medium or high risk category for post operative deep vein thrombosis. If you are found to have a deep vein thrombosis, we would then start you on the standard hospital treatment for deep vein thrombosis. This would involve having a daily injection of another type of heparin, called Tinzaparin and starting warfarin tablets which, you would need to take for six months. The treatment of a deep vein thrombosis does not mean that you need to stay in hospital any longer than normal, as a district nurse can administer the Tinzaparin injections daily at your home. A specialist anti-coagulation outpatient clinic would then see you on a regular basis to monitor the dose of your warfarin.

The information above is summarised in a flow diagram as follows:

```
ADMISSION TO HOSPITAL
EXPLANATION OF TRIAL
SIGNING OF TRIAL CONSENT FORM
CLINICAL ASSESSMENT
```
6. What do I have to do?

There will be no change to management of your care during your hospital stay as each surgical patient receives stockings and heparin after surgery. We will only alter the type of stockings worn by patients, because we wish to know which our patients like the best.

(You may be excluded from the study if the doctors running the trial feel that the use of stockings and/or heparin may be dangerous to your health.)
It will not affect any current treatments that you are receiving. You can continue to take any current medications and a normal diet as directed by your surgical team. You will be asked to fill in a Health Related Quality of Life Questionnaire at the end of the study to help us know your views on the stockings.

7. What is the appliance being tested?

As described above, we aim to compare different types of leg stockings used to prevent post operative deep vein thrombosis after a surgical procedure and blood sample will tested with Thromboelastograph analysis which gives an overall clotting picture of the blood.

8. What are the side effects of taking part?

Stockings, heparin injections and blood tests are all part the routine surgical treatment before and after any operation, this study will not change your treatment or subject you to any additional risk. There are no side effects from wearing leg stockings; they rarely cause itching and minor discomfort. Low dose subcutaneous heparin injections are given to all patients on trial or not and rarely cause side effects. It is used in most adult patients in the post operative period. However, the side effects that heparin can cause are as follows:

- Irritation or damage to the skin at the injection site.
- Bruising or increased bleeding.
- A lowering of platelets in the blood. Platelets are cells which, help to form blood clots.
- A rise in the blood level of potassium.
- Allergic reactions.

Every patient will be closely observed to check that side effects are avoided or treated immediately.

9. What are the possible disadvantages and risks of taking part?
There will be no additional risk to your health by taking part in this study. All the interventions carried out in this study such as: stockings, low dose heparin injections and blood tests are usually performed on all surgical patients. The additional duplex ultrasound scan is painless and risk free. The only disadvantage is to let us know your views by questionnaire.

If we diagnose a deep vein thrombosis, then the appropriate treatment will be commenced in accordance with the Hammersmith Hospitals Trust’s Protocol (as described above). Any other condition that is diagnosed as a result of this trial will be treated by your surgical team or result in a referral to another team for treatment.

10. What are the possible benefits of taking part?

We do not know if the new stocking types used are better than the currently used stockings. In the post operative period you would be followed more closely than normal for the detection of a deep vein thrombosis as a result of the additional tests implemented for the study.

We hope that all treatments will benefit patients. However, this cannot be guaranteed. The information we get from this study may help us to prevent future patients from developing a deep vein thrombosis.

11. What happens when the research study stops?

We shall provide the preferred stockings to all of our patients.

12. What if something goes wrong?

Any complaints about the treatment you receive as part of this trial can be discussed with the clinical research fellow.

It is very unlikely that any harm should come to you as a result of wearing a different type of leg stocking. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms may be available to you.
13. Will my taking part in this study be kept confidential?

All information, which is collected, about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it (unless it is necessary to send information to your GP).

14. What will happen to the results of the research study?

The results of the study will be used to formulate the ‘Charing Cross Guidelines for Post Operative Deep Vein Thrombosis Prevention’. These guidelines will help to prevent DVT in future post operative patients. The results of the trial will be published in leading medical journal after completion of the study, a copy of this will be available to you from the Department of Vascular Surgery at the Charing Cross Hospital. You will not be identified in a report or publication. A copy of the results will available to Medi UK who have supplied the stockings for this study.

15. Who is organising and funding the research?

This study has been organised by the Professor R. Greenhalgh and Mr A Davies in the Department of Vascular Surgery of Imperial College of Science, Technology and Medicine. This is not a sponsored study, the department or doctors involved will not be paid for including you in this study. The research is funded by a charitable trust via Imperial College.

16. Who has reviewed this study?

This trial has been reviewed by the Riverside Research Ethics Committee, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH.

17. Contact for further information.
If you require further information, please contact Mr A Howard, Clinical Research Fellow or Mrs A Williams, Specialist Vascular Nurse, at the Department of Vascular Surgery, 4th Floor, Charing Cross Hospital, Fulham Place Road, London.

We would like to thank you if you have decided to help by taking part in our study. You will be given a copy of the patient information sheet and a signed consent form to keep.
Appendix D

Patient Consent Form

Comparing Anti-Embo1ic Stockings for the Prevention of Deep Vein Thrombosis

Patient Name: ................................................. Patient ID Number: .................................

The patient must complete the whole of this sheet by initial1ing the boxes

I have read the patient information sheet

I have had the opportunity to ask questions and discuss the study

I understand that my participation is voluntary and that I am free to withdraw at any time without giving reason, without my medical care or legal rights being affected

I understand that sections of my medical notes may be looked at by doctors from Charing Cross hospital and possibly by members from regulatory authorities where it is relevant to the research. I give permission for these individuals to have access to my records

Do you give permission for your General Practitioner (GP) to be notified of your participation in this trial?

YES NO

I fully agree to take part in the study.

Signed by patient: ..........................................................

Name in block letters: ..........................................................

Date of consent: ..........................................................

Copy of consent to be placed in patients hospital notes.
Appendix E

Trial baseline sheet

Recruiting Consultant
Speciality:
Planned operation:
Date:

Patient details
Name/address in full:
Hospital number:

Weight: kg/st
Height: cm/ft
BMI:

Past Medical History
Deep vein thrombosis
Pulmonary embolus
Coagulopathy
Coag FHx
Smoking
Hx of VVs
Hx of # leg/Sx
Mobility
Recent flight
Malignancy
Medication
Pre-operative duplex

Baseline Form

Admission: / / , Operation: / / , Ward
First Scan: / / , Time Day . Bkd Y/N
Final Scan: / / , Time Day . Bkd Y/N

Tel:

Left/Right Date: / /
Type: 
Number of years:
CEAP
Surgery type
Bed bound
Chair bound
Housebound
Full
Duration Date: / /
Diagnosis Date: / /
Warfarin Aspirin name:
HRT name:
Steroids name:
Others:

Normal
Thrombus Scarring
Recannalised
Obstruction
Venous anomaly

(Attach copy of duplex diagrammatic findings)

Yes No

Yes
Yes
Yes
Yes

Yes No

Yes
Yes
Yes
Yes

Yes No

Yes
Yes
Yes
Yes

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No

Yes No
## Appendix F  Randomisation sheet

### Patient details

Name in full: 

### Checklist

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<tr>
<td>Signed consent form</td>
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<tr>
<td>Pre-operative duplex</td>
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### Stratification

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<tr>
<td>Speciality</td>
<td>Neuro □</td>
<td>Ortho □</td>
<td>Other □</td>
</tr>
</tbody>
</table>

Date of randomisation □/□/□

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kendall thigh length stockings</td>
<td>□</td>
</tr>
<tr>
<td>Medi thigh length stockings</td>
<td>□</td>
</tr>
<tr>
<td>Medi knee length stockings</td>
<td>□</td>
</tr>
</tbody>
</table>
### Appendix G

**Surgery and post-surgery sheet**

<table>
<thead>
<tr>
<th><strong>Patient details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name in full:</strong></td>
</tr>
<tr>
<td><strong>Hospital number:</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Prophylaxis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stocking type</strong></td>
</tr>
<tr>
<td>KTL</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong></td>
</tr>
<tr>
<td>Time: 12hr pre-op</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Heparin complication:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding - Wound: Yes No</td>
</tr>
<tr>
<td>- Major: Yes No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GCS complication:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Operative details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of operation:</strong></td>
</tr>
<tr>
<td>/ /</td>
</tr>
<tr>
<td><strong>Type of operation:</strong></td>
</tr>
<tr>
<td><strong>Duration of operation</strong></td>
</tr>
<tr>
<td>hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Post operative period</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mobilisation</strong></td>
</tr>
<tr>
<td><strong>Pre-op</strong> cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Post operative duplex</strong> (Attach copy of duplex diagrammatic findings)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date performed</strong></td>
</tr>
<tr>
<td>/ / /</td>
</tr>
<tr>
<td><strong>Post operative day</strong></td>
</tr>
<tr>
<td>5 Yes</td>
</tr>
<tr>
<td><strong>Post operative DVT</strong></td>
</tr>
<tr>
<td><strong>Right</strong> : Proximal Distal</td>
</tr>
<tr>
<td><strong>Left</strong> : Proximal Distal</td>
</tr>
<tr>
<td>IVC</td>
</tr>
<tr>
<td>C.IliacV</td>
</tr>
<tr>
<td>E.IliacV</td>
</tr>
<tr>
<td>C.FemoralV</td>
</tr>
<tr>
<td><strong>Pulmonary embolus</strong></td>
</tr>
<tr>
<td>Clinically: Yes No Day</td>
</tr>
<tr>
<td>VQ: Yes No Equivocal</td>
</tr>
</tbody>
</table>
Appendix I  Patient stocking satisfaction questionnaire

This questionnaire asks you for your views about your stockings or bandages. Please read the questions carefully, and then place a tick in one box below the statement that best describes your answer. If you are unsure about how to answer, please give the best answer you can. In order help us assess the types of stockings or bandages used, please be as frank with your answer as possible.

Patient Name: ___________________________ Sex: ________ Age: ________

Pressure Level: 
TED 3LB ________ Full Length ________
I 4LB ________ Knee Length ________
II ________
III ________

Duration worn: ________ months ________ days Date: ________ 2002

Please do not tick more than one box per question.

1. Do you feel the stockings/bandages cause you discomfort?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

2. Do you feel the stockings/bandages make your legs itch?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

3. Do you feel the stockings/bandages make your legs feel hot?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

4. Do you feel the stockings/bandages are tight?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

5. Do you feel the stockings/bandages slip down?

<table>
<thead>
<tr>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
</table>
6. Do you feel the stockings/bandages are unhygienic to wear?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

7. Do you feel your stockings/bandages look unsightly to wear?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>

8. Do you feel your stockings/bandages are difficult to remove and put back on, if performed by yourself without the help of another person?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
</table>
Appendix J  

Patient stocking compliance diary sheet

The compliance diary sheet was laid out as follows*:

**How many days did you stay in hospital?** □ Days

**Please fill in the date of leaving hospital.** Date □

Please place a single mark for each day and night in a box to record the number of hours that your stockings have been worn:

<table>
<thead>
<tr>
<th>WEEK 1</th>
<th>DAYTIME</th>
<th>NIGHT TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days of the week that stockings are worn</strong></td>
<td><strong>None of the time</strong> (0 hours)</td>
<td><strong>None of the hours at night</strong> (0 hours)</td>
</tr>
<tr>
<td>Monday --/--/2002</td>
<td>A little of the time (less than 4 hours)</td>
<td>Little of the hours at night (less than 4 hours)</td>
</tr>
<tr>
<td>Tuesday</td>
<td>Some of the time (between 4 to 8 hours)</td>
<td>Some of the hours at night (between 4 to 8 hours)</td>
</tr>
<tr>
<td>Wednesday</td>
<td>Most of the time (8 to 12 hours)</td>
<td>Most of the hours at night (8-12 hours)</td>
</tr>
<tr>
<td>Thursday</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunday</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table reduced in size to fit page layout for thesis binding*
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES</td>
<td>Anti-embolic stockings</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>ATIII</td>
<td>Anti-thrombin III</td>
</tr>
<tr>
<td>CDU</td>
<td>Colour Doppler ultrasound</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear nose and throat surgery</td>
</tr>
<tr>
<td>GCS</td>
<td>Graduated compression stockings</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GIT</td>
<td>Gastrointestinal surgery</td>
</tr>
<tr>
<td>ICS</td>
<td>International consensus statement</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>IPC</td>
<td>Intermittent pneumatic compression</td>
</tr>
<tr>
<td>LDUH</td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ration</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PTS</td>
<td>Post-thrombotic or post-phlebitic syndrome</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SNAD</td>
<td>sodium N-[10-(2-hydroxybenzoyl)amine decanoate</td>
</tr>
<tr>
<td>TF</td>
<td>Tissue factor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>TFPI</td>
<td>Tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>THRIFT</td>
<td>Thromboembolic Risk Factors Consensus Group</td>
</tr>
<tr>
<td>3LB</td>
<td>Charing Cross three layer bandaging</td>
</tr>
<tr>
<td>4LB</td>
<td>Charing Cross four layer bandaging</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
</tbody>
</table>
List of presentations and publications resulting from this study

Presentations at national and international meetings


Invited chapters


Publications

Abstracts


Papers

‘Randomised clinical trial of low molecular weight heparin with thigh-length and knee-length antiembolism stockings for patients undergoing surgery.’ A Howard, D Zaccagnini, A Williams, M Ellis, AH Davies, RM Greenhalgh. BJS 2004;90:842-847. (copy included)
Acknowledgements

I would like to thank all of the staff in the Department of Vascular Surgery at Charing Cross Hospital, in particular my research supervisor Professor Roger M Greenhalgh, and also Mr Alun Davies for his support. I would also like to thank Mary Ellis, the Principal vascular technology scientist for her help, venous duplex training and the extra work that this project produced. All the patients described in this thesis were under the care of the Department of Surgery at Charing Cross Hospital. I would like to thanks all the surgical consultants from departments who helped with this study from breast and oncology, ENT (Ear, Nose and Throat surgery), gastrointestinal, neurosurgery, orthopaedic, urology and vascular surgery. These consultants included: Professor SPF Hughes (Orthopaedic, Reconstructive and Trauma Surgery), Mr A Wallace (Orthopaedic, Reconstructive and Trauma Surgery), Mr R Coombes (Orthopaedic, Reconstructive and Trauma Surgery), Mr A Forrester (Orthopaedic, Reconstructive and Trauma Surgery), Mr J Hucker (Orthopaedic, Reconstructive and Trauma Surgery), Mr R Strachan (Orthopaedic, Reconstructive and Trauma Surgery), Mr R Springall (Gastrointestinal Surgery), Mr N Theodorou (Gastrointestinal Surgery), Mr T Christmas (Urological Surgery), Mr J Ramsey (Urological Surgery), Mr PM Clark (ENT Surgery), Mr W Grant (ENT Surgery), Mr K O’Neale (Neurosurgery), Mr N Mendoza (Neurosurgery), Professor J Van Dellen (Neurosurgery), Mr D Peterson (Neurosurgery), Mr HD Sinnet (Breast and Oncology Surgery), Mr JA Lynn (Breast and Oncology Surgery), Mr R Cummins (Breast and Oncology Surgery).
I am especially grateful to Dr Nina Salooja for haematological advice and Ms Louise Brown for randomisation of trial patients.

I would like to thank Medi UK (Hereford, England) for supplying their stockings for this study. Medi UK played no part in the gathering, analysis and presentation of data in this study.

The work described in this thesis was performed over a three-year period whilst employed as a Clinical Tutor in Surgery at Charing Cross Hospital, Imperial College of Science, Technology and Medicine. The work described is all original and my own work.

The Riverside Ethical Committee approved all the clinical trials include in this thesis.
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graduated compression stockings. BJS 1988;85:1228-31


Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery

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Correspondence to: Professor R. M. Greenhalgh (e-mail: r.greenhalgh@imperial.ac.uk)

Background: This was a randomized clinical trial to determine the efficacy and safety of a ‘blanket’ protocol of low molecular weight heparin (LMWH) and the best length of antiembolism stocking, for every patient requiring surgery under general anaesthesia.

Methods: Of 426 patients interviewed, 376 agreed to be randomized to receive one of three types of stocking: thigh-length Medi thrombexin® climax™ (Medi M Hereford, LTK), knee-length thrombexin™ climax and thigh-length Kendall T.E.D.™ (Tyco Healthcare UK, Redruth, UK). All patients received LMWH thromboprophylaxis. Duplex ultrasonography was used to assess the incidence of postoperative deep vein thrombosis (DVT).

Results: No postoperative DVT occurred in 85 patients at low or moderate risk. Nineteen DVTs occurred, all in the 291 high-risk patients: two with the Medi thigh-length stockings, 11 with the Medi knee-length stockings (odds ratio 0.18 (95 per cent confidence interval 0.04 to 0.82); \( P = 0.026 \)) and six with the Kendall T.E.D.™ thigh-length stockings. No patient developed a pulmonary embolism. Stacking groups were similar for age, sex, thromboembolic risk, type of operation and compliance. One significant bleeding complication occurred.

Conclusion: A single protocol comprising LMWH and thigh-length stockings abolished DVT in low- and moderate-risk patients, and reduced the rate of DVT to 2 per cent in high-risk patients.


Paper accepted 23 December 2003
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Introduction

Currently, the most appropriate means of preventing deep vein thrombosis (DVT) in surgical patients are subcutaneous heparin and antiembolism stockings, which offer increased benefit when used in combination. Other pharmacological and physical prophylactic methods exist, but are less effective, less safe or impractical. An audit was conducted in this university hospital of the status of thromboprophylaxis to investigate areas for improvement. Of 106 patients who had undergone surgery, heparin prophylaxis was omitted in 43.0 per cent. The use of antiembolism stockings was also disparate and underprescribed to only 46.2 per cent of patients. A variety of stocking brands and lengths was used with inadequate fitting. The combined use of subcutaneous heparin and stockings was evident in only 24.3 per cent of patients. These findings are similar to other reports in the literature describing poor compliance of DVT thromboprophylaxis.

In order to correct the poor compliance of thromboprophylaxis in the hospital, junior doctors and nurses were tutored in the merits of a single ‘blanket’ protocol of heparin and stockings for all surgical patients. A repeat audit showed a significant improvement in optimal thromboprophylaxis to 88.1 per cent of patients \((P = 0.003)\). The majority of surgical specialties considered low molecular weight heparin (LMWH) to be the best choice for a single-protocol regimen as it is generally more effective, more acceptable to patients owing to the single daily injection,
and now cheaper than low-dose unfractionated heparin. However, surgeons and nurses remained uncertain at what length and design of antiembolism stocking to use in surgical patients.

The aim of the study was to determine the optimal length of antiembolism stockings in surgical patients, and to compare the efficacy and safety of thigh-length and knee-length stockings in the prevention of postoperative deep vein thrombosis (DVT). A single daily subcutaneous injection of 20 mg low-molecular-weight heparin (LMWH), enoxaparin sodium (Clexane®; Aventis Pharma, West Malling, UK), was given to patients on the evening before surgery, except for neurosurgical and orthopaedic patients whose surgeons insisted that they receive the LMWH within 12 h after completion of the operation. Enoxaparin injections were given daily until discharge from hospital.

A record of complications associated with use of stockings and LMWH was kept. All patients who developed a DVT were treated with full anticoagulation with daily LMWH until adequate warfarinization and class-2 compression hosiery, and were referred for haematological follow-up.

Sample size and statistical analysis

Sample size calculations were based on detecting a possible difference in postoperative DVT rates of 20.0 per cent in the knee-length stocking group and 5.0 per cent in each of the thigh-length stocking groups. These calculations, based on 90.0 per cent power at the 5.0 per cent significance level, required 114 patients per group (342 patients in total).

Statistical analysis was performed using the STATA® version 6.0 statistical package (Stata Corporation, College Station, Texas, USA). Logistic regression analysis was used to estimate crude odds ratios (ORs) between the three types of stocking. These ORs were also adjusted for the use of preoperative LMWH.

Results

A total of 426 patients were interviewed for entry into the trial; 39 refused and 11 were medically unable to wear antiembolism stockings or to receive subcutaneous LMWH prophylaxis. Three hundred and seventy-six patients were randomized; their mean age was 58 (range 16–88) years and 218 (58.0 percent) were women. Thromboembolic risk assessment revealed that 291 patients were at high risk, 59 at moderate risk and 26 at low risk. Patients were recruited from a variety of surgical specialties: breast and oncology (73 patients), ENT (13), gastrointestinal (122), neurosurgery (34), orthopaedic (62), urology (58) and vascular venous surgery (14). The patients were randomized into three stocking groups: thigh-length Kendall T.E.D.® (127 patients), thigh-length Medi thrombexin® climax® stockings (128 patients), and knee-length Medi thrombexin® climax® stockings (128 patients). Randomization was stratified by thromboembolic risk (high, moderate and low) and surgical specialty (breast and oncology, ENT, gastrointestinal, neurosurgery, orthopaedic, urological and...
vascular), which produced three similar groups matched for age (P = 0.850), sex (P = 0.998), time of commencement of LMWH (P = 0.280) and thromboembolic risk (P = 0.230). For each stocking group a statistically similar number of patients did not undergo surgery or postoperative venous duplex imaging (P = 0.277) (Fig. 1).

**Trial results**

None of the 85 patients at low or moderate risk developed a DVT when this protocol was used. All postoperative DVTs occurred in patients from the high-risk category. Some 19 (6·5 per cent) of 291 high-risk patients developed a DVT; two were bilateral (Fig. 1). No patient developed pulmonary embolism during the trial.

The Medi thrombexin® climax™ thigh-length stockings were significantly better at preventing postoperative DVT than the knee-length stockings (two versus 11; OR 0·18 (95 per cent confidence interval (c.i.) 0·04 to 0·82); P = 0.026). Five patients developed unilateral DVT and one a bilateral DVT in the Kendall T.E.D.™ thigh-length group (OR 0·5 (95 per cent c.i. 0·18 to 1·41) versus Medi thrombexin® climax™ knee-length stockings; P = 0·190). Although data for Kendall T.E.D.™ thigh-length stockings were not significantly different from those for either of the other two types of stocking, the results were inconclusive owing to a lack of power between the groups. All the DVTs that developed in patients with thigh-length stockings were found in the calf veins (posterior tibial and peroneal veins). The knee-length stockings were also associated primarily with calf-vein DVT, although one proximal DVT was found in the superficial femoral vein of the thigh.

The patients with postoperative DVT included six having orthopaedic surgery, six gastrointestinal surgery,
Two main types of surgery: 'bone cutting' operations as hip (n = 3) and knee (n = 2) replacements, and abdominal surgery (n = 2) and craniootomy (n = 1); and major abdominal surgery including upper gastrointestinal erations (n = 3), lower gastrointestinal operations = 3), nephrectomy (n = 2), cystectomy (n = 2) and ostectomy (n = 1). Of patients undergoing bone-operations, 11 per cent developed a postoperative VT compared with 5-2 per cent of those undergoing major abdominal surgery; the latter all commenced 

VWH prophylaxis before surgery.

The value of preoperative LMWH in reducing the te of postoperative DVT was investigated by means of gistic regression, which showed similar significance when justed for the use of heparin before and after surgery, for Medi thigh-length versus Medi knee-length stockings R 0.19 (95 per cent c.i. 0.04 to 0.88); P = 0.034) and for endall thigh-length versus Medi knee-length stockings R 0.5 (95 per cent c.i. 0.18 to 1.42); P = 0.192). There is weak evidence suggesting that preoperative LMWH is protective in reducing postoperative DVT (OR 0.41 5 per cent c.i. 0.16 to 1.06); P = 0.066). However, this vel of significance was diminished when adjusted for ndomized groups (P = 0.110). Approximately one-half the patients with postoperative DVT in each stockingoup had relevant clinical signs of swelling, tenderness erythema. Age and malignancy were positive risk cators for DVT; the mean age of the 19 patients with VT was 68 (range 45–83) years, and 12 of these d a history of malignancy. All patients who developed VT were treated with full anticoagulation. Warfarin was continued for 6 months under haematological outpatient ic surveillance.

A record of complications associated with the use of cutaneous LMWH and antiembolism stockings showed at only one significant bleeding complication occurred; her complications included two minor haematomas at did not require further management, and minor ot abrasions from stockings in three patients. The mificant bleeding complication developed when a drain is removed on the second day after parotid surgery; the sulting haematoma required further general anaesthesia r surgical evacuation. The patient made a full recovery.

A single protocol was deemed appropriate and nec essary because findings from previous audits had shown that the majority of surgical patients staying in hospita al were at high or moderate risk of thrombembolism. Second, existing protocols prescribe prophylaxis according to risk assessment, which relies on preoperative predictions that may change unexpectedly, such as duration of surgery, postoperative mobility, infection and presence of malignant disease. Antiembolism stockings are effective in the surgical patient, with a reduction in the incidence of postoperative DVT to approximately 11 per cent. Low dose heparin administered via subcutaneous injection is slightly more effective, reducing the DVT rate to around 9 per cent. In combination, subcutaneous heparin and antiembolism stockings are the most practical and effective prophylaxis in surgery. The efficacy, safety and acceptability of these two methods have led to their populari ty in surgical practice. It was proposed that LMWH should be given to all patients having surgery under general anaesthesia, except those with medical contraindications. This policy was accepted throughout the surgical specialties, although orthopaedic and neurosurgeons insisted on delayed heparin administration for their patients. The question arose as to which type of stocking was best in combination with LMWH.

Until this trial, only limited evidence was available to distinguish between the benefits of knee- and thigh-length antiembolism stockings. A number of studies have investigat ed different stockings for effects on venous velocity, patient acceptability and compliance, but only three have compared knee-length with thigh-length stockings for the prevention of postoperative DVT. All three studies were randomized, but the number of patients in each was small and none demonstrated a significant difference. A recent review on antiembolic stockings highlighted some of the benefits of knee-length over thigh-length stockings, but offered no evidence on their efficacy in the reduction of postoperative DVT. The international consensus statement refers to the efficacy of knee-length compared with thigh-length stockings in the prevention of DVT as one of the 'key questions to be answered'. The present study showed that thigh-length antiembolism stockings were better at preventing postoperative DVT than knee-length stockings with the same graduated compression profile.

The standard dose of 20 mg enoxaparin was given to all trial patients because it was simple and previous
studies had shown that increasing the dose of LMWH added no prophylactic benefit but increased postoperative bleeding.\(^{14}\)

In this study, orthopaedic and neurosurgeons at least had the reassurance that the major bleeding problems they feared did not occur. For them to allow LMWH to be given 12 h before surgery could have increased the rate of bleeding whilst lowering the DVT rate. Patients undergoing 'bone cutting' or abdominal surgery are at high risk of thromboembolic complications and therefore require optimal prophylaxis. In the present study, neurosurgical and orthopaedic patients who received only postoperative LMWH had the highest rate of postoperative DVT, approximately twice that of the other specialties where LMWH was given before the operation. The surgical procedure initiates the thromboembolic process and therefore starting the heparin prophylaxis before surgery is probably optimal, although further research in this area is required. LMWH commenced the evening before operation also permits the use of epidural or spinal anaesthesia at the time of surgery.

The combination of a good-quality thigh-length stocking and LMWH for patients undergoing surgery produced a postoperative DVT rate of 2 per cent in high-risk patients and zero in patients at moderate or low risk. This simple and safe protocol for DVT prophylaxis of LMWH and antiembolism stockings can be given to all surgical inpatients. To have a single hospital protocol means that prophylaxis against DVT is less likely to be forgotten. If a specialty insists on a delay in administration or an increased dosage for certain patients, this can be accommodated. Patients with medical contraindications to LMWH or stockings could receive only appropriate prophylaxis.

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Thesis Amendments

Amendments for completion of thesis submitted to the University of London for the degree of Doctor of Medicine, August 2006

“The Prevention of Post-Operative Deep Vein Thrombosis”

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Amendments required:

1. Why the evidence for DVT prophylaxis remains controversial.

2. Discuss the conclusions from the audit and how many patients would be needed to prove safety.

3. Limitations of the study design with reference to:
   
   i. Power calculations
   
   ii. Three pronged randomisation
   
   iii. Stratification of patients
   
   iv. Diagnostic modalities for calf vein DVT
   
   v. Study conclusions
Why the evidence for DVT prophylaxis remains controversial

In recent years, the majority of evidence for the prophylaxis of venous thromboembolism has been summated and reported in numerous consensus guidelines and review articles. These articles stress the importance of risk factors for venous thromboembolism (VTE) and their incorporation into risk stratification systems, upon which the guidelines are reliant, and thereby recommend the appropriate types and intensities of prophylaxis required for patients undergoing a particular treatment. The risk factors reported by the International Consensus guidelines (applied in this thesis) included, presence of varicose veins, general immobility, thrombophilia, trauma, cancer, prior VTE, obesity, infectious disease, increasing age, oral contraceptives, pregnancy and hormone replacement therapy (Nicolaides et al 2001). However, a number of these risk factors have dubious evidence supporting their inclusion, with the obvious knock on effect of affecting the theoretical thromboprophylactic risk and the subsequent prophylaxis given to the patients.

Various studies report different risk factors. For example, a recent meta-analysis that assessed the evidence for post-operative thromboembolic risk factors (Edmonds et al 2004) found that age, obesity, previous VTE, varicose veins, oral contraceptive pill, malignancy, factor V Leiden, general anaesthesia and orthopaedic surgery were all significant risk factors. And interestingly, hormone replacement therapy, ethnicity, gender, chemotherapy, other thrombophilias, cardiovascular factors, smoking and blood type were not significant. However, another study in the Lancet (Sue-Ling et al 1986) reported very different ‘significant’ risk factors: age, euglobulin lysis time, previous abdominal surgery, varicose veins, antithrombin III, smoking and platelet count. These
were all predictive of post-operative DVT. To add to the confusion, a large observational study (Di Minno et al 2005) reported another set of risk factors and separated these into ‘strong’ (history of superficial venous thrombosis, DVT or PE, heart failure and malignancy), ‘moderate and weak’ factors (smoking, history of miscarriage, oestrogen therapy, obesity and varicose veins). Intriguingly, this study reports no difference between sexes for DVT, however the females had consistently more risk factors. The question arises, actually how significant are these risk factors?

The inclusion of varicose veins as a risk factor by the International Consensus Statement (the main guideline used in this study) is controversial. A questionnaire survey (Campbell and Ridler 1995) sent to 363 vascular surgeons revealed that only twenty-nine percent regarded varicose veins as an important risk factor for DVT. Oger et al (1997) reported varicose veins as a risk factor with an odds ratio of 2.56, however like many other studies, the presence of other risk factors are often numerous and potentially confounding. The argument over risk factors and their individual importance will continue to be complex and difficult to prove. Smoking, obesity, immobility are often quoted, but rarely quantified and new risk factors are continually being added, such as intravenous drug abuse in patients under forty years (Syed and Beeching 2005).

Other areas of controversy within the literature surrounding VTE risk factor assessment are the ‘Low risk’ category of patients, the varied age brackets and operation times used for the classification into different risk categories. As previously stated in this thesis the low risk category does not have sufficient evidence to make recommendations in this group, they are a ‘no treatment group by exclusion’. The risk of DVT increases with age and operative time, but the cut-off ages and operation times for separating patients into different risk groups are arbitrary and vary for different guidelines.
Discuss the conclusions from the audit
and how many patients would be needed to prove safety

The audit of venous thromboprophylaxis performed in chapter four of this thesis involved one hundred and seventy-eight patients, all of which were surgical patients at Charing Cross Hospital; already occupying a ward bed or admitted to a hospital bed over a period of forty-eight hours. One hundred and six had all undergone one or more surgical procedures during the current hospital admission, which permitted the use of the International Consensus statement guidelines to be used to assess the risk of post-operative VTE and the appropriateness of prophylaxis application (Nicolaides et al 2001). The audit results were analysed as an overall ‘post-operative’ population (n=106) and also in groups according to their surgical speciality. These subgroups produced groups with a very low number of patients, for example in ENT where n = 4. The audit of the ‘Single Protocol’ produced a significant improvement in overall application of appropriate VTE prophylaxis (figure 4g). However, with only a total of 106 patients there was a possibility that the very audit process and the awareness of the health professionals to the current audit may have improved the compliance of the prophylaxis rather than the change in protocol. Hence, the audit would need greater numbers overall to account for this and repeated on more than one occasion. The numbers required can be calculated from power calculations, an improvement of 20% would require n = 102 in each round of the audit, 30% required n = 34, 40% required n = 21 in each group. Therefore the overall audit results had a statistical power of 76% because n = 34 in the second round of the audit, this was because only certain specialities (breast, gastrointestinal surgery, vascular
and urology) permitted the use of the new protocol. And for ‘surgical speciality’ subgroup analysis each speciality group would require \( n \geq 102 \) patients (DSS Research) to achieve sufficient power.

**Figure 4g - Improvements in DVT Prophylaxis after Education and Introduction of Single Protocol**

In the current health service environment the junior doctors and nurses change posts approximately every 3, 4 or 6 months. Repeated audit at 6 monthly intervals would allow
staffing changes to occur between audits and then the 'real' effects of the single protocol can be evaluated with less bias introduced by audit awareness. In addition, the single protocol was only assessing on certain specialities (breast, gastrointestinal surgery, vascular and urology) that permitted the use of the new protocol, not orthopaedics or neurosurgery that were awaiting the results of the forthcoming trial. This may also have introduced bias into the audit results by not including the very specialities that were most resistant to using the single protocol.

The evidence for the safety of using the single protocol was taken largely from the literature reporting bleeding and stocking complications with DVT prophylaxis. A summary of this literature is provided in the main text of this thesis (chapters 2 and 3). However, during the randomised clinical trial in this study the complications of both LMWH and GCS were recorded and the complication rate was low (chapter 6). If this study contained a control group without any prophylaxis but a placebo then the required numbers would be 473 patients in each group for a complication rate difference of 5% at 90% power and p<0.05 (DSS Research). This control group was not ethically permitted, and therefore the 'observed' complication rate was recorded and compared to traditional controls from the literature. The numbers required for an observation study are much larger, in the region of thousands of patients rather than hundreds like in this study.

Limitations of the study design

with reference to: power calculations, three pronged randomisation, stratification of patients, and diagnostic modalities for calf vein DVT

and study conclusions
i. Power calculations

The power calculations in the study were based on detecting a possible difference in postoperative DVT rates of 20% in the knee-length stocking group and 5% in each of the thigh-length stocking groups. These calculations - based on 90% power at the 5% significance level - required 114 patients per group and 342 patients in total (Stata 6, TX, USA). The results of the trial demonstrated a 9% difference in DVT rate between the Medi thigh and Medi knee-length stockings and a 3% difference between the Medi thigh and the Kendall thigh stockings, this produced a statistical power of 83% and 31% respectively (DSS Research). The numbers required for 90% power at 5% significance, to show a 9% and 3% difference would approximate to 127 and 641 patients in each group respectively.

ii. Three pronged randomisation

In this study we chose the stockings from the UK market leaders Kendall and Medi UK. The study compared Medi thigh and knee-length stockings and we chose to have Kendall thigh length as a 'traditional control' because the majority of the randomised trials in literature used this stocking type. In order to improve the power of the study and keep the recruitment numbers to a minimum, this study could have had a more efficient structure if just two groups were employed, one with thigh and one with knee-length GCS, with 127 patients required for each group. In addition, a better control arm would have been a group without stockings and just LMWH, which may have been ethically permitted.

iii. Stratification of patients
In this study, computer randomisation was performed and this was stratified for surgical speciality and thromboembolic risk, in line with the International Consensus Statement for the Prevention of Venous Thromboembolism (Nicolaides et al. 2001). Patients were recruited from a variety of surgical specialities that included: breast and oncology (n=73), ENT (n=13), gastrointestinal (n=122), neurosurgery (n=34), orthopaedic (n=62), urology (n=58) and vascular surgical patients (n=14) (table 6b). Thromboembolic risk assessment in accordance with the International consensus (Nicolaides et al 2001) revealed 291 patients were high risk, fifty-nine patients were moderate risk and twenty-six patients fell into the low risk category. Stratified randomisation allocated patients into three stocking groups (see table 6c) consisting of patients wearing Medi Thrombexin thigh-length stockings (n=121), Medi Thrombexin knee-length stockings (n=128) and Kendall T.E.D. thigh-length stockings (n=127) (figure 6d). This form of randomisation produced three groups of patients that were statistically similar with regard to demographics and surgical speciality. There was no significant difference in terms of age (P=0.850), gender (P=0.998) (table 6c), thromboembolic risk (P=0.230) (figure 6e) and surgical speciality (figure 6f). In addition, there was no significant difference between groups for compliance with the trial protocol (P=0.277). Figure 6f demonstrates graphically the group similarities for speciality.

However, these similarities do not account for the disparity between groups for the actual types of operation performed. There were potentially many confounding variables produced, for example, by the wide variety of operations, surgeons, surgical techniques, operative times and peri-operative managements. Therefore the actual differences between stocking groups would have been better evaluated by stratifying the randomisation for surgical procedures for each group and standardising the operations and the peri-operative managements performed.
iv. Diagnostic modalities for calf vein DVT

The diagnostic capabilities of duplex for calf vein DVT have been debated regularly over the last decade. Those in favour of duplex proffer the latest developments in power Doppler and zoom technologies. More recently the improved software processing the B mode image, such as high definition zoom, together with Doppler and now power Doppler, has enabled good visualisation of small calf veins and low flow scenarios can
reliably be assessed. The accuracy has been reported to reach between 94 and 97.9% for
detecting acute isolated calf DVT and 97% accuracy (confidence interval 96-98%) for the
diagnosis of proximal DVT (Baumgartner et al 1998 & Keearon et al 1998). The
sensitivity has been reported to reach one hundred percent, specificity 71%, positive
predictive value 71%, achieved with 100% of scans completed successfully (Forbes &
Stevenson 1998). Colour duplex scanning for DVT is non-invasive, time efficient,
acceptable to patients, harmless and repeatable. On the other hand, contrast venography.
is expensive, uncomfortable to the patient, occasionally painful, technically difficult to
perform and exposes the patient to radiation. It is inadequate, impossible to perform or
difficult to interpret in up to ten percent of patients. Isotopic fibrinogen scanning suffers
similar set backs to venography as it is invasive, uncomfortable for the patients,
technically difficult to interpret, involves radiation exposure and it has limited ability to
image proximal DVT in patients with knee and hip replacements due to artefact. Burn et
al (1997) reported how duplex ultrasonography has become increasing prevalent as a first
line diagnostic instrument for the diagnosis of lower limb DVT in UK hospitals and that
venography is used in only a minority of departments as the principal diagnostic
technique.

None of the three available methods are 100% accurate for detecting calf vein DVT,
however for the results of this study to be more accurate we should have employed a
second diagnostic modality to use in conjunction with duplex ultrasound. The
introduction of an invasive investigation in this study may however have reduced patient
recruitment and increased complications. To avoid this the use of the second modality to
assess ‘quality control’ of duplex may have been more feasible.
v. Study conclusions

The results from this study suggested that there was a significant difference between post-operative DVT rates for thigh versus knee-length GCS, there was an improved patient satisfaction with knee-length GCS and that the ‘single protocol’ improved prophylactic compliance. However, due to the borderline power (83%) and limitations in terms of stratified randomisation and calf vein diagnostic techniques, the differences between stocking groups may or may not be real. Further studies would need to undertaken to test the study hypothesis,

*provided LMWH is given to all patients,*

*thigh length anti-embolic stockings are equal to knee-length of the same design in the prevention of post-operative deep vein thrombosis*.

Or to test the hypothesis generated by this study that thigh-length GCS may be better at preventing post-operative DVT than knee length GCS of the same compression profile.

As far as the assessment of patient satisfaction; there was a significant difference for knee length GCS, but further validation of the questionnaire and again further studies would be required to evaluate my findings more thoroughly.

The Single protocol was found to improve the compliance of thromboprophylaxis in surgical patients, however this was only audited (before the randomised trial) in breast, gastrointestinal surgery, vascular and urology because of the reluctance of neurosurgery and orthopaedic specialists to use this protocol at the time of this study. The closing of the audit cycle was, in this case performed by re-auditing only 34 patients (figure 4g).

Therefore a further evaluation of the single protocol is required and was not performed immediately after the trial completion due to time constraints. The Single protocol
became the trust guideline and was later re-audited two years after performing and ‘writing-up’ of this study. This has now been completed in 2006 and once again the DVT prophylaxis across the trust has become disparate and inadequate with an overall surgical compliance rate of 33% for adequate VTE prophylaxis in line with the international guidelines (Nicolaides et al 2001). The compliance rate in medical patients was worse at 8%, giving an overall compliance rate for patients staying in Charing Cross Hospital was 19%. We have therefore, in conjunction with the Picker Institute (Oxford, UK) begun to set up a second study investigating the effect of patient education on VTE prophylactic compliance in hospital.

The current methods of staff education, repeated audit and clinical governance enforcement of the hospital single protocol have continued. Recent rewriting of the Single protocol for the Hammersmith Hospitals NHS Trust has taken place in conjunction with the department of Clinical Governance. A consensus from medical, anaesthetic, haematological and surgical consultants across the trust has been sort and once again achieved, with the necessary adjustments made to the protocol published on the trust intranet. The department of Clinical Governance will audit the VTE prophylaxis at six monthly intervals with the aim of maintaining prophylaxis compliance.

**Additional references**
