Report of the independent expert working group on the prevention of venous thromboembolism in hospitalised patients

A report to Sir Liam Donaldson
Chief Medical Officer
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Description: The Government established an independent expert working group (EWG) to report to the Chief Medical Officer on how current best practice and guidance on managing VTE could be promoted and implemented, and on what resources might be needed to support delivery of any strategy through existing structures. This is the EWG's report.

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The death of patients unnecessarily from venous thromboembolism (VTE) led to the publication of a Health Committee report and the Government’s response, both in 2005. I believe that 2005 will, therefore, be seen as a turning point.

VTE has for many years been a Cinderella issue, and it is not by accident that VTE is known internationally as the silent killer. The Health Committee and the Government recognised that the lack of public awareness about the dangers of VTE was not due to a lack of understanding of what was good practice. In fact, we owe much of what we know today about the prevention and management of VTE to the pioneering work carried out in the NHS in the 1970s and 1980s.

Clear benefits have been established for preventive measures in both surgical and medical patients. I wrote to all doctors in July 2005 informing them of good practice guidance that existed at that time. What was missing was the implementation of good practice.

In 2005, therefore, the challenge was how to encourage widespread adoption of current knowledge in the prevention and management of VTE. The Government response made it clear that much needed to be done and that there were too many preventable deaths from VTE in hospitalised patients. While more data were needed, the evidence suggested that in England around 25,000 people a year died from VTE in hospitals alone. We recognised that there was no systematic approach to identifying and treating those patients at risk from VTE in hospitals and that there was significant room for improvement.

As a result, the Government established an independent expert working group to report to me on how current best practice and guidance could be promoted and implemented, and on what resources might be needed to support delivery of any strategy through existing structures.

I am grateful to have received the report and recommendations of the VTE expert group from Dr Anita Thomas, the group’s Chair. I would like to thank Dr Thomas and her expert group colleagues for the thoroughness of the report and the hard work that went into delivering this to me within a challenging timescale.

The report contains a summary of existing evidence and good practice for medium and low-risk surgical patients and for medical patients. The recommendations in it are sensible and practicable and they will save lives. I commend it to all those involved in the prevention and treatment of VTE in hospitals. This report will complement forthcoming National Institute for Health and Clinical Excellence VTE guidelines on high-risk surgical and orthopaedic patients, due to be published during 2007. I have therefore written to all doctors informing them of the summary of best practice from existing guidance that I have received from the expert group.

VTE is a significant international patient safety issue and, since July 2004 when the Department of Health published Standards for Better Health, healthcare organisations have been charged with continuously and systematically reviewing all aspects of their activities that affect patient safety. Nevertheless, to date, the prevention of VTE has remained unaddressed in too many of our NHS hospitals. I expect this report to be a milestone in developing a systematic approach to preventing VTE in all healthcare systems.

In order to make progress on saving thousands of lives every year, I have also asked Dr Thomas to lead the next phase of this important work by chairing a small implementation working group. This group will develop a national risk assessment tool, and will also provide leadership both within the NHS and the wider healthcare sector in order to assess what needs to be done to ensure that a VTE risk assessment of every patient on admission to hospital becomes a reality.

Sir Liam Donaldson
Chief Medical Officer, England
Sir Liam Donaldson  
Chief Medical Officer, England  

Dear Sir Liam,

In July 2005, you asked me to chair the independent expert working group on venous thromboembolism in hospitalised patients. I was delighted to accept your offer. Venous thromboembolism (VTE) is an extremely important issue of patient safety. At the time of the Health Committee report, it was estimated that VTE caused in excess of 25,000 potentially preventable deaths per annum in UK hospitals – five times the estimated number of deaths each year from hospital-acquired infection. Recent estimates, based on an epidemiological model using extrapolation from European data in both hospital and community settings, suggest a figure of approximately 60,000 preventable deaths each year in the UK.

You had invited an impressive team of experts, including clinical, surgical and research specialists, together with representatives of professions, societies, the public and patients, in order to cover the broad spectrum of VTE-associated issues. You asked the VTE expert group to review and assess existing guidelines on the use of thromboprophylaxis and the effectiveness of interventions, to review current guidelines, seek areas of consensus and report back rapidly to you.

It soon became clear to us that improvement in the prevention and thromboprophylaxis of VTE in England was a broad issue affecting the continuum of care for patients across a diverse health sector that serves a population with a changing demographic profile. In order to best meet our terms of reference concerning hospitalised patients, we therefore took the opportunity to consider VTE in this wider context. We considered the primary, secondary and tertiary care interfaces, public and independent providers, as well as the changing structure of healthcare services.

This approach was later validated by the publication of the White Paper, *Our health, our care, our say*, which was issued halfway through the lifetime of this group. The expert group felt that there was a need to ensure that patients understand and ‘own’ their risk of VTE, that they were empowered to question healthcare professionals about their management, and that they were assured of an effective interface between primary care, institutional care and ongoing management (including prophylaxis) in the community. We recognised links to the White Paper, *Choosing Health*, since there are common risk factors for VTE, stroke, coronary heart disease and cancer. Although VTE was not specifically addressed in this White Paper, choice of a healthy lifestyle could reduce the risk of an individual suffering a VTE event.

The wellbeing of patients is at the heart of this report. The development of accessible information for patients and good communication with patients will be vital if we are to raise public awareness such that an individual understands their own risk profile for VTE and feels able to ask ‘What action is being taken to minimise my risk of VTE in hospital?’

The expert group has focused on assessment of risk for the individual patient, this being a combination of the risk profile of the individual and particular planned procedures or interventions.

It is the role of the National Institute for Health and Clinical Excellence (NICE) to provide national guidance on promoting good health and preventing ill health, and we have worked closely with NICE since we convened. It is our view that the VTE group’s analysis of existing guidelines for orthopaedic and high-risk surgical patients could be seen as part of the evidence that NICE will consider as part of its consultation on VTE guidelines for patients undergoing orthopaedic surgery and other high-risk procedures. The expert group is willing to meet again when NICE begins this consultation, in order to revisit our analysis of existing guidelines and advise the Department on its response.¹

¹ At the Department’s request, the group met on 1 November 2006 and provided advice to the Department.
VTE is a common event in medical patients, and protocols for risk assessment of VTE are significantly less established for medical than for surgical patients; thus, there is the greatest need for a systematic approach for this group, and the expert group therefore makes recommendations for this group of patients.

Our report makes recommendations concerning a systematic and integrated approach to VTE that can be implemented easily. These recommendations are made for all patients in our increasingly diverse healthcare system in primary, secondary and tertiary settings. The recommendations cover the continuum of patient care provided by multidisciplinary teams in primary, secondary and tertiary care.

We also make recommendations concerning local quality control and audit, national quality assurance and impact evaluation, and the education of healthcare professionals. In addition, we comment on the limitations of the current research and health statistics evidence base that might be considered in future work.

This report and recommendations on the prevention and treatment of VTE in hospitalised patients has been made possible by the dedication and enthusiasm of all the members of the VTE expert group over the last eight months. Excellent work was done by three subgroups examining guidelines, interventions, and systems and processes.

We have worked closely with colleagues at the Healthcare Commission, which is now developing an audit strategy for VTE. We have met with the NHS Commercial Directorate, which will now ensure that all contracts for NHS work with the independent sector make explicit reference to the need to meet the Healthcare Commission’s quality assurance standards. We have engaged directly with the independent sector, which is also keen to establish a systematic approach for all aspects of VTE in all care environments.

The Government response to the Health Committee report states: ‘Once the independent expert working group has assessed the current guidance on VTE, the Department will ask that the Healthcare Commission look to seek conformity with this good practice guidance and signal that it intends to include VTE as part of its annual inspection guidance.’

As a result of our contact with the healthcare professional education sector, the Academy of Medical Royal Colleges and Faculties has agreed to include thromboprophylaxis in the new Foundation curriculum for postgraduate medical education and has committed to developing specialist curricula for postgraduate medical training that include VTE-related content appropriate to the specialty.

We have also made contact with Connecting for Health, which will be important in any systemic work on implementation of a comprehensive VTE strategy across the NHS, particularly in respect of clinical knowledge, process and safety.

All stakeholders with whom we have engaged in the course of this consultation have displayed unanimous recognition of the fact that VTE is a serious issue requiring immediate attention where rapid progress can be made in improving patient safety.

I understand that the work of the expert group and this report represent a unique initiative internationally, in that it considers the structures and processes required to deliver a better outcome for patients in relation to VTE, and recommends an evaluation strategy based on health outcomes for patients. It is fitting that this work and report originate in the UK, since much original research on VTE and the modern era of understanding the prevention and treatment of VTE began with work in the NHS in the 1970s.

I hope that this report follows in that tradition and I commend to you this report of the VTE expert working group and its recommendations.

Anita Thomas
Chair, independent expert working group on the prevention of VTE in hospitalised patients
July 2006
Chapter 1

Recommendations

1.1 The VTE expert group has identified four existing guidelines on the treatment and prevention of VTE that we consider to represent best practice. A summary of key points of convergence in existing guidelines is presented at Annex 1 as recommendations for the management of surgical and medical patients.

1.2 There is a huge volume of evidence generated from studies in surgical patients relating to the natural history, pathophysiology, diagnosis, screening, and appropriateness of surrogate end points and prevention of VTE in these patient populations. It is this evidence base that allows us to reach conclusions about defining risk factors, risk populations and the benefits of thromboprophylaxis.

Systems, processes and knowledge base

1.3 The VTE expert group recommends:

- a documented mandatory VTE risk assessment of every hospitalised patient on admission
- this VTE risk assessment be embedded within the Clinical Negligence Scheme for Trusts (CNST)
- improvement of public and professional understanding of VTE at a national level, through improved communication of information to patients and the public, accompanied by improved and coordinated programmes of professional education
- establishment of VTE demonstration centres with an expanded role addressing demonstration of best practice, in order to inform development of comparable local systems in care networks and institutions. Such VTE demonstration centres would work together to develop a national risk assessment strategy, local quality control measures, audit of local practice, and would provide centralised educational material to support local educational programmes (eg working with the National Centre for Anticoagulation Training)
- core standards be set by the Department of Health for the NHS and independent sector in order to ensure that there is ultimately 100% compliance with the requirement for risk assessment of each and every adult admitted to hospital in England. These should be articulated in Standards for Better Health for the NHS and in Independent health care: national minimum standards
- compliance with such standards be monitored by the Healthcare Commission through its assessment and inspection procedures. This would form part of an institution’s self-assessment, with a separate analysis by the Healthcare Commission to test the validity of these responses
- the Department of Health refers responsible healthcare institutions that have no protocols for mandatory assessment and documentation, or have incomplete implementation of risk assessment, to the new expanded local thrombosis demonstration centres for further discussion and advice regarding best practice
- evaluation of the impact on patients and the public of any future VTE strategy and associated implementation, including:
  - the development of a systematic approach to ensuring compliance with national quality assurance standards
  - a communication strategy to promote better understanding
  - a refinement of VTE-related health outcome measures (better VTE ‘metrics’), and
  - improvement in public and patient awareness and provision of guidelines about VTE risk (to include development of the existing VTE web pages on the Department’s website at www.dh.gov.uk/vte)
Thromboprophylaxis strategy

1.4 The VTE expert group recommends that

- **all medical patients** should, as part of a mandatory risk assessment, be considered for thromboprophylaxis measures; in particular, patients likely to be in hospital for longer than four days and with reduced mobility, with either severe heart failure, respiratory failure (due either to exacerbation of chronic lung disease or pneumonia), acute infection, inflammatory illness or cancer (with additional risk factors for VTE) should be considered for the following regime:
  - heparins (both unfractionated and low-molecular-weight forms) are effective preventive treatments. Low-molecular-weight heparins are the preferred prophylactic method
  - aspirin is not recommended for thromboprophylaxis in medical patients
  - mechanical methods of prophylaxis have not to date been appropriately evaluated in acutely ill medical patients, and thus are not recommended at present

- **all high-risk surgical/orthopaedic patients** should be managed according to the available evidence. Publication of the NICE clinical guideline on the prevention of venous thromboembolism in patients undergoing orthopaedic surgery and other high-risk procedures is scheduled for April 2007

- **intermediate-risk surgical patients** or those with concomitant medical conditions should, as part of a mandatory risk assessment, be considered for the following thromboprophylaxis measures:
  - graduated compression stockings combined with heparins (both unfractionated and low-molecular-weight forms)
  - aspirin is not recommended for thromboprophylaxis in intermediate-risk surgical patients

- **low-risk surgical patients** do not require specific prophylaxis other than early mobilisation on account of duration or nature of the surgical procedure, unless other factors are present which increase overall risk and thus place them in intermediate or high-risk categories:
  - aspirin is not recommended for thromboprophylaxis in low-risk surgical patients
Chapter 2
VTE epidemiology and future evaluation and improvement of healthcare

Epidemiology

2.1 VTE comprises deep vein thrombosis (DVT), pulmonary embolus (PE) and the related sequelae of post-thrombotic syndrome (PTS) and pulmonary hypertension (PH).

2.2 The epidemiology of VTE is described below in two ways: the first approach is based on the number of diagnosed cases and the second approach is based on epidemiological modelling. The first approach, based on numbers diagnosed, is limited and may represent a significant underestimate of true incidence and prevalence of VTE for three reasons: the silent nature of the disease and difficulty making the diagnosis, inability to take into account undiagnosed clinical disease and clinical sequelae (including recurrence, PTS, PH and sudden death from untreated or undiagnosed disease), and the use of region-specific rates for the country of origin of the study rather than true countrywide data. Such representative and comprehensive data do not yet exist but are necessary for the evaluation of the impact of preventive strategies and for public health planning and cost assessment.

2.3 The second approach uses epidemiological modelling. Most deaths due to PE occur without antecedent clinical signs of thrombosis, and less than 10% of patients with autopsy-detected PE have a definitive diagnosis of PE that was made during the lifetime of the patient. In addition, only 29% of patients who survive an initial embolic event are diagnosed with PE. These data indicate that it is neither practical nor feasible to identify all VTE cases within healthcare systems. Modelling can provide estimates of the total burden of disease (diagnosed and undiagnosed cases, including sudden deaths).

2.4 One example of epidemiological modelling and resultant estimates of diagnosed and undiagnosed clinical burden of VTE using EU and UK-specific data is described briefly below. The VTE Impact Assessment Group in Europe (VITAE) model was developed by clinical and epidemiological thrombosis specialists working across Europe and the US and used a comprehensive set of inputs to derive, for each country, estimates of total VTE events (DVT, PE, PTS, PH and death) and expected numbers of prophylaxis users in each country, together with related complications and associated costs.

2.5 The total annual burden of VTE across the 25 member states of the EU (population of 454 million) was estimated to be 640,000 symptomatic deep-vein thromboses (DVT) and 383,000 pulmonary emboli (PE). VTE-related deaths were estimated at 480,000 annually. Of these deaths, 34,450 (7%) patients had been diagnosed with VTE and treated, 163,050 (34%) were estimated to be sudden fatal PE, and 281,000 (59%) followed undetected PE. The annual population death rate from VTE was just over 0.1%. In the UK, with 60 million inhabitants, this equates to over 60,000 deaths annually.

2.6 The majority of deaths were sudden or unexpected and occurred prior to any therapy being commenced. Therefore, the impact of appropriate preventive therapy on morbidity and mortality could be substantial.

Future evaluation and improvement of healthcare

2.7 In order to measure the impact of any strategy to prevent VTE in hospitalised patients in England, it is important to establish baseline metrics for measuring the success of any VTE strategy. We have a number of sources of data collection to consider. However, because of under-reporting of VTE, these data are not sufficiently robust to enable secure conclusions to be drawn.

- We urge the Department of Health to initiate research to establish an accurate measure of the number of deaths from VTE both in hospitals and in the wider community.
2.8 The key sources of data available are:

- **General Practice Research Database (GPRD)** (www.gprd.com)
  The GPRD is a large, UK-wide computerised longitudinal database of anonymised medical records in primary care. Data are available from over 3 million active patient records.

- **Hospital Episode Statistics (HES)** (www.hesonline.nhs.uk)
  HES is a large database containing personal, medical and administrative details at patient-record level of all individuals admitted to and treated in NHS hospitals in England. HES links with the Office for National Statistics official death records for numbers of episodes that result in death within 30 days.

  ONS publishes the number of deaths by cause, using the International Classification of Diseases (ICD-10).

2.9 The main findings from these sources are that:

- the number of persons on the GPRD with VTE has been decreasing since 1996.
- the number of persons on the GPRD with PE has been decreasing since 1996.
- the number of persons on the GPRD with DVT has been decreasing since 1996.
- the number of persons on the GPRD with VTE and pulmonary hypertension varied between 1996 and 2003 and has been increasing since.
- the number of persons admitted to hospital with any diagnosis mentioning VTE was around 74,000 in 2004/05, a 1% decline on the previous year. A large proportion of these were emergency admissions (86%).
- in 2003/04, there were around 21,000 episodes of hospital care with any diagnosis mentioning VTE that resulted in a registered death on the ONS death database.
- ONS mortality statistics for VTE-related conditions show a variable number of deaths since 2001, with the lowest figure of around 6,900 deaths in 2004.

2.10 In addition, data are available from the **VERITY registry**. VERITY is a UK, prospective observational registry established in 2001 to develop and improve the management of patients with VTE. Ninety hospitals with outpatient treatment facilities in the UK are enrolled in VERITY. The total number of patients enrolled is 39,199; there are 41,766 VTE episodes and 14,663 follow-up episodes recorded, making this the second largest VTE registry in the world. VERITY data offer a unique insight into risk factors for symptomatic VTE in UK hospitals enrolled in VERITY.

2.11 Findings are published annually. The registry records patient demographics, diagnostic strategies and treatment for patients presenting with a suspected VTE to hospitals with an outpatient treatment facility. Outpatient management of patients with suspected VTE was a major development, and the ultimate aim is to facilitate ‘benchmarking’ for VTE (ie the continuous systematic search for and implementation of best practice) in order to improve patient care.

2.12 The last VERITY data analysis in 2005 described findings on 27,179 patients, including 6,124 patients with a final diagnosis of VTE. The database included information on over 1,400 hospitalised patients who developed VTE during a medical inpatient stay, or following surgery, and 800 patients with cancer and 76 pregnant women who developed VTE.

2.13 VERITY data reveal that VTE occurs more commonly in older patients in this cohort: 59% of patients with VTE were aged between 50 and 80 years. Three additional risk factors were strongly associated with VTE: a personal history of VTE, medical or surgical inpatient stay, and cancer.

2.14 Of those patients with a history of major surgery in the preceding four weeks presenting back to hospital with a suspected VTE, 31% were found to have suffered a VTE. The majority had undergone orthopaedic procedures, and the source of referral was out of hospital in 76% of cases.

2.15 Of 1,451 cancer patients investigated for VTE, 56% were found to have VTE. In contrast, of the 19,459 non-cancer patients, 25% had VTE. A two-fold higher incidence of VTE in cancer patients is in keeping with epidemiological estimates. In terms of absolute numbers, the most common forms of cancer (breast, prostate, colorectal and lung) have the highest number of cases of VTE, but the highest rates of VTE occur in patients with pancreatic, upper GI tract and CNS tumours.

2.16 Symptomatic VTE occurred in 79 pregnant women, with 61 cases of DVT and 18 of PE.
Chapter 3
VTE in the wider context

3.1 A number of VTE-related issues fall outside the initial remit of the expert working group but are referenced here in order to provide an overall context within which the work of the expert group is set. These issues concern immobility and travel-related VTE, inherited conditions predisposing to VTE, and VTE related to hormone treatment, pregnancy and the puerperium. In addition, mention is made here of the Department of Health’s Better Blood Transfusion initiative and supporting committee structure.

Immobility and travel-related VTE

3.2 A possible link between VTE, DVT and long-haul air travel was suggested by reports in medical journals in the 1950s and has aroused significant media interest in recent years. However, a direct link with air travel remains controversial, with no conclusive evidence to suggest that the aviation environment is a causative risk factor. More information on the cabin environment may be available in due course from a European research network. Recent evidence suggests that VTE may be associated with any form of long-distance travel (of four or more hours), whether by air, car, coach or train.

3.3 The exact cause of travel-related VTE is uncertain, but experts agree that immobility is a major risk factor, and observe that individuals with an adverse personal risk profile for VTE are those most likely to develop travel-related VTE.

The expert group endorses current recommendations that prolonged periods of immobility be avoided, and that simple exercise (such as getting up and walking around) be taken regularly, no matter what form of long-distance travel is undertaken. We also endorse the recommendation that thromboprophylaxis is not indicated routinely, unless travellers have a known susceptibility to VTE.

Inherited conditions predisposing to VTE

3.4 Ongoing research by a consortium of medical research scientists (the WRIGHT group) under the auspices of the World Health Organization, a summary report of which was published in December 2006, may resolve some of the current controversy. Initial UK data suggest that neither the lower oxygen availability nor the pressurised cabin atmosphere increases the risk of DVT. There are no scientific data to assess the prevalence of the suggested phenomenon of ‘e-thrombosis’. As with travel-related DVT, the expert group endorses the recommendation that people do not sit immobile for prolonged periods and that simple exercise be taken regularly.

Pregnancy and the puerperium

3.5 A number of inherited abnormalities predispose to development of venous thromboembolism. Consideration of the existence of these genetic thrombophilias is important in certain clinical situations (early onset spontaneous thrombosis, thrombosis in pregnancy, and recurrent thrombotic episodes with no obvious cause or at peculiar anatomical locations). However, there is no evidence that routine screening for such abnormalities in the general hospital population would provide any advantage and it is not recommended. Patients with known thrombophilias should be judged at higher risk of VTE in any assessment for prophylaxis.

3.6 PE remains the leading cause of maternal death in the UK. Successive reports have highlighted failure to recognise risk factors for VTE and failure to employ adequate thromboprophylaxis.

3.7 Guidelines on thromboprophylaxis for women at risk of VTE during pregnancy, labour and after normal vaginal delivery were issued by the Royal
College of Obstetricians and Gynaecologists (RCOG) in January 2004 (www.rcog.org.uk, Green-top guideline no. 37).

**Oral contraception and VTE related to hormone treatment**

3.8 The use of the combined oral contraceptive pill and hormone replacement therapy increases the risk of thrombosis. Use of such agents should be considered in risk assessment and appropriate thromboprophylaxis should be provided.

3.9 Hormonal contraceptive methods are used by 29% of women in the UK aged 16–49 years. Use of combined oral contraception is associated with an increased risk of VTE. Less is known of the risks of VTE with progestogen-only methods. The relative risk of venous thromboembolism is increased with combined oral contraceptive use. Nevertheless, the rarity of venous thromboembolism in women of reproductive age means that the absolute risk remains small (1–15 in 100,000). Combined oral contraceptives containing levonorgestrel or norethisterone are associated with a lower risk of venous thromboembolism than those containing desogestrel or gestodene.

3.10 Guidelines were issued by the RCOG in October 2004 (www.rcog.org.uk, Green-top guideline no. 40).

**DH Better Blood Transfusion arrangements**

3.11 The Health Committee report and recommendations on VTE comment positively on the Department of Health’s committee structure and teamwork related to blood transfusion.

3.12 The VTE expert group was not tasked with examining the relationship of the work on Better Blood Transfusion (BBT) and the prevention of VTE in hospitalised patients. However, during our consideration of recommendations regarding improved systems and processes for the treatment and prevention of VTE in hospitalised patients, we found some helpful examples in the BBT work.

3.13 Three of the five main processes supporting BBT work are directly relevant to our recommendations. These are:

- ensuring that the work is an integral part of NHS care
- providing better information to patients and the public sector
- regular review/monitoring of the work and supporting structures and systems

3.14 We suggest that the Department may wish to take account of the lessons learned in implementing BBT, as work on improvement in the treatment and prevention of VTE in hospitalised patients is taken forward.
Chapter 4
Indicative resources

Resources required for the introduction of a systematic approach to the treatment and prevention of VTE in hospitalised patients

4.1 Our terms of reference asked us to indicate what resources might be needed to support delivery of any VTE strategy through existing structures. We have recommended the establishment of VTE demonstration centres with an expanded role addressing demonstration of best practice, in order to inform development of comparable local systems in care networks and institutions. Such VTE demonstration centres would work together to develop a national risk assessment strategy, local quality control measures, audit of local practice, and would provide centralised educational material to support local educational programmes (eg working with the National Centre for Anticoagulation Training).

4.2 Such demonstration centres would need to be based within hospitals or networks with an existing track record of excellent VTE management. In providing an estimate of potential costs and benefits, we have used the example of the establishment of one VTE demonstration centre for two years. Leadership will be needed for demonstration centres, and we provide estimates for the provision of a national VTE consultant lead and a VTE project manager.

4.3 We suggest that the development of a VTE demonstration centre in an expanded role over two years will cost around £240,000; provision of a VTE consultant lead and a VTE project manager will cost approximately £150,000; and central development of educational resources £60,000.

4.4 We were not asked to look at the wider costs/savings of every hospital risk assessing all their hospitalised patients for VTE. It will be for the Department of Health to look at this level of detail as it implements our recommendations. However, we are aware from discussions with the NHS Litigation Authority (NHSLA) that in the last 10 years around £68 million has either been paid or is outstanding for VTE claims. The amount paid to date represents 1.9% of all clinical negligence claims where the allegedly negligent act occurred during this period. As a result, there is likely to be a clear cost benefit to NHS trusts in reduced Clinical Negligence Scheme for Trusts (CNST) contributions if VTE is managed effectively.
5.1 This report presents a summary of the expert group’s work and includes recommendations on the development of a mandatory risk assessment of each and every hospitalised patient, recommendations for thromboprophylaxis based on a consensus of existing guidelines, and a systematic and coordinated national programme of patient, public and professional education.

5.2 The expert group recommends that these initiatives be supported by the development of VTE demonstration centres to promote best practice, with an expanded role to include local quality control, audit and the development of educational resources and programmes for multiprofessional VTE clinical teams. The group also recommends a set of national standards to support local quality control and national quality assurance, assured by the Healthcare Commission, and that a VTE risk assessment be embedded within the CNST. Finally, the expert group recommends an evaluation of the outcome of these actions on patient health and wellbeing.
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Annex 1
Analysis of points of convergence drawn from existing guidelines

1 Major general surgery (including gynaecological and cancer surgery)
- Heparins (both unfractionated and low-molecular-weight forms) are effective preventive treatments.
- Mechanical methods of prophylaxis are proven to prevent deep-vein thrombosis; combined with unfractionated heparin, mechanical methods show a synergistic efficacy effect. Mechanical methods alone as first-line preventive treatment are the preferred choice when antithrombotics are contraindicated.

2 Major orthopaedic surgery
Total hip replacement
- Low-molecular-weight heparins are the most effective preventive treatment following hip replacement surgery, started in the peri-operative period and continued for at least 10–12 days. This may require an out-of-hospital treatment period, improved efficacy being shown if the treatment is continued for an extended out-of-hospital period.
- Aspirin shows limited efficacy in hip fracture patients, but should not be considered as an effective preventive treatment after total hip replacement surgery.
- Mechanical methods should not be prescribed as first-line preventive treatment alone, but are the preferred choice when antithrombotics are contraindicated.

Total knee replacement
- Low-molecular-weight heparins are the most effective preventive treatment after knee replacement, started in the peri-operative period and continued for 10–12 days; this may require an out-of-hospital treatment period.
- Aspirin should not be considered as an effective preventive treatment after total knee replacement surgery.

3 Medical patients (including heart failure, acute respiratory disease, acute infectious disease and cancer)
- Heparins (both unfractionated and low-molecular-weight forms) are effective preventive treatments. Low-molecular-weight heparins are the preferred preventive treatment because of a superior adverse-effect (bleeding) profile.
- Mechanical methods of prophylaxis are unproven in acutely ill medical patients.

Hip fracture surgery
- There is limited evidence on the safety and efficacy of pharmacological or mechanical preventive treatment.
- Aspirin shows limited efficacy in hip fracture patients, but should not be considered as an effective preventive treatment after any major orthopaedic surgery.
Annex 2

Analysis of existing VTE guidelines

The aims and processes for this guidelines review were developed and provided to the expert subgroup as a programme outline, detailing the objectives, the criteria for guideline inclusion and the approach to assessing study inclusion.

Aims
The subgroup identified its aims as:

- identify current guidelines for VTE prevention
- document areas of agreement/disagreement between guidelines
- give summary recommendations for VTE prophylaxis for hospitalised patients

Process
Guidelines were identified by a systematic MEDLINE review. Irrelevant manuscripts were discarded by the subgroup and accepted guidelines were reviewed and areas of agreement/disagreement summarised in four areas:

- general surgery
- gynaecological surgery
- orthopaedic surgery
- medical inpatients

A summary document was drafted and informed the agenda for a telephone conference, which took place on 20 December 2005.

1 Guideline search

Search strategy

In addition, bibliographies of certain journal articles were searched by hand to locate additional inclusions. The relevance of the articles was assessed with the use of a hierarchical approach based on title, abstract and then review of the published paper.

Guideline selection
The subgroup Chair and his assistant evaluated independently papers for possible inclusion, and any disagreements were resolved by discussion. The complete search was made available to the rest of the subgroup members for their review.

Results
The process of study selection is outlined below. Multiple searches were conducted, to ensure appropriate and specific inclusion of potential articles. The final search is shown in Appendix 1 of this Annex.

The search yielded 624 citations. After their titles were scanned, 32 potentially eligible papers remained. After review of abstracts, an additional nine papers were excluded because they contained guidelines relating to cardiology, another 11 papers were not guidelines, and four papers were not related to VTE. After review of the full article, an additional five papers were excluded because: they were earlier versions of the same guideline (n=2), they were treatment guidelines (n=1), they were related to childhood thrombosis (n=1), or stroke (n=1). One guideline on elderly patients was excluded as it offered a summary of the American College of Chest Physicians (ACCP) guidelines only. This left two guidelines (search numbers 251 and 447) on the prevention of VTE in hospitalised patients from the formal search.

Three additional inclusions were identified through searching by hand. One guideline was identified from the British Committee for Standards in Haematology (BCSH) Guidelines on the use and monitoring of
heparin (2006). Thus, the six guidelines for review are:

Identified by electronic database search:


Identified by hand search:


2 Guideline review

Data extraction

Information on the therapeutic areas specified within the programme outline (namely general surgery, gynaecological surgery, orthopaedic surgery and medical inpatients) was extracted from the guidelines.

The desired information, namely the specific recommendations for the prevention of venous thromboembolism, was abstracted from each guideline and confirmed by reviewer consensus and sent to the remaining subgroup members for verification.

Assessment of guideline content

The content of the six guidelines differs. The ACCP, ICS, BCSH and SIGN guidelines include a review of the evidence and provide formal recommendations for all four target patient groups. In contrast, the BOA guides to best practice for total hip and knee replacement are limited to joint arthroplasty and do not provide a review or formal recommendations.

Assessment of guideline quality

Although no formal assessment of the quality of the guidelines was conducted, specific methodology has been described in the literature that allows a formal guideline quality assessment.2,3,4

Three obvious ways to assess quality include:

- reporting the type of professionals and stakeholders involved in the development process
- the strategy to identify primary evidence
- an explicit grading of recommendations according to the quality of supporting evidence

Of the six guidelines identified in the current search, two do not appear to fulfil these criteria. The BOA guides to best practice for total hip and knee replacement do not appear suitable for a quality assessment, because they contain no methodology, no formal evidence review and offer no graded recommendations.

Age of guidelines

Older guidelines, by definition, will not include up-to-date clinical evidence on the prevention of VTE. Considerable progress has been made in the last five years in a number of key clinical areas in the prevention of VTE, which warrants review and consideration. These advances include, for example, meta-analyses that provide reliable estimates of the rates of symptomatic VTE after orthopaedic surgery,5,6 a large randomised trial programme describing the efficacy and safety of fondaparinux,7 a large randomised trial that provides reliable data on the rate of fatal pulmonary embolism after surgery,8,9 and the reporting of three large, well-conducted randomised trials assessing heparin and fondaparinux in the prevention of VTE in acutely ill medical patients.10,11,12

The six guidelines were published between 1999 and 2006. They are listed here from the most recent: BCSH (2006); ACCP (2004); SIGN (2002); ICS (2001); BOA – hip (1999); BOA – knee (undated).

Grading of recommendations

The grading of recommendations in the ACCP, ICS, BCSH and SIGN guidelines follows a similar approach, and is based on the levels of evidence, ranging from the highest Grade A recommendation to a Grade C recommendation (or Grade D in the case of the SIGN guideline), with Grade A generally related to high-quality meta-analyses or randomised, controlled trials and Grade C based on high-quality systematic reviews or well-conducted case control or cohort studies.

The grade of recommendation also includes a grading of the level of evidence in the form of a number in the SIGN guideline, ranging from 1++ (representing high-quality meta-analyses) to 4 (representing expert opinion).
In the ACCP guideline, the additional number refers to the certainty that the benefits do, or do not, outweigh the risks, burdens and costs. A strong recommendation is given a Grade 1. If the magnitude of the benefits and the risks, burdens and costs is less clear, a weaker, Grade 2 recommendation is made (shown in detail in Table 1).

Comparison of recommendations for the prevention of venous thromboembolism

The recommendations provided within the ACCP, ICS, BCSH and SIGN guidelines are provided in detail below for each of the four therapeutic areas.

The main findings are summarised in Table 2, to allow cross-comparison.

Differences between the guidelines include:

- distinction between low, moderate and high-risk general surgery, most notably in the ACCP guideline (moderate and high risk are presented in Table 2)
- use of recommendations against an agent in ACCP (indicated in red in the table)
- formal recommendations for alternative approaches when heparins are contraindicated

General surgery

**Similarities**

All four guidelines provide similar levels of recommendation for heparin, both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH).

The BCSH guidelines were limited to heparins and therefore do not contain recommendations for mechanical methods. The ACCP and ICS guidelines offer similar recommendations for mechanical methods, with the ACCP suggesting a lower quality of evidence (1C). The SIGN guidelines recommend mechanical methods only in cases of heparin contraindication.

**Discrepancies**

The notable discrepancy is the recommendation for aspirin in the SIGN guideline, although the recommendation for the use of aspirin is only in cases of heparin contraindication.

**ACCP guideline**

The following text refers to the advice given in the ACCP guideline.

In low-risk general surgery adult patients who are undergoing a minor procedure, are 40 years of age or less, and have no additional risk factors, recommend against the use of specific prophylaxis other than early and persistent mobilisation (Grade 1C+).

**Moderate-risk**

General surgery patients are those patients undergoing a non-major procedure and are between the ages of 40 and 60 years or have additional risk factors, or those patients who are undergoing major operations and are <40 years of age with no additional risk factors. Recommend prophylaxis with low-dose unfractionated heparin (LDUH), 5000 U bid or LMWH ≤3400 U once daily (both Grade 1A).

**Higher-risk**

General surgery patients are those undergoing non-major surgery and are >60 years of age or have additional risk factors, or patients undergoing major surgery who are >40 years of age or have additional risk factors. Recommend thromboprophylaxis with LDUH, 5000 U tid or LMWH, >3400 U daily (both Grade 1A).

In high-risk general surgery patients with multiple risk factors, recommend that pharmacologic methods (ie LDUH, tid or LMWH, >3,400 U daily) be combined with the use of graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC) (Grade 1C+). In general surgery patients with a high risk of bleeding, recommend the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases (Grade 1A). In selected high-risk general surgery patients, including those who have undergone major cancer surgery, suggest post-hospital discharge prophylaxis with LMWH (Grade 2A).

**ICS guideline**

The following text refers to the advice given in the ICS guideline.

**Low-risk**

Patients (ie those without risk factors undergoing minor surgery): the data are insufficient to make any recommendations. On the basis of risk/benefit ratio and extrapolation from studies in moderate-risk patients, it is the practice in some countries to use graduated elastic compression stockings (GCS) in addition to early ambulation and adequate hydration.

**Moderate-risk**

Patients (ie those undergoing major surgery, aged over 40 years, without any additional risk factors): the use of low-dose heparin or LMWH are Grade A recommendations for all moderate-risk
patients. Alternative Grade A recommendations are: IPC used continuously until the patient is ambulant; GCS; or a combination of both. Further studies are needed to assess the effect of GCS and/or IPC in addition to pharmacological methods, and to assess the combined effects of different pharmacological methods such as heparin plus aspirin versus heparin alone. The use of dextran or aspirin is based on meta-analysis. However, dextran and aspirin are not the methods of choice in moderate-risk patients, because of their limited efficacy on DVT prevention, the anaphylactoid reactions and danger of cardiac overload associated with the former, the high dose of aspirin (1000–1500 mg per day) required and the fact that oral medications are not possible for several days in patients having abdominal surgery.

High-risk patients (ie those undergoing major surgery, aged over 60 years or with additional risk factors): all should receive prophylaxis as for moderate-risk patients (Grade A recommendation). In addition to single modalities, such as low-dose heparin or LMWH, combined modalities of pharmacological and mechanical methods should be considered, as they may be more effective (Grade B recommendation).

SIGN guideline
The following text refers to the advice given in the SIGN guideline.

The preferred methods of prophylaxis (because they reduce mortality as well as fatal PE) in patients undergoing major general or gynaecological surgery who are at significant risk of VTE are: sc low-dose UFH (5000 IU, 8–12 hourly) or sc LMWH (according to manufacturer’s instructions) (Grade A).

In patients undergoing major general or gynaecological surgery, GCS can be substituted for UFH or LMWH, when these agents are contraindicated (Grade A).

GCS can be combined with UFH or LMWH in patients undergoing general or gynaecological surgery who are at high risk due to the presence of multiple risk factors (Grade A).

In patients undergoing major general or gynaecological surgery, IPC followed by GCS can be substituted for UFH or LMWH, when these agents are contraindicated (Grade A).

Aspirin (150 mg/day orally, rectally or by nasogastric tube) is an alternative to UFH or LMWH, when these agents are contraindicated in patients undergoing major general or gynaecological surgery who are at significant risk of VTE (Grade A).

Intravenous dextran 40 or 70 is a possible alternative prophylaxis of VTE in high-risk patients undergoing major general or gynaecological surgery (Grade A).

BCSH guideline
The following text refers to the advice given in the BCSH guideline.

Patients undergoing major non-orthopaedic surgery should be considered for LMWH or UFH at the recommended prophylactic dose (Grade A).

Gynaecological surgery

Similarities
The guidelines provide similar levels of recommendation as per general surgery.

Discrepancies
The notable discrepancy is the recommendation for aspirin in the SIGN guidelines, although the recommendation for the use of aspirin is only in cases of heparin contraindication.

ACCP guideline
The following text refers to the advice given in the ACCP guideline.

For gynaecological surgery patients undergoing brief procedures of ≤30 minutes for benign disease, recommend against the use of specific prophylaxis other than early and persistent mobilisation (Grade 1C+).

For patients undergoing laparoscopic gynaecological procedures, in whom additional VTE risk factors are present, recommend the use of thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC or GCS (all Grade 1C). Recommend that thromboprophylaxis be used in all major gynaecological surgery patients (Grade 1A).

For patients undergoing major gynaecological surgery for benign disease, without additional risk factors, recommend LDUH, 5000 U bid (Grade 1A). Alternatives include once-daily prophylaxis with LMWH, ≤3400 U/d (Grade 1C+), or IPC started just before surgery and used continuously while the patient is not ambulating (Grade 1B).

For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, recommend routine prophylaxis with LDUH, 5000 U tid (Grade 1A), or higher doses of LMWH (ie >3400 U/d) (Grade 1A). Alternative considerations include IPC alone, continued until hospital discharge.
(Grade 1A), or a combination of LDUH or LMWH plus mechanical prophylaxis with GCS or IPC (all Grade 1C).

For patients undergoing major gynaecological procedures, suggest that prophylaxis continues until discharge from the hospital (Grade 1C).

For patients who are at particularly high risk, including those who have undergone cancer surgery and are >60 years of age or have previously experienced VTE, suggest continuing prophylaxis for two to four weeks after hospital discharge (Grade 2C).

ICS guideline

The following text refers to the advice given in the ICS guideline.

Low-risk patients may receive prophylaxis. GCS used in addition to early ambulation and adequate hydration are Grade C recommendations.

Moderate-risk patients: low-dose unfractionated heparin (5000 units 12 hourly), LMWH or IPC are Grade A recommendations. The addition of GCS based on extrapolation from studies in general surgery is a Grade C recommendation.

High-risk patients: low-dose heparin (5000 units 8 hourly) or IPC used continuously for at least five days are Grade A recommendations. The use of combined modalities should be considered in high-risk patients with cancer (Grade C recommendation).

SIGN guideline

The following text refers to the advice given in the SIGN guideline.

As per general surgery.

BCSH guideline

The following text refers to the advice given in the BCSH guideline.

As per general surgery.

Orthopaedic surgery

Similarities

All four guidelines provide similar levels of recommendation for heparin, both UFH and LMWH.

The ACCP and BCSH guidelines, the most recently published, provide recommendations for the factor Xa inhibitor, fondaparinux. ICS provide a Grade A recommendation for recombinant hirudin, a drug not widely used.

Discrepancies

The notable discrepancy is the recommendation for aspirin in the SIGN guideline with a Grade A recommendation, versus the ACCP Grade 1A against the use of aspirin.

ACCP guideline

The following text refers to the advice given in the ACCP guideline.

For patients undergoing elective total hip replacement (THR), recommend the routine use of one of the following three anticoagulants:

- LMWH (at a usual high-risk dose, started 12 hours before surgery or 12–24 hours after surgery, or 4–6 hours after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day)
- fondaparinux (2.5 mg started 6–8 hours after surgery), or
- adjusted-dose vitamin K antagonist therapy (VKA) started preoperatively or the evening after surgery (international normalisation ratio (INR) target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A)

Have not recommended the use of fondaparinux over LMWH and VKA, or the use of LMWH over VKA, because place a relatively low value on the prevention of venographic thrombosis, and a relatively high value on minimising bleeding complications.

Recommend against the use of aspirin, dextran, LDUH, GCS, IPC or foot pumps as the only method of thromboprophylaxis in these patients (Grade 1A).

For patients undergoing elective total knee replacement (TKA), recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (all Grade 1A).
Have not recommended fondaparinux over LMWH and VKA, or LMWH over VKA, because place a relatively low value on the prevention of venographic thrombosis and a relatively high value on minimising bleeding complications. The optimal use of IPC is an alternative option to anticoagulant prophylaxis (Grade 1B).

Recommend against the use of any of the following as sole methods of thromboprophylaxis: aspirin (Grade 1A); LDUH (Grade 1A); or VFP (Grade 1B).

For knee arthroscopy, suggest clinicians do not use routine thromboprophylaxis in these patients, other than early mobilisation (Grade 2B).

For patients undergoing arthroscopic knee surgery who are at higher than usual risk, based on pre-existing VTE risk factors or following a prolonged or complicated procedure, suggest thromboprophylaxis with LMWH (Grade 2B).

For patients undergoing hip fracture surgery (HFS), recommend the routine use of fondaparinux (Grade 1A), LMWH at the usual high-risk dose (Grade 1C+), adjusted-dose VKA (target INR, 2.5; INR range, 2.0 to 3.0) (Grade 2B), or LDUH (Grade 1B).

Recommend against the use of aspirin alone (Grade 1A).

If surgery will likely be delayed, recommend that prophylaxis with either LDUH or LMWH be initiated during the time between hospital admission and surgery (Grade 1C+). Recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (Grade 1C+).

ICS guideline

The following text refers to the advice given in the ICS guideline.

THR: adjusted-dose warfarin, LMWH, foot pump and recombinant hirudin are Grade A recommendations. 

TKR: LMWH is a Grade A recommendation, superior to warfarin and UFH, although the residual DVT frequency remains high. Further studies are required for mechanical methods.

HFS: there are too few comparative studies in this group to make secure recommendations. The studies that exist are consistent with those from THR, from which recommendations could be reasonably extrapolated.

SIGN guideline

The following text refers to the advice given in the SIGN guideline.

Patients undergoing THR or TKR or other elective major orthopaedic surgery should receive thromboprophylaxis: mechanical (GCS ± IPC, foot pumps), pharmacological (aspirin or heparin or warfarin), or both (Grade A).

HFS: early surgery (within 24 hours) is recommended where possible, to reduce the risk of DVT and fatal PE after hip fracture (Grade C).

Mechanical prophylaxis (IPC or foot pumps) should be considered, to reduce the risk of asymptomatic DVT after hip fracture. There is no evidence for the efficacy of GCS in hip fracture patients (Grade A).

All patients with hip fracture should receive aspirin (150 mg orally, started on admission and continued for 35 days) unless contraindicated (Grade A).

Heparin should be reserved for selected patients at high risk of VTE after hip fracture due to multiple risk factors or contraindications to routine mechanical prophylaxis and/or aspirin (Grade A).

BCSH guideline

The following text refers to the advice given in the BCSH guideline.

Patients undergoing major elective orthopaedic surgery should be considered for LMWH (or fondaparinux) at recommended prophylactic dose for at least 7–10 days (Grade A).

Thromboprophylaxis with LMWH (or fondaparinux) at recommended prophylactic dose should be considered for hip fracture patients (Grade A).

Other/general medical inpatients

Similarities

All four guidelines provide Grade A recommendations for LMWH.

UFH carries a Grade A recommendation in the ACCP and ICS guidelines only. The ACCP and the SIGN recommendations reflect the limited evidence for mechanical methods in medical patients, with Grade 1C and C respectively.

ACCP guideline

The following text refers to the advice given in the ACCP guideline.
In acutely ill medical patients who have been admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, recommend prophylaxis with LDUH (Grade 1A) or LMWH (Grade 1A).

In medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant prophylaxis, recommend the use of mechanical prophylaxis with GCS or IPC (Grade 1C+).

ICS guideline
The following text refers to the advice given in the ICS guideline.

These guidelines cover patients with acute medical illnesses, such as heart failure, chronic respiratory disease or severe chest infection, as well as critically ill patients. Prophylactic low-dose subcutaneous unfractionated heparin or high-dose LMWH prophylaxis are Grade A recommendations in these general medical patients with disease-related risk factors and/or additional patient-related risk factors (Grade A recommendation).

Two large, randomised, double-blind controlled studies have provided strong evidence that chronic respiratory disease and congestive heart failure significantly increase predisposition to DVT. Single daily doses of high-dose LMWH have proven to be most effective for prophylaxis in these patients and are a Grade A recommendation.

There are no reported trials of mechanical methods of prophylaxis, such as GCS or IPC, in medical patients. Although there is no reason to believe that such methods would be less effective than in surgical patients, further studies are needed before evidence-based recommendations can be made.

While the risk of VTE increases with age, age of more than 65 years does not in itself constitute sufficient risk to merit routine prophylaxis in medical geriatric patients in the absence of other risk factors.

SIGN guideline
The following text refers to the advice given in the SIGN guideline.

In general medical patients who are immobilised in hospital due to acute illness, especially those with heart failure, respiratory failure, infections, diabetic coma, inflammatory bowel disease, or nephritic syndrome, or who are in intensive care, prophylaxis of VTE with low-dose UFH or LMWH should be considered. LMWH carries a lower risk of bleeding (Grade A).

In general medical patients at significant risk of VTE, in whom heparin is contraindicated, GCS may be considered (Grade C).

Mini-dose warfarin is recommended for prophylaxis of thrombosis in cancer with central venous catheters (Grade A).

Low-dose warfarin is recommended for prophylaxis of thrombosis during chemotherapy in stage IV breast cancer (Grade A).

BCSH guideline
The following text refers to the advice given in the BCSH guideline.

Recommendation: medical patients determined to be at high risk of VTE should be considered for thromboprophylaxis with LMWH at recommended prophylactic dose (Grade A).

3 Summary
A preliminary consensus was reached, resulting in this Guideline Assessment Document.

The main findings are:
- only four sets of guidelines were produced by systematic review with formal evidence-based graded recommendations
- general and gynaecological surgery: all four sets of guidelines provide similar levels of recommendation for heparin, both UFH and LMWH
- orthopaedic surgery: all four sets of guidelines provide similar levels of recommendation for heparin, both UFH and LMWH. The notable discrepancy is the recommendation for aspirin in the SIGN guideline with a Grade A recommendation, versus the ACCP Grade 1A against the use of aspirin
- medical inpatients: all four sets of guidelines provide Grade A recommendations for LMWH
- there were significant differences between the guidelines with regard to levels of risk and interventions, the main difference being the use of heparin or aspirin in high-risk orthopaedic surgery
- risk assignment and interventions for medical patients are even less well defined than for surgical patients
Table 1. ACCP approach to grades of recommendations*

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Methodological strength of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Clear</td>
<td>Randomised controlled trials (RCTs) without important limitations</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C+</td>
<td>Clear</td>
<td>No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1B</td>
<td>Clear</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws**)</td>
<td>Strong recommendation; likely to apply to most patients</td>
</tr>
<tr>
<td>1C</td>
<td>Clear</td>
<td>Observational studies</td>
<td>Intermediate-strength recommendation; may change when stronger evidence is available</td>
</tr>
<tr>
<td>2A</td>
<td>Unclear</td>
<td>RCTs without important limitations</td>
<td>Intermediate-strength recommendation; best action may differ, depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2C+</td>
<td>Unclear</td>
<td>No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies</td>
<td>Weak recommendation; best action may differ, depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2B</td>
<td>Unclear</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws)</td>
<td>Weak recommendation; alternative approaches likely to be better for some patients under some circumstances</td>
</tr>
<tr>
<td>2C</td>
<td>Unclear</td>
<td>Observational studies</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

* Since studies in categories B and C are flawed, it is likely that most recommendations in these classes will be at level 2. The following considerations will bear on whether the recommendation is Grade 1 or Grade 2: the magnitude and precision of the treatment effect; patients’ risk of the target event being prevented; the nature of the benefit and the magnitude of the risk associated with treatment; variability in patient preferences; variability in regional resource availability and healthcare delivery practices; and cost considerations (see Table 2). Inevitably, weighing these considerations involves subjective judgement.

** These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow up.
### Table 2. Guideline comparison

Please note: coloured text in the table indicates a recommendation against the use of an agent/method.

<table>
<thead>
<tr>
<th>General*</th>
<th>Gynaecology</th>
<th>Orthopaedic (THR/TKR)</th>
<th>Orthopaedic (HF)</th>
<th>Medical patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Grade</td>
<td>Agent</td>
<td>Grade</td>
<td>Agent</td>
</tr>
<tr>
<td>ACCP</td>
<td>LMWH and UFH</td>
<td>1A</td>
<td>LMWH</td>
<td>1C**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1C</td>
<td>UFH</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1B</td>
<td>IPC</td>
<td>1A</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ICS</td>
<td>LMWH and UFH</td>
<td>A</td>
<td>LMWH</td>
<td>A</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SIGN</td>
<td>LMWH and UFH</td>
<td>A</td>
<td>LMWH</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Aspirin†</td>
<td>A</td>
<td>Aspirin†</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>GCS/IPC†</td>
<td>A</td>
<td>GCS†</td>
<td>A</td>
</tr>
<tr>
<td>BCSH</td>
<td>LMWH and UFH</td>
<td>A</td>
<td>LMWH</td>
<td>A</td>
</tr>
</tbody>
</table>

* Moderate and high-risk patients described
** Recommendation is 1A if malignant disease
# Only recommended for high-risk patients (multiple risk factors) and those with contraindications to mechanical methods and/or aspirin
† Recommended for those with contraindications to heparins
Risk and risk assessment for prophylaxis in surgery and acutely ill medical patients

Surgery

For surgery, the concept of low, moderate and high-risk procedures, coupled with the concept of at-risk patients because of, for example, age, previous history of VTE, or cancer, has been in the literature for many years.

The ACCP guideline provides four specific risk categories for surgery patients (low, moderate, high and very high) that are aligned with reported rates of VTE (split into four levels of importance: calf DVT; proximal DVT; clinical PE; and fatal PE, shown in Table 3). These allow specific risk profiles to be created according to the overall risk, and appropriate thromboprophylaxis to be recommended.

The ICS guideline offers a different approach, showing three risk levels (low, moderate and high) for four patient groups: general surgery, gynaecological surgery, obstetrics and medical patients (shown in Table 4). The recommendations for surgical and medical patients are based on assignment to these risk groupings.

Medical patients

Risk assignment and thromboprophylaxis recommendations for medical patients are not as well defined in the literature as for surgical patients. However, three large, well-designed, randomised, placebo-controlled studies have provided high-quality data showing the risk of VTE and have shown the efficacy and safety of thromboprophylaxis in well-defined groups of acutely ill, hospitalised and immobilised medical patients. These randomised studies have confirmed that hospitalised patients with acute medical conditions are at significant risk of VTE. The inclusion criteria and outcomes (clinically important VTE) are documented in Table 5.

Despite the consensus-group recommendations included in this review (that at-risk medical patients should receive thromboprophylaxis), there is currently no consensus as to which patients are at risk, and many patients may not receive appropriate thromboprophylaxis.

A recent review by an expert international panel attempts to synthesise the data from the literature for medical patients and provide a risk assessment model for VTE\(^1\) (see Table 6).

---

### Table 3. ACCP risk categories

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Surgery</th>
<th>Age</th>
<th>Additional risk factors</th>
<th>Calf DVT</th>
<th>Proximal DVT</th>
<th>Clinical PE</th>
<th>Fatal PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Minor</td>
<td>&lt;40</td>
<td>None</td>
<td>2%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>0.002%</td>
</tr>
<tr>
<td></td>
<td>Minor Non-major</td>
<td>40-60</td>
<td>Yes</td>
<td>10–20%</td>
<td>2–4%</td>
<td>1–2%</td>
<td>0.1–0.4%</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>&lt;40</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Non-major</td>
<td>&gt;60</td>
<td>+/-</td>
<td>20–40%</td>
<td>4–8%</td>
<td>2–4%</td>
<td>0.4–1.0%</td>
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<tr>
<td></td>
<td>Major</td>
<td>&lt;60</td>
<td>Yes</td>
<td></td>
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<td></td>
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<td>&gt;40</td>
<td>+/-</td>
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<tr>
<td></td>
<td>Major</td>
<td>&lt;40</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Non-major</td>
<td>&gt;40</td>
<td>Prior VTE, active</td>
<td>40–80%</td>
<td>0–20%</td>
<td>4–10%</td>
<td>0.2–0.5%</td>
</tr>
<tr>
<td></td>
<td>Major (hip</td>
<td>&gt;40</td>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arthroplasty,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hip fracture,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>major trauma,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>spinal cord)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

\(^{1}\) For medical patients.
Table 4. ICS risk categories

<table>
<thead>
<tr>
<th>Risk category</th>
<th>General surgery</th>
<th>Gynaecology</th>
<th>Obstetrics*</th>
<th>Medical patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Major general surgery, age &gt;60</td>
<td>Major gynaecological surgery, age &gt;60</td>
<td>History of DVT/PE</td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Major general surgery, age 40–60 and cancer or history of DVT/PE</td>
<td>Major gynaecological surgery, age 40–60 and cancer or history of DVT/PE</td>
<td>Thrombophilia</td>
<td>Age &gt;70</td>
</tr>
<tr>
<td></td>
<td>Thrombophilia</td>
<td>Thrombophilia</td>
<td>Thrombophilia</td>
<td>Congestive heart failure (CHF)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Major general surgery, age 40–60 without other risk factors**</td>
<td>Major gynaecological surgery, age 40–60</td>
<td>Age &gt;40</td>
<td>Immobilised patient with active disease</td>
</tr>
<tr>
<td></td>
<td>Minor surgery, age &gt;60</td>
<td>Major gynaecological surgery, age &lt;40 on oestrogen therapy</td>
<td>Cardiac failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor surgery, age 40–60 with history of DVT/PE or on oestrogen therapy</td>
<td>Minor surgery, age &gt;60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Major general surgery, age &lt;40</td>
<td>Minor gynaecological surgery, age &lt;40 without any other risk factors**</td>
<td>Age &lt;40 without any risk factors</td>
<td>Minor medical illness</td>
</tr>
<tr>
<td></td>
<td>No other risk factors**</td>
<td>Minor gynaecological surgery, age 40–60 without any other risk factors**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor surgery, age 40–60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No other risk factors**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The risk of DVT in obstetric patients with pre-eclampsia and the other factors is unknown, but prophylaxis should be considered.
** The risk is increased by infectious disease, presence of varicose veins, general immobility.
Minor surgery: operations other than abdominal lasting less than 45 minutes. Major surgery: any intra-abdominal operation and all other operations lasting more than 45 minutes.

Table 5. A comparison of the principal randomised trials of thromboprophylaxis in acutely ill medical patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Drug</th>
<th>Expected stay</th>
<th>Inclusion criteria</th>
</tr>
</thead>
</table>
| MEDENOX      | 1999 | Enoxaparin | ≥6 days, immobilised | Age ≥40
|              |      |           | for ≤3 days and |– CHF (NYHA III/IV) |
|              |      |           |                |– acute respiratory illness |
|              |      |           |                |– infection or inflamed bowel, rheumatic/arthritis disorder |
|              |      |           |                |plus one risk factor |
| PREVENT      | 2003 | Dalteparin | ≥4 days, immobilised | Age ≥40
|              |      |           | for ≤3 days and |– CHF (NYHA III/IV) |
|              |      |           |                |– acute respiratory illness |
|              |      |           |                |– infection or inflamed bowel, rheumatic/arthritis disorder |
|              |      |           |                |plus one risk factor |
| ARTEMIS      | 2003 | Fondaparinux | ≥4 days | Age ≥60
|              |      |           | and |– CHF (NYHA III/IV) |
|              |      |           |                |– acute respiratory illness |
|              |      |           |                |– acute infectious or inflammatory disease |
|              |      |           |                |and |
|              |      |           |                |no other risk factor |

Outcomes: proximal DVT + symptomatic VTE (at day 14–21)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.1%</td>
<td>2.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>6.6%</td>
<td>5.0%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

RRR -50%; P<0.037
RRR -50%; P<0.002
RRR -50%; P<0.085
Table 6. Risk assessment of medical patients

Annex 2 – Appendix 1
This Appendix describes the results of the search of electronic databases undertaken by the guidelines subgroup.

References – Annex 2
1 Remit of the analysis

The terms of reference for this analysis were defined as: ‘Current evidence, best practice and recommendations for the use of specific interventions such as pharmacological, aspirin, and mechanical devices etc.’

In order to fulfil this remit, an approach was formulated that would allow an objective, evidence-based summary of current data that would describe the efficacy and safety of different methods of VTE prevention. This approach involved:

- documenting the endpoints that have been employed in clinical trials:
  - efficacy endpoints (including death, fatal PE, clinical VTE, venographic and isotopically detected (asymptomatic) DVT, ventilation-perfusion (V/Q) scan-detected PE)
  - safety endpoints (including major, clinically significant bleeding, minor bleeding and other significant bleeding events)
- determining for each prophylactic agent/modality the volume of evidence for each endpoint
- establishing the strength of evidence available for each agent, with respect to the efficacy and safety parameters defined, the volume and quality of evidence, and consideration of the long-term morbidity associated with VTE (including post-phlebitic syndrome and thromboembolic pulmonary hypertension)

2 Search strategy

No formal search strategy was employed. A complete literature review of all studies published in the field of thromboprophylaxis was beyond the remit of this subgroup, and would be a duplication of the work ongoing by the National Institute for Health and Clinical Excellence (NICE).

Rather, the remit of this subgroup was to assess current evidence and practice. To this end, previously published evidence-based reviews, especially formal meta-analyses and literature summaries published as part of clinical guidelines for VTE prevention, such as the American College of Chest Physicians (ACCP) guidelines, were assessed. Particular focus was placed on published meta-analyses. Meta-analysis includes a formal literature review, identification of studies of acceptable quality, and a formal analysis of outcomes. Therefore, high-quality meta-analyses published in high-impact journals that have formed part of international guideline assessments for VTE prevention for both surgical and medical patients were identified. Their findings, reviewed in conjunction with individual clinical trials, offer the best assessment of the benefits and risks of prophylactic antithrombotic treatments.

This review is based on evidence already presented within structured reviews and guidelines. Data were derived from three principal documents:

- Health Technologies Assessment (HTA) Vol. 9, No. 49 (2006)

In addition, literature reviews using searches of PubMed, review articles and subsequent hand-searching of references was conducted.

3 Interventions review

Background

Most hospitalised patients have one or more risk factors for VTE and these risk factors are usually cumulative. The rationale for thromboprophylaxis is based on the high prevalence of VTE, the adverse consequences of VTE, and the efficacy and effectiveness of prophylaxis. These principles and the scientific evidence base are summarised in Table 1.
Methods of thromboprophylaxis include mechanical and pharmacological approaches.

**Mechanical approaches**
Mechanical methods increase mean blood flow velocity in leg veins and reduce venous stasis. The methods include:
- intermittent pneumatic compression (IPC) devices
- graduated compression stockings (GCS)
- mechanical foot pumps (FPs)

**IPC**
IPC devices evacuate blood from lower-extremity vessels in an automated fashion. A microprocessor directs pressurised air into segmental diaphragms secured around the leg for a fixed period of time. The compression is delivered in a sequential manner up the leg, producing a wave-like milking effect to evacuate leg veins. Sequential devices are more effective than single-chamber ones. The compression is set to cycle regularly and devices are available for feet, calves and/or thighs.

**GCS**
The exact mechanism by which GCS function is unknown. However, it is suggested that they exert graded circumferential pressure from distal to proximal and, when combined with muscular activity in the limb, displace blood from the superficial to the deep venous system via the perforating veins. It is argued that this effectively increases the velocity and volume of flow in the deep system, thereby potentially preventing thrombosis. The improper application of stockings may potentially cause complications, such as oedema of the legs, DVT and arterial ischaemia. Stockings may be contraindicated for medical reasons, but the extent to which the leg shape may limit effectiveness has not been addressed. Recommendations regarding the ideal length of stockings to use (knee-length or full-length) are not available.

**FPs**
The sole of the foot contains a plexus of veins, the *venae comitantes* of the lateral plantar artery, and normal weight-bearing expels blood from this plexus, causing a pulse of blood to pass through the deep veins of the lower leg, which reduces venous stasis and liberates fibrinolytic factors from the venous endothelial wall. The foot-pump system reproduces the rhythmic expression of blood from the plexus when a patient cannot bear weight.

**Pharmacological approaches**
Pharmacological antithrombotic agents prevent the formation of a venous thrombus and/or restrict its extension by directly altering the process of blood coagulation. The most common agents used are unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) (warfarin). The major disadvantage of pharmacological prophylaxis is the risk of bleeding, which is a particular concern in surgical patients (for example because of the risk of joint haematomas following joint replacement surgery and intracranial
Definition of outcomes in clinical trials

To assess the value of a given antithrombotic agent, it is essential that endpoints for the assessment of efficacy and also for the assessment of any potential adverse events, especially bleeding complications, are included.

**Mortality and fatal pulmonary embolism**

An important trial endpoint is that of a reduction in death and/or fatal PE. However, confirmation of PE requires autopsy, and only a few antithrombotic agents have been assessed to the extent that there is a clear demonstration that their use is associated with a significant reduction in fatal PE in well-designed randomised clinical trials. However, when meta-analyses are undertaken of methodologically sound clinical trials where PE has been included as one of the endpoints in the study, then a number of agents, on this basis, have been shown to possess antithrombotic efficacy.

**Symptomatic and asymptomatic VTE**

Beyond the endpoint of fatal PE is the clinical endpoint of symptomatic VTE, whether it is DVT or PE, confirmed by objective diagnostic tests. As an alternative strategy, asymptomatic endpoints using screening with sensitive tests that are able to diagnose DVT, such as fibrinogen uptake (FUT) scanning, venography or ultrasound, have been employed. Trials employing these endpoints are clinically relevant because asymptomatic thrombosis will predict both symptomatic DVT and potentially fatal PE. Moreover, meta-analyses have been conducted, which have allowed pooling of the small numbers of symptomatic events found and these have provided meaningful results showing risk reductions of symptomatic VTE events of similar levels to venogram-detected DVT.

**Safety endpoints**

When considering safety endpoints in clinical trials, consistent assessment of bleeding is difficult. Because bleeding is an expected complication of operation, blood loss per se both intra-operatively and in the early post-operative period, and consequent requirement for transfusion, are difficult surrogate markers for assessment of bleeding risk for an antithrombotic agent in the peri-operative setting. Wound haematoma and bleeding at the operation site, although potentially expected in a normal surgical procedure, may increase in frequency as a result of antithrombotic therapy. Such differences are important to identify, as their occurrence outside the controlled setting of a clinical trial may have important adverse consequences.

Few peri-operative pharmacologic prophylaxis trials have used endpoints that assess the potential impact of excessive bleeding on surgical outcome. However, such endpoints, which include the need for re-operation secondary to bleeding, the need for surgical evacuation of wound haematomas, or consequences of bleeding which result in either

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drugs</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect inhibitors of FIIa and/or FXa</td>
<td>Via antithrombin (AT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UFH</td>
<td>s.c. injection bid</td>
<td>s.c. injection tid</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>0.2 mL (5000 IU)</td>
<td>0.2 mL (5000 IU)</td>
</tr>
<tr>
<td></td>
<td>Danaparoid sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux (anti-Xa only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Via heparin cofactor (HC-II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermatan sulphate (anti-lla only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct inhibitors of FIIa</td>
<td>Recombinant hirudin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hirudin derivatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Action on coagulation factor synthesis</td>
<td>Vitamin K antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drugs</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium heparin</td>
<td>s.c. injection bid</td>
<td>s.c. injection tid</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>s.c. injection od</td>
<td>s.c. injection od</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>20 mg (2000 IU)</td>
<td>40 mg (4000 IU)</td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>2500 IU</td>
<td>5000 IU</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>2500 IU</td>
<td>3500 IU (cancer); 4500 IU (ortho)</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>s.c. injection od</td>
<td>s.c. injection od</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td></td>
</tr>
</tbody>
</table>
anastomotic dehiscence, wound dehiscence, or arthroplasty joint sepsis, may represent more important endpoints in ‘real-world’ clinical practice. This situation is contrary to that seen in medical patients receiving thromboprophylaxis, where bleeding would not be expected.

Critical review of the literature, data extraction and evidence levels

Information on the endpoints used for each therapeutic agent in the therapeutic areas previously specified within the analysis of existing VTE guidelines (see Annex 2), namely general (and gynaecological) surgery, orthopaedic surgery and medical inpatients, was extracted independently by the assistant on the subgroup chair’s instruction.

Further consideration was given to the volume of evidence for each agent. An important part of the analysis has been making the distinction between three different types of data sources:

- individual, high-quality randomised controlled trials
- meta-analysis of randomised controlled trials
- lower-quality studies

The fact that most studies are comparisons between active agents (e.g. LMWH vs. UFH) and that, in many cases, an uncontrolled use of background agents (e.g. aspirin vs. placebo in hip fracture, with patients receiving prophylactic heparin) is reported, limits this assessment. However, what is described is a current, objective, evidence-based summary of the efficacy and safety of different methods of VTE prevention.

Summary tables are provided starting on page 39, offering an indication of the strength and volume of evidence for each intervention. Where individual randomised trials and/or meta-analysis have shown the effect, the volume of patients is shown as an order of magnitude.

General surgery
Summary tables on page 39.

Risk of VTE in general surgery patients

In early studies published mainly in the 1970s and 1980s,²–⁷ the observed rate of DVT among general surgical patients not receiving prophylaxis varied between 15% and 30%, with rates of fatal PE between 0.2% and 0.9%. The current risk of thromboembolic complications in general surgery is unknown, because studies without prophylaxis are no longer performed in these patients.⁸

The ACCP venous thromboembolism guidelines surmise that more rapid mobilisation, greater use of thromboprophylaxis, and other advances in peri-operative care may tend toward reducing the thromboembolic risk. However, the increasing sophistication of surgery, including, for example, the performance of more extensive operative procedures in older and sicker patients, the more frequent use of pre-operative chemotherapy in cancer patients, and the shorter lengths of stay in hospital (leading to shorter durations of prophylaxis) may heighten the risk of VTE in contemporary patients undergoing inpatient general surgery.⁸

Data review

Data in this section are derived from six principal sources:

1. three meta-analyses describing UFH⁴,⁵ and LMWH⁶ in the prevention of VTE in general surgery
2. ACCP venous thromboembolism guidelines (2004)⁸
3. Health Technologies Assessment Vol. 9; No. 49 (2006)⁹
6. a literature review

Intervention: low-dose unfractionated heparin

Randomised studies

The International Multicentre Trial (1975)¹² randomised 4121 patients older than 40 years undergoing major surgical intervention, to a control group or to receive low-dose unfractionated heparin (LDUH), 5000 U commenced 1 to 2 hours before operation and continued three times daily in the post-operative period until the patient was fully mobile.⁸ The primary endpoint in this study was autopsy-proven fatal PE. Approximately 70% of patients who died underwent autopsy. The trial demonstrated a considerable reduction in the frequency of fatal PE (16 patients in the control group vs. two in the LDUH group) and provided the first evidence that heparin-based thromboprophylaxis not only prevented DVT, but was also able to reduce the frequency of fatal PE and have a significant impact on improving surgical outcome.
Meta-analysis

Although several individual randomised trials in general surgery were large enough to be able to demonstrate a reduction in DVT with peri-operative heparin, a meta-analysis of 46 randomised clinical trials in general surgery, which compared therapy with LDUH with no prophylaxis or placebo, provided important confirmatory data with respect to fatal PE (see Table 4) and DVT (see Figure 1).

The meta-analysis showed that the rate of:

- all-cause mortality was significantly reduced (from 4.2% to 3.2%; OR, 0.8; number needed to treat (NNT), 97)
- fatal PE was significantly reduced (from 0.8% to 0.3%; OR, 0.4; NNT, 182)
- symptomatic PE was significantly reduced (from 2.0% to 1.3%; OR, 0.5; NNT, 143)
- DVT was significantly reduced (from 22% to 9%; OR, 0.3; NNT, 7)
- bleeding events was significantly increased (from 3.8% to 5.9%; OR, 1.6; number needed to harm (NNH), 47)

These findings in general surgery patients were verified in another large meta-analysis. Pool data from 24 randomised trials showed the rate of fatal PE was reduced from 0.7% to 0.2% with UFH, with the rate of wound haematomas increasing (6.3% vs. 4.1% in control subjects; OR, 1.6; NNH, 45), although the rate of major bleeding did not increase.

While both meta-analyses concluded that the administration of heparin, 5000 U tid, was more efficacious than that of 5000 U bid, without increasing bleeding, this was based on indirect comparisons, and there do not appear to be any studies that directly compared these two regimens.

Intervention: low-molecular-weight heparin

**Randomised studies**

LMWH has been extensively investigated since the first report of its use for the thromboprophylaxis in man in general surgical patients by Kakkar et al. in 1982.

In a recent (2005) large, randomised, double-blind study, 23,078 surgical patients (85% general or gynaecological) over 40 years requiring thromboprophylaxis for surgery lasting not less than 30 minutes were randomly assigned to LMWH (3000 IU, od) or UFH (5000 IU, tid), for a minimum of five days. The autopsy rate was 70%. The primary outcome measure, autopsy-proven fatal PE up to 14 days after the end of prophylaxis, occurred in 0.15% of cases, with no significant difference between the treatment groups (Figure 2).

**Meta-analysis**

A meta-analysis reported in 2001 reviewed studies that randomised more than 44,000 general surgical patients in trials using LMWH and LDUH.

**LMWH vs. placebo or no treatment**

- No significant reduction in overall mortality rate (n = 5142; RR 0.54 (0.27–1.10))
- A significant reduction in clinical VTE (n = 4890; RR 0.29 (0.11–0.73))
- A significant reduction in clinical PE (n = 5456; RR 0.25 (0.08–0.79))
- A significant reduction in asymptomatic DVT (n = 513; RR 0.28 (95% CI, 0.14–0.54))
- The rate of bleeding events was significantly increased (see Figure 3)
**LMWH vs. UFH**

The comparison of LMWH with UFH showed that LMWH and LDUH provided roughly equal efficacy and safety, but with a significant reduction in clinical VTE with LMWH, compared with UFH (RR 0.71 (0.51–0.99)). See Figure 4.

**Intervention: fondaparinux**

The selective inhibitor of Factor Xa, fondaparinux, has also been evaluated in patients undergoing abdominal surgery.

**Randomised studies**

In a single trial of general surgical patients (most for malignant disease), there was no substantial difference in either efficacy of thromboprophylaxis or bleeding complications in patients who received fondaparinux commenced post-operatively or LMWH commenced pre-operatively. The primary outcome measure was a composite of DVT, detected by bilateral venography, and symptomatic, confirmed DVT or PE, up until day 10. The main safety outcome measure was major bleeding during treatment. Among 2048 patients evaluable for efficacy, the rate of VTE was 4.6% (47/1027) with fondaparinux, compared with 6.1% (62/1021) with dalteparin, a non-significant relative risk reduction (RRR) of 24.6%. Major bleeding was observed in 3.4% (49/1433) of patients given fondaparinux and 2.4% (34/1425) given dalteparin (P = 0.122).

Figure 1. Meta-analysis findings showed that the rate of DVT was significantly reduced by comparable levels in general, orthopaedic and urological surgery patients

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Odds Ratio (± 95% confidence interval)</th>
<th>Risk Reduction (± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td>67% ± 4</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td>68% ± 7</td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td>75% ± 15</td>
</tr>
<tr>
<td>ANY TYPE</td>
<td></td>
<td>68% ± 3</td>
</tr>
</tbody>
</table>

Figure 2. Recent large, randomised trial findings of fatal pulmonary embolism, compared with International Multicentre Trial

Prevention of fatal pulmonary embolism

\[ P < 0.005 \]

\[
\begin{align*}
\text{Autopsy confirmed fatal PE (n=2076)} & \quad 0.8 \\
\text{Low-dose heparin tid (n=2045)} & \quad 0.1 \\
\text{Control (n=2076)} & \quad 0.16 \\
\text{Low-dose heparin tid (n=11,536)} & \quad 0.15 \\
\text{LMWH qd (n=11,542)} & \quad 0.8 \\
\end{align*}
\]


Figure 3. Rate of bleeding events

\[
\begin{align*}
\text{LMWH better} & \quad \text{LMWH worse} \\
\text{Asymptomatic DVT} & \quad n = 513, RR = 0.28 (0.14–0.54) \\
& \quad P < 0.001, P_H = 0.91 \\
\text{Clinical PE} & \quad n = 5456, RR = 0.25 (0.08–0.79) \\
& \quad P < 0.018, P_H = 0.99 \\
\text{Clinical thromboembolism} & \quad n = 4890, RR = 0.29 (0.11–0.73) \\
& \quad P < 0.009, P_H = 0.67 \\
\text{Death} & \quad n = 5142, RR = 0.54 (0.27–1.10) \\
& \quad P < 0.09, P_H = 0.50 \\
\text{Major haemorrhage} & \quad n = 5456, RR = 2.03 (1.37–3.01) \\
& \quad P < 0.001, P_H = 0.68 \\
\text{Total haemorrhage} & \quad n = 5431, RR = 2.06 (1.77–2.39) \\
& \quad P < 0.001, P_H = 0.24 \\
\text{Wound haematoma} & \quad n = 5242, RR = 1.88 (1.54–2.38) \\
& \quad P < 0.001, P_H = 0.65 \\
\text{Transfusion} & \quad n = 5054, RR = 1.53 (1.28–1.82) \\
& \quad P < 0.001, P_H = 0.54
\end{align*}
\]

Intervention: mechanical methods
Although mechanical methods of prophylaxis have been assessed in general surgical patients, few trials of high methodological quality have evaluated their efficacy, and all trials have included small numbers of patients.

Meta-analysis
The recent Health Technologies Assessment meta-analysis9 analysed all studies published up to 2001 and reviewed all surgical groups together. This analysis showed that mechanical methods reduced the risk of DVT by two-thirds, and by half when added to a pharmacological agent. These findings were similar for each type of mechanical method and for each surgical group. Extensive tables can be found in the published report that detail the studies and their individual findings.

IPC
In the most recent meta-analysis (2005) assessing the effectiveness of IPC to prevent DVT in postoperative patients, 2270 patients were identified in 15 eligible studies, 1125 and 1145 in the IPC and no prophylaxis group respectively.22 Although IPC devices reduced the risk of DVT by 60% (relative risk 0.40, 95% CI 0.29–0.56; p <0.001) in comparison with no prophylaxis, only four of these studies (427 patients) had enrolled general surgery patients.

GCS
GCS are the most widely used and investigated mechanical antithrombotic agents. The majority of studies of stockings for the prevention of VTE have been on general surgical patients. Table 5 shows the results of randomised controlled trials comparing the incidence of DVT in general surgical patients.23 The overall incidence of DVT was 51 (7%) of 748 in the treatment group, compared with 144 (19%) of 757 in the control group. The odds ratio was 0.31, with a relative risk reduction of 64% (95% CI 53 ± 73) in patients wearing stockings.

A Cochrane meta-analysis24 identified 16 randomised controlled trials of GCS that met the strict inclusion criteria for study quality, and this analysis included four studies of general surgery patients, three of which had been included in the analysis shown in Table 5 (Allan et al 1983; Holford 1976; Scurr et al 1987), with an additional study from 1971 included.25 In the treatment group (GCS) of 624 patients, 81 developed DVT (13%) in comparison with 154 (27%) developed DVT, Peto’s odds ratio 0.34 (95% confidence interval 0.25, 0.46) favouring treatment with GCS.
Seven studies looked at combined pharmacological and mechanical methods: in the treatment group (GCS plus another method) of 501 patients, 10 (2%) developed DVT, whereas in the control group of 505 patients, 74 (15%) developed DVT, Peto’s odds ratio 0.24 (95% confidence interval 0.15, 0.37).

**FPs**

No studies describing the efficacy of FPs in general surgery were described.

**Comments on interpretation of mechanical methods studies**

There are a number of difficulties in the interpretation of these analyses. Firstly, the overall findings of the meta-analyses are based on grouping different patient groups together, including general, orthopaedic, neurosurgery, obstetrics and gynaecology, and cardiology patients. Secondly, variations within the included trials, including the use of opposite limb as the control, differing background prophylactic methods used in trials, the age difference in some of the trials, and the fact that most studies used radioactive fibrinogen uptake (FUT) assay to screen for DVT post-operatively, limits the interpretation of the findings.

Nonetheless, considering the evidence available, no trials have demonstrated that mechanical methods of thromboprophylaxis, alone, are able to reduce the frequency of fatal PE or the frequency of PE in general surgical patients.9, 10 Recent analyses suggest that their use is associated with a 50% reduction in the rate of DVT, compared with control.9, 23, 24 When used in combination with LDUH, they appear to be of benefit, with studies reporting a 75% reduction in the rate of DVT identified among patients using combined LDUH and GCS compared with LDUH alone.24

Table 5. Results of randomised controlled trials of graduated compression stockings in preventing deep vein thrombosis in general/abdominal surgery

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Diagnostic test</th>
<th>Cases</th>
<th>Control</th>
<th>Odds ratio</th>
<th>P value</th>
<th>No. needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-intestinal surgery</td>
<td>1985</td>
<td>FUT</td>
<td>11 of 99 (11%)</td>
<td>2547 (31.3%)</td>
<td>0.11 (0.009-0.12)</td>
<td>0.01</td>
<td>6</td>
</tr>
<tr>
<td>1987</td>
<td>FUT</td>
<td>8 of 70 (11%)</td>
<td>26 of 70 (37%)</td>
<td>0.22 (0.06-0.77)</td>
<td>0.08</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>FUT</td>
<td>4 of 49 (8%)</td>
<td>12 of 49 (24%)</td>
<td>0.44 (0.16-0.94)</td>
<td>0.05</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>FUT</td>
<td>15 of 57 (26%)</td>
<td>37 of 57 (65%)</td>
<td>0.88 (0.16-0.88)</td>
<td>0.07</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>FUT</td>
<td>9 of 51 (18%)</td>
<td>6 of 51 (12%)</td>
<td>0.38 (0.06-0.80)</td>
<td>0.02</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>FUT</td>
<td>5 of 45 (11%)</td>
<td>11 of 45 (24%)</td>
<td>0.43 (0.15-0.92)</td>
<td>0.04</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>FUT</td>
<td>7 of 54 (13%)</td>
<td>6 of 54 (11%)</td>
<td>0.41 (0.12-0.92)</td>
<td>0.06</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>FUT</td>
<td>11 of 73 (15%)</td>
<td>1 of 73 (2%)</td>
<td>0.12 (0.009-0.11)</td>
<td>0.00</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>FUT</td>
<td>2 of 83 (2%)</td>
<td>12 of 83 (14%)</td>
<td>0.19 (0.02-0.87)</td>
<td>0.04</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>FUT</td>
<td>51 of 53 (96%)</td>
<td>144 of 53 (86%)</td>
<td>0.83 (0.58-1.16)</td>
<td>0.00</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>1984</td>
<td>FUT</td>
<td>11 of 13 (8%)</td>
<td>3 of 13 (23%)</td>
<td>0.21 (0.03-0.89)</td>
<td>0.04</td>
<td>10</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1984</td>
<td>FUT</td>
<td>7 of 73 (9%)</td>
<td>11 of 73 (15%)</td>
<td>0.21 (0.03-0.89)</td>
<td>0.04</td>
<td>10</td>
</tr>
</tbody>
</table>

### Summary: general surgery

**Intervention comparison: LDUH vs. placebo**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>&gt;10^3 patients</td>
<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^3 patients</td>
<td>&gt;10^5 patients</td>
</tr>
</tbody>
</table>

*‘Bleeding events’* | >10^3 patients   | >10^5 patients|

**Intervention comparison: LMWH vs. placebo**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>&gt;10^3 patients</td>
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<tr>
<td>Fatal PE</td>
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<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>&gt;10^3 patients</td>
<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^3 patients</td>
<td>&gt;10^5 patients</td>
</tr>
</tbody>
</table>

**Intervention comparison: LMWH vs. UFH**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>&gt;10^3 patients</td>
<td>–</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>&gt;10^3 patients</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>&gt;10^5 patients</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>–</td>
<td>&gt;10^5 patients</td>
</tr>
</tbody>
</table>

**Intervention comparison: fondaparinux vs. LMWH**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
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<td>–</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^3 patients</td>
<td>–</td>
</tr>
</tbody>
</table>

**Intervention: mechanical methods vs. control**

**IPC**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial*</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^3 patients</td>
<td>&gt;10^5 patients</td>
</tr>
</tbody>
</table>

*Studies tend to be lower quality and non-blind

**FPs – no evidence**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial*</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Orthopaedic surgery
Summary tables on page 47.

Risk of VTE in major orthopaedic surgery
The ACCP guidelines state that patients undergoing major orthopaedic surgery, which includes hip (THR) and knee (TKR) arthroplasty and hip fracture surgery (HFS), represent a group that are at particularly high risk for VTE. Randomised clinical trials have demonstrated that the rates of venographic DVT and proximal DVT 7 to 14 days following major orthopaedic surgery in patients who received no prophylaxis are approximately 40–60% and 10–30% respectively (see Table 6).26

HFS patients are at very high risk of VTE. After HFS, the rates of total and proximal DVT, which were derived from eight prospective studies using routine contrast venography, were approximately 50% and 27% respectively, without prophylaxis.26 The rate of fatal PE was reported to be in the range of 1.4–7.5% within 3 months after HFS, a range higher than that seen after hip or knee arthroplasty. In a population-based autopsy study of 581 patients who died after hip fracture in 1953–92, PE was consistently the fourth leading cause of death, accounting for 14% of all deaths.27

In terms of VTE prevention, evidence shows that total knee arthroplasty (TKA) differs from THR in several important respects. The ACCP guidelines indicate that, without prophylaxis, the rate of venographic DVT is higher after TKA than after THR, although TKA patients appear to experience lower rates of proximal DVT and symptomatic VTE. The BCSH guidelines28 indicate that, following THR, the incidence of fatal PE is at least 0.37%, as shown in the Norwegian Hip Arthroplasty Registry of 67,548 patients.29 This figure applies to patients who are receiving standard thromboprophylaxis with LMWH and the BCSH guidelines on heparin suggest that unprotected patients would be expected to have a mortality rate of around three times that frequency. Although prospective registries confirm that the incidence of fatal PE may have declined over recent years, this decline is not to the degree found in previous retrospective British studies with incomplete follow-up and data collection, and are therefore contentious and not accepted internationally.30, 31

There are a number of subtle issues, including the timing of the first peri-operative dose, duration of prophylactic treatment and definition/assessment of study endpoints, that can influence study outcome and therefore require careful consideration when evaluating orthopaedic surgery. The exact timing of prophylaxis exerts an effect on clinical efficacy and safety, and it has been shown that substantial differences in VTE risk reduction can be achieved through optimising the dosing schedule. Although venography is routinely undertaken at the clinical trial centre, it is common in orthopaedic thromboprophylaxis studies that the interpretation of the venogram for the purposes of the trial findings is undertaken by the lead investigators or by an independent venogram adjudication committee at a remote site. The criteria used across studies differ, and this can significantly impact on the efficacy assessment.

Data review
Data in this section are derived from six principal sources:
1. a meta-analysis describing UFH in the prevention of VTE (1988)32
2. ACCP VTE guidelines (2004)26
3. Health Technologies Assessment (HTA) Vol. 9; No. 49 (2006)33
4. BCSH Guidelines on the use and monitoring of heparin (2006)28
5. a literature review

Table 6. Rates of deep vein thrombosis and pulmonary embolism following major orthopedic surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>7-14 Days</th>
<th>1-3 Months</th>
<th>1-7 Days</th>
<th>1-Day</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>42–57</td>
<td>11–15</td>
<td>5–27</td>
<td>0–14</td>
<td>0–20</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>41–45</td>
<td>3–10</td>
<td>1–5</td>
<td>1–3</td>
<td>0–17</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>10–14</td>
<td>2–6</td>
<td>1–2</td>
<td>4–9</td>
<td>0–17</td>
</tr>
</tbody>
</table>

*DVT rates are based on the use of mandatory venography in prospective clinical trials published since 1976. These rates are derived from prospective clinical trials where patients received either a prophylaxis regimen that included enoxaparin or standard prophylaxis. Adapted from Chest, 2007, Volume 131 (4), 95S-96S. Source: Reproduced with permission of the American College of Chest Physicians in the format newsletter/e-newsletter via Copyright Clearance Center.
Intervention: low-dose unfractionated heparin

Meta-analysis\textsuperscript{32} of mixed orthopaedic surgery patients showed that:

- UFH significantly reduced by two-thirds all efficacy outcomes in the orthopaedic surgery subgroup (fatal PE, clinical PE, asymptomatic and clinical DVT) (see Figure 5)
- there was an overall 21% reduction in mortality described for all surgery patients
- for heparin vs. placebo, excessive bleeding and need for transfusion was increased relatively by one-half to two-thirds; the absolute increase was around 2%
- bleeding endpoints were noted to be incompletely described and inadequate in many of the trials included in the meta-analysis; nonetheless, bleeding was significantly increased in those patients receiving heparin compared with controls

Intervention: low-molecular-weight heparin and unfractionated heparin

LMWH has been compared with UFH in numerous studies. Several meta-analyses have shown at least equivalence in safety and efficacy and some have shown a small but significant advantage in efficacy for LMWH.

\textit{THR}

For THR, at least three meta-analyses\textsuperscript{34–36} and three clinical studies\textsuperscript{37–39} have established that LMWH is more efficacious than LDUH.

Meta-analysis of studies reported between 1984 and 1991,\textsuperscript{34} comparing LMWH with standard heparin for post-operative prophylaxis in general and orthopaedic studies, showed that for all surgical studies the relative risk (LMWH vs. heparin) was:

- DVT = 0.74 (95% CI 0.65–0.86)
- PE = 0.43 (95% CI 0.26–0.72)
- major bleeding = 0.98 (95% CI 0.69–1.40)

Comparable relative risks were observed for the general and orthopaedic surgery studies separately.

In a more recent and extensive meta-analysis restricted to THR patients alone,\textsuperscript{36} all the thromboprophylaxis approaches were compared. Fifty-two studies, in which 10,929 patients had been enrolled, met the inclusion criteria and were included in the analysis. The studies are shown in Table 7.

The rates of distal, proximal and total DVT; symptomatic and fatal PE; minor and major wound-bleeding complications; major non-wound-bleeding complications; and total mortality were determined for each agent in each study.

Fatal PE:

- compared with the placebo, no agent was associated with a significantly different risk of fatal PE

Symptomatic PE:

- the rates were lowest with warfarin (0.16%), pneumatic compression (0.26%) and LMWH (0.36%), and were significantly lower than placebo (1.51%; p <0.0001)
- warfarin and LMWH were significantly lower than aspirin (1.28%) and LDUH (1.36%; p <0.0083)

Figure 5. Reduction in asymptomatic DVT in orthopaedic surgery correlates with reduction in fatal PE
Table 7. Meta-analysis of total hip replacement patients alone

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Mean Age (yr.)</th>
<th>Mean Percent Male</th>
<th>Mean No. of Days Postop. Venography Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-molecular-weight heparin</td>
<td>21</td>
<td>5512</td>
<td>66</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>Warfarin</td>
<td>12</td>
<td>1493</td>
<td>63</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>8</td>
<td>687</td>
<td>62</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Low-dose heparin</td>
<td>11</td>
<td>1859</td>
<td>66</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Pneumatic compression</td>
<td>5</td>
<td>431</td>
<td>64</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Placebo</td>
<td>13</td>
<td>947</td>
<td>67</td>
<td>42</td>
<td>10</td>
</tr>
</tbody>
</table>


Distal DVT:
- pneumatic compression was associated with the lowest risk (7.7%), significantly lower than the risks with warfarin (17.1%) and aspirin (19.7%) (P = 0.0007 and P = 0.0001 respectively)
- LMWH (9.6%) was significantly lower than the risks with warfarin and aspirin (P = 0.0047 and P = 0.0005 respectively)

Proximal DVT:
- warfarin and LMWH were associated with the lowest risk (6.3% and 7.7% respectively)
- warfarin and LMWH were significantly lower than pneumatic compression (13.3%) (P = 0.0004 and P = 0.0059 respectively) and low-dose heparin (19.0%) (P = 0.0047 and P = 0.0023 respectively)

Major bleeding:
- LDUH was associated with the highest risks of major wound bleeding (2.56%) and total major bleeding (3.46%)
- both risks were significantly higher than the risks with the placebo and all other agents (p <0.0001)
- there were no significant differences between any of the other agents and the placebo, or among the agents, with regard to the risk of major wound bleeding, major non-wound bleeding or total major bleeding

Minor bleeding:
- the risks of minor wound bleeding were highest with LMWH (8.9%) and LDUH (7.6%) and were significantly higher than placebo (2.2%) (p <0.05) and pneumatic compression stockings (1.1%) (p <0.0083)
- the risks of total minor bleeding with LMWH, LDUH and warfarin were higher than the risk with the placebo (p <0.05) and for LMWH (10.5%) and LDUH (13.5%) were significantly higher than the risk with pneumatic compression stockings (4.1%) (P = 0.0013 and P = 0.0022 respectively)

TKR
There are extensive data describing LMWH prophylaxis efficacy and safety after TKR. In particular, two recent meta-analyses showed that LMWH was superior to LDUH and warfarin, without an increased risk in bleeding. The studies showed that LMWH prevents more venographic DVT and proximal DVT than warfarin

Hip fracture
A recent Cochrane review described 10 trials of 826 patients that compared UFH with control, and four trials of 471 patients that compared LMWH with control in hip fracture. The analysis noted that trial quality was disappointing, with the majority showing methodological defects.

- There was no significant difference in overall mortality in the heparin group (46/420 (11%) versus 35/423 (8%); Peto odds ratio 1.39; 95% confidence interval 0.86 to 2.23)
- There were insufficient data to confirm the efficacy of either agent in the prevention of PE
There was a reduction in the incidence of lower-limb DVT (121/511 (24%) versus 203/519 (39%); Peto odds ratio 0.41; 95% confidence interval 0.31 to 0.55)

Data were inadequate for all other outcomes, including wound complications

There is insufficient evidence from five trials, involving 644 patients, to establish if LMWH was superior to UFH

**Intervention: low-molecular-weight heparin and warfarin**

THR

Five randomised clinical trials directly compared adjusted-dose warfarin with LMWH.43–47 The ACCP guidelines pooled the findings and showed rates of all DVT for LMWH of 20.7% (256/1238) vs. 13.7% (238/1741; p <0.0002) for warfarin. There was no difference in proximal DVT rates. Major bleeding used different definitions in the five studies, but was 3.3% in the vitamin K antagonist therapy (VKA) recipients and 5.3% in the LMWH recipients.

In a large, non-blinded clinical trial of more than 3000 THR patients randomly given either enoxaparin, 30 mg subcutaneous (sc) bd, started post-operatively, or warfarin dose-adjusted for an international normalisation ratio (INR) of 2.0 to 3.0, the in-hospital incidences of symptomatic, objectively documented VTE were 0.3% and 1.1% respectively (p <0.008). At three months, the rate of overall VTE was not significantly different. There was no difference in major bleeding.

TKR

Six randomised clinical trials directly compared VKA with LMWH.43, 45, 46, 49–51 The ACCP guidelines pooled the findings and showed DVT rates for VKA of 48% vs. 33% for LMWH, and proximal DVT rates of 10.4% vs. 7.1%. In two of these studies, there was a higher risk of bleeding, but not major bleeding, among LMWH recipients.

Two meta-analyses, conducted in 1998 and 2001, confirmed the superior efficacy of LMWH over both LDUH and warfarin, without an increased risk in bleeding.45, 41 LMWH prophylaxis within 12 hours after surgery may be associated with a small increase in wound haematomas.

**Intervention: fondaparinux**

A meta-analysis of four multicentre, randomised, double-blind trials in patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture (N = 7344) was performed to determine whether a subcutaneous 2.5 mg, once-daily regimen of fondaparinux sodium starting 6 hours after surgery was more effective and as safe as approved enoxaparin regimens in preventing VTE. The primary efficacy outcome was VTE up to day 11, defined as DVT detected by bilateral venography or documented symptomatic DVT or PE. The primary safety outcome was major bleeding.

Fondaparinux significantly reduced the incidence of VTE by day 11 (182 (6.8%) of 2682 patients) compared with enoxaparin (371 (13.7%) of 2703 patients), with a common odds reduction of 55.2% (95% confidence interval, 45.8% to 63.1%; P <0.001); this beneficial effect was consistent across all types of surgery and all subgroups

Major bleeding was significantly more common with fondaparinux when the first dose of fondaparinux was given within 6 hours following surgery.

A post-hoc analysis was conducted of the principal phase III findings in major orthopaedic surgery to determine the effect of fondaparinux on an alternative composite efficacy outcome of clinically relevant VTE. When the composite outcome of any proximal DVT, symptomatic proven DVT or PE was calculated, the level of risk reduction was almost identical to that seen for the primary study outcome that incorporated asymptomatic distal DVT, with a common odds reduction of 49.6% favouring fondaparinux

**Intervention: aspirin**

The Anti-platelet Trialists Collaboration meta-analysis first suggested that aspirin and other antiplatelet agents are effective in preventing post-operative VTE.53 However, this interpretation was subject to further analysis and limitations include the fact that none of the studies used routine contrast venography as an outcome measure and, compared with other prophylaxis regimens such as LDUH, antiplatelet drugs provided less protection.

In the Pulmonary Embolism Prevention (PEP) Trial,55 13,356 HFS patients in five countries were randomised to receive either 160 mg aspirin or placebo, starting before surgery in 82% of patients and continuing for 35 days thereafter. Additional prophylaxis with GCS, LMWH or LDUH was used in 18%, 26% and 30% of patients respectively. The results are summarised in Figure 6.
The primary efficacy endpoint of the trial – vascular deaths – was not reduced by aspirin (hazard ratio 0.72, 95% CI 0.29 to 1.79).

Fatal PE and DVT were both significantly reduced by the addition of aspirin, each by an absolute risk reduction of 0.4%.

Fatal and non-fatal myocardial infarction or stroke, as well as all-cause mortality, were not reduced.

There was a significant increase in wound-related and GI bleeding, and in the need for blood transfusion among the aspirin-treated patients.

In the subgroup of 3424 patients who also received prophylaxis with LMWH, no significant difference in the rate of symptomatic VTE was detected between aspirin and placebo recipients.

Aspirin was associated with a 12 per 1000 excess of transfused bleeds among patients also receiving subcutaneous heparin (increase of 48%).

In the additional group of patients who underwent THR/TKR, no significant difference in the rate of symptomatic VTE was detected between aspirin and placebo recipients.

Figure 6. PEP study principal findings

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (n=6679)</th>
<th>Placebo (n=6677)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep-vein thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venographic</td>
<td>33</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Other objective</td>
<td>36</td>
<td>49</td>
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</tr>
<tr>
<td>Proximal</td>
<td>26</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>43</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Any deep-vein thrombosis</td>
<td>69 (1-0%)</td>
<td>97 (1-5%)</td>
<td>29% (3-48) reduction; p=0.03</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>31</td>
<td>59</td>
<td></td>
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<tr>
<td>Probable</td>
<td>15</td>
<td>22</td>
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<tr>
<td>Fatal</td>
<td>18</td>
<td>43</td>
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</tr>
<tr>
<td>Non-fatal</td>
<td>28</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Any pulmonary embolism</td>
<td>46 (0-7%)</td>
<td>81 (1-2%)</td>
<td>243% (18-60) reduction; p=0.002</td>
</tr>
<tr>
<td>Any venous thrombo-embolism</td>
<td>105 (1-6%)</td>
<td>165 (2-5%)</td>
<td>36% (19-500) reduction; p=0.0003</td>
</tr>
</tbody>
</table>


Figure 7. Frequencies of DVT and PE with aspirin

- Aspirin
- Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>% of patients with symptomatic VTE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip and knee replacement</td>
<td>1.1%</td>
<td>p=0.2047</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1.4%</td>
<td>p=0.2041</td>
</tr>
<tr>
<td></td>
<td>1.6%</td>
<td>p=0.003</td>
</tr>
<tr>
<td></td>
<td>2.5%</td>
<td></td>
</tr>
</tbody>
</table>
The risk reduction for symptomatic VTE from 2.5% to 1.6% was about 30%. This is about half of that described for LMWH and one-third from fondaparinux (see Figure 7).

This reduced risk of VTE was matched by an increased risk of transfusion, gastrointestinal bleeding and wound bleeding (see Figure 8).

**Intervention: mechanical methods**

The HTA meta-analysis, grouping all surgical patients together, showed that mechanical methods reduced the risk of DVT by two-thirds, and by half when added to a pharmacological agent in surgical patients grouped together. These findings were similar for each type of mechanical method and for each surgical group.

However, it is clear that special caution should be exercised when interpreting the risk reductions ascribed to mechanical methods of prophylaxis. As noted in the ACCP guidelines, most trials were not blinded, increasing the chance of diagnostic suspicion bias. The fact that many trials were not blinded suggested that these studies should be regarded (in this current analysis of evidence) as lower-quality studies. In the majority of early studies, fibrinogen leg scanning to screen for DVT was employed; the ACCP guidelines state that mechanical prophylaxis may have factitiously lowered the 10–30% false-positive rate seen with the use of FUT caused by venous pooling, while the rate remained unchanged in the non-mechanical treatment/control group. Finally, because of relatively poor compliance with all mechanical options, they may not perform as well in routine clinical practice as in research studies in which major efforts are made to optimise proper use.

**THR**

Mechanical methods have been studied in THR patients, including GCS and IPC. Two studies have suggested that FPs appear to be effective at reducing the risk of total DVT. The different mechanical prophylaxis methods may confer risk reductions against DVT of 20–70%. It is generally accepted that this risk reduction is lower than anticoagulant-based prophylaxis, especially for preventing proximal DVT.

Poor compliance, improper use of the devices, patient intolerance, and the inability to continue prophylaxis after hospital discharge are thought to be factors limiting the usefulness of IPC. Although studies have suggested efficacy, the published experience is small, and these modalities are not recommended for primary prophylaxis.

**TKR**

There are limited data that suggest GCS provide little or no protection in TKA patients. Four small studies suggest that IPC devices provide efficacious prophylaxis in TKA patients. The ACCP guidelines suggest that these devices are most effective when applied either intraoperatively or immediately post-operatively, and are worn continuously, at least until the patient is fully ambulatory. Combined prophylaxis using IPC and either LMWH or adjusted-dose VKA has not been studied in a randomised clinical trial.
Evidence for FP usage was summarised in the ACCP guidelines: the use of an FP was considerably less efficacious than LMWH in two trials but shown to have some efficacy in two other small clinical trials among TKA patients. In a more recent study, FPs and LMWH were equally ineffective, with a 54% overall rate of DVT in the LMWH group, which was higher than expected. The rate of proximal DVT in this study was low, but there were two PE-related deaths in the FP group.

Duration of thromboprophylaxis after orthopaedic surgery

Well-designed prospective studies that investigated short-duration prophylaxis after THR/TKR were unable to provide reliable estimates of the risk of symptomatic VTE because of small patient samples. Larger studies have methodological limitations because: data on thromboembolic events were obtained retrospectively; patients did not receive anticoagulant therapy; the anticoagulant regimen was not specified; and the duration of prophylaxis was at least three weeks. A recent meta-analysis of THR/TKR identified 17 studies of adequate quality: four clinical outcome studies with 6089 patients who had three months of follow up; and 13 venographic outcome studies with 7080 patients who had venography 7 to 10 days after surgery. The findings were:

- in clinical outcome studies, the three-month incidence of non-fatal VTE was 3.2% (95% CI, 2.0–4.4%), and the three-month incidence of fatal PE was 0.10% (95% CI, 0.02–0.20%)  
- the post-prophylaxis incidence of non-fatal VTE was 2.2% (95% CI, 1.4–3.0%), and the incidence of fatal PE was 0.05% (95% CI, 0–0.12%)  
- the post-prophylaxis incidence of symptomatic VTE was higher after hip replacement than after knee replacement (2.5% vs. 1.4%; P = 0.02)

To summarise, in patients who undergo hip or knee replacement and receive short-duration anticoagulant prophylaxis, symptomatic non-fatal VTE will occur in about one in 32 patients and fatal PE will occur in about one in 1000 patients within three months of surgery. These findings suggested the need for extended-duration thromboprophylaxis.

Recent meta-analyses have established the efficacy of extended-duration prophylaxis on symptomatic VTE events. The first analysis concluded that extended thromboprophylaxis with LMWH following lower-limb arthroplasty results in a significant 50% reduction in the odds of developing clinical VTE events. It has also shown that the overall reduction in venographic events was very similar to the reduction in clinical events, further supporting the evidence that venographically diagnosed DVT is a good surrogate endpoint for clinical VTE events (see Figure 9).

The subsequent analysis included LMWH and UFH and identified nine studies of 3999 patients that met the inclusion criteria – eight were conducted with LMWH and one with UFH. The primary outcome was symptomatic VTE, including DVT and PE. Secondary outcomes were symptomless proximal and distal DVT detected by venography, all-cause mortality, and adverse events including major and minor bleeding.

- Extended-duration prophylaxis for 30–42 days significantly reduced the frequency of symptomatic VTE (1.3% vs. 3.3%, OR 0.38; 95% CI 0.24–0.61, numbers needed to treat (NNT) = 50)

Figure 9. Review: prolonged prophylaxis – lower-limb arthroplasty, comparison: LMWH vs. placebo; outcome: clinical VTE

There was a greater risk reduction in patients undergoing hip replacement (1.4% vs. 4.3%, 0.33; 0.19–0.56, 34) compared with knee replacement (1.0% vs. 1.4%, 0.74; 0.26–2.15, NNT = 250).

A significant reduction in venographic DVT was also observed (9.6% vs. 19.6%, 0.48; 0.36–0.63, NNT = 10).

There was no increase in major bleeding.

There was an excess in minor bleeding (3.7% vs. 2.5%, 1.56; 1.08–2.26, numbers needed to harm (NNH) = 83).

Summary – orthopaedic surgery

**Intervention comparison: LDUH vs. placebo**

**Mixed orthopaedic patients**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>&gt;10^4 patients</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>&gt;10^4 patients</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
</tr>
</tbody>
</table>

**Increases in:**

| ‘Bleeding events’ | >10^4 patients | >10^4 patients |

---

**HFS (LDUH + LMWH)**

<table>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
</tr>
</tbody>
</table>

**Increases in:**

| ‘Bleeding events’ | –                | >10^4 patients |

---

**Intervention comparison: aspirin vs. placebo**

**HFS**

<table>
<thead>
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<tbody>
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<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
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</table>

**Increases in:**

| ‘Bleeding events’ | >10^4 patients |

---

**THR/TKR**

<table>
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<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
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</table>

**Increases in:**

| ‘Bleeding events’ | >10^4 patients |

---

**Intervention comparison: LMWH vs. aspirin**

**THR**

<table>
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<tr>
<th>Reductions in:</th>
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<tr>
<td>Asymptomatic DVT</td>
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<td>&gt;10^4 patients</td>
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</table>

**No difference in:**

| ‘Bleeding events’ | >10^4 patients |

---

**HFS**

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
</tr>
</tbody>
</table>

**Increases in:**

| ‘Bleeding events’ | >10^4 patients |

---

**Notes:**

- Randomised trial: Results from randomised trials.
- Meta-analysis: Results from meta-analyses.
- >10^4 patients: Results based on a sample size of at least 10^4 patients.
- No evidence: No evidence found for the intervention comparison.
### Intervention comparison: LMWH vs. UFH

**THR**

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<td>&gt;10^5 patients</td>
</tr>
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<td>Asymptomatic DVT</td>
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<td>&gt;10^4 patients</td>
</tr>
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<table>
<thead>
<tr>
<th>No difference in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
</tr>
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**TKR**

<table>
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<td>&gt;10^4 patients</td>
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<tbody>
<tr>
<td>Major bleeding</td>
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### Intervention comparison: LMWH vs. warfarin

**THR**

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<td>Death</td>
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<tr>
<td>Fatal PE</td>
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</tr>
<tr>
<td>Symptomatic VTE</td>
<td>&gt;10^4 patients</td>
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</tr>
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<table>
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<tr>
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<tbody>
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**TKR**

<table>
<thead>
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<td>Death</td>
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</thead>
<tbody>
<tr>
<td>Major bleeding</td>
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</table>

### Intervention comparison: fondaparinux vs. LMWH

**THR/TKR/HFS**

<table>
<thead>
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<th>Reductions in:</th>
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<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
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<table>
<thead>
<tr>
<th>Increases in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
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</table>
### Intervention: mechanical methods vs. control

#### THR: GCS

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<th>Reductions in:</th>
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<th>Meta-analysis†</th>
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<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^1 patients</td>
<td>&gt;10^1 patients</td>
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</tbody>
</table>

Increases in:

| Major bleeding | –                 | –              |

*Studies tend to be lower quality and non-blind
†Meta-analyses tend to group different surgical groups

#### THR: IPC

<table>
<thead>
<tr>
<th>Reductions in:</th>
<th>Randomised trial*</th>
<th>Meta-analysis†</th>
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</thead>
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<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^1 patients</td>
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</table>

Increases in:

| Major bleeding | –                 | –              |

*Studies tend to be lower quality and non-blind
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#### THR: FPs

<table>
<thead>
<tr>
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</thead>
<tbody>
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</table>

Increases in:

| Major bleeding | –                 | –              |

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#### TKR: GCS

<table>
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</thead>
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<td>Asymptomatic DVT</td>
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Increases in:

| Major bleeding | –                 | –              |

*Studies tend to be lower quality and non-blind
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#### TKR: IPC

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</table>

Increases in:

| Major bleeding | –                 | –              |

*Studies tend to be lower quality and non-blind
†Meta-analyses tend to group different surgical groups

#### TKR: FPs

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</table>

Increases in:

| Major bleeding | –                 | –              |

*Studies tend to be lower quality and non-blind
†Meta-analyses tend to group different surgical groups

#### LMWH (6 weeks) vs. LMWH (in-hospital)

<table>
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<tr>
<td>Asymptomatic DVT</td>
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<td>&gt;10^4 patients</td>
</tr>
</tbody>
</table>

No difference/increases in:

| Major bleeding | >10^3 patients | >10^3 patients |

Minor bleeding in:

| >10^3 patients | >10^3 patients |

*Studies tend to be lower quality and non-blind
†Meta-analyses tend to group different surgical groups
General medical inpatients
Summary tables on page 55.

Risk of VTE in hospitalised medical patients

VTE causes substantial mortality in hospitalised patients and is most prevalent in those admitted for reasons other than surgery. More than half of symptomatic VTE and around three-quarters of fatal PE occur in patients hospitalised for non-surgical reasons. Hospitalisation for an acute medical illness is independently associated with about an eightfold increased relative risk for VTE. Hospitalisation for an acute medical illness accounts for almost one-quarter of all VTE events within the general population.

Those acutely ill medical patients at risk of VTE include those with congestive heart failure, respiratory illness, and infectious or inflammatory disease. Such general medical inpatients who are not receiving prophylaxis are at a moderate risk for the development of VTE, with meta-analysis identifying the risk of DVT in internal medical patients who received no thromboprophylaxis to be approximately 19%.

This section reviews the clinical trials performed in medical care, excluding cases of acute ischaemic stroke and acute myocardial infarction, in order to assess the prophylactic efficacy and safety of mechanical and pharmacological agents in such patients.

Data review

Data in this section are derived from four principal sources:

1. The principal meta-analysis in this therapeutic area. This was performed by Mismetti et al., and gives a detailed overview of the studies conducted with heparin (either UFH or LMWH), and the generalised findings. The meta-analysis included an analysis of 17 randomised clinical trials in medical patients, excluding those performed in patients with an acute myocardial infarction or ischaemic stroke, who received either UFH or LMWH.

2. The ACCP guidelines. The ACCP guidelines provide the most detailed review of the literature available. Published in 2004, the ACCP guidelines build on the studies included in the meta-analysis. ACCP identified three additional high-quality, randomised, placebo-controlled trials (known as MEDENOX, PREVENT and ARTEMIS), which had been completed and published since the meta-analysis, and which provide higher-quality data than those studies included in the meta-analysis. Strengths of these three studies are: inclusion of a more defined patient population through the application of more rigorous inclusion criteria; and the use of bilateral venography as the definitive screening method (in MEDENOX and ARTEMIS).

3. The HTA review (Vol. 9; No. 49). The HTA review set out to assess the benefits in terms of reductions in the risks of DVT and PE, and hazards in terms of major bleeding, of: mechanical compression; oral anticoagulants; dextran; and regional anaesthesia in surgical and medical patients. The HTA assessment was conducted on all studies published up to 2001 and includes assessment of oral anticoagulation and mechanical methods in medical patients.

4. A literature review. Searches were conducted to identify additional papers published since the publication of the three data sources outlined above.

Interventions

Ten randomised trials in medical patients have compared a heparin-derived agent (LDUH, LMWH or fondaparinux) with placebo (Table 8). LDUH and LMWH have been directly compared in seven randomised clinical trials (Table 9).

Mortality

LDUH

Two randomised clinical trials have assessed the effect of LDUH on mortality:

- A group of 927 general medical patients were given either LDUH, 5000 U sc bid, or no prophylaxis until they were discharged from hospital or were fully mobile. Randomisation was based on the hospital record number and was subject to recruitment bias, and therefore is not included in the tabulation of randomised studies. An intention-to-treat analysis showed the all-cause mortality rate was 7.8% among those who were randomised to LDUH, and 10.9% in the control group (p <0.05). VTE was not reported.
In a Swedish clinical trial of 11,693 patients admitted to hospital with acute infection, participants were randomised to receive either LDUH, 5000 U sc bid, until hospital discharge, or no prophylaxis. The study showed mortality rates were similar in the heparin and control groups (5.3% vs. 5.6% respectively; p < 0.4). Autopsy-proven PE rates were also similar, but there were fewer non-fatal VTE events in the LDUH group (116 vs. 70 respectively; p < 0.001)

LMWH

Three randomised clinical trials have included an assessment of the effect of LMWH on mortality:  
- In 270 medical patients, there was a 4.4% mortality rate by 10 days in both the placebo and LMWH groups.  
- In 2474 patients who had been admitted to hospital with an acute medical condition and randomised to receive LMWH or placebo for up to 21 days, the overall in-hospital mortality rate was 10% in both groups.  
- In the MEDENOX trial, mortality rates at 14 days were seen in 4.4%, 4.3% and 3.3% respectively, in the placebo, enoxaparin 20 mg, and enoxaparin 40 mg recipients

UFH vs. placebo

In five older studies comparing with placebo/no intervention, LDUH at high prophylactic doses reduced the relative risk of FUT-detected DVT by approximately 70%, without an increased risk of bleeding, compared with placebo.

Symptomatic VTE/asymptomatic VTE

UFH or LMWH

A meta-analysis offers the best overall data review of the efficacy and safety of UFH or LMWH in the prevention of symptomatic and asymptomatic VTE.  
- There was no effect on mortality with heparin  
- Prophylaxis with heparin (UFH and LMWH) was associated with a 52% RRR to placebo in clinical PE  
- Heparin was associated with a 56% risk reduction relative to placebo in systematically detected DVT of the lower limbs  
- There was no significant increase in the incidence of major haemorrhage  
- In trials comparing UFH with LMWH, there was no significant difference between the two types of anticoagulant with respect to the incidence of DVT, clinical PE, and mortality  
- LMWH reduced the risk of major haemorrhage in comparison with UFH (relative risk: 0.48, P = 0.049)

LMWH/fondaparinux vs. placebo

The most modern, well-conducted studies, known as MEDENOX, PREVENT and ARTEMIS, provide data on combined endpoints of VTE, both asymptomatic and symptomatic (Table 10).  

In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, enoxaparin, either 20 or 40 mg sc once daily, was compared with placebo in 1102 hospitalised medical patients, most of whom had congestive heart failure, acute respiratory failure, or an acute infection.

- The rates of DVT detected by venography or duplex ultrasonographic scanning (DUS) between days 6 and 14 were 14.9% in the 288 patients receiving placebo, 15.0% in the 287 patients receiving enoxaparin 20 mg, and 5.5% in the 291 patients receiving enoxaparin 40 mg (p < 0.001 for enoxaparin 40 mg vs. placebo)  
- The protection observed with enoxaparin 40 mg daily, extended to each of the major medical subgroups, including those with acute infection, heart failure and respiratory failure  
- Major bleeding occurred in 1.1%, 0.3%, and 1.7% of the patients respectively

The PREVENT Thromboprophylaxis Study compared the efficacy and safety of prophylaxis with the LMWH dalteparin, 5000 U sc once daily, with matching placebo in 3706 hospitalised medical patients who were at moderately high risk for VTE. Prophylaxis was continued for 14 days, and a DUS was routinely obtained before day 21. The primary endpoint was the development of symptomatic VTE, sudden death, and/or DUS-screened proximal DVT.

- This endpoint was reached in 2.8% of dalteparin recipients, compared with 5.0% of those in the placebo group (RRR, 45%; 95% CI, 20 to 62%; p < 0.0015; NNT, 46)  
- Two patients in the placebo group developed fatal PE by day 21, compared with none in the dalteparin group  
- Major bleeding occurred in 0.5% and 0.2% respectively of the dalteparin and placebo patients
The ARTEMIS study assessed the thromboprophylaxis efficacy of the synthetic Factor Xa inhibitor fondaparinux, 2.5 mg sc, od in a blinded, placebo-controlled study in acutely ill medical patients.\textsuperscript{104} The primary outcome was a composite of DVT detected by routine venogram between days 6 and 15 and symptomatic VTE.

- The endpoint occurred in 10.5\% and 5.6\% respectively of the patients who received placebo and fondaparinux ($p <0.029$)
- Fatal PE, a secondary outcome, was also significantly reduced in the fondaparinux recipients (5 vs. 0 events)
- Major bleeding was seen in 0.2\% of patients in both groups

**Mechanical methods**

No randomised clinical trials have evaluated mechanical methods of prophylaxis in general medical patients (evidence provided by ACCP\textsuperscript{1} and HTA assessment\textsuperscript{2}).
Table 8. Summary of findings of randomised trials of heparin-derived agents versus placebo (or not agent) in acutely ill medical patients

<table>
<thead>
<tr>
<th>Primary author or trial name</th>
<th>Gallus</th>
<th>BELCH</th>
<th>CADE</th>
<th>GARDLUND</th>
<th>DAHAN</th>
<th>IBARRA-PEREZ</th>
<th>BERGMANN</th>
<th>MEDENOX</th>
<th>PREVENT</th>
<th>ARTEMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Single-centre, randomised, double-blind, two parallel group</td>
<td>Single-centre, randomised, double-blind, two parallel group</td>
<td>Single-centre, randomised, single study</td>
<td>Single-centre, phase II, randomised, double-blind, two parallel group</td>
<td>Single-centre, randomised, double-blind, two parallel group</td>
<td>Multicentre, randomised, double-blind, two parallel group</td>
<td>Multicentre, randomised, double-blind, two parallel group</td>
<td>Multicentre, randomised, double-blind, two parallel group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient inclusion criteria</td>
<td>Congestive heart failure (CHF)</td>
<td>&gt;40 years, &lt;80 years plus hospitalised with heart failure or chest infection</td>
<td>&gt;55 years plus hospitalised with medical ward or coronary care unit</td>
<td>&gt;50 years plus hospitalised with an acute infectious disease</td>
<td>&gt;40 years plus hospitalised with an acute medical illness</td>
<td>Mean age 76 years, expected stay &gt;6 days, immobilised for ≤3 days and CHF (New York Heart Association NYHA III/IV), acute respiratory illness, or infection or inflamed bowel, rheumatic/arthritic disorder plus one risk factor</td>
<td>Multicentre, randomised, double-blind, two parallel group</td>
<td>Multicentre, randomised, double-blind, two parallel group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient number</td>
<td>26</td>
<td>100</td>
<td>131</td>
<td>11,693</td>
<td>270</td>
<td>192</td>
<td>2472</td>
<td>1102</td>
<td>2472</td>
<td>839</td>
</tr>
<tr>
<td>Test drug</td>
<td>UFH 5000 IU, sc, tid</td>
<td>UFH 5000 IU, sc, tid</td>
<td>UFH 5000 IU, sc, tid</td>
<td>Enoxaparin 60 mg, sc, od</td>
<td>UFH 5000 U, sc, bd; ASA; GCS</td>
<td>Nadroparin 7500 IU, sc, od</td>
<td>Enoxaparin 20 mg or enoxaparin 40 mg, sc, od</td>
<td>Fondaparinux 2.5 mg, sc, od</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>No agent</td>
<td>No agent</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Treatment duration</td>
<td>11 days</td>
<td>14 days or discharge</td>
<td>10 days or until ambulant or until DVT or PE episode</td>
<td>Maximum 21 days or discharge</td>
<td>10 days</td>
<td>Until ambulant</td>
<td>Maximum 21 days or discharge</td>
<td>6–14 days</td>
<td>Maximum 21 days or discharge</td>
<td>6–15 days</td>
</tr>
<tr>
<td>Follow-up</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>21 days</td>
<td>None</td>
<td>None</td>
<td>14 days (ie day 21)</td>
<td>90 days (day 83 to 110)</td>
<td>14 days (ie day 21)</td>
<td>30 days (ie day 21)</td>
</tr>
<tr>
<td>VTE measurement (primary efficacy criteria)</td>
<td>Isotopically detected DVT (FUT at day 11)</td>
<td>Isotopically detected DVT (FUT at entry and every other day)</td>
<td>Isotopically detected DVT (FUT at entry and every day)</td>
<td>Autopsy-documented PE</td>
<td>Isotopically detected DVT (FUT at entry and every day) or documented symptomatic DVT or PE</td>
<td>Autopsy-documented PE</td>
<td>VTE at day 14: venographically detected DVT or documented symptomatic DVT or PE</td>
<td>Venographically detected DVT or documented symptomatic DVT or PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE rate (test) VTE (control) Bleeding</td>
<td>9.1%</td>
<td>4.67%</td>
<td>0.44%</td>
<td>2%</td>
<td>0.57%</td>
<td>3%</td>
<td>2.5% (heparin)</td>
<td>0.81%</td>
<td>5.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>NK</td>
<td>4%</td>
<td>10%</td>
<td>0%</td>
<td>11.1%</td>
<td>13.7%</td>
<td>14.9%</td>
<td>%</td>
<td>10.5%</td>
<td></td>
</tr>
</tbody>
</table>
### Table 9. Summary of findings of randomised trials of heparin-derived agents vs. placebo (or not agent) in acutely ill medical patients

<table>
<thead>
<tr>
<th>Primary author or trial name</th>
<th>HARENBURG</th>
<th>AQUINO</th>
<th>FORETTE</th>
<th>PRIME</th>
<th>EMSG</th>
<th>HARENBURG</th>
<th>PRINCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Single-centre, randomised, double-blind, two parallel group</td>
<td>Multicentre, randomised, open study</td>
<td>Multicentre, randomised, open study</td>
<td>Multicentre, phase III, randomised, double-blind, two parallel group</td>
<td>Multicentre, phase IV, randomised, double-blind, two parallel group</td>
<td>Multicentre, phase III, randomised, open (blinded central reading), two parallel group</td>
<td></td>
</tr>
<tr>
<td>Patient inclusion criteria</td>
<td>&gt;40 years, &lt;80 years plus hospitalised with acute medical illness plus immobility &gt;7 days</td>
<td>Various and elderly</td>
<td>Mean age 83 years plus hospitalised with an acute medical illness plus immobilised</td>
<td>&gt;18 years plus hospitalised with an acute medical illness, with recent mobility reduction and an additional predefined risk factor for VTE</td>
<td>&gt;18 years plus &gt;20 kg body weight plus hospitalised with an acute medical illness, with recent mobility reduction (&lt;3 days)</td>
<td>&gt;40 years plus recent immobility plus hospitalised with acute heart failure (III or IV), respiratory disease, infectious disease, rheumatic disease, or inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Patient number</td>
<td>665</td>
<td>99</td>
<td>295</td>
<td>959</td>
<td>442</td>
<td>1968</td>
<td>665</td>
</tr>
<tr>
<td>Test drug</td>
<td>LMWH (1.5 aPTT units), sc, od</td>
<td>Nadroparin 3075 IU, sc, od</td>
<td>Nadroparin 3075 IU, sc, od</td>
<td>Enoxaparin 40 mg, sc, od</td>
<td>Enoxaparin 20 mg, sc, od</td>
<td>Nadroparin 36 mg, sc, od</td>
<td>Enoxaparin 40 mg, sc, od</td>
</tr>
<tr>
<td>Control</td>
<td>UFH 5000 IU, sc, td</td>
<td>UFH 10,000–15,000 IU, sc, bid</td>
<td>UFH 5000–7500 IU, sc, tid</td>
<td>UFH 5000 IU, sc, td</td>
<td>UFH 5000 IU, sc, bd</td>
<td>UFH 5000 IU, sc, td</td>
<td>UFH 5000 IU, sc, td</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7–12 days</td>
<td>10 days</td>
<td>28 days</td>
<td>7 days</td>
<td>10 ± 1 days</td>
<td>8–11 days</td>
<td>10 ± 2 days</td>
</tr>
<tr>
<td>Follow-up</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>14 days (day 21)</td>
<td>None</td>
<td>None</td>
<td>30 days (day 40)</td>
</tr>
<tr>
<td>VTE measurement (primary efficacy criteria)</td>
<td>Clinical investigation, serial impedance plethysmography, and ultrasound</td>
<td>Ultrasound-detected DVT</td>
<td>Documented symptomatic DVT or PE</td>
<td>VTE at day 7: ultrasound-detected DVT before and at end of study treatment ± confirmatory venography or documented symptomatic DVT or PE</td>
<td>VTE at day 10: isotope detected DVT (PFT at entry and every day) or documented symptomatic DVT or PE</td>
<td>Symptomatic DVT or asymptomatic proximal DVT by ultrasound or clinical PE by high-probability scan</td>
<td>VTE at day 10: DVT confirmed by venography in +ve D-dimer/fibrin monomer test or clinical signs or documented symptomatic PE</td>
</tr>
<tr>
<td>VTE rate (test) VTE (control)</td>
<td>3.6% 4.5%</td>
<td>2.0% 2.0%</td>
<td>2.1% 2.7%</td>
<td>0.2% 1.4%</td>
<td>4.8% 4.6%</td>
<td>0.74% 0.51%</td>
<td>8.4% 8.4%</td>
</tr>
</tbody>
</table>

*and one additional risk factor for VTE
Table 10. A comparison of the principal randomised trials in acutely ill medical patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>Year</th>
<th>Inclusion criteria</th>
<th>Outcomes: proximal DVT + symptomatic VTE (at day 14–21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEEDONY</td>
<td>Enoxaparin</td>
<td>1999</td>
<td>Age ≥40 Expected stay ≥6 days, immobilised for ≤3 days and – CHF (NYHA III/IV) – acute respiratory illness or – infection or inflamed bowel, rheumatic/arthritis disorder and plus one risk factor</td>
<td>Enoxaparin 2.1% Placebo 6.6% RR~50% P=0.037</td>
</tr>
<tr>
<td>PREVENT</td>
<td>Dalteparin</td>
<td>2003</td>
<td>Age ≥40 Expected stay ≥4 days, immobilised for ≤3 days and – CHF (NYHA III/IV) – acute respiratory illness or – infection or inflamed bowel, rheumatic/arthritis disorder and plus one risk factor</td>
<td>Dalteparin 2.6% Placebo 5.0% RR~50% P=0.002</td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>Fondaparinux</td>
<td>2003</td>
<td>Age ≥60 Expected stay ≥4 days and – CHF (NYHA III/IV) – acute respiratory illness – acute infectious or inflammatory disease and no other risk factor</td>
<td>Fondaparinux 1.5% Placebo 3.4% RR~50% P=0.085</td>
</tr>
</tbody>
</table>

Summary – medical patients

**Intervention comparison: UFH vs. placebo**

<table>
<thead>
<tr>
<th>Reductions in</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>&gt;10^3 patients</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>No difference in:</td>
<td>Bleeding episodes</td>
<td>–</td>
<td>&gt;10^3 patients</td>
</tr>
</tbody>
</table>

**Intervention comparison: LMWH vs. UFH**

<table>
<thead>
<tr>
<th>Reductions in</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>No difference in:</td>
<td>Major bleeding</td>
<td>–</td>
<td>&gt;10^4 patients</td>
</tr>
<tr>
<td></td>
<td>Minor bleeding</td>
<td>–</td>
<td>&gt;10^4 patients</td>
</tr>
</tbody>
</table>

**Intervention comparison: LMWH vs. placebo**

<table>
<thead>
<tr>
<th>Reductions in</th>
<th>Randomised trial</th>
<th>Meta-analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>–</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>&gt;10^4 patients</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>No difference in:</td>
<td>Major bleeding</td>
<td>&gt;10^4 patients</td>
<td></td>
</tr>
</tbody>
</table>
References


43. RD Heparin Arthroplasty Group. 'RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty', *JBJS*, 1994; 76: 1174–85.


Background

The Health Committee inquiry into VTE heard considerable evidence that many doctors are unaware of the extent of VTE, how readily it can be prevented, and that VTE was generally not regarded as an educational priority.

On the basis of this evidence, the Health Committee recommended that:

VTE, its prevention, the implementation and adherence to guidelines relating to thromboprophylaxis, including counselling and risk assessment, be given more prominence in undergraduate education, Continuing Professional Development (CPD), and other relevant aspects of medical and paramedical training. In addition, NHS Trusts should ensure that all physicians and surgeons receive training about the subject.

VTE is generally taught within the curricula and the teaching programmes of the various members of the healthcare teams. However, from the evidence presented to the Health Committee, the question has arisen as to whether or not there is a general appreciation of the relative importance of VTE. General consensus suggests that undergraduate medical education is strong on pathophysiology of thrombosis, but weak on epidemiology, patient management and integrating these different strands of knowledge. This is not just at undergraduate level but also post-qualification and as part of continuing professional development (CPD). The Academy of Medical Royal Colleges has now included thromboprophylaxis in curricula for postgraduate medical training, and the Chief Medical Officer has already written to the Council of the Heads of Medical Schools regarding inclusion in undergraduate curricula. With regard to nursing, much as medical education at undergraduate level, the relevant educational institutions determine their own curriculum.

However, the amount of educational material provided to other healthcare groups is uncertain. It is felt that appropriate perception of the importance and the knowledge of VTE is critical to successful implementation of widespread prevention strategies. The remit of this subgroup was to establish in education terms what is available, what gaps there are, how these could be remedied, and then how a broader strategy of education could be implemented across the healthcare community and this implementation assessed.

From data gathered, it is clear that there is a relative paucity of education about VTE and its prevention. VTE may be taught at undergraduate level, but the content of the taught material is individually dependent upon the institution. At postgraduate level and within CPD programmes, VTE teaching is again variable. Information is available on the internet from interested groups but is likely not to be a widely used resource and, furthermore, is of variable quality and complexity. We are only aware of one specific teaching course on VTE and its prevention.

In addition, we received opinion that, generally, in NHS management with regard to VTE there is a lack of awareness that this is a significant clinical problem, and that, rather than education per se, financial and ‘performance’ concerns form a more persuasive argument.

Draft proposals

On the basis of opinion sought to date, tested in a teleconference and at a meeting of the systems and processes subgroup, it was observed that:

- Initially, general practice was excluded from this exercise as the primary target of the Health Committee recommendations was secondary care. However, in discussions it is apparent that primary care needs to be involved in the education process. This is to improve general awareness, deal with the potential roll-out of
thromboprophylaxis into the community after early discharge (not just extended prophylaxis) and allow patient concerns to be addressed appropriately. A clear strategy for delivery of GP-based education will require future consideration once the secondary care-orientated approach is defined.

- Education of hospital staff and assessment and initiation of thromboprophylaxis are of major importance. The educational process has two key elements:
  - an understanding of the importance of VTE prophylaxis, in order to motivate individuals to take action
  - providing knowledge about what to do and how to do it in relation to both assessment for VTE risk and appropriate use/implementation of thromboprophylaxis measures

- We have identified four key groups of staff:
  - nursing staff – this group is likely in the main to be performing risk assessment and the first point of contact
  - medical staff – this group will predominantly be prescribing, carrying out ‘extended’ assessment, if required, and/or referring on for advice
  - pharmacy – in relation to ‘policing’ and checking for correct doses, etc. In addition, pharmacists would also be a good group to involve in the audit process
  - management – to raise the profile of the problem so that appropriate resources are available and the importance of VTE prevention is recognised

- There are three specific educational tasks:
  - How to educate staff.
    Training should not be mandatory. There should be a performance framework, and implicit in this would be the requirement for VTE training for specific groups of staff. Institution induction could be used as an opportunity for a short VTE training session. There are two broad approaches: ‘top down’ or ‘bottom up’ for key groups of staff. ‘Top-down’ education would involve educating senior staff first, ensuring that VTE prophylaxis is discussed at relevant meetings, and developing ‘champions’, including relevant managers. It would also involve thrombosis committees, where they exist. The ‘bottom-up’ approach involves training larger numbers within wards and directorates, and making sure that VTE prophylaxis is in the junior medical staff induction programmes.
    Principal strategies include:
    - development of core educational materials, so that it is possible to convey the right information in no more than 15 minutes. To cover all groups, two sets may be required: one each for ‘top-down’ and ‘bottom-up’ teaching. We believe that these core educational materials should be formulated centrally by consensus agreement
    - development of a standardised core assessment tool and use of this tool to educate through ward-based piloting of use
    - development of a standardised counselling guide/patient information leaflet for counselling and educational use
    - development of appropriate ‘screen savers’ for intranets
    - development of graded internet-based or other e-learning accreditable competency modules/educational packages for those concerned with thromboprophylaxis (akin to the transfusion models and modules being drawn together for the National Patient Safety Agency (NPSA) on anticoagulant use).

- A lead pharmacist should be identified in each Trust, possibly the one already associated with the anticoagulation service. As well as basic education and training, there will be a need for more specialised training for a small number of staff, such as the lead doctor, nurse and pharmacist in each Trust. Each Trust needs an educational champion and a thromboprophylaxis lead at departmental level. It will be necessary to publicise the relevant academic meetings and promote attendance.

- Ensuring that education happens (and adding incentives/pressure as required).
  This could be supported by various regulatory bodies, such as the NPSA, the Clinical Negligence Scheme for Trusts (CNST) or the Healthcare Commission, the latter having application in the independent sector.
  It was noted that, from a managerial perspective, this would be of major importance and drive any Trust ‘support’ for thromboprophylaxis implementation.
and education. Without some form of quality or financial incentive, appropriate training was unlikely to occur. There was universal agreement that this type of incentive was likely to have a major impact on the final effectiveness of implementation, not just that of education delivery.

- **Measuring** the outcome of education programmes.

  Education is a means to an end (in this case, the proper assessment of all patients and the appropriate thromboprophylaxis). Hence the end rather than the means should be assessed. In other words, education should not be enforced directly but Trusts should **want** to do it in order to perform well on measures of assessment or prophylaxis quality and completeness.

- Public education is a very important component and this is alluded to above. Currently, there are many generally accessible sources of information on VTE (>2.6 million hits for DVT and >1.1 million for VTE on Google search engine). However, the information provided is of variable quality and directed at a variety of target audiences, with the possibility of inconsistency and misconception. A public awareness campaign would be an important step in implementing the VTE strategy for both patients and staff. A public education process would be a key supportive measure in ensuring promotion of staff-based education/training, as well as underlining clear importance in terms of general awareness.

  Any public awareness campaign should be centrally formulated and standardised before widespread public dissemination to ensure consistency with other educational materials used for this strategy.

- General awareness of VTE can also be raised by considering implementing the recommendation in the Health Committee report to notify by letter the original surgeon and/or physician should a patient develop VTE or die as a consequence of VTE (paragraph 33 of the Health Committee report).
Annex 5
Terms of reference of the independent expert working group

The VTE independent expert working group is asked to:

- consider how current best practice and guidance can be promoted and implemented and what resources might be needed to support delivery of any strategy through existing structures. This should include consideration of the need to promote or clarify existing guidance on the use of:
  - mechanical devices (foot pumps)
  - aspirin
  - other pharmacological preparations (heparin or other anti-Xa agent)
- recommend action for implementation pending publication of National Institute for Health and Clinical Excellence (NICE) VTE clinical guidelines in 2007

In making its recommendations, the expert working group should limit its recommendations to implementation of existing VTE guidance and good practice. It is the role of NICE to make recommendations on new guidance.

The group is asked to submit its report and recommendations to the Chief Medical Officer by July 2006 (earlier if possible).
Annex 6
Membership of the independent expert working group

Dr Anita Thomas, PhD, FRCP
Title: Consultant Physician, Plymouth Hospitals NHS Trust
Role: Chair

Dr Anita Thomas is a consultant physician at Plymouth Hospitals NHS Trust, specialising in acute internal medicine and care of older people. Dr Thomas was a member of the team that prepared the successful bid for the new Peninsula Medical School at the Universities of Exeter and Plymouth. She has twice served on Council of the Royal College of Physicians, examines for the College, and is a lead assessor for the General Medical Council professional performance procedures.

Dr Thomas is a board member of the Postgraduate Medical Education and Training Board (PMETB), Chair of the PMETB statutory Training Committee and a member of the Food Standards Agency Scientific Advisory Committee on Nutrition (SACN), and was a member of the Expert Group on Vitamins and Minerals (EVM). She is a member of the Lowermoor subgroup of the Committee on Toxicity, reporting on the health effects of the Camelford water pollution incident.

Professor Paul Gregg, MD, FRCS, FRCS (Ed)
Title: Consultant Orthopaedic Surgeon and Professor of Orthopaedic Surgical Science, James Cook University Hospital, Middlesbrough
Role: Representing the British Orthopaedic Association

Professor Paul Gregg is the past president of the British Orthopaedic Association and the author of papers on thromboprophylaxis in orthopaedic surgery.

Dr Andrew Miller
Title: General Physician, Mayday Healthcare NHS Trust, Croydon
Role: Representing the British Thoracic Society

Dr Andrew Miller, who trained at Oxford University, has been consultant general and chest physician at Mayday University Hospital since 1983. He is a national authority and guideline developer on pulmonary embolism, and represents both the British Thoracic Society and the Royal College of Physicians on the working party.

Dr Jonathan Boyce, DM, FRCP, FFPH
Title: Head of External Outputs, Healthcare Commission
Role: Representing the Healthcare Commission

Dr Jonathan Boyce trained in medicine at Oxford, and then in public health in London. He was Director of Health at the Audit Commission for several years before joining the Healthcare Commission in 2004.
Mr John Scarpello, MD, FRCP
Title: Consultant Physician, Department of Diabetes and Endocrinology, University Hospital of North Staffordshire, Stoke-on-Trent
Role: Representing the National Patient Safety Agency as their Deputy Medical Director

Ms Rebecca Brown, SRN, DN Cert, MHS Cert
Title: Anticoagulation Course Leader/Nurses’ Representative
Ms Rebecca Brown is an anticoagulation nurse specialist and a course tutor on the University of Hertfordshire thromboprophylaxis course. She is also an executive member of CLOT (Clinical Leaders of Thrombosis) and a course tutor in anticoagulation for nurse specialists and pharmacists.

Mr Alistair Flowerdew MBBS, MS, FRCS
Title: Medical Director, Salisbury NHS Foundation Trust
Role: Representing the NHS Confederation
Mr Alistair Flowerdew is the executive responsible for clinical governance at Salisbury NHS Foundation Trust and is currently undertaking a project to develop a consistent VTE prophylaxis strategy in this acute hospital trust to increase patient safety. He was previously a full-time consultant general surgeon at West Dorset General Hospitals NHS Trust and practises surgery part time in Salisbury.

Dr Roopen Arya, BMBCh, MA, PhD, FRCP, FRCPath
Title: Consultant Haematologist, King’s College Hospital, London
Dr Roopen Arya is a consultant and lead clinician in haematological medicine and the clinical lead for clinical thrombosis and anticoagulation services at King’s College Hospital.

Dr Trevor Baglin, MB, ChB, PhD, FRCP, FRCPath
Title: Consultant Haematologist, Department of Haematology, Cambridge University Hospitals NHS Foundation Trust
Dr Trevor Baglin is clinical director for haemostasis and thrombosis at Addenbrooke’s Hospital in Cambridge. He has developed a multidisciplinary team for the treatment of bleeding and thrombotic disorders, promoting out-of-hospital care and self-management. His main research interests are in the regulation of thrombin generation and the use of laboratory tests to measure thrombosis risk. Dr Baglin is Chair of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology.

Dr Alexander Cohen, MBBS, MSc, MD, FRACP
Title: Honorary Consultant Vascular Physician, Department of Surgery, Guy’s, King’s and St Thomas’ School of Medicine, London; Vascular Physician, University Hospital Lewisham and St George’s Hospital, London
Dr Alexander Cohen is a member of the International Union of Angiology, the International Society on Thrombosis and Haemostasis, the British Society for Haemostasis and Thrombosis, the Cochrane Review Group for Systemic Overviews, the Internal Medicine Society of Australia and New Zealand, and the Formulary Committee at Guy’s, King’s College, Lewisham and St Thomas’ Hospitals. He has written and co-authored over 170 papers and abstracts since 1990.
Dr Cohen is a regular editor for the peer-reviewed journals *Thrombosis and Haemostasis*, *Journal of Thrombosis and Haemostasis* and *The Lancet* and a reviewer for the NHS Centre for Reviews and Dissemination and the *Drug and Therapeutics Bulletin*. He is an adviser as a vascular physician and epidemiologist to the UK Government Select Health Committee, on the all-party Working Group on Thrombosis and to the Department of Health and NHS on the prevention of VTE. He is also an adviser to the thrombosis charity Lifeblood.

Professor David Fitzmaurice, MD, FRCGP
Title: GP and Professor of Primary Care, Department of General Practice and Primary Care, University of Birmingham
Professor David Fitzmaurice is director of anticoagulation training courses accredited by the University of Birmingham, Chair of the Anticoagulation Working Party of the Primary Care Cardiovascular Society, and medical adviser to AntiCoagulation Europe.
Dr Beverley Hunt, MB, ChB, FRCP, FRCPath, MD

Title: Acting Co-director of Pathology, Department of Haematology and Lupus Unit, Guy’s and St Thomas’ NHS Foundation Trust

Dr Beverley Hunt is medical director of Lifeblood, the thrombosis charity, and head of service for laboratory haematology and molecular diagnostics in the Departments of Haematology, Pathology and Rheumatology at Guy’s and St Thomas’ NHS Foundation Trust. Dr Hunt is an expert in the management of VTE and gave evidence at the Health Select Committee.

Dr Peter Jackson, PhD, FRCP, FFPM (Dis)

Title: Clinical Pharmacologist, University of Sheffield

Dr Peter Jackson is reader in clinical pharmacology and therapeutics at the University of Sheffield and a general physician at Sheffield Teaching Hospitals NHS Foundation Trust, and he heads the Sheffield Hypertension Clinic. He is a member of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment for the Food Standards Agency and the Department of Health, and heads a NICE appraisal panel. Dr Jackson is secretary to the Specialist Advisory Committee in Clinical Pharmacology and Therapeutics, Chair of the regional training committee and programme director.

Dr Jackson is also a long-term member of, and currently secretary to, the Board of Examiners for the Diploma in Pharmaceutical Medicine examination. His research interests lie in the absolute risk approach to disease prevention and he was a member of the group developing the ‘Sheffield Table’. He is currently undertaking a Cochrane review of the use of aspirin in the primary prevention of vascular disease.

Professor Ajay Kakkar, BSc, MBBS (Hons), PhD, FRCS

Title: Professor of Surgical Science and Consultant Surgeon, Barts and The London, Queen Mary’s School of Medicine and Dentistry

Professor Ajay Kakkar joined Barts and the London in July 2004 and leads the newly established Centre for Surgical Science. His research focuses on: the prevention and management of VTE, with particular interest in the cancer patient; the use of antithrombotic agents, and in particular the low-molecular-weight heparins, for the prolongation of survival in patients with malignant disease; and the role of the activated coagulation serine proteases and their receptors (Factor Vlla/Tf, Factor Xa/PAI-1 and thrombin/PAI-1/3) in tumour growth invasion metastasis and angiogenesis through the techniques of gene analysis, gene transfer, standing molecular biological techniques and protein expression.

Squadron Leader Ed Nicol, BMedSci, BM, BS, MRCP, RAF

Title: Specialist Registrar in Cardiology and General Internal Medicine, Royal Brompton and Harefield NHS Trust

Dr Ed Nicol is a specialist registrar in cardiology and general internal medicine and a Royal Air Force Medical Officer. He is a Royal College of Physicians associate tutor and junior doctor representative on the committee responsible for advising on issues relating to frontline implementation to junior medical staff. Dr Nicol is an adviser on aviation-related issues in VTE.

Professor John Pasi, MB, ChB, PhD, FRCP, FRCPath, FRCPCH

Title: Professor of Haemostasis and Thrombosis, Centre for Haematology, Institute of Cell and Molecular Science, Barts and The London, Queen Mary’s School of Medicine and Dentistry

Professor John Pasi has been actively involved in the development of national policy and guideline formulation across a broad range of haemostatic and thrombotic disorders, including acting as adviser to the Health Committee of the House of Commons. Along with these activities, he has a longstanding interest in clinical training and has been active in developing newer models of training initiatives.
Mr David Warwick, MD, FRCS, FRCS (Orth)

Title: Consultant Orthopaedic Surgeon, Southampton University Hospitals NHS Trust

Mr David Warwick has been researching orthopaedic thromboembolism since 1991. This work led to a Hunterian Professorship at the Royal College of Surgeons and a doctorate from the University of Bristol. He has published 17 papers in peer-reviewed journals, has written several invited articles and has presented at dozens of national and international meetings. He is a co-author of the THRIFT guidelines (1998), the International Consensus Statement (International Union of Angiology, 2001) and forthcoming International Consensus Statement revision.

Mr Warwick reviews papers on orthopaedic thrombosis for the Journal of Bone and Joint Surgery and is co-author of the latest edition of Apley’s System of Orthopaedics and Fractures. He lectures regularly on orthopaedic thromboembolism in Britain and abroad. Most recently he has been an invited instructor at the American Academy of Orthopaedic Surgeons and a witness to the UK parliamentary inquiry into thromboembolism.

Mr Geoff Pope

Title: Patient Adviser, Citizens Advice
Role: Representing Citizens Advice

Dr Simon Gibbs

Title: Cardiologist, Hammersmith Hospital, London
Role: Representing the British Cardiac Society

Dr Simon Gibbs is a senior lecturer in cardiology at the National Heart and Lung Institute, Imperial College London. He is honorary consultant cardiologist at Hammersmith Hospital, where he is lead clinician for the pulmonary hypertension service, which is designated by the National Specialist Commissioning Advisory Group (NSCAG). He has a long-standing clinical and research interest in the pulmonary circulation, and is involved in guideline development for pulmonary hypertension.

Ms Sally Clarke

Title/role: Victim of VTE

Observers and Secretariat

Professor Tom Treasure, MD, MS, FRCS

Title: Professor of Cardiothoracic Surgery, Guy’s Hospital
Role: Observer, representing NICE

Professor Tom Treasure is Chair of the NICE Guideline Development Group (with the National Collaborating Centre for Acute Care) for prophylaxis of VTE/PE in patients undergoing surgery.

Dr Mercia Page

Title: Observer
Role: Representing NICE

Dr Jayne Spink

Title: Observer
Role: Representing NICE

Dr Sunjai Gupta, OBE

Title: Observer
Role: Department of Health

Dr Denise O'Shaugnessy

Title: Observer
Role: Department of Health

Tim Brown

Title: Secretariat
Role: Department of Health
Subgroups

Guidelines
Trevor Baglin (Chair)
Peter Jackson
John Scarpello
Adrian Newland
Paul Gregg
Tom Treasure (Observer)

Interventions
Ajay Kakkar (Chair)
David Warwick
Ander Cohen
Tom Treasure (Observer)

Systems and processes
Jonathan Boyce (Chair)
Roopen Arya
Ed Nicol
John Pasi
David Fitzmaurice
Beverley Hunt
Rebecca Brown
Annex 7
Useful links

Academy of Medical Royal Colleges
The objective of the Academy of Medical Royal Colleges is to coordinate the work of the Medical Royal Colleges and Faculties.
www.aomrc.org.uk

British Cardiovascular Society
The British Cardiovascular Society was established in 1922 and is a charitable body. The Society is involved in education, the setting of clinical standards and research into heart and circulatory diseases.
www.bcs.com

British Committee for Standards in Haematology
The British Committee for Standards in Haematology (BCSH) is a sub-committee of the British Society for Haematology. The primary purpose of the BCSH is to provide haematologists with up-to-date advice on the diagnosis and treatment of haematological disease by producing evidence-based guidelines using a well-defined BCSH process.
www.bcshguidelines.com

British Orthopaedic Association
The British Orthopaedic Association provides education and practice management services for orthopaedic surgeons and health professionals.
www.boa.ac.uk

British Society for Haematology
The objectives of the British Society for Haematology are to advance the practice and study of haematology and to facilitate contact between people interested in haematology.
www.b-s-h.org.uk

Chief Medical Officer
The Chief Medical Officer (CMO), Sir Liam Donaldson, is the UK Government’s principal medical adviser and the professional head of all medical staff in England. The website provides up-to-date information on key public health and clinical quality issues and provides access to CMO reports and publications.
www.dh.gov.uk/cmo

Citizens Advice
Citizens Advice helps people resolve their legal, money and other problems by providing free information and advice from nearly 3,400 locations and by influencing policymakers.
www.citizensadvice.org.uk

Department of Health
The Department of Health has a dedicated web page for VTE.
www.dh.gov.uk/vte

General Practice Research Database
The General Practice Research Database (GPRD) is a large, computerised database of anonymised longitudinal medical records from primary care. The GPRD collects data from over three million active patient records from primary care.
www.gprd.com

Healthcare Commission
The Healthcare Commission promotes improvement in the quality of the NHS and independent healthcare.
www.healthcarecommission.org.uk

Hospital Episode Statistics
Hospital Episode Statistics (HES) is a large database containing personal, medical and administrative details of all patients admitted to and treated in NHS hospitals in England. HES also links with the Office for National Statistics’ official death records for numbers of episodes that result in death within 30 days.
www.hesonline.nhs.uk

House of Commons Health Committee on the Prevention of VTE in Hospitalised Patients
The second report of the session 2004/05, together with formal minutes, oral and written evidence, was published on 23 February 2005 and can be viewed online.
Human Tissue Authority
The Human Tissue Authority is a new public body. Its role is to inform the public and the Secretary of State for Health about regulating the storage and use of human organs and tissue from the living, and the removal, storage and use of tissue and organs from the deceased, for specified health-related purposes and public display. Its remit extends to England, Wales and Northern Ireland.
www.hta.gov.uk

Lifeblood: The Thrombosis Charity
Lifeblood was created with the philosophy of collaboration, openness and information sharing. It is governed by four trustees, supported by a multidisciplinary group, who are recognised as leaders in thrombosis care and research within the UK.
www.thrombosis-charity.org.uk

National Centre for Anticoagulation Training
The National Centre for Anticoagulation Training provides theoretical and practical training in all aspects of anticoagulation, with courses accredited through the University of Birmingham and aimed at all healthcare professionals.
www.anticoagulation.org.uk

National Institute for Health and Clinical Excellence
The National Institute for Health and Clinical Excellence (NICE) was formed on 1 April 2005, when the National Institute for Clinical Excellence took on the functions of the Health Development Agency to create a single ‘excellence-in-practice’ organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
www.nice.org.uk

National Patient Safety Agency
The National Patient Safety Agency (NPSA) is a Special Health Authority created to coordinate the efforts of all those involved in healthcare, and, more importantly, to learn from patient safety incidents occurring in the NHS.
www.npsa.nhs.uk

NHS Confederation
The NHS Confederation brings together the organisations that make up the modern NHS across the UK. It works with its members to transform health and health services for the better.
www.nhsconfed.org

NHS Direct
NHS Direct provides a gateway to health information on the internet.
www.nhsdirect.nhs.uk

NHS gateway for local services
This site links to local NHS services in England and provides national information about the NHS. The new NHS search engine allows searches of over 600,000 web pages that provide NHS and health information. There are also contact details on the website for local services, including doctors, dentists, opticians, pharmacies and walk-in centres.
www.nhs.uk/england

NHS Litigation Authority
The NHS Litigation Authority (NHSLA) is responsible for handling negligence claims made against NHS bodies in England. It also monitors human rights case law on behalf of the NHS. Since April 2005, the NHSLA has been responsible for handling family health services appeals. In August 2005, it acquired the further function of coordinating equal pay claims on behalf of the NHS.
www.nhsla.com

Office for National Statistics mortality statistics
The Office for National Statistics publishes the number of deaths by cause, using the International Classification of Diseases (ICD-10).
www.statistics.gov.uk/statbase/Product.asp?vlnk=618

Royal College of Obstetricians and Gynaecologists
The Royal College of Obstetricians and Gynaecologists is dedicated to encouraging the study and advancement of the science and practice of obstetrics and gynaecology.
www.rcog.org.uk

Thrombosis Research Institute
The Thrombosis Research Institute is a multidisciplinary organisation concerned with the inter-related problems of thrombosis and atherosclerosis.
www.tri-london.ac.uk

VERITY
VERITY is a national VTE registry that will enable healthcare professionals to develop and improve the treatment of VTE through increasing knowledge and sharing good practice.
www.verityonline.co.uk